

Frostbite: management update

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Summary

The popularity of winter sports is leading to an increase in the number of subjects exposed to environmental pathologies such as frostbite. This is the reason why the patient's profile is changing from the classical descriptions of adults with pre-existing conditions, basically those with cognitive impairment that prevented them from a proper protection against cold or as an occupational illness in working routines related with low temperature exposures. Nowadays these disorders occur mainly in healthy athletic young patients who expose themselves voluntarily to the cold environment, both for professional or amateur aims. Frostbite can occur as a single pathology or can take part in a more complex clinical picture that includes more serious conditions, as hypothermia or trauma. In addition to this fact, it is not uncommon that frostbite appears in exhausted and dehydrated subjects. The likelihood of such injuries taking place in remote areas further complicates its management, primarily because of the delay in diagnosis and definitive treatment. Sequelae after frostbite are common and potentially limiting for the posterior sports career. In recent years, efforts have been made to establish algorithms intended for rescue and expedition doctors to manage mountain medical care based on scientific evidence. Current recommendations include prompt identification and immediate medical care, followed by early hospital treatment if necessary and specific long-term rehabilitation programmes. This review attempts to describe current knowledge of the physiopathology and the clinical aspects of frostbite, in addition to new management perspectives, from in-situ emergency care through to hospital treatment.

Key words:

Frostbite. Rewarming. Iloprost. Amputation.

Actualización en el manejo de las congelaciones

Resumen

La popularidad de los deportes de montaña conlleva que cada vez haya más individuos expuestos a patologías ambientales como son las congelaciones. De esta forma, el perfil de los pacientes está variando respecto a las descripciones clásicas, donde se consideraban lesiones propias del adulto con patología de base, principalmente alteraciones cognitivas que le impedían protegerse adecuadamente del frío, o bien como una enfermedad laboral en profesiones relacionadas con la exposición a las bajas temperaturas. Actualmente esta patología se presenta más frecuentemente en jóvenes sanos y deportistas que se exponen voluntariamente al ambiente frío para la práctica deportiva. Las congelaciones pueden presentarse como una patología aislada o formando parte de un cuadro clínico más complejo, que puede incluir la hipotermia o patología traumática. Añadido a este hecho, es frecuente que se presenten en individuos debilitados por la fatiga y la desnutrición. La posibilidad de que esta patología tenga lugar en entornos remotos añade complejidad a su manejo y empeora el pronóstico debido al retraso del tratamiento definitivo. Las secuelas tras las congelaciones son frecuentes y potencialmente limitantes para la práctica deportiva posterior. En los últimos años se han hecho esfuerzos para basar los algoritmos de actuación de las patologías de montaña en la evidencia científica, destinados tanto al público deportivo como al personal sanitario. En síntesis, estos versan en la identificación y tratamiento inicial tempranos seguidos de tratamientos hospitalarios administrados de forma precoz en caso de ser necesarios y programas de rehabilitación específicos y prolongados. La presente revisión trata de describir las recomendaciones actuales, desde la identificación y clasificación de las congelaciones hasta los nuevos avances en el manejo sobre el terreno, médico inicial y hospitalario de las mismas.

Palabras clave:

Congelación.
Recalentamiento. Iloprost.
Amputación.

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Definition and background

Frostbite is the most common local injury due to cold and normally occurs when part of the body is exposed to temperatures below the freezing point of intact skin¹, which is estimated to be around -0.55°C^2 , without proper protection and for a sufficiently long period of time³. Frostbite has typically been described as an occupational injury (e.g. due to military, mining or industrial tasks), and as characteristic of subjects with permanent or transitory cognitive impairment that prevents them from protecting themselves against the cold⁴. In the last years, the rate among young, healthy adults has increased due to the popularity of winter sports such as skiing, mountaineering, ice climbing and technical climbing/alpinism, at both professional and amateur levels. The incidence among winter mountaineers appears to be very high, as much as 37% in the only study published⁵. Moreover, given that the subjects most frequently affected are aged between 30 and 49 years⁶ and usually are physically active, frostbite leads to a substantial interruption in their normal activity. It is worth considering that in most cases it leads to long-term sequelae, particularly if subject's daily activities require exposure to low temperatures to ensure they are carried out safely, or if their job involves constant environmental low temperatures (e.g. ski patrollers, mountain guides, avalanche forecasters and workers involved in cold-chain maintenance).

Frostbite is among the most common consultation causes at Mount Everest medical post (27.5% of traumatic injuries) and Denali medical post (18.1% of total injuries)⁷, although these data probably underestimate the actual number of cases, since the number of mild injuries not requiring medical attention is unknown. It is also worth noting that it is the most frequent reason for evacuation from Everest Base Camp⁸ and the leading cause of injury at altitude in the Karakoram mountain range⁹. Around 80 cases of frostbite are registered per year at Chamonix Hospital, two thirds of which are diagnosed as superficial.

Risk factors

Since human beings have limited physiological strategies to protect themselves against the cold, any situation that compromises the body's protection capacity in the general population (alcohol abuse, mental illness, very young and very old age, etc.) is considered a risk factor for frostbite. Other intrinsic characteristics of individuals, such as pathologies that affect the vascular bed, neuropathies, Raynaud's syndrome, smoking, genetic predisposition (DD genotype for the angiotensin-converting enzyme) and previous history of frostbite, are predisposing factors that are widely described in the literature^{1,4,10}. Other factors include preventable actions such as wearing external body piercing jewellery and constrictive elements (rings, snowboard bindings, elastic clamps, etc.)¹¹.

It has been suggested that a lack of appropriate clothing and equipment among those who practice sports in cold and high-altitude conditions and the absence of a competent guide can lead to this kind of injury⁵, but more investigation is required to confirm this assumption. Any adverse event involving immobilization in a cold environment, including spinal injuries and fractures of large bones, increases the risk

of frostbite due to the increased exposure time and the possibility of vascular impairment. With respect to environmental factors, the absolute temperature reached and exposure time are relevant, especially the latter, given that the severity of frostbite is related to the length of time the tissue has been frozen^{1,6}. Incidence increases at altitude, particularly from 5100 meters above sea level, due to local factors such as haemoconcentration, a rise in vascular permeability and dehydration, and potential cognitive impairment secondary to hypoxia that can delay or limit self-protection reflexes⁹.

Location of injury

Distal areas are the most unprotected from the cold and the most exposed; in addition, the high surface-area-to-volume ratio of fingers makes retaining body heat very difficult, so hands and toes account for up to 90% of frostbite injuries. With respect to alpine climbing, when the terrain verticality is such that crampons and ice axes are required, heat loss by conduction from the distal parts of the extremities is accelerated by contact with snow and ice, which is associated with repetitive trauma during the ascent. Nose, ears and lips cool down more slowly than the extremities¹², but may be affected if the area is not properly protected; other areas may be affected due to exposure in specific situations (e.g. the perineum in subjects sitting on metal surfaces, the penis in Nordic skiers and the knees in prolonged resuscitation manoeuvres)^{5,10}.

Physiopathology of frostbite

The pathogenesis of frostbite is based on local ischemia, cellular injury and destruction caused by ice crystal formation, and damage resulting from reperfusion after rewarming.

The skin's initial vasomotor response to cold is vasoconstriction, which preserves the core temperature against cutaneous heat loss. The intensity of this phenomenon depends on the severity of the cold and the individual's intrinsic vasomotor response. Secondary ischemia resulting from this process and neuronal cooling cause the initial clinical alterations in sensitivity. If exposure continues, secondary vasodilatation takes place due to the reduction in smooth muscle sensitivity to adrenergic stimuli in five to 10 minute cycles¹³. This process occurs to provide a certain amount of local protection against cold stress. The extent of this phenomenon varies between individuals and increases with exposure, and it has therefore been suggested that there is some grade of acclimatisation to cold¹¹. In the context of extremely low temperatures, freeze/thaw cycles result in a thrombotic stage, which causes a progressive local ischemia. This involves cellular death and endothelial destruction, which, in turn, activate a pro-inflammatory response that nourishes the oedema, platelet aggregation and thrombosis cycle¹⁴. If the extremity continues to cool down, arteriovenous shunts may open and generate a non-irrigated distal area that protects the central compartment from further temperature loss, thus sacrificing peripheral zones that are not essential for survival¹⁴.

On the other hand, if the skin continues to cool down, extracellular crystals cause extracellular oncotic pressure to increase, which can lead to dehydration, altered electrolytic balance, lysis and cellular death; if

the reduction in temperature occurs rapidly, intracellular crystals may appear. These may expand and generate mechanical cell destruction by disrupting the organisation of the cellular membrane and intracellular organelles¹.

During the rewarming process, inflammatory changes start taking place, with the appearance of oedema, vasodilation and vascular stasis preceding platelet aggregation and thrombosis, whose clinical manifestations are blisters and severe pain. Prostaglandins and thromboxane appear to play an important role in this process, and these molecules are emerging pharmacological targets for frostbite. After this process, and depending on the grade of the secondary microvascular impairment this sequence can result in two different situations: recovery with blood clot dissolution, resulting in viable tissue, or vascular collapse that results in cellular necrosis and the appearance of dry gangrene¹⁵. At this point, tissue damage is irreversible.

The consequences of refreezing a previously rewarmed area are devastating because of the massive cellular destruction caused by the formation of crystals in previously damaged tissue^{14,16}.

Clinical manifestations

In the early stages, alarm symptoms are frequent and often feel unpleasant: a cold sensation and hyperaesthesia or hypoaesthesia are common, though not always present. The affected area becomes numb until frostbite is established, at which point there is a total loss of sensitivity and anaesthesia.

Clinical examination at this point shows a waxy tissue that is yellowish-white or spotted, and differentiating mild from severe injuries is complex.

The rewarming process is painful in most cases and may even require the use of opioid analgesics to control the pain. The tissue at this point is hyperaemic and, depending on the severity, blisters will appear within six to 24 hours; distally located, serum-filled blisters suggest a superficial injury, while proximal, haematic blisters may indicate a deeper injury^{1,14}. Blisters can persist for seven to 10 days if not drained. The appearance of any sensation (e.g. paraesthesia, pain or a stinging sensation), oedema and the capacity of skin to warp under local pressure are associated with a better outcome¹¹, although they do not change its clinical management. Severe frostbite can lead to local infection and systemic involvement. Black eschars are a sign of gangrene in deep tissue.

Classification

There are various proposals for classifying frostbite based on different criteria, including depth of injury, topography and clinical outcome. Given the wide spectrum of injury severity, from reversible changes after rewarming to cellular destruction, it is possible to establish a simple retrospective classification in superficial or deep frostbite based on the preservation or loss of damaged tissue after recovery¹⁶, normally between three weeks and two months after injury. The Wilderness Medical Society guidelines suggest this same classification, but prospectively, after rewarming, based on the probability of tissue loss (Table 1).

Cauchy *et al.* (2001) proposed a predictive scale based on three aspects: topographic extension after first rewarming and, after 48 hours, the presence and aspect of blisters and radiotracer uptake in a bone scan (Table 2).

Table 1. Criteria for Classification of superficial or deep frostbite.

Superficial frostbite	No or minimal anticipated tissue loss, corresponding to 1st- and 2nd-degree injury
Deep frostbite	Deeper injury and anticipated tissue loss, corresponding to 3rd- and 4th-degree injury

According to McIntosh SE, *et al.*, Wilderness Medical Society Practice Guidelines for the Prevention and Treatment of Frostbite, *Wilderness Environ Medicine*. 2014;25:4.

Table 2. Grading score for severity of frostbite injury.

	Grade I	Grade II	Grade III	Grade IV
Extent of initial lesion at day 0 after rapid rewarming	Absence of initial lesion	Initial lesion on distal phalanx	Initial lesion on intermediary (and) proximal phalanx	Initial lesion on carpal/tarsal
Bone scanning at day 2	Useless	Hypofixation of radiotracer uptake area	Absence of radiotracer	Absence of radiotracer uptake area on the carpal/tarsal
Blisters at day 2	Absence of blisters	Clear blisters	Haemorrhagic blisters on the digit	Haemorrhagic blisters over carpal/tarsal
Prognosis at day 2	No amputation	Tissue amputation	Bone amputation of the digit	Bone amputation of the limb +/- systemic involvement +/- sepsis
Sequelae	No sequelae	Fingernail sequelae	Functional sequelae	Functional sequelae

According to Cauchy E, *et al.*, Retrospective study of 70 cases of severe frostbite lesions. A proposed new classification scheme, *Wilderness Environ Med*. 2001;12:248.

This classification, which makes early prognosis possible, was designed in the context of injuries in the French Alps, where there is an effective rescue system that facilitates access to hospitals with the capacity to carry out complex radiological examinations within a short period. In more remote environments, immediate specialised medical attention is not possible within 48 hours of injury, so the outcome is estimated based on clinical examination alone, and the amount of tissue loss is highly unpredictable.

***In-situ* treatment of frostbite**

Emergency treatment should be initiated as soon as frostbite is suspected. General recommendations from the International Commission for Alpine Rescue (CISA-IKAR) and the Medical Commission of the International Climbing and Mountaineering Federation (UIAA MedCom) for immediate treatment must be adapted to each particular situation¹⁷:

- Move out of the wind.
- Consider turning back.
- Drink fluids (warm if possible).
- Remove boots, but consider that there may be problems replacing them if swelling occurs.
- If wet, replace socks and gloves with dry ones.
- Warm by placing foot/hand in companion's armpit/groin for 10 minutes only.
- Replace boots.
- Give one aspirin or ibuprofen to improve circulation (if available and not contraindicated)
- Do not rub the affected part, since this may cause tissue damage.
- Do not apply direct heat.

If sensation in the affected area returns, it is worth acting on the assumption that previous prevention strategies failed and that continuing to expose the affected body parts under the same conditions is dangerous. If this does not happen, medical treatment may be needed and rewarming in a warm shelter or protected area is recommended.

Treatment of frostbite in base camp, hut or protected area

In the event that transferring the patient to a healthcare centre is difficult or will take too long (over two hours¹⁸), rewarming must be started *in situ*, as long as there is no possibility of refreezing and the environment allows for this procedure to be carried out safely¹⁹. Although walking with established frostbite in the foot is not recommended, self-evacuation in remote areas may be necessary, and the priority is to reach a safe location protected from the cold, rather than remaining immobile in a hostile environment. If an assisted rescue is possible, the extremity should be protected and immobilised with a non-compression bandage. The objective is to reach a safe place, where rapid rewarming can be initiated, considering that the use of heat sources during the transfer should be avoided. Incidentally, frostbite can rewarm spontaneously during attempts to keep the victim warm during transport; in this case, it is not recommended that slow rewarming is actively avoided, but it is imperative to ensure that refreezing does not occur, since this would reduce the possibility of viable tissue¹.

In general, frostbite, as a local injury, must be treated after life-threatening conditions and systemic disorders such as hypothermia and trauma.

Frostbite rewarming

Rewarming must be started as soon as possible and carried out in a water bath (ideally with a diluted antibacterial agent) at a generally accepted temperature of 37°C-39°C²⁰. Considering that the benefits of faster rewarming are not clear, higher temperatures should be avoided, since they cause more pain and may produce associated burn wounds¹⁹. Conversely, slow rewarming with lower water temperatures can induce ice crystal fusion, and thus create larger structures that are more damaging to tissue.

Reperfusion criteria are recovery of sensation, normal or red/purple coloration at the distal part of the extremity and pliability of the affected tissue, which occur after 30 minutes to 1 hour of hydrotherapy^{11,17}. Active movements inside the heating vessel are beneficial during rewarming². Patients must be informed of the possibility of pain intensification and macroscopic changes of the injury during this process. Early treatment is essential for bone reperfusion and posterior viability²¹ and the absence of recovery of sensation after rapid rewarming is a predictive factor for poor prognosis².

Water baths should be continued twice a day. The affected area should be kept clean and dry, and the extremity should be elevated above heart level to prevent oedema and venous stasis⁴. Massage and rubbing are not recommended, as mechanical stress on the injured area can cause further damage.

Injuries may present different grades of severity in the same limb, so keeping graphic records can be useful for the clinical monitoring of the evolution of injuries. It can be assumed that if there is loss of tissue, it will be more distal than the damage initially observed²².

Basic treatment *in situ*

The use of NSAIDs is justified in order to reduce the oedema that can compromise blood flow and local circulation²³. Acetylsalicylic acid irreversibly inhibits thromboxane-A2 synthesis in platelets, so many authors recommend its use^{15,17}, although others prefer the administration of ibuprofen¹. There are no studies that demonstrate the superiority of one treatment over the other.

Oral vasodilators have been recommended on a theoretical basis and because of the low risk associated with their use. The capacity of pentoxifylline to increase erythrocyte deformability may improve blood flow in the damaged area if prescribed as an adjunctive therapy two to six weeks after injury²⁴. Buflomedil is an alpha-adrenergic receptor inhibitor with good results in isolated cases that have not been reproducible in subsequent studies²⁵. There is currently no scientific evidence to recommend the use of either medication^{14,15}.

Antibiotic coverage should be reserved in cases of associated cellulitis or potentially contaminated injuries, or where there are septic or traumatic concomitant pathologies that require it, since frostbite itself is not an infectious disease and antibiotic prophylaxis does not prevent secondary infections.

In-situ treatment with heparin has not demonstrated efficacy in modifying the clinical course of frostbite, but it might be recommended to prevent deep vein thrombosis if prolonged immobilization of the patient is needed in the case of frostbite in the lower limbs.

There is consensus in favour of using needles to drain clear blisters if movement is restricted and for conservative management of haemorrhagic blisters, since there is assumed to be deep structural damage underlying them^{1,2}. In any case, blisters drain spontaneously within a few days. After treatment of the wound, the area should be cleaned, dried, covered with a topical aloe vera gel²⁶ and protected with a non-compression bandage that allows oedema to form without restricting blood flow. Dressings should be changed at least every six hours¹¹, although this depends on the availability of supplies and the specific conditions prior to evacuation.

Frostbite usually occurs in patients who are debilitated by fatigue, dehydration and undernourishment, all of which limit the body's capacity to produce heat¹². During treatment, it is important to maintain acceptable levels of blood volume, orally if the patient is alert and intravenously if not, especially if clinical signs of dehydration are present, in which case small saline boluses are recommended¹⁴. In the presence of hypothermia, secondary to the suppression of vasopressin, larger volumes may be necessary, ideally warmed before infusion². Rest and nutrition are essential for recovery, especially for patients in remote locations who face long return journeys.

The use of hyperbaric chambers at high altitude (>3500 m) has been proposed to prevent secondary intense vasoconstriction due to hypoxia and improve the benefits of in-situ treatment and rewarming²⁷.

Supplementary oxygen is recommended above altitudes of 4500 m¹¹ or if arterial oxygen saturation is lower than 90%, since tissue recovery depends to a great extent on sufficient tissue oxygenation¹⁴.

Low-molecular weight dextran reduces blood viscosity and prevents microthrombi formation and could be a good therapeutic tool in the future considering their low anaphylactic risk and for those patients who are not good candidates for iloprost or thrombolytic therapy.

Advanced medical treatment in the field

Recent publications of isolated cases suggest that emerging therapies reserved for hospital treatment, such as iloprost and rt-PA (human recombinant tissue plasminogen activator), could be used in the field in the future for severe frostbite through resource-limited treatment strategies²², although there are no randomised trials that justify this procedure at present. It would be particularly useful to develop optimal in-situ medical care, particularly for patients with severe frostbite who are not close to a hospital, and since the therapeutic window of these drugs is the first 12-48 hours.

Need for evacuation

If frostbite is considered the only reason to assess the possibility of evacuation, mild frostbite (grade I) does not justify ending the activity, but prevention strategies should be improved and the potential risk for refreezing assessed. Grade II frostbite does not require urgent evacua-

tion, but the need for medical care on the field requires the activity to be discontinued for treatment and the regular application of dressings. Severe frostbite (grades III/IV) is a medical emergency in which a delay in treatment worsens prognosis, increases the risk of amputation and risks further systemic involvement.

Hospital management

The anamnesis of a patient admitted to hospital with frostbite should include the time the injury occurred (although this can be difficult to define), the moment in which first rewarming took place, and the type and frequency of any medical treatment received.

Complementary examinations are not required as routine in mild frostbite. For severe frostbite with a risk of tissue loss, angiography can show residual vascular occlusions after rewarming, thus allowing local thrombolytic treatment to be carried out and its effectiveness monitored²⁸. The tendency to use Doppler ultrasounds to evaluate blood flow is becoming more popular these days, with angiography being reserved for when vascular interventions are required.

Scintigraphy with Tc99 can predict surgical indication and the extent of tissue loss after 48 hours of injury in 84% of cases²⁹. While the application of this technique makes it possible for the patient to find out the extent of their injury and their prognosis at an early stage, waiting for the natural demarcation of necrosis is still recommended before surgery is carried out.

Nuclear magnetic resonance makes it possible to view soft tissues, vessels and ischemic areas clearly and noninvasively²⁹, although there is little experience of its use in frostbite.

Patients with severe frostbite who are attended within the first 12-24 hours in a hospital with intensive-monitoring capacity are candidates for thrombolytic treatment with rt-PA, either intravenous or intra-arterial with catheter guidance in the absence of contraindications. The aim is to restore arterial flow by eliminating thrombotic residues when distal tissues are still viable, and thus significantly reduce the number of amputations^{30,31}. Although there are published dosage recommendations², no comparative studies have been made to strongly support a specific infusion titration. In addition to the possibility of bleeding, the most relevant secondary effect is the appearance of post-reperfusion oedema that can lead to compartment syndrome by raising interstitial pressure¹⁰.

Infusion of vasodilators prior to rt-PA reverts the vasospasm associated with frostbite without any additional adverse effects^{32,33}. An open-label study showed that coadministration of heparin and rt-PA, both in intravenous or intra-artery delivery, appears to be a safe and effective practice for reducing vascular microthrombi formation³⁴. Treatment with rt-PA should end when blood flow is restored in the distal vessels (observed with angiography) or after 48 or 72 hours in the absence of recovery^{31,33}. Those patients at risk of tissue loss with a complete angiographic response have a very good prognosis³⁵.

Given the good results of this intervention in several case reports and published studies, it seems that patients with severe frostbite should be rapidly evacuated to hospital in order to take advantage of the therapeutic window, although there is a shortage of randomised trials to support these measures^{28,34,36}.

Table 3. Comparison between different thrombolytic management regimes.

Reference	Cases (n)	Grade of injury	Initial treatment	Type of administration	Drug	Dosage	Study type	Amputation rate
Wexler et al. 2017 ⁴¹	6	No data	Rapid rewarming	Intra-venous	tPA+/-aspirin+/-warfarin+/-heparin	initial bolus dose followed by a 6-hour infusion of tPA	Retrospective case review	24.6%
Jones et al. 2017 ⁴²	7	No data	No data	Intra-venous	tPA + heparin +/- coumarin +/- antiplatelet	tPA at 0.15mg/kg IV bolus+ tPA. IV infusion (0.15 mg/kg) over 6h up to a total dose of 100mg. After: heparin+/-coumarin+/-antiplatelet agent	Retrospective case review	27.5%
Tavri et al. 2016 ³⁵	13	At risk of tissue loss	?	Intra-arterial	t-PA	27,5 mg (12-48 mg) during 34h (12-72h)	Retrospective review	20,5%
Cauchy et al. 2016 ⁴³	20	Severe	Rapid rewarming+ 250 mg aspirin +buflovedil 400 mg for 1 hour.	Intra-venous	Aspirin + tPA + iloprost	tPA 100 mg, single dose + iloprost 2 ng/6 h+ Aspirin 250 mg	Retrospective case review	27.3% for grade 3, 44.4% for grade 4
	41	Severe	Rapid rewarming+ 250 mg aspirin +buflovedil 400 mg for 1 hour.		Aspirin + buflovedil	After, daily treatment of aspirin and buflovedil		62.5% for grade 3, 100% for grade 4
	58	Severe	Rapid rewarming+ 250 mg aspirin +buflovedil 400 mg for 1 hour.		Aspirin + iloprost	Aspirin and IV iloprost 2 ng/6 h		4.9% for grade 3, 66.7% for grade 4
Ibrahim et al. 2015 ²⁸	3	Severe	Rapid rewarming+fluid replacement	Intra-arterial	tPA + heparin	tPA 4 mg bolus+infusion 1mg/hr+ heparin until PTT 50-70 s for maximum 48 h	Retrospective case review	0%
Handford et al. 2014 ²	-	Severe	-	Intra-arterial	tPA + heparin	tPA 3 mg over 15 min followed by constant infusion of 1 mg/h. Maximum 48h of no improvement + 500 units/hr heparin for 4 hours	Review	No data
Cauchy et al. 2011 ²¹	16	Severe frostbite (grade3/4)	Rapid rewarming of the areas with frostbite plus 250 mg of aspirin and IV administration of buflovedil (400 mg)	Intra-venous	Aspirin + iloprost + tPA	250 mg of aspirin + iloprost (2 ng per kilogram per minute for 6 hours per day) for 8 + tPA (100 mg) for the first day	Prospective, randomized, open-label Controlled trial	19%
	15	Severe frostbite (grade3/4)	Rapid rewarming of the areas with frostbite plus 250 mg of aspirin and IV administration of buflovedil (400 mg)		Aspirin + buflovedil	250 mg of aspirin and buflovedil (400 mg for 1 hour per day) for 8 days		60%
	16	Severe frostbite (grade 3/4)	Rapid rewarming of the areas with frostbite plus 250 mg of aspirin and IV administration of buflovedil (400 mg)		Aspirin + iloprost	250 mg of aspirin plus a prostacyclin (0.5 - 2 ng of lprost per kilogram of body weight per minute for 6 hours per day)		0%
Johnson et al. 2011 ³⁶	11	Severe	No data	Intra-venous	tPA + heparin	0.15mg/kg bolus + 0.15mg/kg/h6h to a maximum of 100mg. Followed with heparin to PTT 2X control for 3-5 days	Retrospective case review	59%
Bruen et al. 2007 ³¹	6	Patients with perfusion defects	Immediate rewarming and fluid resuscitation as appropriate	Intra-arterial	tPA + heparin	tPA initial rate of 0.5 to 1.0 mg/h + Heparin at 500 U/h until normal perfusion or maximum 48 h	Retrospective case review	10%
	26	Varying degrees of injury severity. Not treated with thrombolytic therapy	Immediate rewarming and fluid resuscitation as appropriate	-	-	-		41.5%
Twomey et al. 2005 ³⁴	13	No data	Rapid rewarming	Intra-venous	tPA + heparin	0.15 mg/kg bolus + 0.15 mg/kg/h6h to a maximum of 100 mg. Followed by IV heparin to PTT 2 control for 3-5 days, then Coumadin 4 weeks	2 Groups Arterial Venous Prospective, open label, unblinded	19% (not reported by route of administration)
	6	No data	Rapid rewarming	Intra-arterial	tPA + heparin	0.075 mg/kg/h 6 h. Repeated additional 6 h if repeat scan abnormal		19% (not reported by route of administration)

On the other hand, iloprost is a prostacyclin analogue with vasodilator and antiplatelet properties that has been associated with reductions in digital amputations in severe frostbite, so many authors recommend its intravenous administration as a first-line treatment^{22,29}. Dose titration in published clinical experiences is based on the appearance of adverse effects within the therapeutic range (starting at 0,5-2 ng/kg/min, with 0,5 ng/kg/min increases every 30 minutes until the maximal toleration rate is achieved and maintaining its infusion 6 hours/day for 5-8 days), with consideration for the fact that the patient must be maintained in the supine position to prevent orthostatic hypotension²¹. The effect of its association with rt-PA is not well known, although in accordance with a recent randomized trial it seems to be optimal in grade IV frostbite within the first 12 hours²¹. Contraindications of its use include unstable angina, recent cardio-vascular events and increased risk of bleeding. The advantages of iloprost over rt-PA are that it does not require interventionist procedures, the therapeutic window is larger, it can be administered in patients with trauma and intensive monitoring, other than blood pressure monitoring, is not required.

Tetanus vaccination is recommended, according to the usual schedule.

If amputation is required, surgical intervention must be delayed until viable tissue can be demarcated accurately, provided that an emergency justification for proceeding (e.g. gangrene, sepsis and compartment syndrome). This measure is justified by the possibility that tissue initially considered non-viable is restored³⁷ and the risk of surgical trauma interfering with the healing of proximal tissues⁴⁶. This is not carried out in normal conditions until at least four to six weeks after injury, including in patients receiving thrombolytic therapy, which can imply the need for psychological support.

Sequelae

Sequelae after frostbite are common and occur independently of its severity. In a study of 30 patients with grade II frostbite, 63% were found to have sequelae after four to 11 years from injury (cold sensitivity 53%, digital numbness 40%, reduction in touch sensitivity 33%)³⁸. It is estimated that sensitivity disturbances are present for at least four years in nearly all those who have suffered from frostbite¹¹.

Chronic pain secondary to frostbite is very common and is usually refractory to conventional analgesics. It sometimes responds to drugs designed for neuropathic pain (e.g. amitriptyline and gabapentin). Despite efforts to treat later symptoms (e.g. pain, paraesthesia and numbness) with chemical and surgical sympathectomies, there is no clear indication for their use.

Other common problems include hyperhidrosis, secondary to an abnormal response of the sympathetic system, trophic alterations in skin and fanerae, digital flexor retraction and high susceptibility to future cold-related injuries. Alterations of skin colouration, ranging from depigmentation to local cyanosis, are not uncommon.

Long-term sequelae include osteoporosis, and where the frostbite affected the joints, osteoarthritis with damaged joint surfaces and a decline in joint mobility with tendinous retractions of the flexor musculature³⁹.

Digital amputations (partial or total) involve functional limitations to daily life and sporting activities, given the alteration in the normal biomechanics of the limb. Gait will be severely impaired if frostbite affects the metacarpophalangeal joint in the foot. Risk factors related to amputation include duration of exposure to cold, absence of proper equipment, exposure to cold in remote areas, presence of infection and delay in treatment.

There is a broad consensus on the need to prioritise an early multidisciplinary rehabilitation programme for patients who have undergone amputation, including prompt controlled mobilisation to prevent tendinous retraction and reach optimal levels of functional recovery^{10,15}, and long-term, non-aggressive treatment⁴⁰ (Table 3).

Conclusions

Frostbite is no longer primarily an occupational pathology or characteristic of subjects with cognitive impairment. It has become a common cause of morbidity among healthy young adults who voluntarily expose themselves to cold, usually while practising winter sports. Knowledge of activity planning, survival skills and cold protection is strongly recommended as basic prevention tools. Early recognition of frostbite is essential to ensure prompt diagnosis and early initial treatment, since a delay in first rewarming is associated with a worse prognosis. At present, in-field treatments are relatively basic and can be initiated by non-qualified subjects with the proper training. New perspectives are focusing on improving initial care by applying advanced treatments under medical supervision. For superficial frostbite, there is no need for further complementary tests beyond the clinical monitoring of the injury. For severe frostbite, scintigraphy with Tc99 is a good prognosis predictor after 48 hours of injury. Angiography is both an imaging and a therapeutic tool, but less invasive options such as MRI and ultrasound appear to be good alternatives when direct thrombolysis is not required. Emerging hospital treatments have a therapeutic window that needs to be known to take fast and optimal decisions regarding patient evacuation, considering the rescue time lapses and the hospital resources of each mountain area and country. Surgical interventions must be delayed until there is a clear demarcation of the necrotic area. Long-term sequelae are prevalent among subjects with frostbite, even in non-severe injuries. A multidisciplinary approach to caring for patients with frostbite is needed in the management of long-term functional sequelae.

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