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The use of intravenous tPA for the treatment of severe frostbite

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ABSTRACT

Objective: tPA and anticoagulation for treatment of severe frostbite have been reported suggesting differences in imaging techniques, route of tPA administration and management of patients after tPA infusion. This is a report of our results following a protocol of Tc-99m scanning, intravenous tPA administration, followed by either systemic anticoagulation or antiplatelet therapy.

Methods: Patients admitted to our burn center between February 13, 2015 and February 13, 2016 for frostbite who met inclusion criteria were treated with Tc-99m scan and intravenous tPA followed by systemic anticoagulation or antiplatelet therapy. Inclusion criteria included rewarming had not started more than 24 h prior to the scan and no contraindications to the use of tPA.

Results: Fifteen patients met inclusion criteria and 12 were treated according to the protocol. Nine received scans with 2 showing normal perfusion. Seven displayed perfusion defects and received intravenous tPA. Five recovered fully after tPA. Two who showed improved but abnormal scans after tPA experienced bleeding complications necessitating stopping heparin/Coumadin. Those two went on to partial amputation of digits.

Conclusion: The use of intra-arterial or intravenous tPA along with angiography or Tc-99m scanning followed by systemic anticoagulation or antiplatelet therapy may be beneficial to patients suffering frostbite.

1. Introduction

Treatment for frostbite has remained relatively unchanged for many years. The immediate care involves rapid rewarming of the affected body part with circulating water at a temperature of 40–42 °C (104–107.6 °F) until rewarming is complete [1]. Following rewarming, the body part is wrapped in bulky, atraumatic dressings and the areas of tissue necrosis are allowed to demarcate over several weeks. Amputations are then performed at the levels of demarcation. Loss of digits and

Abbreviations: tPA, Tissue Plasminogen Activator; PRU, P2Y12 Reaction Units.

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portions of the nose and ears are common in the treatment of severe frostbite [2,3].

Frostbite injures tissues through (1) damage of the cell membrane and, (2) progressive tissue ischemia [4,5]. Thrombolytic therapy offers a directed therapy by potentially restoring blood flow in the microcirculation and reversing tissue ischemia, as demonstrated in a rabbit model by Salimi et al. [6].

While various thrombolytic measures have been tried, recent interest has been shown in the use of Tissue Plasminogen Activator (tPA) for the treatment of frostbite. This naturally occurring substance converts plasminogen to plasmin. Plasmin then lyses the fibrin occurring in blood clots. With this lysis the blood clot is dissolved and blood flow is restored. Commercially available recombinant tPA has already found application in the treatment of ischemic stroke, myocardial infarction and pulmonary embolism. The first report of the clinical use of tPA for thrombolysis in treating frostbite in humans occurredng in 1992 [7]. Since then, reports of the successful use of tPA have continued to be published with treatment protocols outlining its administration by both the intravenous and intra-arterial routes, Table 1 [8–15].

We have utilized a modified version of the protocol published by Johnson et al. in 2005 for the treatment of patients presenting to our verified burn center with severe frostbite, (Table 2) [12]. This study describes our experience with specific attention to patient outcomes, amputation rates and complications seen with the use of tPA and anti-coagulation in this patient population.

2. Methods

Following IRB approval, a retrospective chart review was performed of patients treated for frostbite at our verified burn center between February 13, 2015 and February 29, 2016. Inclusion criteria were ages $\geq$18 years, admission for frostbite with rewarming in less than 24 h prior to the initiation of the treatment protocol. Exclusion criteria included pregnant patients, prisoners, a contra-indication to the use of tPA, or delay between rewarming and potential institution of tPA. Table 2 describes the treatment protocol.

Patients with a diagnosis of frostbite were identified electronically. Data was abstracted from the electronic medical record and the institutional burn quality database. Data collected included demographics, history of drug and alcohol use, mental health diagnoses and a history of diabetes mellitus, body areas involved in the frostbite injury, Tc-99m scan results, protocol treatments given and outcomes including surgical procedures (amputations), number of and body areas undergoing amputation, and complications related to tPA administration.

Statistical analysis of the data was performed using SAS 9.4.

3. Results

Thirty-eight patients were identified as being treated for frostbite. Twenty were males and the mean age for all patients was 39.4 $\pm$ 12.64 years (range 19–79). Twenty-three patients were treated as out-patients leaving 15 admitted for in-patient treatment. Seven of the 15 admitted patients had pre-existing psychiatric disorders, 2 with diabetes mellitus and 2 more had HgA1c levels in the pre-diabetic range. At the time of their admission, 3 of the 15 patients tested positive for recreational drugs, 2 of the 15 with alcohol and 5 of the 15 with both drugs and alcohol.

Twelve patients were treated according to the protocol, (Table 3). Three of these twelve patients had digital pulses detected with Doppler and therefore, did not receive scans. All three had uneventful recoveries.

Of the 9 patients receiving scans, 2 showed normal perfusion and did not receive tPA infusion. They both recovered with no complications.

Seven patients received intravenous tPA infusions. Three had normal repeat scans and went on to full recovery without complications. All three were placed on Coumadin for one month. The remaining 4 showed interval improvement on repeat scan. Of those 4, 2 went on to full recovery without complication. One of these 2 patients was placed on Coumadin for a month. The other was placed on clopidogrel and aspirin for a month because of a history of frequent falls and, therefore, a relative contra-indication to Coumadin anti-coagulation. The remaining 2 experienced bleeding complications while on heparin and, thus, had their anti-coagulation stopped but were not placed on anti-platelet therapy. These two patients were treated early in our protocol development and both went on to develop necrosis of digits with amputations. The amputations performed on these 2 patients were at levels demonstrated on the repeat scan and at levels more distal than predicted by the initial scan. As a result of our experience with these two patients, we modified the protocol as described by Johnson and added anti-platelet therapy for cases where anti-coagulation with either heparin or Coumadin was felt to be contra-indicated.

4. Discussion

Historically, treatment for frostbite injury has been to immediately warm the affected body part in a whirlpool bath set at 40–42 °C until rewarming has been accomplished [1]. This is followed by gentle wound care and analgesia, allowing the areas of dry gangrene to demarcate in anticipation of amputation to be performed several weeks to months following the original injury [2,3]. The results of this approach are often debilitating for the patient and unrewarding for the practitioner. New treatments, such as the application of thrombolytic therapy that result in tissue preservation and minimize functional impairments, are being studied.

Frostbite produces tissue injury through two mechanisms. First, direct cell membrane damage through the formation of extra-cellular ice crystals leading to cellular dehydration and eventually cellular death. The second, and perhaps more important mechanism, is progressive tissue ischemia through the formation of micro-emboli and damage to the endothelial lining of the capillary bed and fibrin deposition [4,5]. It is this second mechanism that thrombolytic therapy (directed at lysing the fibrin clot) followed by anti-coagulation therapy