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Deep Frostbite: The Question of Treatment

Y Epstein[1*], T Falick Michaeli[2*], A Rivkind[3], S Efrati [4], J Haik[5,6]

[1]Heller Institute of Medical research, Sheba Medical Center, Tel Hashomer and the Sackler Faculty of Medicine, Tel Aviv University, Israel

[2]Department of Developmental Biology and Cancer Research, IMRIC, Hebrew University Hadassah Medical School, Jerusalem, Israel

[3]Department of General Surgery and Trauma Unit of Hadassah Medical Center, Ein Karem, Jerusalem, Israel

[4]The Institute of Hyperbaric Medicine, Assaf Harofeh Medical Center, Zerifin, Sagol School of Neuroscience, Tel-Aviv University, and the Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

[5]Department of Plastic and Reconstructive Surgery, The Burn Unit, Sheba Medical Center, Tel Hashomer, and the Sackler Faculty of Medicine, Tel Aviv University, Israel

[6]The Talpiot Medical Leadership Program, Sheba Medical Center, Tel Hashomer and the Sackler Faculty of Medicine, Tel Aviv University, Israel

[*]First two authors equally contributed to the manuscript.

[*]**Corresponding Author:** Y Epstein, Heller Institute of Medical research, Sheba Medical Center, Tel Hashomer and the Sackler Faculty of Medicine, Tel Aviv University, Israel. Email: Yoram.Epstein@sheba.health.gov.il

*T Falick Michaeli, Department of Developmental Biology and Cancer Research, IMRIC, Hebrew University Hadassah Medical School, Jerusalem, Israel. Email: tal.michaeli@mail.huji.ac.il

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Abstract

Within the spectrum of peripheral cold injuries, frostbite is the most serious lesion in many cases leading to the amputation of fingers or a limb. Frostbite is becoming increasingly prevalent due to an increase in outdoor activities such as skiing, hiking, and mountaineering, affecting fit, active individuals who are in the prime of their lives. The pathophysiology of frostbite is well characterized; it involves two main pathways: (a) intracellular changes that lead to cell death, (b) tissue ischemia and thrombus formation. Besides the recommendation of aggressive warming of the affected tissues, other adjuvant treatments administered in the post thawing stage have been suggested. Here we discuss the pathophysiology of frostbite, tools for assessment of injury severity and the current approaches on patient medical management in the field and during hospitalization.

Keywords: Cold related injuries; Frostbite; Hyperbaric Oxygen (HBO); Prostacyclin; Thrombolytic agents

Pathophysiology

Exposure to cold can lead to various injuries that are subsequent to the related hypothermia and can affect organs in several manners within the human body. The most devastating injury is frostbite injury which develops when a person's skin temperature drops to sub-zero levels. The severity of changes observed within the tissue due to frostbite injury depend on the freezing rate, the duration of freezing, the extent of injury, and the thawing rate [1]. One of the ways to characterize frostbite is to divide the injury into four pathologic phases that overlap. The phases are: the pre-freeze phase, freeze-thaw phase, vascular stasis, and late ischemic phase [2]. The pathophysiologic mechanism that underlies frostbite injury has been studied in several model systems throughout the literature. There are two general mechanisms underlying frostbite injury, which occur simultaneously. The first is direct cellular damage, which is formed during the initial freeze process. The second is the delayed process mediated by progressive tissue ischemia which is attributed to thrombus formation and inflammatory response (Figure 1) [3,4].

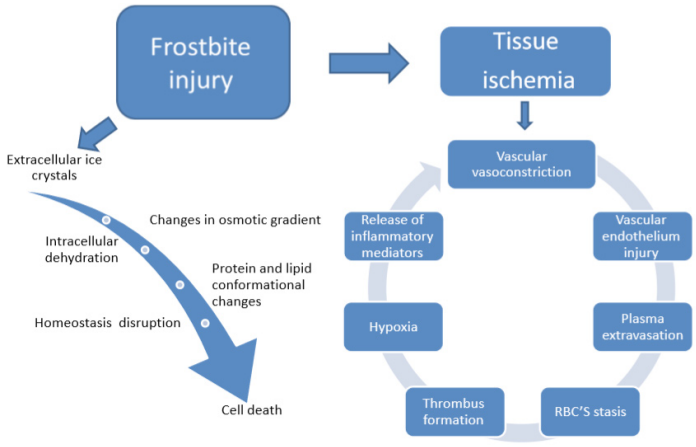

Figure 1: Pathophysiology of frostbite.

Unless freezing is very rapid, the initial freezing injury leads to the formation of extracellular ice crystals. These crystals directly damage the cell membrane and change the osmotic gradient across it, resulting in the extraction of free water out of the cells, causing intracellular dehydration and subsequent cell death. Notably, dehydration of cells causes changes in both protein and lipid conformation, as well as abolishing intracellular homeostasis. As the temperature of the tissue continues to fall, intracellular ice forms, which expand and cause mechanical destruction of the cells in the tissue.

The second mechanism, involving tissue ischemia, is considered to contribute more to the clinical outcome than the direct mechanical injury. Micro-vascular function is compromised as the skin cools, resulting in the vasoconstriction of arterioles and venules. Endothelial cells are injured and separated from the arterial wall lamina, allowing plasma extravasation that causes vascular slowing and erythrocyte stasis [5]. Arterioles and venules become thrombosed, and irreversible tissue hypoxia occurs. These events promote the release of inflammatory mediators. The release of prostaglandins and thromboxane A2 trigger a vicious cycle of further vasoconstriction, platelet aggregation, and blood vessel thrombosis, which prolongs the damage within the suffering tissue [3].

Improper thawing may also contribute to tissue's damage. The deleterious effects of partial thawing and refreezing may lead to increased blood viscosity and vasoconstriction, thromboembolism after rewarming, tissue edema, increased compartment space pressure, neutrophil activation, bleb formation, and cellular death [3,4]. It has been suggested that Reactive Oxygen Species (ROS) play a role as reperfusion injury mediators in this process [4].

Classification

Historically, the classification of frostbite severity consists of four grades indicating the depth of the injury [2]. First-degree frostbite (superficial skin) is characterized by a numb central white plaque with surrounding erythema. Edema and hyperemia develop in the injured areas, with no blisters or tissue loss. Second degree frostbite describes injuries with blisters, surrounded by erythema and edema, which usually fill with fluids during the first 24 hours. Vesicle formation and superficial skin sloughs may occur after or during rewarming of the injured area, with no necrosis developing. Third degree frostbite (full thickness and subcutaneous tissue) causes hemorrhagic blisters, local edema, and grayish-blue discoloration of the affected area that result in a hard black eschar two weeks after the initial injury and skin loss down to subcutaneous layer. Fourth degree frostbite is characterized by a complete necrosis, deep cyanosis without development of vesiculation or local edema. Necrosis of subcutis, loss of tissue, tendon, and bone are apparent. In many cases, however, a general approach is advisable, since evaluating the severity and depth of injury may be difficult. Therefore, frostbites are generally classified as superficial (degrees 1 and 2- partial thickness) and deep (degrees 3 and 4- full thickness) [4,6,7].

At the onset of injury, most injuries appear similar, therefore, final tissue loss, prognosis, and the probability of amputation could not be predicted [8]. Clear cut demarcation of ischemic tissue from viable tissue is established 3-6 weeks after initial exposure and therefore, final decision for amputation should not be taken at the early stage of the offset of injury [1,9]. Accordingly, Cauchy, et al. (2001) suggest a useful classification, based upon a retrospective study constructed mainly on the topography of the lesions and on technetium imaging. That classification consists of four grades of injury: Grade 1 relates to injuries that require no hospitalization and full recovery is expected. Grades 2-4 injuries have an increased risk of amputation and, therefore, require hospitalization. Grade 2 frostbite will usually require soft tissue amputation. Grade 3 involves bone amputation, while grade 4 leads to large amputation with systemic effects [8].

Imaging

Precise assessment of tissue viability is often difficult to achieve. Several radiological techniques have been recommended to improve the process of surgical management in frostbite cases. Routine imaging studies early in the diagnosis and treatment of frostbite have been questioned in their reliability to determine both the extent and the amount of tissue damage and in predicting tissue demarcation at this stage because transitory vascular instability may last 2-3 weeks after the frostbite injury, the most promising studies have used triple phase bone scanning and MRI/MRA [1]. A large retrospective study of 92 patients with severe frostbite of the extremities showed that ^{99}Tc bone scans obtained during the first few days of injury accurately indicated the level (toe, hand, or arm) of amputation in 84% of the cases [10]. The benefit from

using these scans was also demonstrated in case reports [11,12].

Case reports suggest that MRA is superior to ^{99}Tc bone scans, allowing direct visualization of occluded vessels and better delineation of viable tissue than bone scans [13]. However, in order to properly compare the efficiency of the two imaging methods, a large scale study should be performed.

In a recently published paper it was suggested to use a novel imaging method, microangiography, in the assessment of severe frostbite injury [14]. In this paper a strong positive correlation was found between the microangiography studies and predicting the amputation level of the patients.

Treatment

The treatment of frostbite can be divided into three phases: pre-thaw field care, immediate hospital care, and post-thaw treatment.

Pre-Thawing Field Care

Pre-hospital care is focused on protecting the frostbitten part from a mechanical trauma and preventing thawing until definitive rewarming can be secured. The patient should be moved to a shelter, away from the wind, and be provided with warm fluids. Wet clothing including boots, socks, and gloves should be removed and the patient should be dressed with dry clothing. The cold extremity should be placed in an armpit or groin to warm it and prevent further cooling. Rubbing the affected area, which once was highly accepted, is prohibited because it may cause mechanical trauma and direct tissue injury. Definitive treatment in the field is not encouraged since thawing and refreezing may result in a more extensive injury. Thus, the decision of treating frostbite in the field should only be made and initiated when there is no risk of refreezing [4,5]. Rapid evacuation to a clinic equipped with adequate facilities to treat frostbite is of utmost importance; this was established to improve prognosis.

Immediate Hospital Care – Rewarming

Rapid rewarming in warm water is of importance since the initial treatment is aimed at melting the ice crystals formed within the cells and the reestablishment of effective blood flow to the affected areas. The quickest and best treatment is rewarming in a water tank at a temperature of 38–42 ˚C (ideally: 40 ˚C) [2]. Circulation of water around the frozen tissue will help maintaining the required temperature. Warming the patient in colder temperatures might lead to hypothermia resulting in sustained vasoconstriction, and an increase of ice crystals size in the affected region, and thereby contribute to tissue damage. Rewarming with higher temperatures may produce a burn wound. A mild antibacterial agent (hexachlorophene or providone-iodine) should be added to the water [4]. Rewarming is complete when the involved skin takes on a red or purple appearance and becomes soft and pliable to the touch. This result is usually accomplished in 15-30 minutes but may take longer when injury is extensive; in these cases, immersion should be continued until thawing is complete [6]. Indeed, this has become the cornerstone of early treatment for all severities of frostbite [1,6].

Clear or milky blisters that appear in the affected area contain prostaglandins and thromboxanes that may damage underlying tissue [15]. The formation of hemorrhagic blisters represents structural damage to the superficial dermal plexus. Common practice in a hospital setting is to debride the clear or milky blisters, followed by applying a moisturizing agent such as topical Aloe Vera, a potent anti-prostaglandin agent, every 6hrs. [1]. Debridement limits further tissue damage and improves visualization of the underling tissue. Hemorrhagic blisters should be left intact to prevent desiccation of the underlying tissue. It is important to point out that comparative studies have not been performed and recommendations are based on common practice.

Active motion during rewarming may also help to reestablish blood flow in the affected area, but active massaging should be avoided. An injured leg should be elevated and the affected sites should be loosely dressed with either a Vaseline gauze and local antibiotic treatment or an advanced dressing that will keep the wound clean and moist. In addition to local warming, general body warming is important. As thawing is painful, analgesics may be needed. Ibuprofen (400 mg orally, every 12 hours) is recommended for its selective anti-prostaglandin activity. Aspirin may be less beneficial in frostbite because it blocks all prostaglandins including some prostacyclins, which are beneficial for wound healing. It is noteworthy that these treatments are recommended to be given in the field when frostbite injury is severe and in the absence of contraindications. Oral administration allows it to be easily taken and relatively safe [5,9].

Post-Thaw Hospital Care

Several adjuvant therapeutic modalities have been suggested attempting to alleviate or diminish the progressive ischemia in frostbite, preserving tissue viability by enhancing blood perfusion to the affected limbs, and improving oxygenation. These treatments usually include Hyperbaric Oxygen (HBO), prostacyclin infusion (e.g. iloprost), and thrombolytic agents (e.g. Tissue Plasminogen Activator tPA) [4,5].

Hyperbaric Oxygen Treatment (HBOT)

The rationale of treating frostbite with hyperbaric oxygen is due to the increased amounts of dissolved oxygen in plasma, which is directly proportional to the partial pressure of inhaled oxygen. This might have immediate beneficial effects, as the increased local tissue oxygen tension improves and maintains the viability of the affected and adjacent tissues, which in turn facilitates vascular and cellular regeneration [16-18]. HBOT increases the

deformability and flexibility of red blood cells [18] and diminishes edema formation in post ischemic tissues [19]. Additionally, it diminishes microorganism proliferation, activates antimicrobial agents, and activates the immune system and has a bacteriostatic effect [16-18]. Ledingham first reported hyperbaric oxygen as a mode of treatment for frostbite in 1963 [20]. Nevertheless, data on HBOT in frostbite are still anecdotal and very limited; since the first published case over 50 years ago, only 25 cases of frostbitten patients treated in this manner have been reported in the literature [20-33]. Several case reports have reported positive results in terms of digits' salvage [33,34]. Nevertheless, in the Haik et al case-series, despite being treated with HBO daily, 50% of the patients needed amputation due to irreversible necrotic damage, starting five days after injury [32]. Further investigation is warranted regarding the role of HBOT in frostbite therapy.

Thrombolytic agents

The use of thrombolytic agents in frostbite, such as a Tissue Plasminogen Activator (tPA), is to treat microvascular thrombosis in order to enhance the tissue's perfusion. Since the first report by Cauchy, et al. (2000) on the treatment of frostbite with tPA [35], 15 reports have been published that include a combination study including the treatment of 128 patients with tPA and other thrombolytic agents [33-47]. In some of the reports, a combination of treatment modalities has been administered [35,45]. It has been concluded that overall continuous Intra-Arterial (IA) infusion of thrombolytic agents may be beneficial in frostbite cases with severe perfusion defects demonstrated by angiography, by restoring, at least partially, blood perfusion to the affected tissue, and thus lowering the risk for amputation [40,45-47]. The Bruen, et al. (2007) retrospective study reported that administering tPA within 24 hours of injury reduced digital amputation rates from 41% to 10% ($P<0.05$) [36]. Amputation rate correlates closely with angiographic findings [40]. The dose of tPA and the route of administration have not been delineated, though several protocols based on personal clinical practice are suggested in the literature [6,15,37,47]. As the potential risks of tPA include bleeding and compartment syndrome, this treatment modality should be undertaken in an intensive care unit [15]. It has been suggested that the use of intra-arterial or intravenous tPA along with an angiography or Tc-99m scanning may be beneficial [46]. Noteworthy, a recent publication on 18 patients has not shown statistically significant results on amputation levels that would support the hypothesis of the efficacy of thrombolytic therapy. The patients suffered injuries ranging from second degree deep to third degree and did not differ significantly on the level of amputation with or without tPA treatment [48].

Iloprost

Iloprost is a prostacyclin analogue with vasodilatory properties that mimics the effects of sympathectomy [15]. The physiological idea of using iloprost in the treatment of frostbite is its effect on platelet aggregation that results in decreased microvascular occlusion. Its activity as a vasodilator improves blood supply to collateral vessels [49]. The protocol currently in use for the administration of ilioprost was suggested in 2011 by Cauchy, et al. [35].

Groechenig (1994) was the first to publish his experience with iloprost treatment of 5 patients suffering frostbites (grades 2-3) [49]. Although no patient required amputation, this treatment was abundant until Cauchy et al. recently reported their experience with 32 patients suffering from various degrees of frostbite; it is noteworthy that half of the patients were treated also with tPA [35]. Although these authors showed a lower amputation rates for patients treated with iloprost vs. iloprost and tPA (0% vs. 3.1%, respectively), this is probably due to the more severe cases in the latter group [35]. In the case series that was described by Haik, et al. (2015), a partial success with iloprost treatment (in combination with HBOT) was noted; two of the four patients were discharged from the hospital with only minor lesions that did not need any surgical intervention and the two other patients needed major surgical intervention [32]; it is noteworthy, however, that the former two patients had a milder grade of injury. A recently published review examining whether or not an infusion of iloprost can be used to treat frostbite with a favorable outcome could not unequivocally recommend for the use of iloprost, though the authors pointed out that it may reduce the risk of amputation after frostbite [50].

Other Treatment Modalities

Other treatment modalities that have been suggested are: surgical lumbar sympathectomy, vasodilators, low molecular weight dextran, and antibiotics. However, there is still no recorded evidence regarding the efficacy of those treatments and their added value [6].

Discussion

Frostbite is a thermal injury that can occur when temperatures drop low enough for tissue to freeze. While all exposed tissues may be affected, the feet and the hands account for most injuries reported. On rewarming, tissue inflammatory response develops which is often associated with tissue loss. The extent of the tissue loss reflects the severity of exposure and affects the patient's management. Classification of these injuries helps in assessing tissue viability. Until recently, the treatment of frostbite injuries has been limited to supportive care only, including local rewarming, local disinfection, the use of topical dressing, pain control, and NSAID (mostly ibuprofen) administration [6].

After screening the literature on adjuvant treatments for frostbite, no definitive conclusions could be reached about the effectiveness of these various suggested treatments due to small

sample sizes and limited data. Nevertheless, adjunctive treatments are under ongoing studies and the cumulative clinical experience hint to some beneficial therapeutic effects, at least in the milder cases of frostbite, with these treatments.

Conclusion

Overall, frostbite presents a great clinical management challenge. The cumulative data in the literature is insufficient to recommend any of the adjuvant treatments as helpful beyond an effective thawing treatment and a conservative treatment with topical dressing. Therefore, in light of the available literature and treatment modalities, no conclusive conclusion can be drawn, nor can a gold standard of care be set. Based on the clinical outcome in patients receiving adjunctive treatment, it seems that the success of the adjuvant treatments depends on the grade of the injury. While the lower grades of frostbite (grades 1–3) might be responsive to adjuvant treatment, deep frostbite may not be responsive and may ultimately result in amputation of the affected site. Further investigation and large-scale studies must be performed in order to provide well evidenced based recommendations and protocols.

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