Managing inflammation by means of polymeric membrane dressings in pressure ulcer prevention

Author:
Amit Gefen

Inflammation is the immediate normal response of the immune system to localised microscopic cell damage that precedes macroscopic tissue damage. Inflammation is triggered by secretion of chemokines that attract immune system cells to the sites of cell damage and facilitate their extravasation through increase in capillary permeability. The increased permeability of capillary walls in the inflammatory state consequently causes fluid leakage from the vasculature and, hence, oedema and associated pain. Polymeric membrane dressings (PolyMem®, Ferris Mfg. Corp.) are multifunctional dressings that focus and control the inflammation and oedema, and reduce pain. The literature reviewed in this article suggests that by having these effects on the inflammatory response, especially in fragile patients, the PolyMem dressing technology may facilitate repair of micro-damage in cell groups, which counteracts the evolution of damage to a macroscopic (tissue) level. Reducing the spread of inflammation and oedema in tissues appears to be a unique feature of PolyMem dressings, which supports repair of cell-scale damage under intact skin and tilts the delicate balance between the counteracting damage build-up and tissue repair mechanisms, thus promoting reversibility and self-healing.

Inflammation, a critical phase in tissue repair and healing, is the immediate normal response of the immune system to localised microscopic damage (death of a group of cells), which precedes macroscopic tissue damage. Inflammation is triggered by secretion of chemokines, which are specific cytokines (signalling/messenger molecules also called chemo-attractant molecules) that attract immune system cells, for example, white blood cells (WBCs) to the sites of cell damage, for clearance of cell debris and for confronting pathogens if they are invading *[Figure 1]*.

The inflammatory response should normally stop when it has cleared the cell debris. When the inflammation response is inadequate, repair of tissue damage becomes impossible, particularly since the invaders or damaged cells remain behind. Adequate inflammation implies that the immune system needs to be sensitive and responsive to localised cytokine release as cells break down in the onset of damage. One of the factors that may prematurely halt inflammation is failure of the immune system to detect a local rise in cytokine levels, which may occur if systemic, baseline cytokine levels are atypically high. Indeed, in neuromuscular conditions, such as post spinal cord injury (SCI), the function of the immune system is damaged and the inflammation response becomes abnormal. In the chronic phase of SCI, in particular, as bidirectional communication no longer exists between the nervous, endocrine and immune systems, both endocrinal and immune impairments form. In particular, people with an SCI are often found to be in a perpetual low-grade inflammatory state, which is elevated to an even further extent when other health complications are present, including infections (Allison and Ditor, 2015).

It is well known that the deterioration of the body systems post-SCI exhibit similarities to the progressive degenerative phenomena that are characteristic to normal aging, with the difference being the timescale of the deteriorative changes. Examples of such deteriorative changes include considerable muscle and bone atrophy, fat

Amit Gefen *is Professor of Biomedical Engineering, Department of Biomedical Engineering, Tel Aviv University, Israel*

infiltration into muscles, skin thinning and loss of anchoring between skin layers, all of which take place in healthy older people over decades. In individuals with an SCI, however, these changes all occur within a few months to just a couple of years (Gefen, 2014a). Interestingly, like in SCI, chronic inflammation is tightly correlated with aging as well (Jenny, 2015).

The specific causes and effects for chronic inflammation in aging are not yet clear. A number of theories have been developed that attempt to define the role of chronic inflammation in aging, including redox stress, mitochondrial damage, immunosenescence, endocrinosenescence, epigenetic modifications and age-related diseases. However, thus far, no single theory is able to explain all aspects of aging; instead, it is likely that multiple processes contribute and that all are intertwined with inflammatory responses. The overall outcome, however, is that older people are, much like the neuromuscularly impaired patients, likely to be found at a perpetual low-grade inflammatory state.

Chronic low-level inflammation is not only metabolically 'expensive' as the immune system is in a continuous over-active state, but also, the ongoing low-level inflammation could reduce the local sensitivity of the immune system to local release of chemokines due to breakdown of cells in the onset of a pressure ulcer (pressure injury in the US and Australia), including a deep tissue injury. Clearly, when the immune system is unresponsive to ongoing cell death processes, and no inflammation is triggered to clear out the cell debris and stop the necrosis-apoptosis cycle, tissue damage grows and spreads faster, and so the damage cascade is overall intensified.

Under such chronic inflammation (as in aging or neuromuscular conditions), locally secreted chemokine signals that result from onset of a pressure ulcer, and which require a 'true' inflammation response from the immune system, may be left unnoticed by the chronically active and, hence, less-sensitive immune system. As the early cell damage may not attract a response from WBCs to start a repair process, the damage will likely intensify and expand from the micro-scale of cells to the macroscopic tissue level *[Figure 2]*, and become irreversible. Much like in Aesop's fable *The Boy Who Cried Wolf*, the chronicity of the inflammatory state in neuromuscular disabilities and aging may compromise the ability of the immune system to detect true events of cell damage requiring local activation of the processes described in *Figure 1*, such as immune cell extravasation and migration.

The practical conclusion would be that in individuals with neuromuscular conditions and in older people, there appears to be a potential benefit in managing the levels of chemokines release and, hence, the chronic inflammation process prophylactically, in order to support the sensitivity of the immune system to local rise in chemokine levels when cell death occurs, in the early stage of a pressure ulcer.

The polymeric membrane dressings commercially known as PolyMem® dressings (Ferris Mfg. Corp.) are the brand name to which the majority of published literature refers when reporting the benefits in use of this category of dressing technology. PolyMem dressings are multifunctional dressings comprising a hydrophilic polyurethane matrix that contains a mild, non-toxic wound cleanser, soothing moisturiser (glycerin), a superabsorbent polymer and, in some versions, also silver and a semi-permeable backing film. The polyurethane foam membrane in the dressing provides a porous structure that draws fluids from existing wounds, controls water loss and, therefore, facilitates moist wound-healing conditions. There is experimental evidence in the literature that suggests that in a rodent model, the design and structure of the PolyMem dressing material inhibits the activity of nociceptive neurons in the epithelium (Beitz et al, 2004). As mentioned earlier, the immune and peripheral neural systems are strongly coupled, which may explain the reported reduction in inflammation at the region of the dressing, as well as the often observed decrease in oedema and pain (Hayden and Cole, 2003; Beitz et al, 2004).

Given these effects, from an inflammation management standpoint, applying a PolyMem dressing appears to be beneficial for topically depressing the perpetual chronic inflammation in neuromuscular conditions and older people: Applying the dressing may theoretically increase the local sensitivity of the immune system to cell death events in at-risk anatomical sites, early enough, at the onset of the pressure ulcer damage spiral when damage is still limited to microscopic groups of cells *[Figures 1,2]*.

The purpose of this review is to analyse the evidence in the literature that points to the plausible enhancement of sensitivity of the immune system and the benefits of applying PolyMem dressings at sites such as the sacrum and heels prophylactically. In addition, the literature suggests that PolyMem promotes improved activation of localised inflammation when damage has occurred. There is also evidence to the value of containing the inflammatory response and limiting it to the affected sites, so that collateral cell and tissue damage is prevented. Together with application of standard care procedures, including

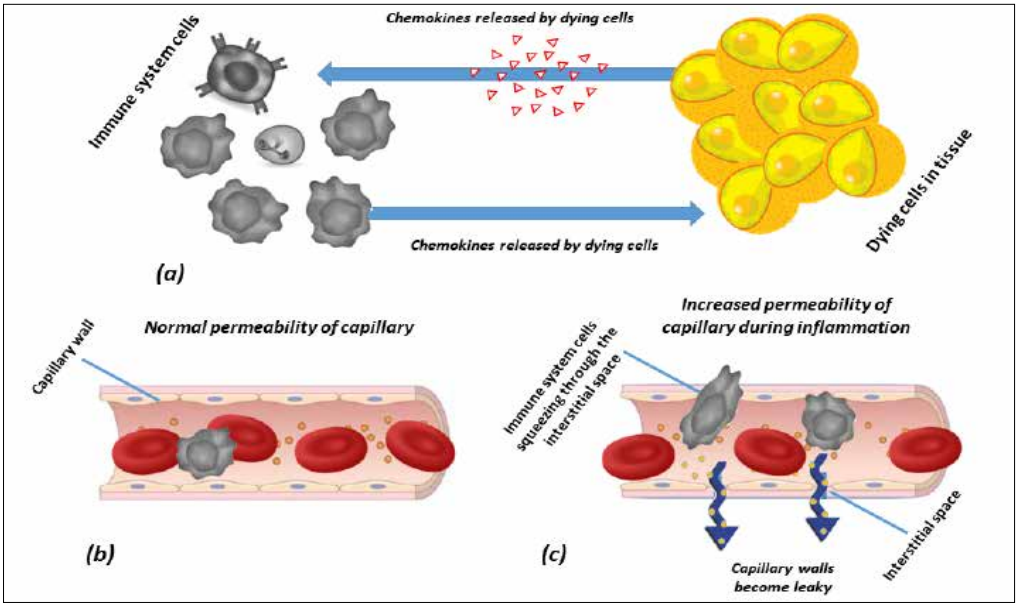


Figure 1. The role of chemokines in attracting immune system cells in order to clear away cell debris: (a) Damaged cells release chemokines (symbolised as colored triangles) that act as inflammatory signals, attracting immune system cells to the site of microscopic tissue damage. The release of chemokines also acts to increase the permeability of capillaries above the basal level (b), which then enables extravasation-infiltration of white blood cells to the damaged region, but also cause the walls of capillaries to become leaky (c).

prescription of adequate support surfaces, routine visual skin assessment and repositioning, the literature reviewed in this article suggests that presence of the PolyMem dressings may facilitate repair of the micro-damage (for which local inflammation is a critical stage) before the micro-damage continues to evolve to macroscopic, tissue-scale damage. Accordingly, by summarising published pre-clinical and clinical evidence, this paper demonstrates that applying PolyMem dressings prophylactically and, therefore, locally managing inflammation may support the body in repairing a reversible micro-damage prior to the stage when damage becomes irreversible.

Polymeric membrane dressings focus and moderate inflammation

Published experimental evidence demonstrates that the unique design, structure and material composition of the PolyMem® dressings focuses the inflammatory response to the primary site of tissue damage and also subdues the activity of nociceptive neurons in the epithelium (Kahn, 2000; Beitz et al, 2004). Subduing nociceptive neurons moderates the response of the spinal dorsal root ganglia mechanism that is responsible for generating inflammation, oedema, pain, itching and burning, which suggests that the effect of PolyMem is both local and central. Specifically, using a rat model, it has been shown that the PolyMem dressing (but not standard gauze or foam dressings) induces spinal cord Fos expression in laminae III and IV of the dorsal horn of naive (non-injured) animals which, therefore, indicates both a deep tissue and a central nervous system effect (Beitz et al, 2004). Dorsal horn neurons receive noxious and non-noxious stimuli sensory information from primary afferents that innervate the skin, as well as deeper tissues of the body (Todd, 2010). Accordingly, the work reviewed above, particularly the Beitz experiments where stab wounds were inflicted in rodents and subsequent healing has been assessed, highlights that the effect of the PolyMem dressing applies not only to skin, but also to subcutaneous fat and skeletal muscle tissues, even though the PolyMem products are always used superficially (Kahn, 2000; Beitz et al, 2004; Weissman et al, 2013).

The Kahn (2000) study employed rabbit models to assess healing of controlled inflicted traumatic injuries and also examined human injury cases treated with PolyMem dressings (without compression). Interestingly, they demonstrated that the PolyMem dressing is clinically effective even when placed on intact skin. For example, when PolyMem dressings were used to treat patients with traumatised tissues and bruises, the area directly beneath the dressing was not tender and appeared normal, while areas outside the dressing perimeter were typically discoloured (ecchymosis), indurated and tender (which are clinical signs of acute inflammation). This could relate back to the

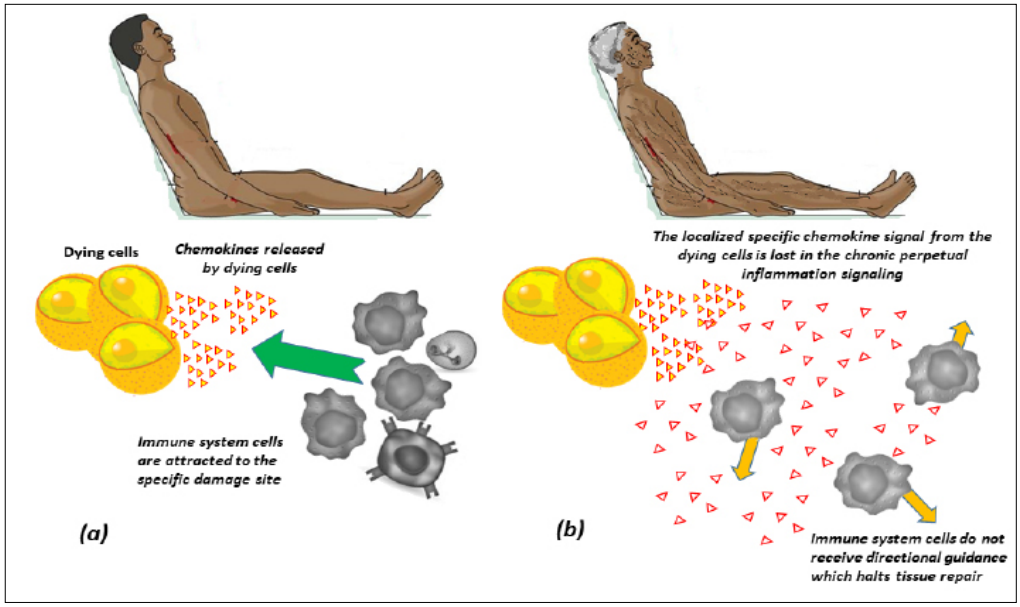


Figure 2. Illustration of the potential consequences of chronic perpetual inflammation on sensitivity of the immune system in responding to localized cell death in the early phase of formation of a (micro-scale) pressure ulcer: (a) Normally, the chemokines released by the dying cells in the micro-injury site (symbolized as colored triangles) should attract immune system cells (white blood cells [WBCs]) to the specific damage site, and as the WBCs leave the capillaries and migrate in the tissue (chemotaxis), they are guided by the concentration gradient of the released chemokines to reach the correct location of the micro-damage. (b) In the state of chronic, perpetual inflammation such as in the elderly, the localized specific chemokine signal from the dying cells is lost in the chronic perpetual inflammation signaling and the WBCs do not receive adequate directional guidance, which in turn halts the repair process. As no effective intervention is taken by the immune system in this case, cell damage continues and spreads, and damage may become macroscopic and irreversible.

animal work of Beitz and colleagues (2004), which pointed to mechanisms for inflammation control associated with use of PolyMem, as detailed above. There have been additional case studies which indicated that applying PolyMem dressings over deep tissue injuries (under intact skin), as well as on subdermal contusions, hematomas and sprains accelerated healing (Burkhard, 2010). Moreover, it has been reported that 80% of category 1 pressure ulcers, where the skin is intact, resolved within 4 days after PolyMem dressings have been applied, whereas following standard care protocols (without prescription of PolyMem) these pressure ulcers typically heal within 2 weeks (Wilson, 2010).

Furthermore, the pain associated with the aforementioned pressure ulcers was eliminated as quickly as 2 hours post initial use of the product (Wilson, 2010). In one interesting and relevant patient case, reported by Schmid et al (2010), the PolyMem dressing has been replaced by a conventional dressing during the course of treatment post-knee replacement surgery. Within 2 hours from the above replacement of dressings, swelling had returned, the patient was complaining about increased pain and consumed pain relief medications after not using these for a week while PolyMem had been applied. These symptoms resolved promptly as soon as PolyMem has been reapplied (Schmid et al, 2010). With regard to prevention of medical device-related pressure ulcers, PolyMem has recently been reported to contribute to the reduction in prevalence of injuries caused by tracheostomy devices (O'Toole et al, 2017).

Taken together, the work by Kahn (2000) and the above-listed case and case series studies form the basis for the hypothesis that the PolyMem dressing technology has a distinctive prophylactic value, as PolyMem can support repair of micro-damage under intact skin. This then allows the body to self-heal by reversing injurious events that otherwise may lead to clinically significant (macroscopic) pressure ulcers. Nevertheless, it is noteworthy that in the pyramid of clinical evidence, the relevant work reported so far is not at the top of the hierarchy, i.e. there are no randomised clinical trials (RCTs) that were specifically designed to test inflammation control by dressings. Therefore, we stress that the above is still a hypothesis which requires further testing.

The value in inflammation management for pressure ulcer prevention

In the build-up of tissue damage, inflammation, which is triggered by chemokines released from dying cells *[Figure 1],* as well as by release of calcitonin gene-related peptides (CGRPs) from nociceptive neurons (neurogenic inflammatory signals), may develop rapidly and spread to healthy tissues surrounding the initial damage site.

While the inflammatory phase of wound healing is a prerequisite for successful tissue repair, uncontrolled inflammation and excess oedema have been shown to cause peripheral cell and tissue damage, hinder healing of the primary wound and increase pain. Secondary tissue damage due to inflammation and formation of oedema may proceed after the initial injury (Weissman et al, 2013), which emphasises the need to manage and contain the inflammation response (but not depress it completely). The latter applies not only with regard to existing wounds, but is also extremely relevant and important in the process of micro-damage self-repair (i.e. spontaneous repair), as related to pressure ulcer prevention.

Specifically, as tissue damage is the outcome of a cell death rate exceeding the rate of tissue repair in a certain patient and a given anatomical site, topical management of inflammation appears to be vital in modulating the cell death rate, which should contribute to a better likelihood of prevention. As explained in the introduction to this article, PolyMem dressings appear to be beneficial for topically depressing the perpetual chronic inflammation in neuromuscular conditions and older people, though this still requires further research through laboratory work and RCTs.

Based on the body of evidence so far (as reviewed earlier in the article), and while appreciating that it is still limited, the author surmises that in the more fragile populations, applying the PolyMem dressings may increase the local sensitivity of the immune system to cell death events in at-risk anatomical sites early enough, at the onset of the pressure ulcer damage spiral. If increased sensitivity of the immune system is to be achieved in fragile patients by applying PolyMem dressings prophylactically to anatomical sites, such as the sacrum and heels, this may promote activation of localised inflammation in these patients that is closer to a normative response when micro-damage (first cell death events) occurs; a more focused inflammation, which is contained to the primary damage sites is then expected. Further research is warranted to provide the clinical evidence of such effectiveness in RCTs.

It should be noted that managing inflammation, though being a critical component, is just one requirement in pressure ulcer prevention that needs to be met together with other design specifications. Hence, in addition to inflammation management, a good prophylactic dressing also creates adequate biochemical, biomechanical and biothermal environments at the skin surface and in the subdermal tissues at risk. In particular, prophylactic dressings should lower exposure to tissue distortions and deformations, optimise tissue temperatures and manage moisture levels.

The PolyMem dressings are compliant and flexible, thus providing cushioning to weight-bearing tissues (Denyer, 2009). Clearance of wetness through immediate absorption followed by evaporation from the PolyMem dressing is a fundamental microclimate control and skin protection mechanism (Smith et al, 2012; Woo et al, 2017), which contributes to preventing maceration of the skin. In general, the clearance of wetness from the skin surface further minimises elevated frictional forces, which may harmfully distort skin and internal tissues, since wet skin has a greater friction coefficient with contacting materials (Gefen 2011, 2014b; Shaked and Gefen, 2013). The reduction in frictional forces is the effective outcome of internal interactions between the PolyMem dressing components, namely, a hydrophilic polymer with super-absorbance properties, which clears moisture away from the skin surface, together with glycerin and surfactant that contribute to lubrication and a smoother micro-topography of the skin area protected by the dressing.

Alleviation of skin and soft tissue loads at weight-bearing sites via the above mechanisms (cushioning and microclimate control) reduces the risk for deformation-inflicted cell and tissue damage, and the extent of damage if such occurs. Thermal isolation, which is further provided by the PolyMem dressing (and which foam dressings generally provide) prevents the sites at risk from cooling (Jones and Harding, 2009), which supports blood perfusion that is also essential for an effective inflammation response (cold temperatures promote vasoconstriction). Management of the biomechanical and biothermal conditions which are physiologically coupled (Gefen, 2011; Shaked and Gefen, 2013; Zeevi et al, 2017) is generally

important and in the case of the PolyMem, complements the inflammation management function of this specific technology.

Conclusions

The current literature that can be used to evaluate the prophylactic potential of inflammation management by dressings is sparse, much of it is case and case series studies and venues of publications are mostly conferences with less methodological work published in journals. With that being said, at this time, based on the existing literature reviewed here, applying PolyMem dressings prophylactically appears to support the body in repairing a reversible micro-damage prior to the stage where damage becomes irreversible.

Since these dressings are non-adherent, theoretically they are well suited for prophylactic use. Dressing changes are comfortable and atraumatic which ensures that presence of the dressing prophylactically over prolonged periods and routine replacements are not irritating the skin. Reducing the spread of inflammation in tissues through nociceptor inhibition, as reviewed above, is a unique feature of PolyMem dressings which supports repair of cell-scale damage under intact skin, and hence, tilts the delicate balance between the counteracting damage build-up and tissue repair mechanisms, leading to reversibility and self-healing.

Additional basic, bioengineering and clinical research, across all levels of the evidence pyramid, is definitely required to establish deeper understanding of the underlying mechanisms and increase the base of evidence for the prophylactic value in inflammation management. WINT

Disclosure

This literature review was funded by an Unrestricted Educational Grant from Ferris Mfg. Corp.

References

Allison DJ, Ditor DS (2015) Immune dysfunction and chronic inflammation following spinal cord injury. *Spinal Cord* 53(1): 14-8

Beitz AJ, Newman A, Kahn AR et al (2004) A polymeric membrane dressing with antinociceptive properties: analysis with a rodent model of stab wound secondary hyperalgesia. *J Pain* 5(1): 38–47

Burkhard R (2010) *Efficient Reduction of Swelling and Bruising on Severe Sports Injuries When Using Polymeric Membrane Dressings*. European Wound Management Association Meeting, Geneva, Switzerland. Poster #218, May 26–28, 2010

Denyer J (2009) *Polymeric Membrane Dressings in the Management of Infants with Epidermolysis Bullosa* (EB). European Wound Management Association Meeting, Helsinki, Finland. Poster #100, May 20–22, 2009

Gefen A (2011) How do microclimate factors affect the risk for superficial pressure ulcers: a mathematical modeling study. *J Tissue Viability* 20(3): 81–8

Gefen A (2014a) Tissue changes in patients following spinal cord injury and implications for wheelchair cushions and tissue loading: a literature review. *Ostomy Wound Manage* 60(2): 34–45

Gefen A (2014b) From incontinence associated dermatitis to pressure ulcers. *J Wound Care* 23(7): 345

Hayden JK, Cole BJ (2003) The effectiveness of a pain wrap compared to a standard dressing on the reduction of postoperative morbidity following routine knee arthroscopy: A prospective randomized single-blind study. *Orthopedics* 26(1): 59–63

Jenny NS (2012) Inflammation in aging: cause, effect, or both? *Discov Med* 13(73): 451–60

Jones V, Grey J, Harding K (2006) Wound dressings. *BMJ* 332(7544): 777–80

Kahn AR (2000) A superficial cutaneous dressing inhibits inflammation and swelling in deep tissues. *Pain Med* 1(2): 187

Minematsu T, Yamamoto Y, Nagase T et al (2011) Aging enhances maceration-induced ultrastructural alteration of the epidermis and impairment of skin barrier function. *J Dermatol Sci* 62(3): 160–8

O'Toole TR, Jacobs N, Hondorp B et al (2017) Prevention of tracheostomy-related hospital-acquired pressure ulcers. *Otolaryngol Head Neck Surg* 156(4): 642–51

Schmid P (2010) *Reduction of Edema and Pain on Surgical Wounds with Polymeric Membrane Dressings*. European Wound Management Association Meeting, Geneva, Switzerland. Poster #317, May 26–28, 2010

Shaked E, Gefen A (2013) Modeling the effects of moisture-related skin-support friction on the risk for superficial pressure ulcers during patient repositioning in bed. *Front Bioeng Biotechnol* 1: 9

Smith D, Houle H, Searls L (2012) *Hypergranulation Tissue, A Challenging Problem with an Easy Solution*. Wild On Wounds Conference, Las Vegas, Nevada. Poster #21, September 11–14, 2012

Todd AJ (2010) Neuronal circuitry for pain processing in the dorsal horn. *Nat Rev Neurosci* 11(12): 823–36

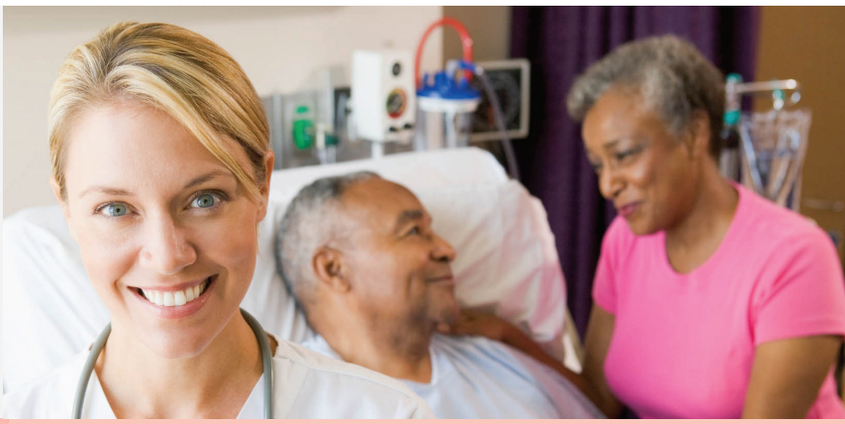
Weissman O, Hundeshagen G, Harats M et al (2013) Custom-fit polymeric membrane dressing masks in the treatment of second degree facial burns. *Burns* 39(6): 1316–20

Wilson D (2010) *Application of Polymeric Membrane Dressings to Stage I Pressure Ulcers Speeds Resolution, Reduces Ulcer Site Discomfort and Reduces Staff Time Devoted to Management of Ulcers*. Symposium on Advanced Wound Care – SPRING, Orlando, FL, USA. Poster #CS-128, April 17-20, 2010

Woo KY, Beeckman D, Chakravarthy D (2017) Management of moisture-associated skin damage: A Scoping review. *Adv Skin Wound Care* 30(11): 494–501

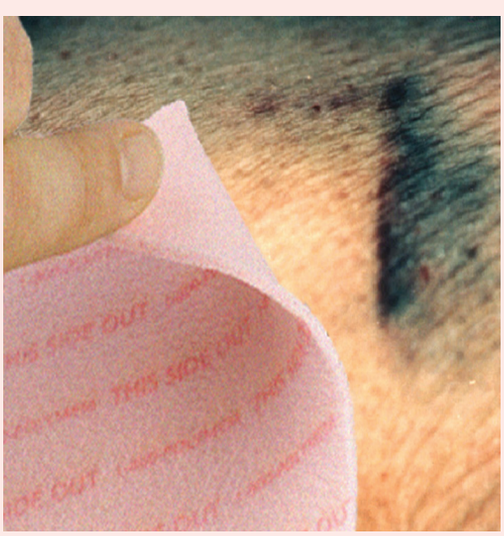
Zeevi T, Levy A, Brauner N, Gefen A (2017) Effects of ambient conditions on the risk for pressure injuries in bedridden patients - multiphysics modeling of microclimate. *Int Wound J*. In press (available online), DOI: 10.1111/iwj.12877

PolyMem® wound dressings are designed to focus inflammation to where it is needed – the wound site – while minimizing inflammation where it isn't needed, in uninjured tissue surrounding the wound.[1]



PolyMem®

more healing • less pain



Reduced bruising without compression

Focusing the inflammatory process helps reduce secondary cell damage and pain caused by the typical swelling and bruising usually observed beyond the wound site.[1,2,3]

PolyMem has been shown to reduce secondary cell damage by reducing the recruitment of adjacent inflammatory nerve endings (also referred to as nociceptors or free nerve endings).[1] These populous nerve endings, found in the epidermis, dermis, muscle, joints and viscera, are responsible for triggering and spreading the inflammatory reaction into surrounding uninjured tissues.[4,5,6,7,8] The spreading of inflammation is often clinically evidenced by increased temperature, bruising, swelling, increased sensitivity to stimuli, and pain beyond the immediate zone of injury.[5,7]

References:
1. Beitz, AJ, Newman A, Kahn AR, Ruggles T, Eikmeier L. A Polymeric Membrane Dressing with Antinociceptive Properties: Analysis with a Rodent Model of Stab Wound Secondary Hyperalgesia. The Journal of Pain. Feb 2004;5(1):38-47
2. Knight KL. Chapter 3. Inflammation and Wound Repair In Cryotherapy in Sport Injury Management. Human Kinetics. 1995. Champaign, IL
3. Merrick MA. Secondary injury after musculoskeletal trauma: a review and update. Journal of Athletic Training 2002;37(2):209-217
4. Clay CS, Chen WYJ. Wound pain: the need for a more understanding approach. Journal of Wound Care. April 2005;14(4):181-184
5. Abraham SE. Pain Management in wound care. Podiatry Management. June/July 2006:165-168
6. Wulf H, Baron R. The Theory of Pain in European Wound Management Association Position Document Pain at Wound Dressing Changes, Medical Education Partnership, London UK, 2002; page 8-11
7. Levine JD, Reichling DB. Chapter 2 Peripheral Mechanisms of Inflammatory Pain. In Wall PD, Melzak R, Editors. Textbook of Pain. 4th edition. Edinburgh, UK: Churchill Livingstone, 1999. pages 59-84.
8. Fields HL. Chapter 1 Introduction & Chapter 2 The Peripheral Pain Sensory System In Pain New York; McGraw-Hill 1987 pages 1-40

Learn more and order at polymem.com

MKL-745 R0 0218