CASE REPORTS

Case Report: Severe Frostbite in Extreme Altitude Climbers —The Kathmandu Iloprost Experience

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Severe frostbite occurs frequently at extreme altitude in the Himalayas, often resulting in amputations. Recent advances in treatment of frostbite injuries with either intravenous or intra-arterial tissue plasminogen activator, or with iloprost, have improved outcomes in frostbite injuries, but only if the patient has access to these within 24 to 48 h postinjury, and ideally even sooner. Frostbitten Himalayan climbers are seldom able to reach medical care in this time frame. We wished to see if delayed iloprost use (up to 72 h) would help reduce tissue loss in grade 3 to 4 frostbite. In a series of 5 consecutive climbers with severe frostbite in whom we used iloprost, 4 of whom received treatment between 48 and 72 h from injury, 2 had excellent results with minimal tissue loss, and 2 had good results with tissue loss less than expected. The 1 patient with a poor outcome likely experienced a freeze-thaw-refreeze injury. This small series suggests that iloprost can be beneficial for severe frostbite, even after the standard 48-h window and perhaps for up to 72 h.

Keywords: climbing, Everest, cold injury, mountaineer, amputation

Introduction

CIWEC Hospital and Travel Medicine Center located in Kathmandu, Nepal, treats many climbers and trekkers each year. Among the more than 200 cases of frostbite recorded in the CIWEC database in the past 5 y (2012–2016), most of the injuries were in mountaineers who were trying to summit or had summited Mount Everest and other 8000 m peaks in Nepal and in Tibet. Time to presentation was usually 72 h or greater until 2012/2013, when helicopter rescue from camp 2 on Mount Everest in Nepal became routine. Since then, climbers have started to present within 48 to 72 h of their frostbite injury. Before our starting to use iloprost in 2014, care was merely supportive. In October 2014 a typhoon in India caused unusually high snowfall in the Annapurna massif during the peak trekking season. Numerous trekkers died near Thorung Pass (5416 m) and some survivors sustained severe frostbite.¹ The Nepal military evacuated 3

Israeli travelers by helicopter with severe grade 4 frostbite and we initiated iloprost treatment 72 h after injury with the first dose at CIWEC and subsequent 4 doses in Israel. Two of the trekkers had amputations but 1 of them recovered completely (Figure 1).

Based on this experience and recent literature suggesting that iloprost could be effective beyond 24 h, we developed a protocol using intravenous iloprost in persons with grade 3 to 4 frostbite who presented within 72 h of injury. We report here our experience with the first 5 climbers to encourage others to consider using iloprost for these devastating injuries in the proper setting.

Background and methods

Thrombolysis is gaining recognition as an effective treatment for severe frostbite injuries. Tissue plasminogen activator (tPA) given intravenously or intra-arterially is effective when given within 24 h of frostbite injury, and with limited warm ischemia duration.^{2–4} In addition, the prostacyclin analogue iloprost given intravenously was effective in a controlled trial and in case reports, and

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Figure 1. Frostbite of both feet, with purplish discoloration involving all toes and extending to mid-metatarsals, with hemorrhagic blisters on toes. Photos: top row at 74 h; bottom row, left and middle photos at 3 mo, right at 1 y. (See text.).

can perhaps be given more than 24 h after frostbite injury, although data are limited.^{5–8} Most patients being evacuated from Himalayan peaks with frostbite do not arrive at the hospital within 24 h, and therefore iloprost may offer a treatment option for these climbers. In order to assess this possibility, we used iloprost in a consecutive series of frostbite patients in the spring Everest climbing season of 2016.

We performed initial evaluations, documented the frostbite injuries with photographs, and obtained informed consent for treatment. Grading of frostbite injury was based on the system proposed by Cauchy et al,⁹ with distal phalanx involvement being grade 2, middle and proximal phalanx grade 3, and metatarsal/metacarpal involvement grade 4. In grade 1, the initial lesion (defined by a grayness or cyanotic anesthetic area of the distal phalanx) vanishes after rapid rewarming.⁹ Each injured digit was graded. All frostbite injuries had spontaneously thawed and rewarming was not necessary. Local care of frostbitten extremities included bulky protective dressings after soaking in warm povidone-iodine-water solution. Blisters were drained if large, and desquamated areas were dressed with sterile nonadherent dressings. Iloprost was mixed with normal saline to a concentration of $0.2 \text{ mcg}\cdot\text{mL}^{-1}$. Infusion was started at $2 \text{ mcg}\cdot\text{h}^{-1}$ for 30 min, then increased by $2 \text{ mcg}\cdot\text{h}^{-1}$ every 30 min to a maximum of $6 \text{ mcg}\cdot\text{h}^{-1}$ for persons 50 kg or less, $8 \text{ mcg}\cdot\text{h}^{-1}$ for persons 75 kg or less, and $10 \text{ mcg}\cdot\text{h}^{-1}$ for persons weighing more than 75 kg, making an infusion rate of approximately $2 \text{ ng}\cdot\text{kg}\cdot\text{min}^{-1}$. Monitoring of patients included heart rate and blood pressure, and we

watched for vasomotor reactions such as headache, tachycardia, palpitations, and nausea; if these developed we reduced the dosage until the patient was able to tolerate the drug. The infusion was continued for 6 h each day for 5 d. We administered aspirin 325 mg daily for 5 d, and cephalexin 500 mg 4 times a day, with 1 person receiving intravenous ceftriaxone $2 \text{ g}\cdot\text{d}^{-1}$ on account of foot cellulitis. We performed local frostbite care daily as described above. This protocol was approved by the Kathmandu CIWEC Hospital ethics committee.

Case reports

Patient demographics and treatment details of the following cases are presented in [Table 1](#).

PATIENT 1

A 49-year-old man presented to our hospital after helicopter evacuation from camp 2 (6400 m) on Everest in May 2016. He had summited and descended to the South Col (8000 m, camp 4), where he spent the night. The next morning he felt cold and was numb in both feet. He removed his shoes to find the socks soggy with sweat and his toes frostbitten. He changed his socks, applied pads to warm his feet, and descended by foot to camp 2. He was evacuated from camp 2 the next morning to Kathmandu. He did not receive any medication before arriving in Kathmandu, where his feet showed purplish discoloration affecting all the toes of the left foot, with a large bleb on the first toe, and purplish discoloration and blebs on toes 1 to 3 of the right foot

Table 1. Patient demographics and treatment details

Patient	Sex	Age (y)	Digits affected	Maximum altitude	Evacuation altitude	Time to iloprost infusion	Side effects of iloprost	Digit loss
1	M	49	3 toes – grade 3; 4 toes – grade 2	8848 m	6400 m	48–72 h	Headache, drop in blood pressure 20 mm	One third of 3 digits
2	M	38	3 toes – grade 3; 4 toes – grade 2	8163 m	4800 m	<48 h	None	None
3	M	21	3 fingers – grade 3; 2 fingers – grade 2	8848 m	5300 m	60 h	None	None
4	M	54	5 fingers – grade 2; 5 toes – grade 3	8848 m	6400 m	48–52 h	Headache, nausea	Partial amputations of 8 digits
5	M	33	1 toe – grade 4 4 toes – grade 3	8848 m	5300 m	66 h	None	One half of 2 digits

M, male.

(Figure 2). His injuries were consistent with grade 3 frostbite of both great toes and the second toe of the right foot, and grade 2 of the third, fourth, and fifth toes of the left foot and the third toe of the right foot. He received 5 d of iloprost treatment and tolerated it well except for mild flushing. Time from injury to iloprost treatment was between 48 and 72 h. At 3 mo and 16 mo, photographs show improvement and finally minimal digit loss of both great toes and the second toe of the left foot (Figure 2). He has resumed mountain climbing.

PATIENT 2

A 38-year-old man summited Manaslu (8163 m) on October 1, 2016. He descended to camp 2 (6000 m) and spent the night. The next day, he descended to base camp (4800 m) in bad weather, and on removing his shoes found frostbite injuries affecting both feet. He thought the freezing injury probably occurred around midday on October 2 and that his feet rewarmed as he continued down to base camp. On October 3, he found his toes were worse and looked blue; he was evacuated by helicopter to Kathmandu. He did not take any medications before evacuation. In Kathmandu his examination showed frostbite injuries of the great toes of both feet with small hemorrhagic blebs, and purplish discoloration of the second to fifth toes of the right foot consistent with grade 3 frostbite of both great toes and the right second toe, and grade 2 of the third, fourth, and fifth toes of the right foot and the fourth toe of the left foot. Time from injury to iloprost was between 32 and 48 h. At 3 mo, he had recovered almost completely except for small areas on both great toes (Figure 3).

PATIENT 3

A 21-year-old male Sherpa climbing Everest sustained frostbite to fingers of both hands on summit day in May 2016. He descended to camp 4, camp 2, and then base camp and was helicoptered out to Kathmandu within 48 h, without receiving any medications. In Kathmandu he was admitted to another facility for 1 day, where his blisters were drained, before being transferred to CIWEC Hospital. Discoloration and blebs involving the fourth and fifth digits of the right hand and the fourth digit of the left hand were consistent with grade 3 frostbite. Grade 2 frostbite was present on third digits of both hands (Figure 4). Time from injury to iloprost was 60 h. He was treated for 5 d and tolerated it well. His fingers recovered completely without tissue loss, and 1 y postinjury he has already summited another 8000 m peak.

Figure 2. Patient 1. Grade 3 frostbite of both great toes and second toe of the right foot, grade 2 of third, fourth, and fifth toes of left foot and third toe of right foot. Photos: top row at 48-72 h; bottom row at 3 mo and 16 mo.

PATIENT 4

A 54-year-old American man summited Everest in May 2016. During descent, he realized that his hands and feet, particularly the right hand and right foot, were frozen.

During the summit push, he used only his right hand to hold onto the ropes. He rewarmed his right hand and right foot at camp 4 (8000 m). The next day, he walked to camp 2 (6400 m) and was evacuated to Kathmandu. He was not sure if refreezing might have occurred during descent to

Figure 3. Patient 2. Grade 3 frostbite of both great toes and right second toe, and grade 2 of third, fourth, and fifth toes of the right foot and fourth toe of left foot. Photos: top left, 32-48 h; top right, 1 mo; bottom row, 3 mo.

Figure 4. Patient 3. Grade 3 frostbite of digits 4 and 5 of the right hand and digit 4 of the left, with grade 2 of third digits of both hands. Photos: top row, at 60 h; bottom row, at 2 mo and 1 y.

camp 2. He had been taking 80 mg of aspirin, a potassium supplement, and a multivitamin daily, and an occasional acetazolamide. On admission, the right foot had black discoloration of all 5 toes extending up to the proximal phalanx, consistent with grade 3 injuries (Figure 5). Similar frostbite injuries were also noted in the second through fifth fingers of the right hand and third finger of the left hand consistent with grade 2 injuries of 5 digits (images of hands not shown). Technetium-99 scintigraphy done immediately after patient arrival (vascular phase only) showed no perfusion in the toes of the right foot, nor in the 5 affected fingers. Time from injury to iloprost was between 48 and 52 h. Iloprost infusion was started and continued for 5 d. He experienced symptoms of flushing and headaches during infusion that required dose reduction during the first 2 d and symptoms resolved. At 3 mo, 8 of 10 of his frostbitten digits were partially amputated (Figure 5, right foot only).

PATIENT 5

A 33-year-old Australian mountaineer summited Everest in May 2016. He descended to camp 4 and spent the

night assisting a fellow climber. In the morning he realized that his feet were frozen, the right more so than the left. On May 20 his feet thawed during the descent to camp 2. He then walked to base camp, where he was evacuated by helicopter to Kathmandu. He did not take any medication during the climb but took some aspirin after getting frostbite. In Kathmandu, on examination there was purplish discoloration of all toes of the right foot extending beyond metatarsophalangeal joints to the dorsum of the foot. There was a ruptured bleb at the base of the first toe (Figure 6), and also increased warmth on the dorsum of the right foot that was ultimately considered to be cellulitis. Frostbite injuries were consistent with grade 4 of the great toe and grade 3 of the second through fifth toes of the right foot. The left foot had only dark discoloration of the tip of the first toe with intact capillary refill in the rest of the toes. He received the standard iloprost treatment as well as ceftriaxone for cellulitis with good resolution. Time from injury to iloprost was 66 h and from rewarming to iloprost 42 h. At 6 mo he had amputation of one half of the first and second toes of the right foot (Figure 6).

Figure 5. Patient 4. Grade 3 frostbite of all toes of the right foot. Photos: top row, at 72 h and 6 d (day 3 of iloprost infusion) bottom row, 1 mo and 3 mo.

Discussion

We wished to see if delayed iloprost use (up to 72 h) would help reduce tissue loss in grade 3–4 frostbite. In the 5 climbers in whom we used iloprost, 2 (patients 2 and 3) had very good results with minimal tissue loss, and 2 (patients 1 and 5) had good results with tissue loss less than expected. The 1 patient with a poor outcome (patient 4), with amputation of 8 of 10 affected digits, may have experienced refreezing that likely occurred after rewarming. This small series suggests that iloprost can be beneficial for severe frostbite, even after the standard 48-h window and perhaps for up to 72 h.

Frostbite is common in climbers at extreme altitude, despite modern, high-quality equipment. Factors contributing to onset of frostbite in this extreme environment include unusually cold temperatures, strong winds, dehydration, vasoconstriction from reduced core body temperature, prolonged exposure of up to 20 h on summit day, prolonged inactivity due to long queues, loss of protective gear, trauma, and severe hypoxemia while climbing over 8000 m with low-flow oxygen. Most persons who sustain frostbite on Everest or other

8000 m peaks do not know exactly when extremity freezing takes place, making treatment decisions difficult. Spontaneous rewarming often occurs as the climber descends to lower altitude and shelter, but refreezing sometimes ensues in particularly bad conditions. Occasionally severe frostbite is due to skin contact directly with metal or with spilled fuel.

The traditional approach for decades was merely prevention of complications, such as infection or repeat trauma, followed by amputation and reconstructive surgery after clear demarcation of necrotic tissue on physical examination, usually over the course of weeks to mo. Multiphase bone scanning with technetium-99m-labeled diphosphonate done on day 2 after rewarming and a second scan done 7 to 10 d later is an established modality to assess the extent of vascular injury, response to treatment, and early prediction of the extent of amputation.^{8,10,11} Single photon emission computed tomography/standard computed tomography (SPECT/CT) has been found to add value to define finer anatomic details before definitive surgical care of frostbite.¹¹ There have been case reports of magnetic resonance imaging

Figure 6. Patient 5. Grade 4 frostbite of right great toe with grade 3 of others. Photos: top row at 66 h, bottom row 3 mo and 6 mo.

and magnetic resonance angiography use in assessment of tissue necrosis and viability that permitted earlier surgical intervention.¹²

The first real advance in frostbite treatment in decades was the use of tPA in a few case reports and then clinical trials. tPA can be given intravenously or intra-arterially,¹³ often in conjunction with selective arteriography, and is most effective if administered within 24 h of injury.⁴ Expedition climbers can rarely reach a hospital within 24 h of injury, and thus they rarely receive tPA treatment.^{2,3,14} Cauchy et al have reported the use of tPA at K2 base camp in 2 patients with successful outcome in 1.¹⁵

Iloprost, a prostacyclin analogue, is a potent vasodilator that also inhibits platelet aggregation^{16,17} and is able to downregulate lymphocyte adhesion to endothelial cells.¹⁸ No serious adverse reactions occurred in a study of 48 patients when iloprost was given intravenously at 2 ng·kg·min⁻¹ for 6 h daily for weeks in patients with peripheral vascular disease.¹⁹ Iloprost also helps improve ischemic pain and reduce amputation rates in patients with severe peripheral vascular disease.^{20,21} The use of

iloprost in frostbite was first described in 1994.²² Cauchy et al⁵ popularized its use with a controlled trial resulting in no amputations in patients treated with iloprost. It has an excellent safety record, and side effects like headache and nausea can usually be managed without discontinuation of therapy. Of our 5 patients, 2 had minor side effects, and 1 had side effects requiring a dose reduction for the first 2 d, but all were able to achieve the optimum dose of 2 ng·kg·min⁻¹. None had significant heart rate or blood pressure abnormalities. Iloprost is given intravenously through an infusion or syringe pump, with monitoring of heart rate and blood pressure, along with monitoring for side effects and symptomatic treatment. Intra-arterial tPA requires advanced facilities complete with arteriography. Although both intra-arterial and intravenous tPA must be given within 24 h of injury, and both have the potential for serious bleeding, iloprost appears to be a safe drug that can be used more than 24 h after frostbite injury.⁸ Since critical time elapses from the occurrence of frostbite to treatment, field use of iloprost should be considered by persons experienced in its use in order to

reduce rates of amputation.¹⁵ For persons summiting Everest, it may still take 36 to 48 h from the time of frostbite to infusion of iloprost at base camp.

LIMITATIONS

Although technetium bone scanning is available in Nepal, it is not on site at CIWEC Hospital. We were not able to perform this pretreatment, since valuable time would be lost. We were also not able to perform it at the end of treatment, as patients were very anxious to return to their home countries as soon as possible. We therefore do not know for certain that amputation was inevitable in these cases, or that iloprost definitely improved perfusion. Use of magnetic resonance imaging and high frequency ultrasound in evaluating the level of severity of frostbite has yet to be explored in Nepal. One of these modalities in evaluating the severity of frostbite and benefit of intervention should be utilized for future cases.

In conclusion, severe frostbite continues to be a problem in extreme altitude mountaineering. New therapies offer more effective treatment options, but survival of tissue is a function of time to treatment, which is often delayed in remote environments. Treatment with iloprost infusion offers hope in delayed presentation of frostbite; whether iloprost infusion can be started on Everest or other 8000 m peaks for better patient outcomes remains to be explored.

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References

- Vadlamudi R, Murphy HA, Pandey P. Benefit of prostacyclin for severe frostbite at altitude in Nepal. Proceedings of the 14th Conference of the International Society of Travel Medicine (CISTM14) Quebec; May 24–28 2015; Quebec City, Canada. International Society of Travel Medicine; 2015:39.
- 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. discussion 51–3.
- 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. discussion 4–5.
- Gonzaga T, Jenabzadeh K, Anderson CP, Mohr WJ, Endorf FW, Ahrenholz 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.
- Cauchy E, Cheguillaume B, Chetaille E. A controlled trial of a prostacyclin and rt-PA in the treatment of severe frostbite. *N Engl J Med*. 2011;364(2):189–90.
- Poole A, Gauthier J. Treatment of severe frostbite with iloprost in northern Canada. *CMAJ*. 2016;188:1255–8.
- Hallam MJ, Cubison T, Dheansa B, Imray C. Managing frostbite. *BMJ*. 2010;341:c5864.
- Handford C, Buxton P, Russell K, Imray CE, McIntosh SE, Freer L, et al. Frostbite: a practical approach to hospital management. *Extrem Physiol Med*. 2014;3:7.
- Cauchy E, Chetaille E, Marchand V, Marsigny B. Retrospective study of 70 cases of severe frostbite lesions: a proposed new classification scheme. *Wilderness Environ Med*. 2001;12(4):248–55.
- 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.
- 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.
- Barker JR, Haws MJ, Brown RE, Kucan JO, Moore WD. Magnetic resonance imaging of severe frostbite injuries. *Ann Plast Surg*. 1997;38:275–9.
- McIntosh SE, Opacic M, Freer L, Grissom CK, Auerbach PS, Rodway GW, et al. Wilderness Medical Society practice guidelines for the prevention and treatment of frostbite: 2014 update. *Wilderness Environ Med*. 2014;25(4 suppl):S43–54.
- Bruen KJ, Gowski WF. Treatment of digital frostbite: current concepts. *J Hand Surg Am*. 2009;34(3):553–4.
- Cauchy E, Davis CB, Pasquier M, Meyer EF, Hackett PH. A new proposal for management of severe frostbite in the austere environment. *Wilderness Environ Med*. 2016;27:92–9.
- Kaukinen S, Ylitalo P, Pessi T, Vapaatalo H. Hemodynamic effects of iloprost, a prostacyclin analog. *Clin Pharmacol Ther*. 1984;36:464–9.
- Fitscha P, Kaliman J, O'Grady J, Sinzinger H. In vivo modulation of platelet deposition on human atherosclerotic lesions by various antiaggregatory prostaglandins. *Folia Haematol Int Mag Klin Morphol Blutforsch*. 1988;115:443–6.
- Della Bella S, Molteni M, Mocellin C, Fumagalli S, Bonara P, Scorza R. Novel mode of action of iloprost: in vitro down-regulation of endothelial cell adhesion molecules. *Prostaglandins Other Lipid Mediat*. 2001;65:73–83.

19. Balzer K, Bechara G, Bisler H, Clevert HD, Diehm C, Heisig G, et al. Reduction of ischaemic rest pain in advanced peripheral arterial occlusive disease. A double blind placebo controlled trial with iloprost. *Int Angiol.* 1991;10:229–32.
20. Arosio E, Sardina M, Prior M, De Marchi S, Zannoni M, Bianchini C. Clinical and circulatory effects of Iloprost either administered for 1 week or 4 weeks in patients with peripheral obstructive arterial disease at Leriche-Fontaine stage III. *Eur Rev Med Pharmacol Sci.* 1998;2:53–9.
21. Vitale V, Monami M, Mannucci E. Prostanoids in patients with peripheral arterial disease: a meta-analysis of placebo-controlled randomized clinical trials. *J Diabetes Complications.* 2016;30:161–6.
22. Groeichenig E. Treatment of frostbite with iloprost. *Lancet.* 1994;344(8930):1152–3.