Comments on “The Use of tPA in the Treatment of Frostbite: A Systematic Review”

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Figure 1. A 71-year-old female with severe frostbite bite of her right foot and hand successfully salvaged with thrombolysis. (a, b) Pre-operative photographs of left and right hand; (c) pre-treatment angiogram of the patient's right hand showing perfusion deficits to right thumb, index and middle fingers and retrograde filling of the right radial artery; (d) photographs 2-months post tPA treatment without any deficits on examination of the hand; and (e) angiogram of patient's right hand after 24 hours of intra-arterial tPA infusion revealing restoration of right index and middle fingers, right thumb and radial artery perfusion.

We have read with interest the recently published article “The use of tPA in the Treatment of Frostbite: A systematic Review” by Dr. Richard Hutchison et al published in the January 2019 issue.¹ We applaud them for their efforts to study this difficult problem and agree with much of their findings. However, we believe their final recommendation to avoid the use of thrombolytics in frostbite patients unless conducting in an active research protocol may be misleading to readers. We have found thrombolysis to be an effective means of limb salvage for severe frostbite at our institution,

which is a tertiary referral center evaluating numerous frostbite victims annually. (Figure 1) We believe their findings might dissuade others from attempting thrombolytic ther-

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Table 1. Summary of Outcomes of Studies Using Thrombolytics in Severe Frostbite.

Author	Year	Design	Level of Evidence	Intervention	Treatment Route	Imaging Modality	Digits at Risk (n)	Amp(n)	Limb Salvage Rate (%)	Complications
<i>Lindford, et al</i>	2017	retrospective, observational cohort study	III	intra-arterial tPA (5mg bolus/0.5 - 1 mg/hr) + therapeutic UFH for 12 hours if contraindication to tPA; iloprost (0.5 - 2.0 ng/kg/min) for 2 - 3 days + UFH + 81 mg ASA for 24 - 72 hours	IATT	Angiography	100	19	81.1%	1 patient developed catheter-site aneurysm that resolved with conservative treatment
<i>Tavri, et al</i>	2016	single-institution case series	III	intra-arterial tPA (1 mg/hr for 48 hours) + UFH + 81 mg ASA for 24 - 72 hours	IATT	Angiography	127	21	83.0%	1 surgical exploration and repair of brachial artery hematoma and pseudoaneurysm
<i>Patel, et al</i>	2017	retrospective chart review	III	Treatment: intra-arterial tPA (25-5 mg/hr for 48 hours) + Heparin(500-1000 U/hr) Control: Topical silver sulfadiazine + gauze + surgery	IATT	Angiography	80	12	85.0%	none
<i>Bruen, et al</i>	2007	retrospective chart review	III	intra-arterial tPA (25-1.0 mg/hr for 24 - 28 hours)	IATT	Angiography	59	6	90.0%	1 retroperitoneal hematoma
<i>Ibrahim, et al</i>	2015	case series	V	intra-arterial tPA (2-4 mg bolus + 1 mg/hr for 48 hours) + UFH + 81 mg ASA for 24 - 48 hours	IATT	Angiography	30	0	100.0%	none
<i>Cauchy, et al</i>	2011	randomized control trial	III	Treatment: rt-PA (100 mg bolus)	IV	Tc-99m triple phase bone scan	159	5	96.9%	Only minor: hot flushes in 55%, nausea 25%, palpitation 15%, vomiting in 5%
<i>Wagner, et al</i>	2011	case report	V	intra-arterial tPA (0.25 mg/hr for 72hours) + UHF (500 U/hr)	IATT	Angiography	8	0	100.0%	none
<i>Johnson, et al</i>	2011	retrospective	III	IV tPA (0.15 mg/kg bolus followed by 0.15 mg/kg/hr for 6 hrs + heparin for 3-5 days	IV	Tc-99m triple phase bone scan	110	43	60.9%	none
<i>Dolbec, et al</i>	2013	case series	V	Intra-arterial thrombolytic therapy	IATT	Angiography	20	10	50.0%	none
<i>Twomey, et al</i>	2005	retrospective	IV	IV tPA (0.15 mg/kg bolus followed by 0.15 mg/kg/hr for 6 hrs + heparin for 3-5 days intra-arterial tPA (0.075 mg/kg/hr for 6 hours)	IV (13) & IATT (6)	Tc-99m triple phase bone scan	174	33	81.0%	hematuria
<i>Saemi, et al</i>	2009	retrospective	V	brachial artery papaverin 30mg/hr + IV heparin 800 U/hr + Intra-arterial tPA (0.5 mg/hr for 24 hours)	IATT	Angiography	10	0	100.0%	none
<i>Nygaard, et al</i>	2017	retrospective	IV	IV alteplase 0.15 mg/kg bolus + 0.15 mg/kg/hr for 6 hours + lovenox Control: traditional care	IV	Tc-99m triple phase bone scan	260 tPA 155 control	16 tPA 16 control	74.0% tPA* 55.0% control*	infection + cellulitis; 2 patients with bleeding complications
<i>Wexler, et al</i>	2017	retrospective	IV	IV tPA 0.15 mg/kg bolus followed by 0.15 mg/kg/hr for 6 hrs + heparin for 3-5 days	IV	Not reported	65	16	75.4%	1 patient w/ nonspecified complications
<i>Jones, et al</i>	2017	retrospective	III	IV alteplase 0.15 mg/kg bolus + 0.15 mg/kg/hr for 6 hours + lovenox	IV	Tc-99m triple phase bone scan	40	11	72.5%	2 patients had bleeding complications necessitating stop of heparin/coumadin
<i>Sheridan, et al</i>	2009	retrospective	V	intra-arterial tPA (1 mg/hr) + therapeutic LMWH	IATT	Angiography	15	1	93.0%	groin hematoma at catheter entry site after 36 hours of lytics
<i>Gross, et al</i>	2012	retrospective	V	warm bath, tPA(0.15 mg/kg bolus + 0.15 mg/kg/hr after bolus + heparin 12 units/kg/hr for 36 hours	IV	Tc-99m triple phase bone scan	10	10	0.0%	none
<i>Gonzaga, et al</i>	2016	retrospective	III	control: conservative therapy Treatment: intra-arterial tPA(0.25-0.5 mg/hr for 48 hours) + Heparin(500 U/hr) + papaverine 30 mg/mL for 24 - 72 h	IATT	Angiography	472	148	68.6%	groin hematoma (3 patients), 1 patient w/ acute renal failure, RUE thrombosis + ischemia
Total					IATT 10 (59%), IV 7 (41%)		1844	346	81.2% overall, 78.7 weighted average	15 total (4.3%) 6 - Hematoma 5 - bleeding 2 - pseudoaneurysms 1 - ischemic limb 1 - acute kidney injury

*Limb salvage rate represents average cohort salvage rate as determined by the Hennespin Score.

**Amp = Amputation defined as amputation of digit or extremity; ASA = Aspirin; IATT = Intra-arterial thrombolytic therapy; IV = Intravenous infusion; tPA = Tissue plasminogen activator; UFH = Unfractionated heparin

apy for frostbite, leading to amputation of salvageable digits or limbs.

While the technique of their systematic review is excellent, we feel they arrived at an erroneous conclusion because their search terms were not broad enough to capture all of the pertinent studies in the literature discussing this therapy in frostbite patients. Hutchison utilized the search terms “frostbite AND tissue plasminogen activator OR tPA OR amputation OR anti-platelet therapy OR extremity salvage.” We performed our own literature review of the same topic with the terms “frostbite AND tissue plasminogen activator OR tPA OR thrombolytics OR fibrinolytics”; returning an additional two relevant articles, which we believe should have been included.^{2,3} These additional articles, both written in 2012, report an additional 30 at risk digits treated successfully with thrombolytics. Our literature search identified a total of 325 patients that were studied and 216 patients with severe frostbite who received thrombolytics.

Furthermore, the recent article failed to examine the aggregate data to determine if this therapy improves limb salvage rates. After analyzing the results of all papers returned by our literature review (Table 1), we found thrombolysis to be effective by reducing amputation rates. We observed a 78.7% weighted average rate of overall limb salvage and a 70.7% rate specifically in the upper extremity and digits. Additionally, our search revealed a low complication rate with the majority being minor bleeding events that resolved with cessation of thrombolytic therapy.

Despite the overall low level of evidence, our analysis of the same studies evaluated by Hutchison plus the additional relevant identified studies returned by our expanded search, reveal that tPA appears to prevent amputation in properly selected frostbite patients. Our current analysis of thrombolytic use in patients with severe frostbite mirrors our excellent clinical experience in this patient group. Figure 1 demonstrates the pre-treatment and post-treatment images and associated angiograms of a 71-year-old female with

severe three extremity frostbite found down outside for several hours. On initial presentation she lacked inflow to her right foot, and bilateral hands. With continuous infusion of tPA for 24 hours to each extremity, perfusion to her digits and foot was restored; avoiding amputation. It is our hope that our findings will encourage others to utilize thrombolytics in similar patients with severe frostbite to prevent amputation.

Ethical Approval

This study was approved by our institutional review board.

Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

Statement of Informed Consent

Informed consent, including photographic consent, was obtained from all individual participants included in the study.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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