

**Management of severe frostbite using iloprost, alteplase and heparin –
a Yukon Case Series**

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Declaration of authors competing interest

The authors have no competing interest to declare.

Data-Sharing Statement

This case series data, the Yukon Frostbite Protocol and Pre-Printed Orders are available upon request to the corresponding author.

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Abstract

Background: Canada’s Yukon Territory is north of 60° latitude with temperatures below -40°C every winter. We identified the need to modernize our frostbite management and implemented a protocol based on the best available evidence in 2015. We present a case series of the patients treated with the protocol since implementation.

Methods: The charts of all patients who presented to Whitehorse General Hospital between February 2015 to February 2020 with Grade 2 to 4 frostbite were reviewed retrospectively by the authors. Grade 2 and 3 frostbite were treated with iloprost while Grade 4 with iloprost, alteplase and heparin. Patients’ demographics, predisposing events leading to frostbite, frostbite severity and number of digits affected and salvaged were reviewed. The time from presentation to the Emergency Department (ED) to treatment initiation was also evaluated.

Results: 22 patients were treated according to the protocol, ten patients with Grade 2 frostbite (45%), five patients with Grade 3 frostbite (23%), and seven patients with Grade 4 frostbite (32%). A total of 142 digits were affected and 113 digits salvaged (80% salvage rate). 29 digits were amputated, all of which were of Grade 4. Extreme winter sports and alcohol use were identified as predisposing events, with alcohol use leading towards more severe frostbite injury. ED presentation to rewarming was 2.4 hours on average. The average time from ED presentation to iloprost initiation was reduced from 32.9 hours (2015) to 2.6 hours (2020).

Conclusion: Our five-year experience has demonstrated the feasibility of advanced frostbite care in a rural and remote centre. We believe the education of the healthcare providers involved, a defined protocol algorithm with visual grading system, and pre-printed orders have contributed to improved frostbite care at our institution.

Introduction

Frostbite can occur rapidly in cold climates, affecting a range of patients from the homeless or unwell, to athletes in extreme sports events. The impact of severe frostbite can be debilitating. Frostbite injuries due to exposure are a result of an initial extracellular freezing injury followed by a reperfusion injury due to vasoconstriction and microthrombosis in affected tissues¹. The severity of injuries can range from mild to severe. A grading system developed by Cauchy et al describes Grade 1 to Grade 4 frostbite^{2,3}. The higher the grade the more proximal the cyanotic changes in the digits and the higher the amputation rate. The foundations of treatment of frostbite have included rapid rewarming⁴ and antithromboxane agents such as topical aloe vera and ibuprofen⁵. More recently, vasodilators and/or thrombolytics have been promoted to address the reperfusion injury caused by vasoconstriction and thrombosis⁶⁻²⁸. Beginning in the 1990s, a growing body of evidence has popularized the use of iloprost in frostbite, first in Europe and now in Canada^{6,11,15,16,21,24,27}. Iloprost, a synthetic prostacyclin analog, is a potent vasodilator, inhibits platelet aggregation, and enhances fibrinolytic activity by releasing endogenous tissue plasminogen activator²⁹. There is but one randomized controlled trial published to this date demonstrating the benefit of iloprost combined with alteplase and heparin¹¹.

Canada's Yukon Territory extends from 60 degrees (°) North (N) latitude to a northern edge near 70°N latitude. It has a mountainous landscape and expected temperatures below -40 degrees Celsius (°C) every winter from November to April. Whitehorse, the capital of Yukon, also attracts elite athletes for extreme outdoor winter sporting events. Given this environment, we identified the need to modernize our frostbite management and implemented a treatment protocol and pre-printed orders based on the best available evidence in February 2015. We published our first 2 cases in the CMAJ in 2016¹⁵. We present here a case series captured since our protocol inception in 2015.

Methods

Yukon Frostbite Protocol

A treatment algorithm (Figure 1) and pre-printed orders were developed by Poole and Gauthier and implemented at Whitehorse General Hospital in 2015. Thereafter, several education sessions were offered to the hospital staff and Yukon communities’ healthcare providers. Patients diagnosed with frostbite in the Emergency Department (ED) were graded using the visual grading system developed by Cauchy et al^{2,3} after rapid rewarming of extremities in hot water. Grade 1 to 4 cases were managed with daily hydrotherapy, debridement and aspiration of clear blisters, topical aloe vera (Aloe Vesta Protective Ointment, ConvaTec), scheduled oral ibuprofen, and pantoprazole. Patients with Grade 2-4 frostbite, presenting within 72 hours of rewarming, received iloprost, and, in addition, those with Grade 4 presenting within 24 hours of rewarming also received alteplase and heparin unless contraindicated. Iloprost (Ilomedin; obtained through Health Canada Special Access Programme) was diluted at a standard concentration of 0.2 mcg/mL and initiated at a rate of 10 mL/hour intravenous infusion to a maximum rate according to patient’s weight for a total of 6 hours or until the end of the 250 mL bag. Alteplase was given at a dose of 15 mg intravenous over 2 minutes then 0.75 mg/kg (maximum 50 mg) over 30 minutes then 0.5 mg/kg (maximum 35 mg) over 60 minutes. Alteplase dosing was later (2017) revised to 0.15 mg/kg over 15 minutes then 0.15 mg/kg/hour intravenous infusion for 6 hours. Patients receiving alteplase also received heparin 60 units/kg intravenous once then 12 units/kg/hour for 6 hours then adjusted as per partial thromboplastin time (PTT) for 72 hours.

Setting

This study was performed at Whitehorse General Hospital, a rural and remote hospital located in the Yukon Territory, Canada. All patients were 18 years and older.

Design

This is a single-centre retrospective case series. We performed a chart review of all consecutive patients who presented to Whitehorse General Hospital with Grade 2 to 4 frostbite and were treated with iloprost as per our protocol, between February 9, 2015 to February 8, 2020.

Data collection

The computer pharmacy system, Meditech, was used to identify patients who had received iloprost or alteplase for frostbite and patients’ charts were retrieved from the hospital health records archives. A data abstraction tool was developed in an Excel worksheet and included patients’ demographics, frostbite severity, limbs affected, and factors known or suspected to affect frostbite treatment outcomes based on previously published studies: patients’ comorbidities, local environmental temperature, body temperature, duration of cold exposure, predisposing event, time from presentation to the ED to rewarming, time from presentation to treatment with iloprost and alteplase and heparin when applicable as well as adverse drug reactions. The local environmental temperature was based on Environment Canada data (<https://climate.weather.gc.ca/>). Patients’ medical records were reviewed independently by two reviewers (Poole and Gauthier). Discrepancies in data collection were further evaluated by a third independent reviewer (MacLennan). Where discrepancies still existed, all three reviewers met to further review chart data and gain consensus.

Exclusion

One patient was excluded from this case series as there was uncertainty in the patient's history as to how long ago the frostbite injury had occurred (possibly an old frostbite injury). This patient presented with fissured and blackened toes, ischemic and dusky in nature. The patient was transferred out of Whitehorse General Hospital to a referral hospital out of territory due to other urgent medical conditions requiring a higher level of care.

Outcomes

The outcome measured was the number of digits salvaged compared to the number of digits affected. We also verified if there was a correlation between the environmental temperature and frostbite severity and duration of cold exposure and severity. We evaluated the time from patients' presentation to the ED to treatment initiation over the years.

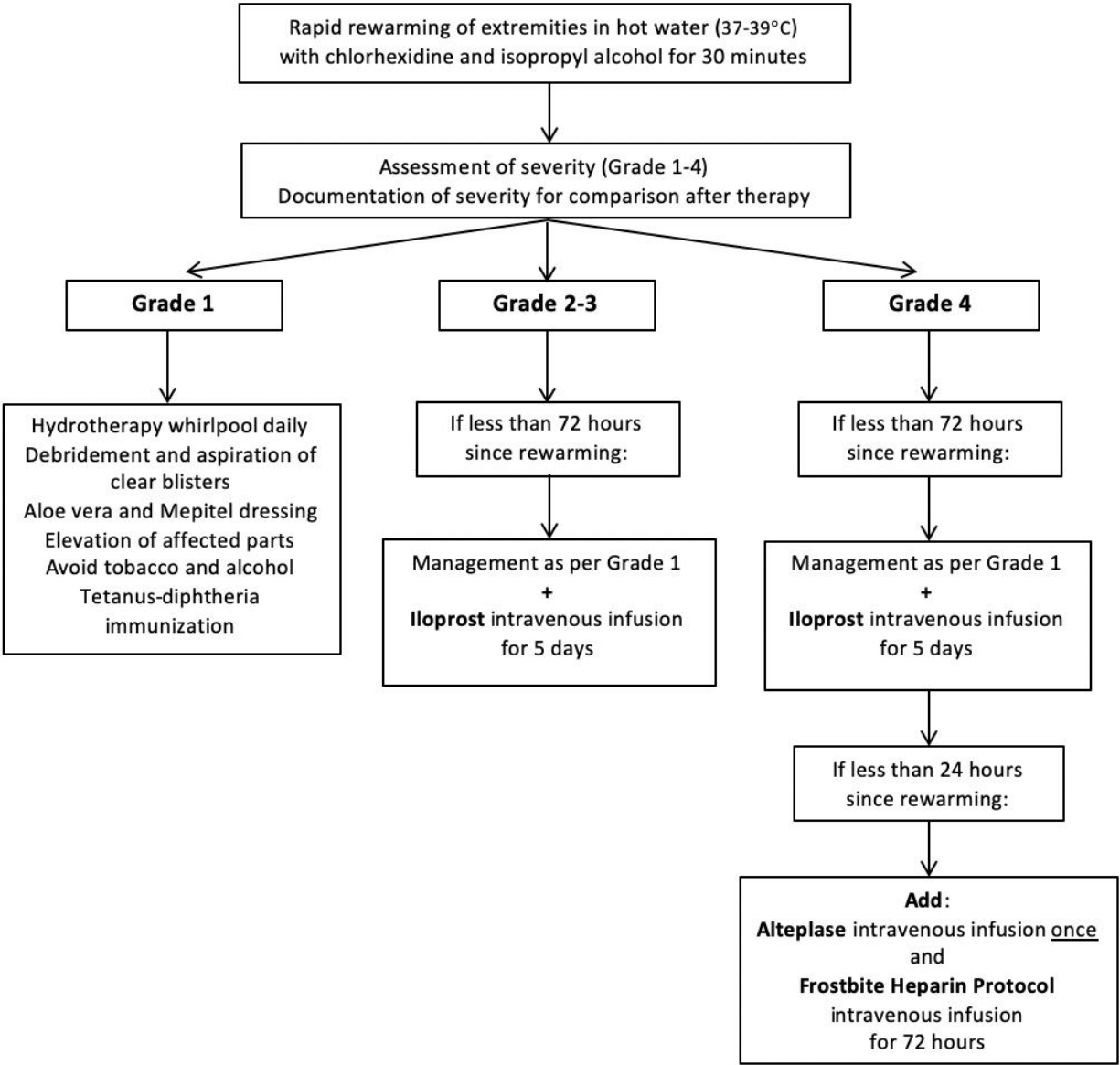
Statistical analysis

Descriptive statistical analysis was performed using Microsoft Excel (version 16.16.22). The One-Way ANOVA tests were performed using the IBM SPSS software (build 1.0.0.1347).

Ethics approval

The Yukon Frostbite Protocol was approved by the Yukon Hospital Corporation Ethics Committee before implementation. The Pre-Printed Orders were approved by the Pharmacy and Therapeutics Committee and Medical Advisory Committee. The authors obtained permission to review the patients' medical records from the Medical Advisory Committee.

Figure 1. Yukon Frostbite Protocol Algorithm



Results

Case series

From February 9, 2015 to February 8, 2020, Whitehorse General Hospital received and treated a total of 22 patients with a diagnosis of Grade 2 to 4 frostbite. The 22 patients were followed by the surgical team for frostbite treatment through to injury resolution. Follow-up included in-person clinic visits, telehealth consultations or emails and photographs. The patients' demographics, the interventions they received and their outcomes are summarized in Table 1.

Eighty-six percent of frostbite cases occurred at temperatures of -21°C and colder, most cases occurring in temperatures between -21°C to -30°C , with no significant correlation between temperature and frostbite severity ($p=0.375$; Figure 2). The exact duration of cold exposure was difficult to determine from patients' histories but ranged from exposure as short as 45 minutes to 64 hours. There was no significant correlation between the duration of cold exposure and frostbite severity ($p=0.409$). Predisposing events leading to frostbite injury fell into three main categories: winter sports, alcohol use and motor vehicle accident/breakdown. Winter sports precipitated 45% of the cases. Eight of the ten patients performing winter sports were participating in the Yukon Arctic Ultra, an endurance running race taking place every year in February. Alcohol use precipitated 27% of the cases, showing a trend towards more severe injury, with 5 of 6 alcohol-related cases being Grade 4 injury (Figure 3).

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Table 1. Patient Demographics, interventions and outcomes

n = 22		
Average age, in years (range)		39 (20 to 78)
Number of male patients		17 (77%)
Number of patients with comorbidities		
	Tobacco smoking	7 (32%)
	Alcohol Use Disorder	7 (32%)
	Diabetes	0
	Peripheral Vascular Disease	0
Average local environmental temperature at the time of the injury in °C (range)		-31 (-14 to -47)
Average body temperature at presentation to the emergency department in °C (range)		36.2 (29.8 to 37.7)
Average duration of cold exposure in hours (range)		20 (0.75 to 64)
Number of patients with freeze-thaw cycle		2 (9%)
Predisposing Event		
	Sport	10 (45%)
	Alcohol use	6 (27%)
	Car accident/breakdown	3 (14%)
	Psychiatric Disorder	1 (5%)
	Work	1 (5%)
	Other	1 (5%)
Number of patients by Grade		
	Grade 2	10 (45%)
	Grade 3	5 (23%)
	Grade 4	7 (32%)
Limbs Involved		

	Number of patients with hands involved only	6 (27%)
	Number of patients with feet involved only	12 (55%)
	Both hands and feet	4 (18%)
Digit Outcomes, Overall		
	Number of digits affected	142
	Number of digits salvaged	113 (80%)
Number of digits affected and salvaged by frostbite severity - Grade 2		
	Number of digits affected	51
	Number of digits salvaged	51 (100%)
Number of digits affected and salvaged by frostbite severity - Grade 3		
	Number of digits affected	27
	Number of digits salvaged	27 (100%)
Number of digits affected and salvaged by frostbite severity - Grade 4		
	Number of digits affected	58
	Number of digits salvaged	29 (50%)

Figure 2. Local environmental temperature at the time of the injury (°C) and number of frostbite cases with corresponding severity

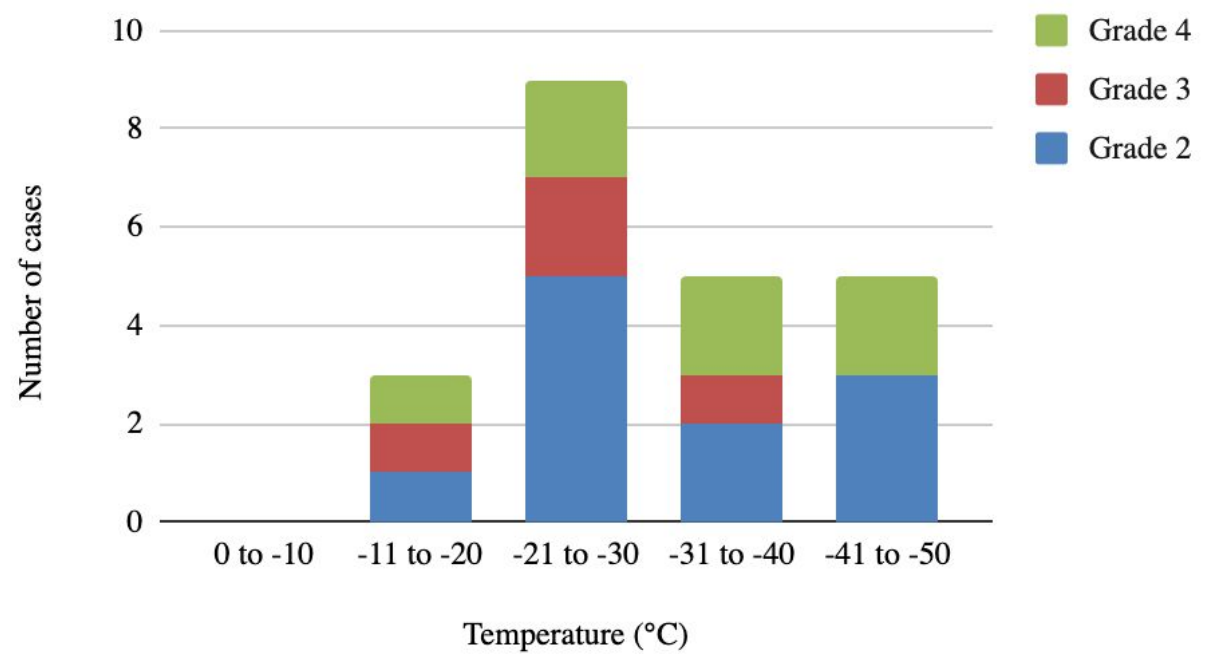
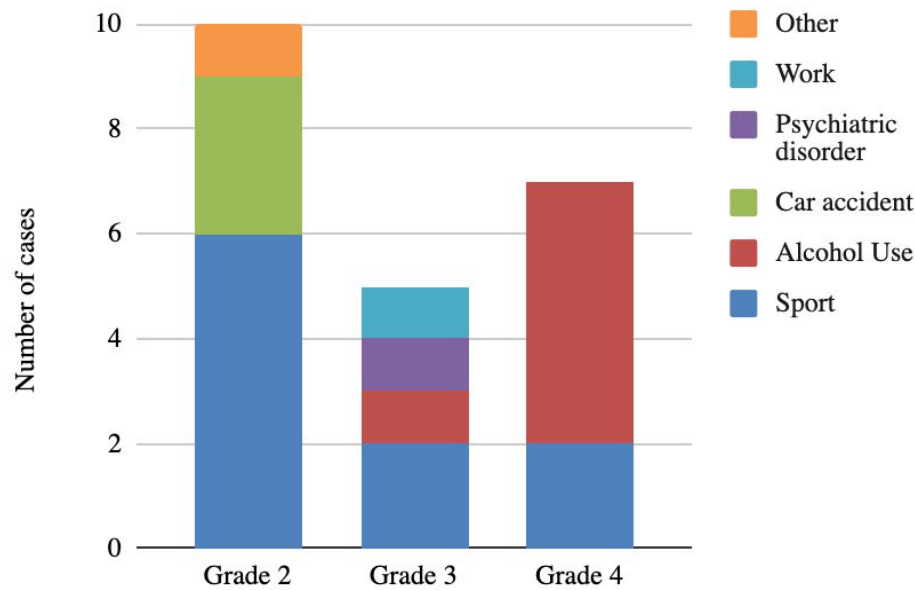


Figure 3. Frostbite severity and predisposing event



The treatment details and adverse drug reactions of the 22 patients in the series are summarized in Table 2. Though the majority of patients were rewarmed rapidly in the ED, nine patients (41%) had rewarmed prior to presentation to Whitehorse General Hospital (ie; passive rewarming, or active rewarming at home or at their community health centre). Most patients received 5 days of iloprost. One patient had frank bleeding below the eye after iloprost infusion but this was possibly due to a recent physical altercation. This patient was also on venous thromboembolism prophylaxis with dalteparin. Another patient receiving iloprost daily developed a perforated duodenal ulcer on day 5 of hospitalization. The patient was receiving scheduled ibuprofen at a dose of 600 mg every 6 hours and was not receiving any gastric protecting agent. Five patients received alteplase and heparin, in addition to iloprost, two of whom had an adverse reaction possibly related to alteplase and heparin. One patient had an acute intramuscular hemorrhage and one had bleeding from traumatic wounds, both requiring blood transfusion.

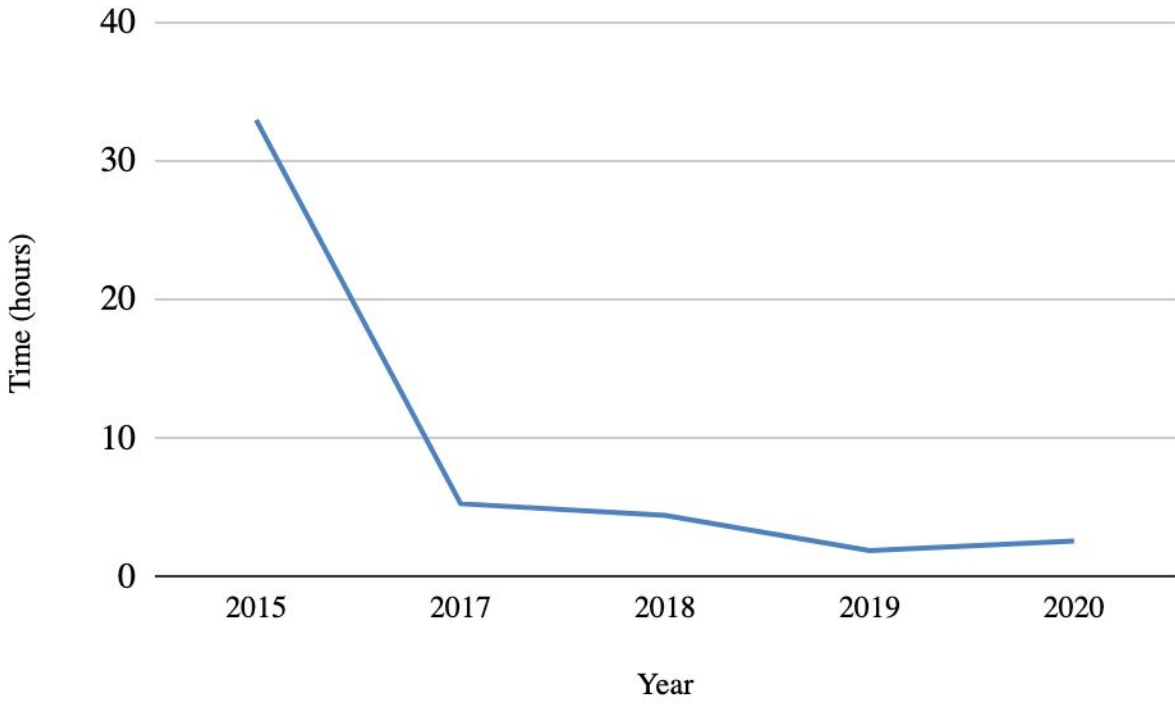
ED presentation (triage) to rewarming was 2.4 hours on average. The average time from ED presentation to iloprost initiation was reduced from 32.9 hours (2015) to 2.6 hours (2020) (Figure 4). There were only 2 years that had Grade 4 cases that met criteria for alteplase treatment, 2017 and 2018. For these two years, time from ED triage to alteplase initiation decreased from 7.4 hours (2017) to 4.6 hours (2018).

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Table 2. Treatment details and adverse drug reactions

Treatment Regimen, number of patients		
	Rapid rewarming	13 (59%)
	Iloprost only	17 (77%)
	Iloprost, alteplase and heparin	5 (23%)
	Topical aloe vera	19 (86%)
	Scheduled oral ibuprofen	22 (100%)
Number of iloprost doses (days) received, number of patients		
	1	2 (9%)
	2	0
	3	3 (14%)
	4	1 (5%)
	5	16 (73%)
Number of patients with 1 or more adverse drug reaction with iloprost, overall		16 (73%)
Number of patients with iloprost adverse drug reactions		
	Headache	11 (50%)
	Flushing	8 (36%)
	Tachycardia (heart rate greater than 100)	8 (36%)
	Nausea	6 (27%)
	Vomiting	2 (9%)
	Dizziness	2 (9%)
	Other	2 (9%)
	Hypotension (blood pressure less than 90/50)	1 (5%)
Alteplase dosing		
	Number of patients who received alteplase 15 mg intravenous over 2 minutes then 0.75 mg/kg (maximum 50 mg) over 30 minutes then 0.5 mg/kg (maximum 35 mg) over 60 minutes	1 (20%)
	Number of patients who received alteplase 0.15 mg/kg over 15 minutes then 0.15 mg/kg/hour intravenous infusion for 6 hours	4 (80%)
Number of patients with 1 or more adverse drug reaction with alteplase, overall		2 (40%)

Figure 4. Average time (hours) from ED presentation to iloprost treatment



Interpretation

This case series demonstrates the efficacy of a treatment protocol including iloprost, alteplase and heparin for digit salvage in Grade 2 to 4 frostbite. Our overall digit salvage rate, Grades 2 to 4 combined, was 80%. Grade 2 and 3 cases had a 100% salvage rate while Grade 4 cases had a 50% salvage rate. There were four patients of 22 who required amputation of digits. Of note, the majority of digits were amputated from one unfortunate patient who lost 19 of 20 digits after a severe case of Grade 4 frostbite. We observed a notable decrease in time to initiation of iloprost and alteplase treatment over the years.

According to Cauchy et al, the risk of amputation is 31% for Grade 2 frostbite, 67% for Grade 3 frostbite and 98-100% for Grade 4 frostbite². In our case series, the overall digit salvage rate was 80% (20% amputation rate) and 50% for Grade 4 frostbite, which suggests that our pharmacologic intervention using iloprost, alteplase and heparin improves the outcomes. Our digit salvage rate is also consistent with Lindford et al, which demonstrated a 74.8% salvage rate using intra-arterial tissue plasminogen activator and iloprost in their 20-case review²¹. In our series, more cases were related to outdoor sports than to psychiatric illness or alcohol use. This is likely distinct from what would be expected in an urban centre. Interestingly, we had no cases of frostbite at temperatures warmer than -14°C, with 86% of cases occurring at temperatures colder than -21°C. This is consistent with the findings by Juopperi et al in Finland³⁰. Considering that Boles et al demonstrated an increased risk of tissue loss in frostbite cases occurring at temperatures equal or below - 23°C³¹, 86 % of our cases were at risk of tissue loss.

As other authors have observed²⁶, our experience demonstrates that having a formal protocol and pre-printed orders led to a decrease in treatment delays. Great efforts were made to educate frontline providers in the ED and community hospitals and health centres. As familiarity with frostbite recognition, grading and management has improved, so has time to treatment initiation. We observed a notable decrease in time to initiation of iloprost and alteplase treatment over the years. This is important progress, as Nygaard et al found that time between rewarming and thrombolytic therapy was a critical window (warm ischemia time), with each hour of delay resulting in a 28% decrease in digit salvage²².

Since the implementation of our protocol we made four substantial changes. One was the decision to treat Grade 2 cases with iloprost. This arose from the difficulty distinguishing some Grade 3 cases from Grade 2 early on. We have been impressed with the continued clinical changes that occur over the first 72 hours following rewarming. Given how well iloprost was tolerated by our patients it was decided to err on the side of possibly overtreating some Grade 2 patients to avoid undertreating or delaying treatment of Grade 3 cases. We also treated many patients with Grade 2 and 3 in an ambulatory setting (outpatient therapy in the ED or Critical Care Department). The third change was a decrease in the alteplase dose. We initially used the Cauchy et al alteplase dosing¹¹ but revised our alteplase dosing in February 2017 based on the Hennepin County Medical Center experience in Minnesota²². The revised alteplase dosing yields a smaller total dose (16% less in an 80 kg patient). We believed the administration would be simpler and there would be less risk of adverse drug events with a smaller dose. We also revised our protocol in April 2018 to include the proton-pump inhibitor pantoprazole following one patient experiencing a perforated duodenal ulcer.

The risks associated with alteplase are notable, and so should remain a treatment reserved for those at highest risk of amputation. Iloprost, however, can be offered to people with any level of cyanosis and thus risk of digit loss (Grade 2 to 4) and can be effective up to 72 hours after rewarming²⁴. Iloprost is not currently commercialized in Canada and only available through Health Canada Special Access Program. There is only one published case report on the use of epoprostenol, another prostacyclin, by an American institution without access to iloprost²⁶. Due to the limited evidence with the use of epoprostenol in frostbite management, we recommend continuing using iloprost and we encourage Canadian hospitals in regions at risk of cold injury to obtain access to iloprost for use in frostbite.

Limitations

Unfortunately, due to the absence of a control group, our case series did not allow us to verify the benefit of iloprost, alteplase and heparin compared to no pharmacologic intervention. Our case series also did not allow us to determine whether the combination of iloprost and alteplase provides additional benefit to either agent alone. Ideally, this question would be addressed in a randomized controlled trial where Grade 4 digit salvage rate is compared between treatment with iloprost alone, alteplase alone, and the combination of both. A national registry would serve to collect all frostbite cases, standardize data selection and demonstrate if there are enough cases to sufficiently power such as study. Further limitation of our series is that it is retrospective in nature and grading of frostbite relies on subjective clinical interpretation. A future study validating clinical grading as compared to advanced imaging would be beneficial.

Conclusion

The protocol developed at our institution has streamlined frostbite management and has resulted in a digit salvage rate comparable with the literature. It has been taken up well by healthcare providers, reducing time to treatment, and decreasing warm ischemia time. The treatment with iloprost for all Grade 2 to 4 injuries, and adding alteplase and heparin within the first 24 hours for all Grade 4 injuries appears to be an appropriate and achievable regimen.

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