Fibrinolytic Therapy for the Management of Frostbite

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Disclosure

I have had no financial relationship over the past 12 months with any commercial sponsor with a vested interest in this presentation.
Learning Objectives for Pharmacists

1. Describe the mechanism of action of tissue plasminogen activator (t-PA) in the management of frostbite.
2. Define the conditions, in which, alteplase might be considered for the management of frostbite.
Learning Objectives for Pharmacy Technicians

1. List the available dosage forms of alteplase.
2. Describe the directions for preparation of alteplase for frostbite therapy.
Frostbite

• Freezing localized thermal injury
• Tissues are exposed to temperatures below freezing point for a sustained period of time

Frostbite

• Frostbite versus frostnip
• Susceptible body parts:
  • Hands
  • Feet
  • Earlobes
  • Nose
Risk factors

• Time of exposure
• Wind and moisture
• Children and elderly
• Intoxication/substance abuse
• Homelessness
• Psychiatric illness

• Dementia
• Diabetes
• Peripheral vascular disease
• Smoking
• Raynaud’s disease
• Neuropathy

Pathophysicsology

Three pathways of tissue freezing:
1) Extracellular formation of ice crystals
2) Hypoxia as a result of cold-induced local vasoconstriction
3) Release of inflammatory mediators

Prendergast HM, Erickson TB. Robert Hedges’ Clinical Procedures in Emergency Medicine and Acute Care. 65;1405-1433.
Pathophysiology

1) Extracellular formation of ice crystals
   • Increase of extracellular oncotic pressure
   • Fluid shifts out of cells
   • Disruption of intracellular metabolism
   • Instability of cell membrane
   • Contributes to inflammatory response

Prendergast HM, Erickson TB. Robert Hedges’ Clinical Procedures in Emergency Medicine and Acute Care. 65;1405-1433.
Pathophysiology

2) Hypoxia as a result of cold-induced local vasoconstriction
   • Body alternates between periods of vasoconstriction and vasodilation
   • As temperature continues to decrease, vasoconstriction persists
   • Increase in blood viscosity
   • Vasospasm
   • Formation of microthrombi

Prendergast HM, Erickson TB. Robert Hedges’ Clinical Procedures in Emergency Medicine and Acute Care. 65;1405-1433.
Pathophysiology

3) Release of inflammatory mediators
   - prostaglandin F$_2$ and thromboxane A$_2$
   - further vasoconstriction leading to cell death
   - Release of these mediators peaks during rewarming, and cycles of recurrent freezing and rewarming increase inflammatory tissue levels
   - Avoid rewarming until refreezing can be prevented

Prendergast HM, Erickson TB. Robert Hedges’ Clinical Procedures in Emergency Medicine and Acute Care. 65;1405-1433.
Clinical Signs & Symptoms

- Superficial frostbite – pale, waxy, numb, poor capillary refill, very painful on rewarming
- Deeper frostbite – hard, solid, blanched, hemorrhagic blisters may be present, no pain or feeling present
  - Severe edema and blistering develop
  - Dry gangrene
  - Tissue sloughing
  - Tissue necrosis
  - Amputation

Prendergast HM, Erickson TB. Robert Hedges’ Clinical Procedures in Emergency Medicine and Acute Care. 65;1405-1433.
Prognosis

• Favorable signs:
  • Intact sensation
  • Normal color
  • Warm tissues
  • Early appearance of clear blisters
  • Edema

• Unfavorable signs:
  • Nonblanching cyanosis
  • Hemorrhagic blisters
  • Impaired sensation
Prognosis

• Delay in seeking medical care >24 hours
  • 85% likelihood for the need of surgical intervention
• Patients seen within 24 hours
  • <30% likelihood of requiring surgical intervention

Prendergast HM, Erickson TB. Robert Hedges’ Clinical Procedures in Emergency Medicine and Acute Care. 65;1405-1433.
Treatment

• Rapid rewarming
  • Immersion in warm water (104.0°F to 107.6°F) for 15-30 minutes
• Elevation
• Debridement
• Thromboxane inhibitor—Aloe vera
• NSAID—Ibuprofen
• Semiocclusive dressings
• Tetanus prophylaxis (if indicated)

Prendergast HM, Erickson TB. Robert Hedges’ Clinical Procedures in Emergency Medicine and Acute Care. 65;1405-1433.
Investigated Pharmacotherapy Options

- Heparin or low-molecular-weight heparin (LMWH)
- Tissue plasminogen activator (t-PA)
- Warfarin
- Vasodilators
- Corticosteroids
- Low molecular weight dextran
Tissue plasminogen activator (tPA)

Evidence and place in therapy
Proposed Mechanism of Action

- tPA converts plasminogen to plasmin
- Plasmin degrades fibrin and fibrinogen
- Clots are dissolved throughout the body

Administration Methods

- **Intravenous (IV) versus intra-arterial (IA)**
  - Both studied
  - No prospective randomized studies comparing the two methods
  - Differences in adverse event rates
  - Dosing differences

Evaluating the Data

Twomey et al.

- single center, non-randomized, prospective trial
- 16 patients
  - 6 patients received IA tPA
  - 13 patients received IV tPA
- Average age of 42.5 years old

Evaluating the Data

Inclusion Criteria
• 18-75 years old with severe frostbite
• No improvement on rapid rewarming in tepid water
• Absent Doppler pulses in limbs and or digits
• No perfusion on the Tc-99m three-phase bone scan

Exclusion Criteria
• Severe hypotension
• Recent trauma or stroke
• Bleeding disorder
• Pregnancy
• Mental incapacity
• Drug/alcohol intoxication
• Repeated freeze–thaw cycles
• > 48 hours of cold exposure

Methods

• tPA dosing:
  • 0.15 mg/kg, followed by infusion of 0.15 mg/kg/hr x 6 hours
• Heparin drip started after tPA completion
  • Titrated 2x control PTT
• Warfarin started day 3-5 and continued x 4 weeks

Results

- 16/19 patients responded to tPA
  - 12/16 patients required amputation in the control group
- 33/174 digits were amputated despite treatment (19%)
  - Control patients: all digits with absent flow on Tc-99m scans were amputated
- Complications:
  - IV tPA group—none
  - IA tPA group—2 reported complications resulting in cessation of therapy

Author’s Conclusion

• tPA therapy is safe
• Reduced predicted digit amputations
• Equivalent results in IV and IA patients
• Non-responders:
  • > 24 hours of cold exposure
  • Warm ischemia times greater than 6 hours
  • Evidence of multiple freeze–thaw cycles

Evaluating the data

Bruen et al.

- Retrospective study
- IA tPA initial rate of 0.5 – 1.0 mg/hr into the extremity via femoral or brachial arterial catheter sheath
- Heparin was administered at 500 units/hr into the intraarterial catheter
- Administration of tPA within 24 hours of injury improved tissue perfusion and reduced amputations

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>tPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digit amputations</td>
<td>97/234 (41%)</td>
<td>6/59 (10%)</td>
</tr>
<tr>
<td>Proximal amputations</td>
<td>14</td>
<td>0</td>
</tr>
</tbody>
</table>

Evaluating the data

Cauchy et al.

- Randomized, prospective study
- 47 patients with severe frostbite included, 407 digits at risk
- Rapid rewarming + aspirin 250mg + Buflomedil 400mg IV

<table>
<thead>
<tr>
<th>Cohort 1</th>
<th>Aspirin 250mg daily da+ buflomedil 400mg daily x 8 days</th>
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</thead>
<tbody>
<tr>
<td>Cohort 2</td>
<td>Aspirin 250mg daily + iloprost 0.5-2 ng/kg/min x 6h per day x 8 days</td>
</tr>
<tr>
<td>Cohort 3</td>
<td>Aspirin 250mg daily + iloprost 0.5 to 2 ng/kg/min x 6h per day x 8 days + tPA 100mg</td>
</tr>
</tbody>
</table>

Results

- **Aspirin + buflomedil**
  - Risk of amputation 60%
  - 9/15 patients

- **Aspirin + iloprost**
  - Risk of amputation 0%
  - 0/16 patients

- **Aspirin + iloprost + tPA**
  - Risk of amputation 19%
  - 3/16 patients

Evaluating the data

Wexler A et al.

- Case series
- 6 patients received tPA as frostbite treatment
- No serious adverse effects from tPA administration
- All 6 patients had improved outcomes
- Patients with diminished response:
  - Unknown duration of cold exposure
  - Drug or alcohol intoxication

Place in Therapy

- Reserved for patients with severe frostbite & at risk for significant tissue loss
- < 24 hours of cold exposure
- No evidence of multiple freeze/thaw cycles
- Little to no improvement with re-warming
- Absent doppler pulses in limbs and/or digits
- Absence of perfusion on angiography

IV Dosing

<table>
<thead>
<tr>
<th>Bolus</th>
<th>Maintenance</th>
<th>Max dose</th>
</tr>
</thead>
</table>
| • 0.15 mg/kg  
• over 2 min | • 0.15 mg/kg/hr  
• over 6 hours | • 100 mg  
• Central line administration preferred |

**IA Dosing**

<table>
<thead>
<tr>
<th>Bolus</th>
<th>Maintenance</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 2-4 mg</td>
<td>• 1 mg/hr</td>
<td>• Continue until evidence of reperfusion or 48 hours</td>
</tr>
<tr>
<td></td>
<td>• Divided amongst catheters</td>
<td></td>
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*Heparin drip also started at 500 mg/hr concurrently through access sheath

Monitoring

• Prior to starting tPA:
  • Baseline assessment of:
    • hemodynamics
    • laboratory data (including coagulation)

• During tPA infusion:
  • Neurological assessments every 15 min
  • Vital sign monitoring every 15 min
  • Maintain blood pressure <180 mmHg (systolic) & <105 mmHg (diastolic)

• After tPA infusion x6 hours:
  • Neurological assessments & vital signs every 30 min x 6 hrs
  • Neurological assessments & vital signs every 1 hr x 24 hrs

Absolute Contraindications

• Any prior intracranial hemorrhage, or known structural intracranial process, cardiovascular disease, or known malignant intracranial neoplasm
• Ischemic stroke within the past 3 months
• Suspected aortic dissection
• Active bleeding or bleeding diathesis
• Recent surgery on spinal canal or brain, recent trauma
• INR >1.7

Relative Contraindications

- Age >75
- Current or recent use of anticoagulation
- Pregnancy
- Traumatic or prolonged cardiopulmonary resuscitation (>10 min)
- Recent internal bleeding (< 2–4 weeks)
- Severe uncontrolled hypertension (systolic > 180/diastolic > 110 mm Hg)
- Dementia
- Remote history of >3 months ischemic stroke
- Major surgery within 3 weeks
- > 24 hour of cold exposure
- Evidence of multiple freeze–thaw cycle
- Warm ischemia time >6 hours
- Platelets < 100,000

Preparation for Administration

• Supplied as sterile, lyophilized powder in 100 mg and 50 mg vials
• Each vial package with diluent for reconstitution (Sterile Water for Injection)
  • 50 mg vial packaged with 50 mL of Sterile Water for Injection
  • 100 mg vial packaged with 100 mL of Sterile Water for Injection
• Swirl, DO NOT SHAKE
• Reconstituted to a concentration of 1 mg/mL
• Beyond use date – 8 hours
Summary

- Safe to use for frostbite patients without contraindications
- May partially or completely restore perfusion to digits at risk for amputation
- Can reduce number of digits requiring amputation
- IV versus IA methods
- Patients with diminished response:
  - > 24 hour of cold exposure
  - Evidence of multiple freeze-thaw cycle
  - Warm ischemia time >6 hours
Guidelines Recommendation

“Although further studies are needed to determine the absolute efficacy of tPA for frostbite injury and to compare intraarterial tPA to IV prostacyclin, we recommend IV or intraarterial tPA within 24 hours of injury as a reasonable choice in a proper facility. Recommendation grade for thrombolytic therapy: 1C.”

Table 2 Summary of initial hospital management of frostbite

1. Treat hypothermia or serious trauma
2. Rapidly rewarm in water heated and maintained between 37° and 39°C (98.6° to 102.2°F) until area becomes soft and pliable to the touch (approximately 30 minutes)
3. Ibuprofen (12 mg/kg per day divided twice daily)
4. Pain medication (eg, opiate) as needed
5. Tetanus prophylaxis
6. Air dry (ie, do not rub at any point)
7. Debridement: selectively drain (eg, by needle aspiration) clear blisters and leave hemorrhagic blisters intact
8. Topical aloe vera every 6 hours with dressing changes
9. Dry, bulky dressings
10. Elevate the affected body part if possible
11. Systemic hydration
12. Thrombolytic therapy: consider for deep frostbite with potential significant morbidity if less than 24 hours after thawing; use angiography for prethrombolytic intervention and monitoring of progress
13. Clinical examination (plus angiography or technetium-99 bone scan if necessary) to assist determination of surgical margins
14. Evaluation by an experienced surgeon for possible intervention

Post-Test Questions for Pharmacists

Which of the following statements best describes the mechanism of action of alteplase in the management of frostbite?

a) Inhibits the formation of stable fibrin clots in patients with frostbite via inhibiting fibrinogen conversion to fibrin
b) Fibrinolysis of vascular thrombosis of frostbitten tissue
c) Prostacyclin analog—causes vasodilation and increased blood flow to affected area
Post-Test Questions for Pharmacists

Which patient would be the most appropriate choice for alteplase therapy?

a) 41 year old male presents with severe frostbite affecting one digit

b) 35 year old male presents with severe frostbite injury 10 hours after injury affecting entire foot

c) 90 year old female with past medical history of GI bleed resulting in ICU admission presents with frostbite affecting all five right hand digits

d) 60 year old female with severe frostbite of left foot presents 36 hours post-injury
Post-Test Questions for Pharmacy Technicians

Which of the following is a correct dosage formulation of alteplase?

a) Powder for solution – 100 mg vial
b) Solution – 100 mg vial
c) Tablet – 100 mg
d) Intranasal spray – 100 mg
Post-Test Questions for Pharmacy Technicians

Directions for reconstitution of alteplase include all of the following, except:

a) Do not shake when reconstituting
b) Reconstitute to a concentration of 1 mg/mL
c) Mix with sterile water for injection
d) Use within 24 hours
References


References


References

