



Research Article

Protocolled thrombolytic therapy for frostbite improves phalangeal salvage rates

Rosemary Elizabeth Paine¹, Elizabeth Noel Turner¹, Daniel Kloda²,
Carolyn Falank¹, Bruce Chung¹ and Damien Wilson Carter^{1,*}

¹Department of Surgery, Maine Medical Center, 22 Bramhall St, Portland, Maine 04102, USA, and ²Department of Radiology, Maine Medical Center, 22 Bramhall St, Portland, Maine 04102, USA

*Correspondence. Email: dcarter@mmc.org

Received 6 December 2019; Revised 27 December 2019; Editorial decision 21 January 2020

Abstract

Background: Frostbite is a cold injury that has the potential to cause considerable morbidity and long-term disability. Despite the complexity of these patients, diagnostic and treatment practices lack standardization. Thrombolytic therapy has emerged as a promising treatment modality, demonstrating impressive digit salvage rates. We review our experience with thrombolytic therapy for severe upper extremity frostbite.

Methods: Retrospective data on all frostbite patients evaluated at our institution from December 2017 to March 2018 was collected. A subgroup of patients with severe frostbite treated with intra-arterial thrombolytic therapy (IATT) were analysed.

Results: Of the 17 frostbite patients treated at our institution, 14 (82%) were male and the median age was 31 (range: 19–73). Substance misuse was involved in a majority of the cases (58.8%). Five (29.4%) patients with severe frostbite met inclusion criteria for IATT and the remaining patients were treated conservatively. Angiography demonstrated a 74.5% improvement in perfusion after tissue plasminogen activator thrombolysis. When comparing phalanges at risk on initial angiography to phalanges undergoing amputation, the phalangeal salvage rate was 83.3% and the digit salvage rate was 80%. Complications associated with IATT included groin hematoma, pseudoaneurysm and retroperitoneal hematoma.

Conclusions: Thrombolytic therapy has the potential to greatly improve limb salvage and functional recovery after severe frostbite when treated at an institution that can offer comprehensive, protocolled thrombolytic therapy. A multi-center prospective study is warranted to elucidate the optimal treatment strategy in severe frostbite.

Key words: Frostbite, Tissue plasminogen activator, Amputation, Digit salvage, Thrombolysis

Background

Severe frostbite is a cold injury that has the potential to cause considerable morbidity and long-term disability. Despite the complexity of these patients, diagnostic and treatment practices lack standardization. The National Burn Repository (NBR) and the National Trauma Data Bank collectively reported about 100 cases each year in the

USA from 2007 to 2014 [1]. However, the true incidence is not known because many facilities do not report to these trauma databases. Frostbite is commonly seen in homeless populations as well as with cold weather recreation and is often associated with the following risk factors: alcohol use, drug abuse, diabetes, dementia and mental illness [2–4].

Traditionally, the treatment of frostbite has been conservative with expectant management, utilizing amputation when necessary [4, 5]. Recently, more aggressive treatment modalities have gained widespread use with impressive clinical outcomes. Still, diagnostic and treatment modalities are highly variable amongst institutions, as there are no large scale, multi-center studies evaluating treatment protocols and associated outcomes [6]. Our institution, Maine Medical Center, treated 17 frostbite patients in the 2017–2018 winter season. Given the acute increase in incidence, we were compelled to rapidly adopt a protocolized treatment strategy in an effort to improve limb salvage. We utilized a standard approach that included catheter-directed intra-arterial thrombolytic therapy (IATT).

Thrombolytic therapy was first used for frostbite in 1992 and has emerged as a promising treatment modality [7]. A 2019 systematic review, including 17 studies, demonstrated overall digit salvage rates of 81.2% [6]. Theoretically, thrombolytic therapy targets the latter pathological effects of frostbite. In the first stage of injury involving direct cellular damage, intracellular freezing results in cell death and extracellular freezing leads to cellular membrane damage. This results in intracellular dehydration, electrolyte imbalances and subsequent cellular death. In the second stage of injury, the coagulation pathway is activated by cellular death [5, 8, 9]. A cycle of vasoconstriction and vasodilation occurs which leads to thrombosis and ischemia. The accumulation of inflammatory mediators, subsequent localized edema and additional platelet aggregation exacerbates this ischemic cycle [5, 8, 9]. The administration of a thrombolytic drug disrupts this cycle [10]. Tissue plasminogen activator (tPA) is most often used and acts by converting plasminogen into plasmin which lyses fibrin clots, thus destroying the thrombi created by the cold injury [10]. In this study, we will examine the demographic characteristics, diagnostic evaluation, treatment modalities and clinical outcomes of our cohort of frostbite patients.

Methods

Study design and data collection

Following approval from the Maine Medical Center Institutional Review Board, we collected retrospective data using the electronic health record and found that 17 frostbite patients were treated from December 2017 to March 2018 (Table 1). Patients were evaluated by the burn service on presentation, which occurred in either the outpatient clinic or the emergency department. Based on clinical assessment, cases were diagnosed as either minor or severe cold injury by an attending burn surgeon. Patients were rewarmed and resuscitated as indicated. We characterized severe frostbite by hemorrhagic blisters, skin necrosis and evidence of perfusion deficits. For superficial cases, no imaging was obtained. If distal perfusion was unclear, then digital Doppler ultrasound was performed. If there was clinical evidence of severe injury with impaired perfusion, interventional radiology was con-

Table 1. Demographics, mechanism of injury and casual factors of our frostbite patients.

Total, n	17
Age, years; median (range)	31 (19–73)
Sex, n (%)	
Male	14 (82.3)
Female	3 (17.6)
Location of injury, n (%)	
Upper extremity	11 (64.7)
Lower extremity	7 (41.2)
Torso	1 (5.9)
Length of stay, days; median (range)	3 (1–59)
Substance misuse, n (%)	10 (58.8)
Homeless, n (%)	4 (23.5)
Psychiatric illness, n (%)	7 (41.2)
Mechanism of injury, n (%)	
Hiking	2 (11.8)
Eluding law enforcement	2 (11.8)
Found down outside	4 (23.5)
Exposure with walking	6 (35.3)
Exposure during car breaking down	1 (5.9)
Lobstering	1 (5.9)
Unknown	1 (5.9)

sulted and patients underwent digital subtraction angiography (DSA) to determine arterial patency [11].

Patients diagnosed with mild frostbite injury were treated with conservative management. Conservative management consisted of supportive care with bedside debridement, local wound care, pain control and occupational and physical therapy. Blisters were unroofed if they were affecting range of motion and/or crossed a joint. Wound care consisted of either silver sulfadiazine, petroleum gauze and an antibacterial ointment or an aloe-based lotion. A multi-modal approach was used for pain, including acetaminophen, non-steroidal anti-inflammatory drugs, gabapentin and opioids. For injuries to the feet, there was no activity restriction implemented and patients were fitted with specialized shoes for ambulation. For injuries to the hands, patients underwent daily occupational therapy to maintain full range of motion.

Angiography and IATT

Patients diagnosed with severe frostbite involving the upper extremities were evaluated for inclusion in our IATT protocol. Inclusion criteria included severe frostbite, rewarming within 24 hours, presentation within 24 hours of injury, upper extremity injury, selective lower extremity injury and lack of contraindications to heparinization. If inclusion criteria were met, then interventional radiology was consulted and DSA performed via femoral artery access to assess for perfusion. If there was diminished perfusion, then tPA was administered via the intra-arterial catheter sheaths to the affected extremities at 0.5 mg/hr to each affected extremity. No bolus dose was administered on initiation of therapy. Systemic heparin infusions were initiated at sub-therapeutic doses of 12 units/kg/hr

in accordance with our institution's low intensity heparin infusion protocol. Heparin was also infused through the outer sheath of each catheter at 40 units/hr to maintain patency and prevent showering of thrombus from the catheter tip. While femoral catheters were in place, patients were maintained on bed rest and monitored in either the surgical intensive or intermediate care units and DSA was repeated every 24 hours. If improvement was noted on repeat angiography then IATT was continued for another 24 hours. IATT was halted and the catheter(s) were removed if no improvement was seen on repeat DSA or after a maximum of 3 days. During and after the completion of thrombolysis, supportive care was provided. At the completion of IATT, the heparin infusion was discontinued and transitioned to a low molecular weight heparin at 1 mg/kg twice daily for 7 days and aspirin at 325 mg for 3 months.

Surgical management differed between patients. Nuclear multiphase bone scintigraphy, or bone scan, was used to assist in surgical planning on select cases to determine macrovascular, microvascular and osseous perfusion [11]. Early surgical management included debridement and skin substitute placement or rotational flaps. Some patients underwent distal amputations and then subsequently required a more proximal amputation. In most cases, tissue was allowed to demarcate and mummify before amputation was performed.

Salvage rates were calculated for each individual who underwent IATT and for the combined cohort. With the assistance of the interventional radiologist, the number of phalanges with decreased perfusion on initial DSA were counted. Operative reports were inspected to determine which phalanges were subsequently amputated. Phalangeal salvage rate was calculated as below. Digital salvage rate was calculated in the same fashion.

$$\left(1 - \frac{\text{\#phalanges amputated}}{\text{\#phalanges with decreased perfusion on initial DSA}}\right) \times 100 = \text{\%phalangeal salvage}$$

Results

Demographic characteristics

Seventeen frostbite patients were treated between December 2017 and March 2018 (Table 1). The median age was 31 years (mean: 34.9, standard deviation [SD]: 15.3, range: 19–73) and 14 (82%) patients were male. Of the cohort, 7 (41%) were treated as inpatients and the remainder were managed at the outpatient burn clinic. Of those treated as inpatients, the median length of stay was 3 days (mean: 13.4, SD: 21.2, range: 1–59). Eleven (64.7%) cases involved the hands, 7 (41.2%) cases involved the feet and one case involved the torso. Substance misuse was involved in a majority of the cases: 10 (58.8%) patients were intoxicated with alcohol or illicit drugs at the time of injury. Four (23.5%) patients within the cohort were homeless at the time of injury and 7 (41.2%) patients had a psychiatric diagnosis.

Table 2. Group demographics and phalange characteristics of our intra-arterial thrombolytic therapy (IATT) frostbite patients^a

Total, n	5
Age, years, media (range)	31 (19–63)
Sex, % male	100
Time from injury to IATT, hrs; median (range)	15.4 (8.8–17.1)
Duration of tPA infusion, hrs; median (range)	62 (50.5–82.2)
Improvement in perfusion by phalange, %	74.5
Total with impaired perfusion on initial angiogram	106
Total with impaired perfusion on final angiogram	27
Phalangeal salvage ^b , %	83.3
Total at risk for amputation	106
Total amputated	14
Time from injury to amputation, days; median (range)	88 (53–192)

^aA total of 5 patients (all male) met eligibility criteria for IATT and a phalangeal salvage of 83% was achieved. Additional IATT and amputation information is reviewed

^bOne patient was lost to follow-up and was excluded from the salvage rate calculation

Interestingly, 2 patients were injured while being pursued by law enforcement. No patients were diabetic.

IATT yielded significant digit and phalangeal salvage rates

Five (29.4%) patients were clinically diagnosed with severe frostbite to the entirety of both hands (Figure 1) and DSA was performed to determine perfusion deficits. DSA confirmed no perfusion to the 106 phalanges and all met inclusion criteria for IATT (Table 2). One patient who underwent IATT, with severe frostbite to the hands, also had minor frostbite to the right calf and torso. It is unclear if IATT contributed to the healing of these other areas. One patient with severe frostbite to the hands was excluded from IATT because he presented several days after injury. Table 3 describes the details of IATT for each patient. The median time from injury to initiation of tPA was 15.4 hours (SD: 3.3, range: 8.7–17.0) and the median duration of tPA infusion was 62 hours (SD: 12.8, range: 50.5–82.2). Based on radiological analysis, initial DSA revealed decreased perfusion to a total of 106 phalanges between the 5 patients. At the completion of angiography, 27 phalanges demonstrated decreased perfusion, resulting in a 74.5% improvement in perfusion after tPA thrombolysis (Figure 2). Fourteen phalanges required amputation, therefore comparing phalanges at risk on initial angiography to phalanges undergoing amputation; we report an 83.3% phalangeal salvage rate (Table 2). When accounting for the number of digits requiring partial amputation, we report an 80% overall digit salvage rate.

Amputations

Of the 5 patients with severe frostbite who underwent IATT, 3 underwent surgical amputation. One patient did not require



Figure 1. Representative clinical photographs of frostbite injury to hands that occurred in two patients, labeled patient 2 (a) and patient 5 (b), upon hospital admission. Each patient presented with severe frostbite to each hand and both met inclusion criteria for intra-arterial thrombolytic therapy

amputation and one patient pursued follow-up care in a neighboring state and was reportedly scheduled for amputation of 2 digits but did not present for surgery. Of the 3 patients, the time from injury to amputation varied, with a median of 88 days (range: 53–192 days). Table 3 describes which phalanges were amputated for each patient undergoing IATT. No patients required complete amputation of any digit, and surgical management differed between patients. Two patients underwent amputation when digits had fully mummified. One patient underwent early amputation of a partial digit but required further amputation of other digits at a later date. One patient underwent 3 surgical procedures: (1) early debridement of 4 partial digits and skin substitute placement; (2) re-amputation of one partial digit, skin substitute placement to another residual digit and rotational flap to another residual digit; and (3) partial amputation of 2 digits.

Twelve patients were treated conservatively. One patient with severe frostbite was excluded from IATT and required

amputation of one distal phalanx. Salvage rate was not calculated for this patient because he did not undergo DSA. Of the remaining 11 patients with minor frostbite, none required amputation.

IATT complications

Three patients developed groin hematomas, with one patient developing a pseudoaneurysm. One patient developed a retroperitoneal hematoma and bacteremia of unclear etiology. All complications were self-limiting and required no surgical intervention.

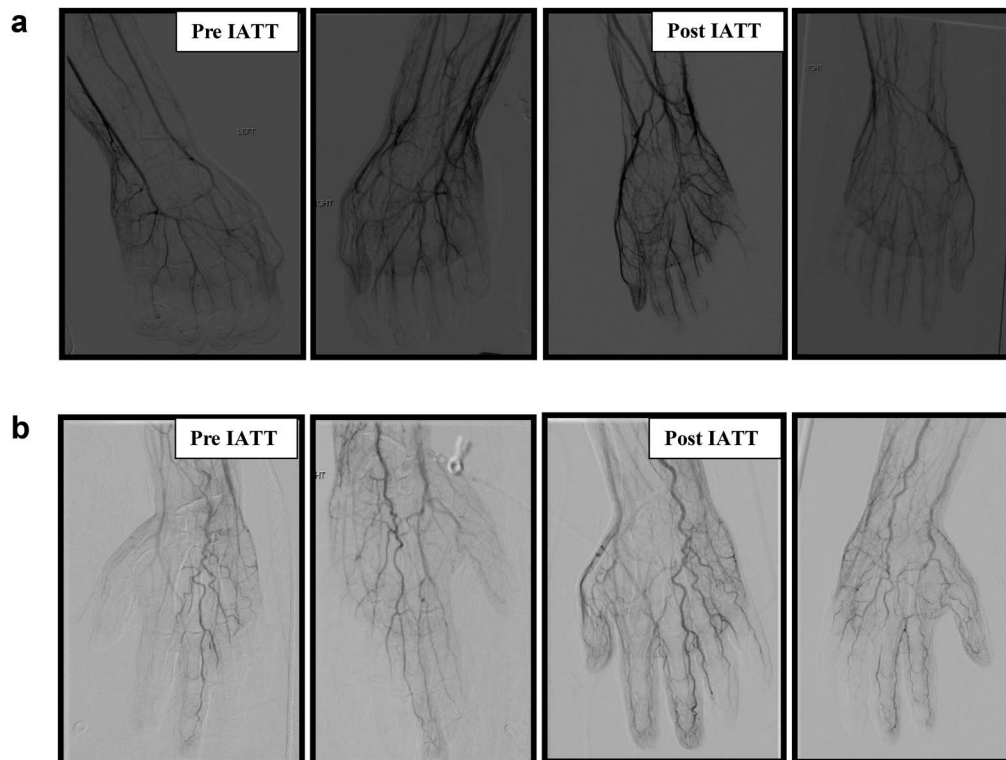
Discussion

Our experience with severe frostbite not only highlighted the utility of thrombolytic therapy, but also demonstrated that a clear protocol for this treatment is important to preserve limb viability. Due to extremely cold temperatures during the

Table 3. Summary of intra-arterial thrombolytic therapy (IATT) data, including duration, complications, perfusion pre- and post-tissue plasminogen activator (tPA), amputations and salvage success by each patient

Patient	1	2	3	4	5
Time from injury to initiation of IATT, hrs	8.75	16.45	17.06	15.38	14.58
Time from presentation to IATT initiation, hrs	5.48	6.07	5.8	7.37	6.4
Duration of IATT, hrs	82.21	63.53	51.08	62.03	50.46
Phalanges without perfusion pre-IATT, n	22	19	22	26	17
Phalanges without perfusion post-IATT, n	1	9	0	8	9
Restored perfusion, %	95.5	52.6	100	69.2	47.1
Amputations, right; n (phalange)	NA	0	0	2 (fifth mid & distal)	2 (fifth, mid & distal)
Amputations, left; n (phalange)	NA	2 (fourth mid & distal)	0	5 (third mid & distal fourth mid & distal second distal)	3 (fourth distal, fifth mid & distal)
Time from injury to amputation, days	NA	192	NA	53	88
Phalangeal salvage rate, %	NA	89.5	100	73.1	70.6
Digital salvage rate, %	NA	90	100	60	70
Complications	Catheter site hematoma	None	Catheter site Hematoma	Retroperitoneal hematoma, bacteremia	Catheter site pseudoaneurysm

NA not applicable

**Figure 2.** Representative angiograms showing digital arteries and distal vascular blush before and after intra-arterial thrombolytic therapy (IATT). (a) Pre- and post-IATT angiogram of patient 2 showing improved perfusion post-IATT. (b) Pre- and post-IATT angiogram of patient 5 presenting with improved perfusion post-IATT

2017–2018 winter season, there was an influx of multiple severe frostbite cases; hence, we were inclined to adopt a standard approach for management of these patients. In previous years, management differed with each case. After reviewing the available literature, we worked in conjunction

with our interventional radiology team to provide protocolized thrombolytic therapy as described above. We believe our patient population benefited from us utilizing a comprehensive protocol for classification of injury, thrombolytic therapy and diagnostic and prognostic imaging. Surgical management

was intentionally delayed and tailored to each patient as needed. We reported a phalangeal salvage rate of 83.3% with IATT. We felt it was important to report based on phalangeal salvage as opposed to partial or complete amputation because it provides further detail regarding the benefits and efficacy of thrombolytic therapy. To our knowledge, we are the first to report phalangeal salvage rate as opposed to digital salvage rate. Our digit salvage rate of 80% describes which digits underwent partial amputation at either the proximal interphalangeal or distal interphalangeal joints and is comparable to digit salvage rates reported in the literature by other centers that employ thrombolytic therapy [6, 12–23]. For these reasons, we believe all patients with severe frostbite should be transferred to a tertiary center with the ability to perform thrombolytic therapy in addition to standard supportive and surgical care.

Gonzaga *et al.* reported a series of 62 patients over 13 years who received IATT, comparing digits at risk on initial angiography with amputation rates, and reported an overall digit salvage rate of 68.6% [12]. They used either urokinase, tPA or tenecteplase, depending on pharmacy availability, along with a vasodilator, either papaverine or nitroglycerin. In patients with restored distal perfusion at completion of angiography, only 2% of patients required partial or complete amputation [12]. Their protocol typically stopped tPA prior to 72 hours; however, if patients continued to show improvement then tPA infusions would continue up to 120 hours. In the 6 patients that underwent tPA infusion 80 to 120 hours, none experienced bleeding complications and no amputations were performed. In a smaller cohort, Tavri *et al.* presented 13 patients who received IATT with tPA and nitroglycerine via femoral access and reported an 83.4% digit salvage rate [13]. They reported complications of 2 groin hematomas and 1 axillary hematoma which required surgical exploration [13]. In a historical review, Patel *et al.* reported on both IATT and conservative management, finding 15% of patients receiving IATT required amputation, compared to 77% of those who received only conservative management [14]. In addition, they noted a decreased length of stay and fewer complications in the IATT group [14]. Bruen *et al.* presented one of the only comparative studies of thrombolysis for frostbite using historical controls. In the treatment group, patients with decreased perfusion on angiography underwent IATT via femoral or brachial access and they found that only 10% of patients received amputations compared to 41% in the historical control group [15].

Twomey *et al.*, in an open-label study, examined both IATT and intravenous thrombolytic therapy (IVTT) with tPA and found no difference in amputation rates between intra-arterial and intravenous groups; however, the design of this open-label trial was not powered to compare the two administration methods but to examine tPA thrombolysis in general [16]. IATT, in combination with systemic heparin infusions, was associated with more bleeding complications than intravenous administration [16]. Jones *et al.* reviewed the effects of IVTT with tPA on frostbite patients with impaired perfusion on bone scan [22]. Of the 7 patients

included in the study, 5 did not require amputation and 2 required partial amputation. Interestingly, the 2 patients that underwent amputation experienced bleeding complications from heparin infusions, had therapy discontinued early and were never commenced on adjuvant anti-platelet therapy. It is unclear if these amputations were related to discontinuation of anticoagulation and anti-platelet therapy [22]. Johnson *et al.* also reported on IVTT with tPA, showing a 41% digit salvage without any bleeding complications [23].

In a systematic review, Drinane *et al.* reviewed 17 studies regarding thrombolytic therapy for frostbite, analysing a total of 345 patients, with nearly equal numbers undergoing IATT compared to IVTT [6]. Limb salvage rates were similar between IVTT and IATT, 77.3% and 76.4%, respectively. Complication rates were also similar between IVTT and IATT, with an overall complication rate of 4.3%. This review demonstrates that thrombolytic therapy is effective and safe [6]. Still, there is variability in when thrombolysis is indicated and how thrombolysis is managed. Management varies in time from injury to initiation of thrombolysis, use of concomitant vasodilators, variable rates of thrombolytic infusion, maximum length of thrombolytic therapy, interval of angiography during thrombolytic treatment, femoral versus brachial access for angiography, anticoagulant and anti-platelet therapy after thrombolysis and the optimal imaging modality used to assess perfusion. Methods for classifying extent of injury are also inconsistent, making comparison between treatment algorithms difficult. A standardized approach to classification, like the Hennepin score, which uses anatomic locations and extent of tissue loss to calculate a predicted salvage rate, is necessary as the treatment of frostbite progresses [24].

Thrombolytic therapy is typically initiated within 24 hours of injury and patients are often excluded from therapy if they present after than this, as late presentation seems to be associated with treatment failure [6]. In a retrospective review, Nygaard *et al.* determined that minimizing time to thrombolytic therapy is important and each hour delayed results in a decreased salvage rate of 28% [25]. Conversely, in a small case series, Al Yafi *et al.* initiated thrombolytic therapy up to 47.75 hours after injury [26]. They did not observe a significant increase in amputation rates among those who waited longer between injury and initiation of thrombolytic therapy [26]. Given these promising results, it may not be necessary to limit inclusion criteria to presentation with 24 hours of injury. Further investigation is warranted to determine optimal timing of thrombolytic therapy. This would be especially consequential in rural areas with long transport times to a tertiary center.

Compared to conventional treatments for frostbite, the results of thrombolytic therapy are impressive—the improved perfusion demonstrated on consecutive angiography and bone scan can be quite dramatic. Given ethical considerations, a prospective clinical trial with conservative treatment controls is not plausible. We are unfortunately limited to comparison between thrombolytic therapy and predicted or historical outcomes. This is a significant limitation to

establishing a clear causative relationship between thrombolysis and decreased amputation rates. Outcomes have clearly improved since the advent of thrombolytic therapy and therefore it seems reasonable to continue investigation of this intervention to determine the treatment regimen that yields the highest limb, digit and phalangeal salvage rates.

Femoral versus brachial access

There is no standardized arterial access site for IATT; however, most centers, including ours, utilize femoral access. Femoral catheterization is associated with several serious complications, including retroperitoneal hematoma, loss of distal pulse, access site hematoma, pseudoaneurysm and arteriovenous fistula [27]. With more recent use of percutaneous techniques, brachial access has been reported as safe and no significant difference in complication rates has been demonstrated between femoral, brachial and radial artery access [28–30]. There are no reports comparing access routes for IATT for the treatment of frostbite.

Bone scan and microangiography

Several institutions complete a diagnostic bone scan in the acute phase and prognostically in the sub-acute phase [31]. Bone scans may predict level of amputation with 84% specificity at approximately 3 days post-injury [32]. In our experience, bone scan did not predict level of amputation; in fact, bone scan overestimated the level of amputation in one case and underestimated the level of amputation in the second case. We therefore found this imaging modality ineffective for its intended purpose. In our opinion, early amputation is generally unwise and it is prudent to allow injured soft tissues to fully demarcate to determine viability for eventual wound closure. The ability to predict level of amputation may be beneficial in offering prognostic data to patients; however, in our practice, bone scanning is time- and resource-consuming without significant clinical benefit. However, given our low utilization of this modality, no conclusions on the efficacy of bone scans can be made from our data. Lacey *et al.* investigated the use of microangiography—a bedside imaging tool utilizing infrared light and peripherally injected indocyanine green to affected tissue to assess tissue damage [33]. They report a strong correlation between microangiography result and future amputation level. The authors suggest that this method may contribute to more expeditious rewarming and thrombolysis due to the ease and speed of the modality [33]. Further investigation is warranted to determine the optimal imaging modalities for frostbite.

Hospital length of stay

We found that other comorbid conditions and socioeconomic status guided length of inpatient hospitalization. Socioeconomic status and substance abuse were noted to be significant factors in a high proportion of our cases, which is consistent with previously published literature [34, 35]. For instance, a

Finnish trial showed that frostbite disproportionately affects the homeless and those with substance abuse problems [34]. All severe cases in our cohort were noted to be under the influence of alcohol and/or illicit substances at the time of their injury. The disinhibition associated with alcohol or illicit drugs likely contributes to prolonged cold exposure and severity of injury. Homeless populations seem to be at an even higher risk given the susceptibility to cold exposure and the high incidence of substance abuse in this population [2]. Interestingly, both patients who were injured while in pursuit by law enforcement tested positive for, and admitted to using cocaine prior to the incident.

In a recent review of the NBR, demographic and socioeconomic issues affecting burn and frostbite patients were analysed. It was found that frostbite patients were more likely to require intensive care, experienced longer lengths of stay and had higher hospital costs than burn patients [35]. The severity of the frostbite injury was not deemed a likely cause of these outcomes. The authors found that increased length of stay and cost is more likely caused by the socioeconomic factors afflicting these patients, leading to disposition issues. Further preventative measures should be explored to avoid cold exposure in these vulnerable populations.

Limitations

Our study has several limitations. First, the retrospective design of this case series introduces certain biases. Second, the non-standardized nature of the clinical assessment introduces bias around patient selection for IATT. Diagnosis of clinical severity was left to the clinical judgement of the attending physician, introducing the issue of inter-rater variability. It is not possible to define whether these patients were under- or over-treated with IATT. Frostbite is an uncommon injury—the small sample size in this study is a limitation. The clinical significance of phalangeal salvage has not previously been defined and thus its relevance to functional outcome in frostbite patients is unknown. Our findings are consistent with previously published thrombolytic therapy digit salvage rates in previous case series [6, 12–23]. However, a multi-center prospective observational study is warranted to elucidate the optimal treatment strategy in severe frostbite.

Conclusions

Thrombolytic therapy has the potential to greatly improve limb salvage and functional recovery after severe frostbite. The frostbite patient with severe injury will benefit from protocolized care at an institution that can offer thrombolytic therapy. Regionalization of these patients to experienced centers will facilitate further robust research in this complicated patient population.

Abbreviations

DSA: Digital subtraction angiography; IATT: Intra-arterial thrombolytic therapy; IVTT: Intravenous thrombolytic

therapy; NBR: National Burn Repository; SD: Standard deviation; tPA: Tissue plasminogen activator

Funding

This project did not receive any internal or external funding.

Availability of data and materials

All data was drawn from review of the identified charts. Anonymized data is available for review upon request and included in this manuscript. It is stored in a secure RedCap database file.

Authors' contributions

REP, DWC and ENT were the primary contributors to the conception, design, data analysis and interpretation of results. DWC, REP, ENT, BC and CF performed data collection and analysis. DK performed analysis of radiological imaging. REP and DWC drafted the manuscript. All authors contributed to revising the manuscript and critical review.

Ethics approval and consent to participate

This project was approved by the Maine Medical Center Institutional Review Board as a retrospective chart review study.

Consent for publication

This manuscript contains images of individual patients. Formal written consent to use these images was obtained from each patient.

Conflicts of interest

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

References

- Nygaard RM, Endorf FW. Frostbite in the United States: An examination of the National Burn Repository and National Trauma Data Bank. *J Burn Care Res.* 2018;**39**:780–5.
- Kowal-Vern A, Latenser BA. Demographic of the homeless in an urban burn unit. *J Burn Care Res.* 2017;**28**:105–10.
- Cauchy E, Davis CB, Pasquier M, Meyer EF, Hackett PH. A new proposal for management of severe frostbite in the austere environment. *J Wilderness Med.* 2016;**27**:92–9.
- Lindford A, Valtonen J, Hult M, Kavola H, Lappalainen K, Lassila R, *et al.* The evolution of the Helsinki frostbite management protocol. *Burns* 2017;**43**:1455–63.
- Mohr WJ, Jenabzadeh K, Ahrenholz DH. Cold injury. *Hand Clinics.* 2009;**25**:481–96.
- Drinane J, Kotamarti VS, O'Connor C, Nair L, Divanyan A, Roth MZ, *et al.* Thrombolytic salvage of threatened frostbitten extremities and digits: A systematic review. *J Burn Care Res.* 2019;**40**:541–9.
- Skolnick AA. Early data suggest clot-dissolving drug may help save frostbitten limbs from amputation. *JAMA.* 1992;**267**:2008–10.
- Morris SE. Cold-induced injury: frostbite. In: Herndon DN (ed). *Total Burn Care*, 3rd edn. Philadelphia: Saunders Elsevier, 2012, 530–5.
- Murphy JV, Banwell PE, Roberts AHN, McGrouther. Frostbite: Pathogenesis and treatment. *J Trauma.* 2000;**48**:171–8.
- Wexler A, Zavala S. The use of thrombolytic therapy in the treatment of frostbite injury. *J Burn Care Res.* 2017;**38**:e877–81.
- Millet JD, Brown RK, Levi B, Kraft CT, Jacobson JA, Gross MD, *et al.* Frostbite: Spectrum of imaging findings and guidelines for management. *Radiographics.* 2016;**36**:2154–69.
- Gonzaga T, Jenabzadeh K, Anderson CP, Mphr WJ, Endorf FW, Arenholtz DH. Use of intra-arterial thrombolytic therapy for acute treatment of frostbite in 62 patients with review of thrombolytic therapy in frostbite. *J Burn Care Res.* 2016;**37**:e323–34.
- Tavri S, Ganguli S, Bryan RG, Jr, Goverman J, Lui R, Irani Z, *et al.* Catheter-directed Intraarterial thrombolysis as part of a multidisciplinary management protocol of frostbite injury. *J Vasc Interv Radiol.* 2016;**27**:1228–35.
- Patel N, Srinivasa RN, Srinivasa RN, Gemmete JJ, Krishnamurthy V, Dasika N, *et al.* Intra-arterial thrombolysis for extremity frostbite decreases digital amputation rates and hospital length of stay. *Cardiovasc Intervent Radiol.* 2017;**40**:1824–31.
- 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**:546–51.
- Twomey JA, Peltier GL, Zera RT. An open-label study to evaluate the safety and efficacy of tissue plasminogen activator in treatment of severe frostbite. *J Trauma.* 2005;**59**:1350–4.
- Ibrahim AE, Goverman J, Sarhane KA, Donofrio J, Walker TG, Fagan SP. The emerging role of tissue plasminogen activator in the management of severe frostbite. *J Burn Care Res.* 2014;**36**:e62–6.
- Wagner C, Pannucci CJ. Thrombolytic therapy in the acute management of frostbite injuries. *Air Med J.* 2011;**30**:39–44.
- Sheridan RL, Goldstein MA, Stoddard FJ, Jr, Walker TG. Case records of the Massachusetts General Hospital. Case 41-2009. A 16-year-old boy with hypothermia and frostbite. *N Engl J Med.* 2009;**361**:2654–62.
- Saemi AM, Johnson JM, Morris CS. Treatment of bilateral hand frostbite using transcatheter arterial thrombolysis after papaverine infusion. *Cardiovasc Intervent Radiol.* 2009;**32**:1280–3.
- Wexler A, Zavala S. The use of thrombolytic therapy in the treatment of frostbite injury. *J Burn Care Res* 2017;**38**:e877–81.
- Jones LM, Coffey RA, Natwa MP, Bailey JK. The use of intravenous tPA for the treatment of severe frostbite. *Burns.* 2017;**43**:1088–96.
- 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**:344–8.
- Nygaard RM, Whitely AB, Fey RM, Wagner AL. The Hennepin score: Quantification of frostbite management efficacy. *J Burn Care Res.* 2016;**37**:e317–22.

25. Nygaard RM, Lacey AM, Lemere A, Dole M, Gayken JR, Wagner ALL, *et al.* Time matters in severe frostbite: Assessment of limb/digit salvage on the individual patient level. *J Burn Care Res.* 2017;**38**:53–9.
26. Al Yafi MN, Danino MA, Izadpanah A, Coegniet E. Using intra-arterial tPA for severe frostbite cases. A observational comparative retrospective study. *J Burn Care Res.* 2019;**40**: 907–12.
27. Sobolev M, Slovut DP, Lee Chang A, Shiloh AL, Eisen LA. Ultrasound-guided catheterization of the femoral artery: A systematic review and meta-analysis of randomized controlled trials. *J Invasive Cardiol.* 2015;**27**:318–23.
28. Heenan SD, Grubnic S, Buckenham TM, Belli AM. Transbrachial arteriography: Indications and complications. *Clin Radiol.* 1996;**51**:205–9.
29. Parviz Y, Rowe R, Vijayan S, Iqbal J, Morton AC, Grech ED, *et al.* Percutaneous brachial artery access for coronary artery procedures: Feasible and safe in the current era. *Cardio Revasc Med.* 2015;**16**:447–9.
30. Benit E, Missault L, Eeman T, Carlier M, Muyldermans L, Materna P, *et al.* Brachial, radial, or femoral approach for elective Palmaz-Schatz stent implantation: A randomized comparison. *Cathet Cardiovasc Diagn.* 1997;**41**:124–30.
31. Manganaro MS, Millet JD, Brown RK, Viglianti BL, Wale DJ, Wong KK. The utility of bone scintigraphy with SPECT/CT in the evaluation and management of frostbite injuries. *Br J Radiol.* 2019;**92**:20180545.
32. Cauchy E, Marsigny B, Allamel G, Verhellen R, Chetaille E. The value of technetium 99 Scintigraphy in the prognosis of amputation in severe frostbite injuries of the extremities: A retrospective study of 92 severe frostbite injuries. *J Hand Surg Am.* 2000;**25**:969–78.
33. Lacey AM, Fey RM, Gayken JR, Endorf FW, Schmitz KR, Punjabi GV, *et al.* Microangiography: An alternative tool for assessing severe frostbite injury. *J Burn Care Res.* 2019;**40**:566–9.
34. Mäkinen TM, Jokelainen J, Näyhä S, Laatikainen T, Jousilahti P, Hassi J. Occurrence of frostbite in the general population—work-related and individual factors. *Scand J Work Environ Health.* 2009;**35**:384–93.
35. Nygaard RM, Endorf FW. Frostbite vs burns: Increased cost of care and use of hospital resources. *J Burn Care Res.* 2018;**39**:676–9.