Compartment syndrome following use of tissue plasminogen activator for frostbite in the setting of concomitant diaphyseal tibia fracture

Noah M. Joseph, MD, MS\textsuperscript{a,*}, Nicholas Alfonso, MD\textsuperscript{b}, Adam G. Hirschfeld, MD\textsuperscript{b}

Abstract
Background: Tissue plasminogen activator (tPA) is a thrombolytic agent increasingly being employed for the treatment of acute frostbite. Although tPA has been shown with success to increase digit salvage rates, data on potential complications, including risk of hemorrhage, is limited. As a result, acute trauma is considered a contraindication to use in many institution-based protocols. Currently, there is a paucity in the literature regarding use of tPA for frostbite in patients with concomitant extremity fractures.

Case presentation: We report the case of a 36-year-old male treated with tPA for frostbite to digits of his bilateral hands in the setting of a concomitant diaphyseal tibia fracture. He subsequently developed acute compartment syndrome in his lower extremity. This was followed by emergent fasciotomy and staged fracture fixation with serial wound debridement and subsequent closure. Despite this complication, the patient went on to early radiographic and clinical union of his tibia fracture. His frostbite wounds healed without functional deficits.

Conclusions: In patients with severe frostbite injury with digital perfusion defects, tPA for thrombolysis may be indicated. Use of thrombolytics for frostbite in trauma patients or those with concomitant extremity fractures requires a multidisciplinary discussion regarding potential risks. Contingency planning is essential to ensure that potential bleeding complications, including development of compartment syndrome, are diagnosed and treated early. Given the paucity in the current literature regarding use of thrombolytics in trauma patients, further study is warranted to inform the surgical community on instances in which the benefits of tPA administration may outweigh the risks.

Level of evidence: Case report; Level V.

Keywords: compartment syndrome, frostbite, tibia fracture, tissue plasminogen activator

1. Background
Frostbite produces tissue injury through extravascular ice crystal formation and intravascular micro-emboli, fibrin deposition, and thrombosis.\textsuperscript{[1,2]} While rewarming therapies are employed to address ice crystal formation, there is increasing interest in the use of tPA in treatment of vascular thrombosis from frostbite.\textsuperscript{[3,4]} Use of tPA for thrombolysis in frostbite has been shown to reduce the rate of digit amputation by 30% in some reports.\textsuperscript{[5,1]} Despite these results, tPA carries a significant risk of bleeding and sequelae thereof, including the development of compartment syndrome (CS) secondary to intracompartamental hemorrhage.

We describe a case of lower leg CS following administration of tPA for frostbite in the setting of concomitant diaphyseal tibia fracture. Although recent trauma can be a contraindication for tPA administration, this is not well defined in the literature. We aim to highlight important considerations for patients with extremity fractures and concurrent frostbite for which tPA may be indicated. This is the first case report describing outcomes from tPA administration for frostbite in the setting of a long-bone fracture. The patient provided informed consent for data concerning this case to be submitted for publication. Institutional Review Board approval was obtained.

2. Case presentation
A 36-year-old male was brought to the emergency department after being found down in the snow 2 hours after sustaining a mechanical ground level fall while intoxicated, injuring his left leg. He denied loss of consciousness and had crawled to the side of a road to signal for help. Upon presentation, he was hypothermic (30.8°C), with frostbite to all digits of bilateral hands (Fig. 1A–D). He also sustained a closed left distal third tibial shaft fracture with a nondisplaced posterior malleolar fracture (Fig. 2A–D). He was intoxicated (serum EtOH 286), and
Figure 1. (A, B) Dorsal and volar views of left-hand frostbite on initial presentation to emergency department. (C, D) Dorsal and volar views of right-hand frostbite on initial presentation to emergency department.

Figure 2. (A–D) Anteroposterior (A, B) and lateral (C, D) radiographs of the tibia showing a distal third oblique tibial shaft fracture. There are concomitant proximal fibula and posterior malleolar fractures as well.
in lactic acidosis (lactate 17.0). His coagulation panel was within normal limits, PTT 30s, INR 1.05, fibrinogen 253mg/dL. His fractured extremity was cool, his compartments were full but compressible, and he denied pain with passive stretch. His pulses were palpable distally and his ankle-brachial index was 1.0. He had Doppler signals in all digits, and palpable radial pulses, however his digits were cyanotic with overlying hemorrhagic bullae.

He was admitted to the intensive care unit for rapid rewarming, fluid resuscitation, and local wound care. His tibial shaft fracture was closed, reduced, and splinted. Surgery was delayed initially to optimize resuscitation.

Eight hours after admission the patient lost digital Doppler signals in bilateral hands with digital thrombosis confirmed on angiography. Multidisciplinary discussion then took place with burn, trauma, and orthopaedic surgery teams regarding use of tPA administration for thrombolysis. Consensus was that the risk of digital limb loss outweighed risk of delayed fixation of the tibia and tPA was administered with return of Doppler signals following thrombolysis. The patient was placed on a heparin drip following the procedure per institutional protocol. Serial compartment checks were performed following tPA administration with plans for tibial fixation 24 hours after thrombolytic therapy.

Fourteen hours after tPA administration, the patient began complaining of increasing left lower leg pain unrelieved by pain medication. Upon evaluation, his anterior and lateral compartments were firm, and he exhibited pain with passive flexion and extension of his ankle and toes. He remained neurovascularly intact. He was diagnosed with CS and was taken emergently to the operating room for 4-compartment fasciotomy and external fixator application of his tibial shaft fracture. Heparin and tPA were discontinued immediately at the time of CS diagnosis. A single-incision fasciotomy was performed of all 4 compartments. A large hematoma was encountered and evacuated from the lateral and posterior superficial and deep compartments. Muscle was assessed intraoperatively and was found to be viable, and contractile. The fasciotomy wound was left open and dressed with a negative-pressure wound vacuum.

The patient’s symptoms improved dramatically following fasciotomy. Further tPA administration was discontinued despite persistent reduced flow on angiography to 4th and 5th digits of bilateral upper extremities. Intravenous heparin was resumed postoperatively. The patient underwent tibial intramedullary nailing, posterior malleolar screw fixation, and wound debridement 48 hours after fasciotomy. He was subsequently taken back to the operating room twice more at 48-hour intervals for repeat irrigation and debridement with wound closure being achieved at final debridement. He was discharged from the hospital 2 days after final wound closure with non-weight-bearing restrictions on his left lower extremity for 6 weeks. Low-molecular weight heparin was prescribed for deep vein thrombosis prophylaxis. At the time of discharge, his digits remained viable managed with bismuth-petrolatum gauze and bacitracin.

At 6-month follow-up, the patient’s bilateral hand frostbite wounds had re-epithelialized with maintenance of digital vascular perfusion (Fig. 3A and B). Bilateral hand function had returned to baseline and without pain. Plain radiographs showed interval bridging callus about the tibia fracture (Fig. 4A–D). His fasciotomy incision had healed without signs of infection (Fig. 5A and B). He was neurovascularly intact without deficits, weight-bearing without pain, and had returned to work as a carpenter.

3. Discussion

tPA has been used with considerable success in decreasing digital amputation rates in patients with frostbite.2–6 While tPA carries a significant risk of hemorrhage, current literature on tPA in frostbite has reported such complications sparingly. We present a unique case in which tPA was used for treatment of frostbite to bilateral upper extremity digits in a patient with a diaphyseal tibia...
fracture. While thrombolysis and reperfusion of his frostbitten digits was achieved using tPA, he subsequently developed CS of his fractured extremity requiring emergent fasciotomy. Although this complication resulted in additional operations related to management of his fasciotomy wound and delayed fracture fixation, the patient ultimately went on to clinical and radiographic union. His digital frostbite injuries healed without deficit or need for amputation.

Figure 4. (A–D) Anteroposterior (A, B) and lateral (C, D) radiographs of the left tibia 6 months postoperatively following intramedullary nailing of diaphyseal tibia fracture, percutaneous screw fixation of posterior malleolar fracture, and closed management of proximal fibula fracture. Interval callus is observed about all 4 cortices consistent with fracture union.

Figure 5. (A, B) Anterior and lateral views of left tibia at 3-month follow-up from 4-compartment fasciotomy for compartment syndrome and intramedullary tibial nailing for diaphyseal tibia fracture.
To our knowledge, CS following tPA administration for frostbite has not yet been described. However, this complication has been reported in select cases following tPA administration for thrombolysis in myocardial infarction, pulmonary embolism, and ischemic stroke.[7–10] Bleeding complications following tPA used in treatment of frostbite have been limited to a few case series. In a review of 62 patients with frostbite treated with intraarterial tPA for digital perfusion defects found on angiography, Gonzaga et al.[4] reported a 67%-digit salvage rate with 3 patients developing catheter-site hematomas. Twomey et al.[5] reported 1 case of hematuria and 1 arterial puncture site bleed, in a cohort of 19 patients receiving tPA for frostbite with a digit salvage rate of 81%.

Due to bleeding risk, recent trauma has been considered a contraindication to tPA administration. Wexler and Zavala[2] reported that recent trauma was an absolute contraindication to tPA therapy in frostbite in their institution-specific algorithm. Others consider trauma a relative contraindication.[3–5] However, this is based on theoretical risk, as no quantified outcomes studies have been published on tPA treatment in the setting of fracture. Jones et al.[10] described a case in which a patient with severe frostbite to bilateral feet in addition to an intertrochanteric hip fracture underwent tPA therapy without bleeding incident. In another report, tPA was administered without complication for thrombolysis in ischemic stroke in the setting of acute rib fractures.[10] Therefore, it may be possible to safely administer tPA in select trauma patients after thorough risk–benefit evaluation. However, further study is needed.

In this case, the patient presented with multiple limb-threatening injuries and several risk factors for the development of CS, including his fracture, although spiral tibial shaft fractures are commonly lower-energy torsional injuries, and his potential coagulopathy secondary to intrinsic liver dysfunction from alcohol use. In such instances, multidisciplinary discussion involving burn, critical care, and orthopaedic surgery teams, is required to make a calculated decision regarding tPA administration and subsequent clinical monitoring. Risks and benefits should be discussed amongst surgical teams and with the patient, to ultimately make an informed decision. Discussion should include the risk of CS and potential sequelae thereof, including subsequent surgeries, wound complications, fracture nonunion, infection, and amputation. In this case, the patient was at risk of multiple digit amputations once the level of tissue necrosis demarcated. At the same time, bleeding risk was considered with the potential for development of CS in his fractured extremity due to the synergistic effects of fracture bleeding, potential alcohol-induced coagulopathy, and use of thrombolytic therapy.

In such instances, contingency planning is required should tPA therapy be initiated in a higher-risk trauma patient, including availability of an orthopaedic specialist, 24-hour operating suite access, frequent compartment checks, and monitoring in an intensive care unit setting. Should compartment syndrome develop, fasciotomy should be performed without delay to prevent irreversible neurovascular damage.

4. Conclusions

We report a case of lower extremity CS following tPA administration for frostbite in the setting of concomitant diaphyseal tibia fracture. Given the theoretical bleeding risk with thrombolytic therapy and the paucity of literature on its use in the trauma patient population, we believe this single case is notable. Bone bleeding from a fracture site may be an acceptable and manageable risk when considering tPA in the setting of an acutely thrombosed peripheral, coronary, or cerebral artery. These risks should be weighed on an individual case basis, as multiple injuries or conditions can have compounded effects. Further research is required to aid in this decision-making process.

References

1. Murphy J, Banwell P, Roberts A, et al. Frostbite: pathogenesis and treatment. J Trauma. 2000;48:171–178.
2. Wexler A, Zavala S. The use of thrombolytic therapy in the treatment of frostbite injury. J Burn Care Res. 2017;38:e877–e881.
3. Jones LM, Coffey RA, Natwa MP, et al. The use of intravenous tPA for the treatment of severe frostbite. Burns. 2017;43:1088–1096.
4. Gonzaga T, Jenabzadeh K, Anderson CP, et al. 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–e334.
5. Twomey JA, Pelvier 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;59:1350–1355.
6. Bruen KJ, Ballard JR, Morris SE, et al. Reduction of the incidence of amputation in frostbite injury with thrombolytic therapy. Arch Surg. 2007;142:546–553.
7. Crick KA, Crick JC, Pulley MT. Hemorrhagic upper extremity complications from tissue plasminogen activator. J Surg Orthop Adv. 2007;16:27–30.
8. Tuna S, Duyumus TM, Mutlu S, et al. Upper extremity acute compartment syndrome during tissue plasminogen activator therapy for pulmonary embolism in a morbidly obese patient. Int J Surg Case Rep. 2015;8C:175–178.
9. Brownlee WJ, Wu TY, Van Dijck SA, et al. Upper limb compartment syndrome: an unusual complication of stroke thrombolysis. J Clin Neurosci. 2014;21:880–882.
10. Dressing A, Greiter Z, Bardutzky J. Safe intravenous thrombolysis after traumatic cardiopulmonary resuscitation with ribs fracture: a case report. Case Rep Neurol. 2017;9:156–160.