12-17-2021

Effectiveness of tPA at reducing amputations in patients with severe frostbite

Kylie Gravatt
James Madison University

Meredith Mahen
James Madison University

Effectiveness of tPA at Reducing Amputations in Patients with Severe Frostbite

Kylie Gravatt, PA-S & Meredith Mahen, PA-S
James Madison University Physician Assistant Studies, Harrisonburg, VA

ABSTRACT

Objective: To determine the efficacy of tissue plasminogen activator (tPA) therapy in reducing the number of limb and digit amputations in patients with severe frostbite.
Introduction: Current treatment regimens for frostbite consist mainly of rapid rewarming measures and wound care. This regimen is unfortunately many times not sufficient in cases of severe frostbite and frequently leads to delayed amputations.
Methods: A search was conducted in Pubmed using the terms "Frostbite"[Mesh]) AND "Tissue Plasminogen Activator"[Mesh]. Articles were chosen based on relevancy to the research question and having a publication date after 2005. Case reports were excluded.
Results: All three studies reported a decrease in incidence of amputation from severe frostbite in those who received tPA. When combining the results among the studies, the total number of at-risk digits was 259 when looking at the patients who received tPA. Of those 259 digits, 189 were salvaged after tPA use, leading to an overall salvage rate of 73%.
Conclusion: TPA therapy shows potential as a new and promising treatment of severe frostbite for a specific subset of patients. If specific measures are met, the benefits seem to outweigh the risks. That being said, further studies are warranted to solidify these results and prove efficacy.

INTRODUCTION

Frostbite occurs after prolonged exposure to subfreezing temperatures. Those with peripheral vascular disease, diabetes, and mental illness are at increased risk for developing frostbite.[1] Severe frostbite frequently progresses to life changing amputations of digits and limbs. Frostbite causes tissue damage and necrosis by directly freezing the tissues and indirectly causing vasospasm and arterial thrombosis.[2] This indirect mechanism consists of the release of inflammatory mediators leading to edema and endothelial injury. The endothelial damage causes the formation of microemboli which in turn prevents dermal blood flow, leading to tissue ischemia.[3]

The current treatment of frostbite aims at limiting the amount of permanent damage through rapid rewarming, wound care, and efforts to enhance tissue viability.[1] Unfortunately, current treatment regimens still frequently lead to delayed amputation. Studies performed as early as 1992 have shown that the use of tissue plasminogen activator (tPA), specifically alteplase, can reduce amputation rates in patients with severe frostbite. Although, this has not been clinically accepted until recently.[4]

Alteplase is a thrombolytic drug that binds to fibrin in the thrombus and converts entrapped plasminogen into plasmin, initiating local fibrinolysis.[5] The reasoning behind its use in the treatment of severe frostbite is its ability to dissolve the dermal microemboli thus leading to increased tissue perfusion.[3] This study aims to look at the efficacy of tPA and heparin, in addition to standard therapy, in reducing the number of limb and digit amputations when compared to standard therapy alone.

PICO

P- Patients ages 8-64 with severe frostbite within the first 24 hours of symptoms and without contraindications to receive thrombolytics
I- tPA and heparin in addition to standard therapy
C- Standard therapy (rewarming)
O- Reduction in limb and digit amputations

CLINICAL QUESTION

For patients ages 8-64 with severe frostbite does tPA and heparin, in addition to standard therapy, reduce the number of limb and digit amputations when compared to standard therapy alone?

METHODS

As outlined in Figure 1, the database Pubmed was used to conduct an initial search. The terms "Frostbite"[Mesh]) AND "Tissue Plasminogen Activator"[Mesh] were used. This search yielded 19 articles and after duplicates were removed, 17 articles remained. These articles were screened based on publication date. One article was removed due to being published prior to 2005. The remaining 16 articles were then screened for relevance to our clinical question. Articles were excluded if the patients were treated with a medication other than tPA, heparin, or aspirin, if they were a single case report, or if they were written in a language other than English. This left 3 full-text articles which were chosen to be included in this quantitative meta-analysis. These articles were chosen based on their comparison of tPA and heparin with standard therapy to standard therapy alone for treating severe frostbite.

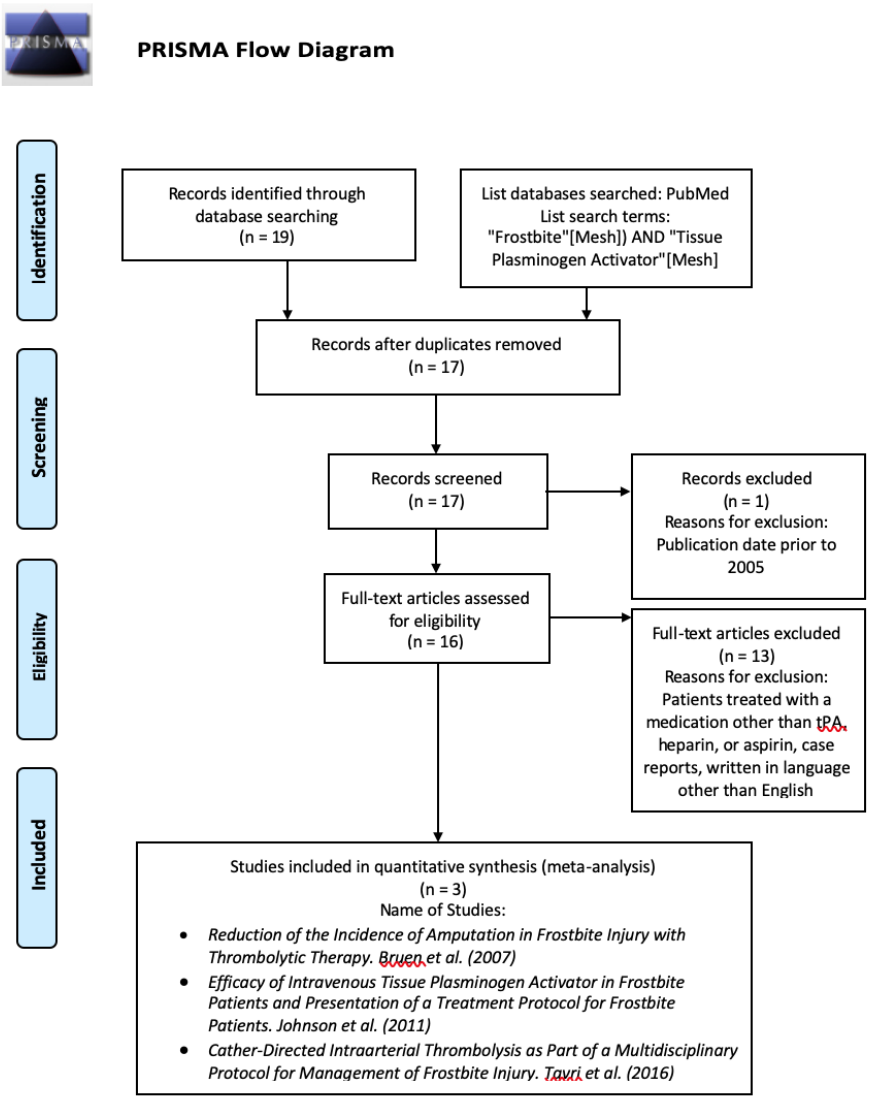

Figure 1. PRISMA flow diagram depicting the article selection process.

RESULTS

Study 1:

Reduction of the Incidence of Amputation in Frostbite Injury with Thrombolytic Therapy. Bruen et al. (2007)[6]

Study Objective

To determine if thrombolytic therapy will decrease the incidence of amputation when administered within 24 hours of exposure.

Study Design

This is a single institution retrospective review of clinical outcomes and resource use at the University of Utah Medical Center burn unit. This is a 12-bed unit, staffed by 3 full time

physicians who provide care to a wide range of burn, soft tissue, and traumatic injuries including frostbite.

Study subjects were identified via data extracted from patient medical records. Data from 2001-2006 was used to identify frostbite patients treated with tPA and data from 1995-2006 was used to identify the control subjects who were not treated with tPA. 32 total patients were identified as being treated for a frostbite injury between 1995 and 2006. Seven of these patients received tPA; 6 within 24 hours of exposure and 1 after 48 hours of exposure. This patient was thus included in the control group since tPA was not received within 48 hours. The mean age of patients treated with tPA was 32.3 and the mean age of all other patients was 37.4. 25 patients were male and 7 were female. 4/6 patients who received tPA were male and 21/26 patients who did not receive tPA were male. The authors used the patient medical records to gather data about exposure circumstances, duration to treatment, and number of digits and proximal extremities involved.

All 32 patients were evaluated by an attending burn surgeon at the time of admission and were given initial therapy including immediate rewarming and fluid resuscitation as appropriate. They then assessed vascular compromise via doppler pulses, capillary refill and skin color. Patients who had absent pulses or who had black or deep purple discoloration of digits underwent a perfusion evaluation via digital angiography. If significant perfusion defects were noted, tPA administration was initiated. Patients were excluded from receiving tPA if they had a history of concurrent trauma, neurological impairment, recent surgery or hemorrhage, or bleeding diathesis. TPA was administered at a rate of 0.5-1.0 mg/hr. Heparin was also administered at a rate of 500 U/hr. Repeat angiograms were obtained to evaluate response to treatment every 8-12 hours. Administration was discontinued when perfusion was achieved or when the total therapy time reached 48 hours. All patients were managed with identical local wound care regardless of receiving tPA or not. They also all were assisted in general range of motion therapy throughout their treatment.

Amputation was done on areas of obvious necrosis or mummification development. Primary study endpoints include number of digit amputations (fingers and toes) and amputations of more proximal joints (ray, transmetatarsal, and below the knee). Secondary endpoints included cumulative length of stay, total costs, cost per involved digit, and cost per digit saved. Outcomes of patients who received tPA were then compared to the outcomes of patients who received standard therapy alone. Statistical analysis was performed using SPSS software, version 14.0. A P value of $<.05$ using the Mann-Whitney U test was considered significant.

Study Results

For the purpose of this research, only primary endpoints were evaluated. As seen in Table 1, for the 26 patients who did not receive tPA, a total of 234 digits were involved. Of those 234 digits, 97 of them required amputation. Resulting in a total of 41% of digits requiring amputation for this group. For the 6 patients who received tPA within 24 hours, there were a total of 59 digits involved. 6 of those 59 digits required amputation; 10% of the digits involved. These results display a 31% decrease in digit amputation rate between the control group and tPA group. These results are statistically significant with a P value $<.05$. Type of amputation was also looked at. In the control group there were a total of 14 proximal amputations done, whereas in the tPA group, no amputations were necessary proximal to the digits.

Table 1: Amputation Outcomes of Patients Who Received tPA Compared With All Other Patients Who Did Not Receive tPA.

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.

Study Critique

This study is a retrospective cohort study and not a randomized control trial (RCT) limiting the significance of this study. The sample size is small at 32 with only 6 patients who received tPA, thus limiting the study further. The mean age was reported for each group but there were no specific ages listed for each patient. This made the study hard to compare to other studies in which age was a factor in determining success of treatment. Perfusion was assessed in this study to determine who received tPA and who did not. Therefore, only patients with inadequate perfusion received tPA and were compared to patients who had adequate perfusion on initial exam. A more reliable comparison would be comparing patients with inadequate perfusion who received tPA to patients with inadequate perfusion who did not receive tPA. There were significantly more men in this study which makes it more difficult to extrapolate data out for women. Lastly, there was no indication of follow up. It is unknown whether patients required amputation later on after their initial hospital stay. A strength of this study is that it has a comparison/control group as opposed to other relevant studies being investigated which do not have a comparison.

Study 2:

Efficacy of Intravenous Tissue Plasminogen Activator in Frostbite Patients and Presentation of a Treatment Protocol for Frostbite Patients. Johnson et al. (2011)[2]

Study Objective

To look at the use of tPA as a safe and effective treatment to reduce the number of digit amputations in severe frostbite injury.

Study Design

The study was a retrospective chart review of 11 patients who were treated at Hennepin County Medical Center (HCMC) Burn Unit between 2008 and 2010. These patients were chosen based on being given the diagnosis of frostbite and being treated with tPA. The patients ranged in age from 19 to 64 years old.

Before being given tPA, the patients were imaged with technetium (Tc)-99m triple-phase bone scintiscan to quantify the extent of frostbite damage. Digits were considered at risk for amputation if the early-phase scan showed decreased perfusion. Each of the 11 patients met the criteria for tPA administration as described in Table 2 below. These patients were administered IV tPA per the protocol at HCMC. This protocol included tPA at a dose of 0.15 mg/kg IV bolus followed by 0.15 mg/kg/h over 6 hours, up to a max dose of 100mg to be given. One hour after completion of tPA administration, a heparin bolus 3000 units IV was given and heparin was continued over 3 to 5 days with the goal of doubling the partial thromboplastin time (PTT) from baseline. A repeat Tc-99m bone scan was performed 24-72 hours after completion of tPA to evaluate the effectiveness and prognosis.

Table 2. Exclusion and Inclusion Criteria for tPA administration.

Inclusion Criteria:	**Exclusion Criteria:**
No improvement on rapid rewarming in tepid water (38-42 C for 15-20 minutes)	Severe Hypertension
Absent Doppler pulses in limbs and/or digits	Recent trauma, stroke, or bleeding disorder
Limited perfusion on Tc-99m 3-phase bone scan	Pregnancy
Less than 24 hours since rewarming has been completed	Mental Incapacity
	Repeated freeze-thaw cycles
	More than 24 hours of cold exposure

Study Results

The results of the Tc-99m triple-phase bone scan for the 11 patients revealed a total of 16 hands and 6 feet that were affected with severe frostbite. These had 73 digits that were determined to be at risk of amputation, as determined by the decreased perfusion on the bone scan. Of the 73 digits, 43 digits resulted in amputation while 30 were able to be saved. This means that 41% of the digits at risk for amputation did not require amputation after the administration of tPA.

Study Critique

This study was limited by the fact that it had a very small sample size of 11 patients. It also only looked at the patients that received tPA for frostbite and did not compare to a control group who only received rewarming treatments for example. The risk of amputation however, is a large risk that limits the possibility of having a control group as they would most likely have a higher incidence of amputation. Other patient factors that were not accounted for in this study and therefore could have had an effect on the need for amputation were: use of tobacco and alcohol, history of diabetes and peripheral vascular disease, and the patient's age. There were no genders reported for the patients making it unclear if there is a gender difference in treatment response. A strength to this study is that it provided specific inclusion and exclusion criteria for administration of tPA.

Study 3:

Cather-Directed Intraarterial Thrombolysis as Part of a Multidisciplinary Protocol for Management of Frostbite Injury. Tavri et al. (2016)[7]

Study Objective

To evaluate intraarterial catheter-directed thrombolysis for prediction and prevention of delayed surgical amputation as part of multidisciplinary management of frostbite injury.

Study Design

This was a single institution retrospective case review series of 13 patients who were treated with intraarterial tPA for frostbite injury between 2009 and 2015. All patients received a

multidisciplinary approach to treatment including evaluation of the injured extremity in regard to skin color, other dermatologic changes, capillary refill, and quality of peripheral pulses determined by both palpation and doppler evaluation. Patients who showed skin discoloration, poor capillary refill (> 3 s), or weak pulses were suggested of having impaired perfusion. Conservative treatment was initiated for patients including rapid rewarming therapy, wound dressings, prophylactic antibiotic treatment, pain control with NSAIDs or opioids, and evaluation of contraindications to receiving tPA therapy. Contraindications included major trauma with increased bleeding risk.

Baseline angiograms were performed on all patients by an interventional radiologist who then made the decision to initiate tPA. TPA was given at a maximum rate of 1mg/extremity/hour with a maximum of 2mg/hour. Concurrent IV heparin was given and titrated to a subtherapeutic PTT goal of 40-60 s, along with daily 81 mg aspirin. TPA was given for a maximum of 72 hours and discontinued when there was complete angiographic response or a lack of any improvement after 72 hours of therapy. The completion angiograms were classified as complete, partial or no response and were compared to the baseline angiograms. They then assessed for association with follow-up amputation rates. Correlations were assessed between amputation outcome and duration of cold exposure, time between exposure and rewarming therapy, and time between exposure and tPA therapy.

Study Results

For the purposes of this study, endpoints other than amputation rates after giving tPA were not reported on. Of the 13 patients in this study, 127 digits were found to be at risk of amputation due to decreased tissue perfusion seen on angiography. Of the 127 digits treated with catheter-directed intra-arterial tPA, 101 had a complete angiographic response, 26 had a partial angiographic response, and zero had no angiographic response. In the end, 106 digits (83.4%) had complete recovery and only 21 digits (16.6%) resulted in amputation.

Study Critique

This study is a retrospective case series and not an RCT. It has no comparison/control group and the sample size is very small. The patients are mostly male so it is unknown if outcomes can apply to women. A strength of this study is that it evaluates angiographic response to tPA and how that correlates with amputation rate. Despite having a small sample size, the number of digits involved was 127, potentially making data more reliable.

DISCUSSION

The treatment of frostbite has typically consisted of rewarming measures regardless of the extent of the tissue damage. These measures when applied to severe frostbite more often than not, result in amputation of the affected digit or limb. TPA has therefore been studied in this review as a possible superior treatment for minimizing amputation rates in severe frostbite. The components of the three studies are summarized below in Table 3.

Table 3. Overview of the studies.

	Study 1: Bruen et al.[6]	Study 2: Johnson et al.[2]	Study 3: Tavri et al.[7]
Patients, n	32 (6 received tPA)	11	13
Population	Mean age of patients: 32.3 (treated with tPA); 37.4 (all other patients) 25 males 7 females	Age range: 19-64 yo No gender reported	Mean age of patients: 33.4 yo Age range: 8-62 yo 11 males 2 females All white
Location	University of Utah Medical Center burn unit. Salt Lake City, UT.	Hennepin County Medical Center (HCMC) Burn Unit. Minneapolis, MN	Division of Vascular and Interventional Radiology, Department of Radiology, University Hospitals and Case Western Reserve University School of Medicine. Cleveland, OH.
Primary Outcome	Incidence of amputation after receiving tPA compared to those who did not receive tPA	Incidence of amputation after receiving tPA	Incidence of amputation after receiving tPA
Medications Administered	tPA at a rate of 0.5-1.0 mg/hr; Heparin at a rate of 500 U/hr	tPA at a dose of 0.15 mg/kg IV bolus followed by 0.15 mg/kg/h; Heparin bolus 3000 units IV	0.5-1 mg tPA/ extremity/hour, with a maximum overall total dosage of 2 mg/hr. Heparin was titrated to a subtherapeutic PTT goal of 40–60 s; Aspirin 81 mg PO daily

All three studies looked at the primary outcome of the incidence of amputation among those who received tPA and Study 1 was the only study that also compared these findings to a control group. When combining the results of this outcome among all three studies, the total number of at-risk digits was 259 when looking at the patients who received tPA. Of those 259 digits, 189 were salvaged after tPA use. This is a salvage rate of 73%. A strength of this review is that it includes a large number of digits at risk of amputation, so while the sample size of each study is small, the number of total digits investigated was large.

Regarding the reliability of these findings, there are several weaknesses to this review including the small overall sample size. As mentioned above, the total number of digits involved was 259, however, the total number of subjects with frostbite who received tPA was only 30.

Study 1 was a retrospective cohort with a treatment group and comparison group. The other two studies were retrospective case reviews that did not include a control or comparison group. That being said, only Study 1 was able to accurately evaluate tPA treatment and compare outcomes to standard rewarming therapy. The other two studies were not able to accomplish any comparison and only served to evaluate the efficacy of tPA through the number of compromised digits before and after treatment. Even though Study 1 had the comparison group, the two groups did not have similar circumstances. The treatment group was determined by patients who did not have adequate perfusion on exam and the control group was determined by patients who did have adequate perfusion on exam. A better and more reliable comparison would include two groups under similar conditions.

There was no standardized dose of tPA used throughout the 3 studies. TPA dosage was determined by hospital protocol. This resulted in patients from different hospitals receiving a different rate and amount of tPA. In addition, the supplemental agent of heparin was not given at a standardized dose either. Each study gave heparin at a dose determined by hospital protocol. Study 3 gave an additional aspirin which was not standard throughout the other two studies.

Ages of patients was also a concern and considered a weakness to the review. Study 1 reported a mean age but not specific ages of patients. Study 2 provided an age range and Study 3 provided an age range and a mean but no specific ages of those treated either. This makes it difficult to stratify information from this review out to the public since it is unknown what ages had benefits to treatment and what ages did not. Similarly, most patients who received tPA were men, making it hard to extrapolate data from this review to women. Study 1 and 3 reported mostly male patients and Study 2 did not report on gender at all.

Lastly, there were no follow up reports throughout the studies making it impossible to determine whether patients required amputations later on due to their injuries. There were also no reports in Study 1 or 2 on whether comorbidities were taken into account including a history of diabetes mellitus, peripheral vascular disease, or alcohol and tobacco use. Study 3 did include these specific comorbidities. These comorbidities could alter outcomes and should be looked at further in future studies.

Studies 1 and 3 reported p values. In study 1 the Mann-Whitney U test was used to calculate the p value and determine statistical significance ($p<0.05$). In study 3, a two-tailed p value was calculated via the Fisher exact test ($p= 0.007$). Whereas in study 2, p values were not obtained, only percentages were used to determine percent of digits salvaged after tPA use.

After reviewing the funding of each study, there does not appear to be any biases. Study 1 was funded internally from its University of Utah affiliation and there were no conflicts of interest identified in Studies 2 and 3.

CONCLUSION

When looking at the incidence of amputation after receiving tPA in those with severe frostbite, there appears to be a decrease in amputation rate compared to those who did not receive tPA. As these studies have shown to be small and few, future studies, particularly randomized control trials (RCTs) should be performed. RCTs with standardized dose protocols would elicit more reliable results. Comparison groups should also be more similar to one another so results are more authentic. Specific age ranges should be used and there should be equal male and female participation to ensure that age and gender variables are taken into account when extrapolating results. Lastly, comorbidities such as diabetes mellitus, peripheral vascular disease, and alcohol and tobacco use should be considered in all patients when looking at results.

It is also important to consider the risk versus benefit of this treatment option. The benefit of not needing to have a limb or digit amputated is a life changing difference. There is of course a potential risk with systemic thrombolysis such as severe bleeding (ie. intracranial hemorrhage), however this risk is small. Study 1 reported that only one patient developed a retroperitoneal hematoma as a complication of therapy that resolved without intervention. Study 3 reported only two patients that developed femoral access site bleeding that was managed conservatively. Only one of those two patients underwent surgical exploration and repair of a brachial artery hematoma. Study 2 did not report any complications.

The American Journal of Neuroradiology reported in 2017 that the approximate cost of IV tPA in the United States is $7000 for a 100mg vial.[8] The treatment of frostbite in these studies only used around an average of 0.1 mg an hour for a couple of days therefore this cost would only be a fraction of that total. While this is still a large amount of money, when looking at the cost of surgery to perform an amputation it can range anywhere from $20,000-$60,000 depending on surgeon, facility, hospital stay length, medications given, and medical supplies used.[9]

The mainstay of treatment for frostbite despite its severity, has consisted of rewarming measures that have not changed for decades. This review into the use of tPA shows that there is potential for a new and promising treatment of frostbite for a specific subset of patients. They must present within 24 hours of injury, show decreased perfusion on scans, and have no contraindications to tPA. If these measures are met, the benefits seem to outweigh the risks, however, further studies are still needed to solidify this.

REFERENCES

1. Zafren K, Mechem CC. Frostbite: Emergency care and prevention. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA, 2020. https://www.uptodate.com/contents/frostbite-emergency-care-and-prevention?search=frostbite%20causes&source=search_result&selectedTitle=1~46&usage_type=default&display_rank=1#H5

2. Johnson AR, Jensen HL, Peltier G, DelaCruz E. Efficacy of intravenous tissue plasminogen activator in frostbite patients and presentation of a treatment protocol for frostbite patients. *Foot Ankle Spec*. 2011; 4(6): 344-348. doi:10.1177/1938640011422596

3. Hutchison RL, Miller HM, Michalke SK. The Use of tPA in the Treatment of Frostbite: A Systematic Review. *Hand (N Y)*. 2019; 14(1): 13-18. doi:10.1177/1558944718800731

4. Skolnick AA. Early data suggest clot-dissolving drug may help save frostbitten limbs from amputation. *JAMA*. 1992; 267(15): 2008-2010.

5. Lexicomp, Inc. Alteplase: Drug Information. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA, 2020. https://www.uptodate.com/contents/alteplase-drug-information?search=alteplase%20MOA&source=panel_search_result&selectedTitle=1~92&usage_type=panel&kp_tab=drug_general&display_rank=1#F132222

6. Bruen KJ, Ballard JR, Morris SE, Cochran A, Edelman LS, Saffle JR. Reduction of the incidence of amputation in frostbite injury with thrombolytic therapy. *Arch Surg*. 2007; 142(6): 546-553. doi:10.1001/archsurg.142.6.546

7. Tavri S, Ganguli S, Bryan RG Jr, et al. Catheter-Directed Intraarterial Thrombolysis as Part of a Multidisciplinary Management Protocol of Frostbite Injury. *J Vasc Interv Radiol*. 2016; 27(8): 1228-1235. doi:10.1016/j.jvir.2016.04.027

8. Leslie-Mazwi TM, Chandra RV, Hirsch JA. To tPA or Not to tPA, That Is the Question. *American Journal of Neuroradiology.* 2017; 38(8): 1464-1466. doi: http://doi.org/10.3174/anjr/A5263

9. What is the Cost of Finger Amputation Surgery? Industrial Safety and Hygiene News Web site.https://www.ishn.com/articles/97845-what-is-the-cost-of-finger-amputation-surgery#:~:text=The%20cost%20of%20surgery%20for,%2C%20anesthetics%2C%20and%20medical%20supplies. Published February 5, 2014. Accessed November 23, 2020.