Preventing and Salvaging the Converted Burn Using a Novel Oxygen Delivering Hydrogel, a Case Report and Subject Review

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Abstract

The bane of a thermal insult is its further progression from a partial thickness to a full thickness injury. Although complex, this phenomenon is orchestrated primarily through the union of unabated inflammation and inadequate tissue perfusion synergizing to effect further cellular destruction and necrosis. Several local and systemic factors have been implicated in this delayed assault on the wound, chief among them are desiccation, ischemia and infection. Understanding the pathogenesis and identifying causative agents would help prevent this process from transpiring, impacting not only treatment decisions but morbidity as well. We present such a case within this context, suggesting that the combination of a desiccating agent (benzalkonium chloride) and smoking resulted in the near total conversion of a deep mixed dermal burn. Furthermore, the author feels that a recently developed oxygen delivering hydrogel (Ozeion) could not only have prevented this condition from progressing but was instrumental in its subsequent reversion, as well as the timely reconstitution of the burnt skin's surface.

Keywords Burn conversion; Desiccation; Oxygen delivering hydrogel

Introduction

The burn wound is a dynamic stage hosting a variety of local and systemic factors whose interplay determines the net effect on the overall healing process. Healing the burn wound can be a particularly complex and challenging task, especially when complicated by burn wound conversion. The latter can be the result of a number of events not least of which is wound desiccation. We present such a case whose thermal burn was converted by the injudicious application of the topical antiseptic benzalkonium chloride and further harmfully impacted by habitual and continuous smoking throughout this ordeal. Nevertheless, the case is noteworthy because the wound, in spite of being a majority full thickness injury was revived and salvaged by 3-weeks' time using a newly reported innovative hydrogel capable of not only humidifying the wound but translocating oxygen directly onto the wound surface [1].

Case Report

The patient is a 47 year old Greek-American chef with borderline hypertension on no medication and a 50 pack year history of tobacco abuse. He burnt himself retrieving a hot metal pan from an oven. He sustained a 4.5 x 6.25 cm mixed (2nd & 3rd degree) deep dermal burn to the mid-medial aspect of the right upper arm. Seen one day after his injury he was clinically estimated to have a 3rd degree burn to the mid-medial aspect of the right upper arm. Seen one day after his injury he was clinically estimated to have a 3rd degree burn to 1% of his total body surface area (TBSA). He was prescribed no other medication. (Photo A-initial burn 1 day post-injury). The following day the patient showed signs of marked improvement in the appearance of the wound. There was no evidence of infection, wound edema, weeping discharge or circumferential erythematous discoloration. The superior upper third, with its white leathery texture consistent with a third degree burn had remained stable and confined, having not breached its inferior border. The subjacent mixed second degree portion had shed its flaking and scaling epithelial layer distally (making room for the neoeithelium), while proximally it demonstrated a denuded moist, pink and painful dermis.

The patient was not seen again for 48 hours (4 days post injury) when a marked visible deterioration in the wound was observed. These discordant findings were the result of a desultory patient decision to stop using the hydrogel as directed, using it occasionally and its stead apply the topical antiseptic, benzalkonium chloride (BC), to prevent infection.

Results

It is apparent from the subsequent series of photos that the subjacent deep dermal burn had converted, being almost completely resurfaced by eschar (Figure 1A-O). As a consequence, the patient was advised to discontinue the use of benzalkonium chloride and resume the original treatment protocol, which although short lived appeared promising. In addition, he was now seen daily to assure compliance, guidance and if necessary appropriate interdiction. In spite of this major setback, the accompanying photos catalogue the metamorphic changes that transpired over the next 17 days as the eschar gradually sloughed, being bowed over and replaced by the underlying neoeithelium. No further complications or adverse events occurred and by day 21 the wound was healed having been resurfaced with no other treatment other than the liberal use of the Oxygen Delivering Hydrogel (ODH) covered with fine mesh gauze. Because the wound healed within 3 weeks there were only mild pigmentedary changes and...
no hypertrophic scarring [2]. Furthermore, the reconstituted skin except for the apical portion was soft and pliable, by week 6 there was little evidence of the original burn injury as the new surface blended into the color and texture of the surrounding skin. These events are remarkable since deeper dermal burns involving the reticulum and extending to full thickness are slow to heal and susceptible to scarring and unstable fragile skin [2,3]. We feel that the ODH played a significant role in not only resuscitating the converted burn but provided the needed hydration and oxygen to hasten the time needed to heal. This can be optimally achieved by applying the hydrogel liberally (Q_H) during the sub-acute phase (first five days) of the reparative process.


Discussion

Pathophysiology

Thermal burns and the heat energy transferred, trigger a spectrum of response in living tissue from protein denaturation to cellular dysfunction and death. The severity of a burn depends not only on temperature and length of exposure but on depth of involvement and area affected (TBSA). This initial response is quickly followed by inflammation and ischemia induced injury [3,4]. The more extensive the burn the greater the likelihood of a vicious inflammatory reaction with multi-organ systemic consequences, shock and cell death. This phase is initiated by the release of cytokines from macrophages and neutrophils and enhanced by the role of oxygen free radicals, a direct result of the action of these messengers and the effects of thermal and radiant energy on cellular and corporal water [4,5]. The sum effect is an increase in vascular permeability and further tissue destruction caused by super oxide, peroxide and hydroxy radicles intoxicating such cellular constituents as proteins, and bi-lipid membranes. Left unsuppressed, these events along with adverse local conditions such as infection or desiccation lead the delayed second assault on the burn wound, effecting conversion and further necrosis within a few days of the initial injury [3-7].

Squelching the inflammatory reaction and preventing burn wound conversion are of paramount importance and among the principle goals of burn care. For the most part burns are not homogenous wounds but rather a consortium of injuries varying in magnitude and severity from third to first degree. Viewed as a mosaic, burns are classically depicted as three concentric circles or zones of injury propagating outward with diminishing intensity, akin to a rock thrown into a body of still water [8]. The epicenter or central core exhibits a zone of necrosis, anoxia and capillary thrombosis. Surrounding this area is a zone of marginal viability, equivalent to a deep dermal (2nd degree) burn and characterized by hypoxia and impaired circulation or stasis. These ‘inner rings’ are then circumscribed by an outer perimeter of hyperemia and normoxia. It is in this precarious intermediate zone where the most vulnerable of these thermally damaged cells reside. It is also the area that will be impacted the most by the local and systematic factors just previously discussed [8].

Practically all aspects of the circulatory system and its vascular tree are damaged or impaired as a consequence of a deep dermal burn. Capillary permeability is increased as the microcirculation loses its vessel wall integrity and acts like a sieve as proteinaceous fluid is leaked into the interstitial space [3-6]. Grossly, this is evidenced by edema and eschar formation, as this collagenous matrix collects along with cellular detritus to fill and then gel over the wound bed which has lost its keratinous epithelial envelope. These eschars sit atop cavernous lakes of varying depths of dermal destruction (2nd, 3rd degree), giving the wound its pebbly appearance. The wound thus graphically displays the classic concentric three tiered zones of injury, each a reflection of the varying grades of impaired and altered blood flow from thrombosis to hyperemia. As a result the cells they service vary in vitality and survivability from necrotic to marginally dysfunctional. In essence the burn wound’s fate is determined by the degree of derangement of its blood supply. Failure to maintain an adequate circulation as a result of thrombosis or capillary obstruction leads to desiccation, ischemia and necrosis as the wound is deprived of oxygen and essential nutrients. The window of opportunity is short lived, 48-72 hours, to prevent and reverse this inexorable march of events towards cell death [4]. It is apparent that the common thread linking all wounding events, burns included, is a disruption in blood flow resulting in stasis and hypoxia. It logically follows that strategies which enhance the bioavailability of oxygen to damaged cells is critical to their sustainability, revitalization and regeneration.

Local Factors

Desiccation

The ensuing inflammatory reaction amplified by reactive oxygen species (ROS), act in concert to affect the loss of capillary and cell wall
This increase in permeability results in cellular dehydration and extra cellular fluid extravasation into the interstitium, manifesting as edema. Unabated this leads to cell shrinkage, hyperosmolarity and apoptosis at the cellular level exacerbated by stasis and the impairment of blood flow extracellularly. The sum effect results in the subversion and destruction of marginally viable cells as the burn wound converts, extending its level of injury [4]. Preventing desiccation and maintaining a moist wound surface would ergo: 1) enhance the delivery of oxygen and nutrition to the wound surface, 2) decrease eschar formation and as a consequence, 3) promote epithelial proliferation and migration along a thin water layer and 4) enhance surface wound defenses by providing oxygen to macrophages and neutrophils, 5) decrease evaporative water loss as well as fund collagen production and angiogenesis by sustaining fibroblast proliferation [9].

Benzalkonium chloride (BC) is a ubiquitous over the counter topical antiseptic used in everything from household cleaners to skin cleansers. As such it fills medicine cabinets and first aid kits as it's marketed as a front line defense for the treatment of minor scrapes and wounds. Nevertheless, its own label warns against its topical application over "large or raw surfaces or blisters." Chemically considered a quaternary ammonium (quart) and a cationic surfactant, it works both as a topical anti-microbial and skin sanitizer. It primarily functions as a biocidal by disrupting the cell membrane and increasing its permeability, causing the leeching out of intracellular contents, leading to cell shrinkage, dehydration and cell death. Moreover, several studies arising from the ophthalmologic literature describe its noxious effects on ocular epithelium, having it serve as the murine model for the development of dry eye [10-13]. When it acts as a surfactant it serves as a hand cleanser to remove dirt and sebum from the skin. However, its continued use can promote dry skin and damage the stratum corneum [7,14]. In a human study of comparable products, Epstein found a statistically significant higher trans epidermal water loss with BC at a concentration of 0.05%. Furthermore, it was the only agent tested which demonstrated visible skin irritation [14]. The patient’s OTC BC product which he applied and left on for several minutes before rinsing had a concentration of 0.13%, nearly 3 x greater.

Smoking

It is generally recognized that smoking is harmful to wound healing, primarily because it acts as a vasoconstrictor. Robson in his study postulated that vasoconstriction played a major role in burn wound conversion threatening cell viability in the zone of stasis [15]. In a classic study Sorensen demonstrated how cigarette smoking significantly increased the infection rate when compared to a cohort of non-smokers [16]. In addition, smoking has also been found to decrease both the function of neutrophils and the rate of collagen synthesis [17]. Although he stopped using the BC he continued to smoke throughout his treatment course at the rate of 2 packs per day.

Taken in aggregate, these local effects were particularly noxious and corrosive to the wound as marginally viable tissue succumbed and was converted to a full thickness injury as the majority of the wound was repaved with eschar. Needless to say, extreme caution should be exercised when applying topicalics locally to the burn wound especially during the acute and sub-acute phase (1-5 days), when many of its cellular constituents are precariously surviving on a knife’s edge.

The Role of Oxygen in Wound Healing

It is widely acknowledged that oxygen is a key requirement to sustain all phases of the healing process. Following coagulation, the presence of oxygen is essential for macrophages and neutrophils to sanitize a wound of debris and bacteria. It is also during the proliferative phase that fibroblasts are induced to produce collagen and ground substance (ECM) the wound’s mortar, and epithelial cells and capillaries (angiogenesis) are stimulated to regenerate, providing the wound’s bricks. Epithelialization is a particularly critical aspect of the healing process in burns especially in partial and superficial burns where healing spontaneously by secondary intention and without the need for biologics or tissue constructs. In fact for a wound to resurface, epithelialization unleashed through mitosis, is observed to occur at 17x its normal resting rate [1,18]. This burst of respiratory activity places a large oxygen burden on the wound.

For a wound to have the best chance of healing the partial pressure in its bed should register a minimum of 30mm Hg and ideally over 40 [1,19,20]. These levels are easily achieved using Hyperbaric Oxygen (HBO). In fact the experience garnered, both clinical and experimental, has demonstrated the capability of HBO to promote neangiogenesis, epithelialization and ultimately wound healing. Indicated and touted for its ability to resolve carbon monoxide poisoning resulting from fires, its other role as a healing accelerator for acute burns and skin grafts is often questioned and remains controversial. This belief is still widely held in spite of the preponderance of evidence to the contrary [21].

Hyperbaric oxygen (HBO) as a recognized modality for deep dermal burns was observed and first reported by Ikeda and Wada in 1965. Treating Japanese coal workers for carbon monoxide poisoning, these clinicians astutely observed rapid healing of their associated second degree skin burns. These observations stimulated and encouraged others to validate their findings. Most recently in 2013, Ganci and coworkers studied and reviewed over twenty different clinical and experimental animal models in an effort to address this issue and definitively determine the efficacy of HBO in this clinical setting. The authors concluded that HBO prevents dermal ischemia, reduces edema as it modulates the precarious zone of stasis, preventing burn wound conversion by sustaining cellular metabolism, all the while enhancing the healing process [22].

Hyperbaric oxygen is administered by transporting and placing a patient in a hermetically sealed chamber which can deliver 100% oxygen at high pressures. These pressures (2-3 atmospheres) are achieved slowly and are necessary to dissolve gaseous oxygen which is inhaled through the lungs. Since hemoglobin is completely saturated at these concentrated pressures, any additional oxygen must be carried and delivered by the blood stream in its dissolved state to the hypoxic wound bed. Upon reaching its destination oxygen, following the laws of physics, diffuses from an area of high to low concentration, suffusing itself into the ischemic tissue. The case that HBO can benefit oxygen deprived tissue, burns included, should no longer be questioned. Rather, can hyperoxemia be achieved solely by inhaling oxygen under pressure from whence it is transported internally by the blood stream or can oxygen be delivered externally to the wound surface independent of its microcirculation?

To thoroughly answer this question we must first look at more primitive life forms in the animal kingdom, insects. Insects it seems have no lungs and receive oxygen through their exoskeleton. Small openings or microtubules in their outer shell allow for the passage of
oxygen directly to their tissues. This diffusion can occur up to a limit of only 12 mm thus restricting and accounting for their diminutive size. The capability of the skin to function as a ‘peripheral lung’ is not restricted to just insects but is also seen in certain amphibia as well. Frogs, for instance, in spite of having lungs, also possess an oxygen permeable skin envelope, which allow them to ‘breathe’ through their skin as well.

Studying the morphology of the human skin and paying particular attention to its circulatory anatomy, Dr. Terrance Ryan of Oxford University made a trenchant observation. He noted that the capillary loops supplying the epidermis are located in the dermis rather far from the papillary projections. He postulated that the metabolic requirements of active tissue necessitate its having its blood supply close by. As a consequence he surmised that the epidermis must be metabolically inactive or ‘inert’ [22]. In fact, the metabolic and thus the oxygen demands of the skin in general are very little. In spite of being the largest organ in the body it receives less than 5% of the cardiac output or just a little over 2 teaspoons (12 ml) of oxygen per minute. Viewed another way, 400 cm² area of skin, around 8x8 inches requires only 0.3ml O₂/min to sustain its basal metabolic needs [23]. With such a scant amount of oxygen needed its plausible to envision a portion of it being supplied externally through the corneum stratum. This may help explain why the dermal capillaries are located a distance from the epidermis.

In spite of being the largest organ, the amount of skin available for oxygen exchange pales in comparison to the combined surface of the alveolar-capillary interface by a factor of 70. What is more, the skin is on average 1.5 mm thick, the alveolus by contrast is less than 1u mm, making it a much more efficient medium for gaseous oxygen diffusion. Nevertheless, approximately 1-2% of the oxygen needed by the body is provided by the skin, which is available for local rather than systemic consumption [23].

Supporting the claim that the skin is not as inert as once thought, that it plays an active, albeit, minor role in oxygen uptake are several studies reviewed by Ludzinsky [24]. One such study cited the maintenance of oxygen levels to the superficial skin in spite of proximal arterial limb occlusion [25,26]. Advances in the sensitivity of cutaneous oxygen measurements confirm oxygen penetration of the corneum stratum down to 0.3 mm of the superficial dermis [26,27]. These findings were most recently corroborated in a study published out of Canada in 2013. This experiment demonstrated the penetration of dissolved oxygen through the plantar surface (a thick skin barrier) in volunteers immersed in oxygen saturated water when compared to controls immersed in regular tap water [28].

Finally, another investigation showed that epidermally stripped porcine skin was permeable to dissolved oxygen when topically applied [29]. Interestingly, this finding is particularly relevant in that this experimental model resembles a deep dermal burn where the superficial layers are vaporized exposing the relatively porous subjacent dermis. These observations have led to the development of another therapeutic tool, topical oxygen therapy, or TOT. Unlike HBO, TOT, can be locally administered via a portable device targeting the ischemic area directly under normobaric pressures thus avoiding many of the systemic risks and complications associated with HBO [19,24]. Moreover, it is capable of delivering oxygen independent of the pulmonary tree and irrespective of the dermal microcirculation. However, to be effective both modalities require gaseous oxygen be converted into its dissolvable homologue to be ‘biologically’ active and ultimately utilized by its target cell [19,25]. Nevertheless, despite these biophysical barriers TOT, like HBO, has been shown to promote the various essential elements of wound healing including angiogenesis and epithelialization [1,20].

**Back to the Future: The Creation of Oxygen Liberating Water**

Billions of years ago the earth’s atmosphere was devoid of oxygen as we now know it. Approximately 2 billion years ago oxygen began appearing in the biosphere as a consequence of both photosynthesis and the catalytic action on water by arch bacteria inhabiting the ancient oceans. This is referred to in geologic history as the ‘Great Oxygenation Event’ and it served as the evolutionary guide and blueprint for the development and creation of Oxygen Liberating Water (OLW).

Although chemically H₂O this water when independently tested had several advantageous distinct biophysical properties in addition to its oxygen generating potential. First, when studied by an outside laboratory its surface tension measured 59 dynes/cm (normal 73) and its freezing point registered at 34 degrees F [26-30]. Taken together these findings indirectly confirmed an altered energy state present within the water molecule affecting the hydrogen bonding forces as well, lowering or weakening them. Second and more importantly, is its catalytic role, facilitating the cleavage of oxygen from the water molecule where it is ensconced, releasing it preferentially to a living organism in oxygen debt along a diffusion gradient.

This phenomena was observed and corroborated when aerobic hydrocarbon digesting bacteria were placed in an anoxic environment below the earth’s surface. The addition of the water (OLW) not only sustained and revitalized these microbes but enabled them to function normally and metabolize their food source, oil. Extrapolating this data and aware of a basic commonality among heterotrophic organisms within nature with respect to basic cellular function (cellular respiration) we proceeded to further test the water and its oxygen evolution mechanism.

Under the auspices of the department of Sports Medicine at the University of British Columbia Medical School in Vancouver, four healthy subjects were placed in a hypoxic tent in which the ambient oxygen content was lowered to produce a SaO₂ of 90% as measured by pulse oximetry. Once stabilized at this level each volunteer was given 600 cc of oxygen liberating water (OLW) to drink. Within 10 minutes of ingestion all 4 subjects registered a modest increase in their SaO₂ with two of the four reaching peak levels of 95%. These elevated levels were maintained for twenty minutes post a second imbibition before returning to baseline (90% SaO₂). Even more significant, was that this experiment was performed twice, a month apart with identical results [1,31]. Although small, these incremental increases were felt to be significant when viewed with the understanding and through the lens of the S-shaped oxyhemoglobin dissociation curve.

Finally, this author in a yet to be published experiment applied the Ozoeon hydrogel to two different sites on the forearm. Once absorbed (under 10 min), a trained technician applied a cutaneous oxygen monitor probe (Radiometer) and measured the paO₂ before and after gel application in the same area. Both times a 25% increase in paO₂ over baseline was observed, it is also important to note that these reading were obtained over an intact corneum stratum. When taken in aggregate, these findings were apodictic of the oxygen delivering capacity present in both the water and the gel. Furthermore, as a consequence of its lower surface tension, the water is less cohesive or

more permeable, allowing it to transgress the skin barrier more readily than other water based solvents. In short, OLW functions in a dual capacity as a drug delivery system with that ‘drug’ being oxygen. Moreover, the oxygen is provided in a form that can be easily taken up by the targeted hypoxic or injured cell. Finally, the hydrogel formulation was chosen as the medium in which to impregnate the wound. Prepared in a variety of ways, we settled on a relatively weak bonding gelling agent or polymer which would not only rapidly dissolve upon contact with the skin, but was less likely to interfere with the unique properties inherent in the OLW. As a consequence, it is able to unload the entrapped water molecules onto the wound bed providing not only a source of hydration, but nascent oxygen as well.

Hydrogels as a group are particularly well suited topicals in which to treat burns for a variety of reasons. First, they are cool and soothing, as well as easily adaptable to any wound surface. Second, being a gel they contribute to the migration and transplantation of neighbouring epithelial cells, facilitating their implantation onto the healing wound surface [20]. Third, they are gentle upon removal an important consideration when dealing with fragile skin and granulating tissue. Fourth, they can protect and hydrate a wound, as well as absorb moderate amounts of exudate or discharge. Fifth, they can contribute to autolysis, scab dissolution and wound debridement. Sixth, an oxygenated hydrogel has the advantage of supporting and transporting Mesenchymal Stem Cells (MSC) dislodged from the traumatized wound surface until they are capable of adherence, differentiation and tissue development [32]. Finally, being over 90% water they can be easily customized by adding a number of different solutes or ingredients including alginates, hydrocolloids, salts, or antimicrobials. Essentially, they can be adjusted and custom tailored to deal with the local needs of a particular wound [1,9].

Conclusion

The wounding event and its response are multifactorial and dependent upon a variety of local and systemic conditions for either its successful resolution or its continued propagation resulting in failure and its complicating sequelae. Nevertheless, these phenomena invoke a near uniform reaction that transcends aetiology and organ system involved. The wound or inciting insult invokes an inflammatory process achieved via a host of mediators that converges with hypoxia as a consequence of impaired perfusion or ischemia, resulting in cellular derangement or destruction. It therefore follows that successful intervention must not only be timely, aimed at subduing or terminating the inflammatory response but at instituting measures that would provide oxygen to injured tissue so as to promote regeneration and enhance the healing process.

When treating a myocardial or cerebral infarct its common practice and widely recognized that early intervention at revascularization is necessary to limit or reverse injury to ischemic tissue. The goal, of course, is to provide blood flow and oxygen along with it. Accepting that paradigm and viewing the skin as an organ, the same biologic goals should be held for it as well. The burn is a ‘stroke’ inflicted upon the skin and since revascularization of the microcirculation is not feasible, other modalities (HBO) that can achieve the same end result need to be closely examined, utilized and employed. Practically speaking, it is logistically challenging to march a critically injured patient followed by an army of caregivers and a flotilla of tubes from a burn unit to a hyperbaric oxygen chamber. Furthermore, many of these patients have sustained pulmonary burns as well and are on ventilator support. Experimentation has shown that the skin, especially one that has lost its ‘impermeable’ epidermal sleeve through a burn is capable of oxygen absorption. Furthermore, if that oxygen can be delivered independent of the host’s respiratory or circulatory status, then we may finally have at hand a novel and revolutionary method of healing burns. Aware that we need just a minimal increase in pO² to heal a wound (greater than 30) or sustain the skin, this goal should be readily achievable by direct oxygen translocation. Finally, I believe that our hydrogel through the clinical response achieved in this and a handful of other cases are not anecdotal but indicative of a new and innovative treatment that is capable of delivering oxygen when applied topically.

The premise of this paper is to first identify instigating and precipitating factors which lead to burn wound conversion and then proffer steps to mitigate and treat it. Chief among them is dehydration, ischemia and its consequence hypoxia, as well as minimizing infection [33,34]. Expeditious attention to the first two will affect the third by decreasing the risk of its development [35]. We contend that the proper application of this gel provides all three. In fact, after just one day of treatment the patient already showed signs of improvement and stabilization of the burn wound (photos A & B). It’s plausible and quite possible that had he stayed on his recommended treatment course he would have had a different and even better result. Echoing Winters, wounds heal optimally in a moist or gel like environment by facilitating epithelialization. Furthermore, if a moist or gel dressing is applied a scab is less likely to occur [33,34]. In all likelihood the eschar that developed was a consequence of both local factors which fuelled and exacerbated the initial inflammatory response. With discontinuance of BC and continued frequent (minimum QID) application of the hydrogel, using no other agents, he went on to heal unimpeded and quickly 17 days later, even though he continued to smoke.

The purpose of this article is to demonstrate the superior healing qualities inherent in a newly developed oxygen delivering hydrogel. In particular, how its early and frequent application can prevent and if indicated treat burn wound conversion quickly, affordably and effectively with minimal residual scarring and sequelae.

References