Overcoming the challenge of overgranulation

Wound repair is a highly complex process. When wounds fail to heal, it is usually the absence of granulation tissue which is the main issue. However, there are times when an overgrowth of tissue can lead to practical management issues. This article will look at the normal wound healing process and seek to identify why the development of ‘overgranulation’ occurs. It will identify potential management strategies and explain why the use of a steroid-impregnated tape (Haelan Tape®, Typharm) may be an appropriate option for wound healing management in this client group.

Alison McGrath

The mechanisms of wound repair following injury are complex, but, as further research is undertaken, clinicians and researchers are developing greater understanding, including how and why these mechanisms are disrupted in certain individuals.

Arguably, the publication of Winter’s study on wound healing (1962) brought about one of the greatest changes in wound management. The research suggested that the maintenance of a moist wound healing environment brought about enhanced wound healing, with increased granulation and re-epithelialisation and improved scar quality. This was in marked contrast to previous approaches to wound management in which dry wound healing was advocated. Since the adoption of this approach, one of the central tenets of wound management has been to facilitate the proliferation of granulation tissue in the wound through the regulation of wound bed moisture and, when required, the provision of additional moisture in the wound healing environment. This is widely accepted as an essential facet of good wound care and a prerequisite to eventual tissue repair.

However, while granulation occurs in an orderly, if occasionally, slow manner in the majority of wounds, in others it can become disorganised resulting in the production of a protruding mass of granular tissue, which appears to inhibit wound closure. This ‘overgranulation’ can be unsightly and distressing to patients, as well as posing a management challenge to clinicians.

This article will look at the potential causes of overgranulation, the methods employed to manage it, focusing on an approach that appears to provide a practical solution.

Normal wound healing
To appreciate why overgranulation occurs, it is important to understand how wound healing takes place in normal circumstances. The healing of wounds is a complex physiological process, which is essential to re-establish the integrity and function of the body (Flanagan, 1996). Although often represented graphically as a linear process, there are in fact many interconnected components which influence the process of healing: many of the cells and chemical prompts involved in the wound healing process have more than one function and may demonstrate altered states of expression depending on their interaction with other elements. For example, macrophages are involved in the immune response to bacterial ingress and removal of non-viable debris, but also have a role within the production of growth factors responsible for tissue regeneration.

For these reasons, it is unsurprising that despite the large amount of research that has been undertaken into wound healing, there are still areas which are not properly understood (Russell, 2000).

The natural healing process is frequently divided into four interconnected stages:

- Inflammation
- Granulation
- Epithelisation
- Maturation.

Inflammation
Inflammation is a vascular and cellular response designed to defend the body against alien substances and to dispose of non-viable tissue. This prepares an environment conducive to the...
formation of new tissue at the site of injury. In acute injury, the inflammatory response is predominantly limited to the area of tissue damage and resolves within three to five days (Hart, 2002).

Following injury, blood constituents leak into the surrounding tissues, activating the coagulation cascade (Kerstein, 1997). Activated platelets become very sticky and adhere to form a platelet plug, which acts as a provisional haemostat. This is strengthened by strands of polymerised fibrin. This clot limits blood loss and provides a fibrinous migratory scaffold for the movement of a variety of cells into the wound site.

On injury, damaged cells release inflammatory mediators such as prostaglandins and histamine from mast cells. Serotonin may also be released, resulting in vasodilation of existing blood vessels and increased cell permeability. This is seen clinically as erythema and localised oedema as fluid leaks into surrounding tissues. Vasodilation and increased vessel permeability enable extravasation of the neutrophils, monocytes, and T and B lymphocytes into the tissues. These are attracted into the wound within hours of injury by the action of the mediators.

Wound cleansing is started by phagocytic macrophages which arrive within 1–2 days, digesting the fibrin and providing a defence against infection. Macrophages and neutrophils are essential for the transition from the inflammatory to proliferative phase of healing.

There are also growth factors that initiate the movement and proliferation of fibroblasts, which in turn lay down the structural protein and collagen for tissue repair (Kerstein, 1997; Morison et al, 1997).

The interleukins (cytokines) are involved in inflammation and wound healing and affect local tissue by increasing tissue adherence and attracting T and B lymphocytes to the site of the injury.

**Granulation**

The construction of new tissue within a wound requires two processes — the formation of a new vascular supply to transport the raw building blocks needed for tissue repair; and the use of these materials to synthesise protein chains into new tissue.

One of the most important cells in this process is the dermal fibroblast. These migrate into the wound and increase in numbers through mitosis. Stimulated by growth factors released by macrophages in the wound, fibrils of reticulin are laid throughout the wound, which are later converted to collagen. Even as collagen is laid down by the fibroblasts, collagenases and other proteolytic enzymes remodel it. Matrix metalloproteinases (MMPs) are a group of enzymes which play an important role in the proliferative phase of healing (Stephens and Thomas, 2002).

In particular, collagenase regulates the balance between collagen synthesis and lysis by facilitating the growth of new connective tissue and the re-absorption of the extracellular matrix (ECM), the temporary filler which physically supports the newly-formed blood vessels and granulation tissue characteristic of the proliferative phase (Edwards et al, 1987; Stephens and Thomas, 2002; Vuolo, 2010). In normal wound healing, the level of production (synthesis) is greater than destruction (lysis), therefore, there is net gain in collagen. As the process continues, this balance is shifted until eventually equilibrium is established.

Local tissue hypoxia acts as the primary stimulus for angiogenesis (Planagan, 1997), along with the release of angiogenic factors from macrophages and platelets, and fibroactin found in the fibrin scab. Endothelial cells in the form of capillary buds grow into the new framework, providing the oxygen and nutrients necessary to fuel cellular proliferation.

Eventually, fibroblasts stimulated by growth factors differentiate into myofibroblasts, which act like smooth muscle fibres and exert greater tension across the wound and result in wound contraction. Large deep wounds may take a considerable length of time to contract and heal. Contraction could be responsible for 40–80% of wound closure in wounds left to heal naturally (Irvin and Challopadhyay, 1978).

This explains the clinical significance of wound edge approximation with external devices such as suture material; mechanical closure of the wound shortens the healing process and can achieve enhanced cosmesis by reducing the need for significant contraction.

**Epithelialisation**

Epithelial migration is initiated soon after injury, as cells adjacent to the damaged area begin to divide and move across the field of injury. In partial thickness wounds, these cells are found in hair follicles and sebaceous glands as well as the neighbouring intact epidermis (Mercandetti and Cohen, 2005).

In deeper wounds, lateral extension of the epidermal keratinocytes across the wound is the primary method of re-paving. These migrating keratinocytes are delicate and require a moist oxygen-rich environment if optimum proliferation and migration is to be achieved.

Numerous factors act as a stimulant to keratinocyte migration, such as altered calcium levels, exposure to damaged extracellular matrix, loss of contact inhibition, alterations in tension within the epithelium and exposure to growth factors.

Once activated, cells dissolve their anchoring structures (these are known as desmosomes and hemidesmosomes) (Santoro and Gaudino, 2005) and deposit proteins called integrins on actin filaments. These enable the cell to ‘stick’ to new tissue. The cell flattens...
and forms projections (pseudopodia, lamellipodia and filopodia), which are used to drag the cell to its new location. The keratinocytes gradually move over the granulation tissue under the level of the scab (if one has formed), and enzymes break down clot and debris.

As the cells migrate, new keratinocytes are formed behind this leading edge by the stimulation of growth factors. This process continues until the advancing keratinocytes meet their counterparts moving in from the other direction, at which point contact inhibition causes them to stop migrating and reform anchor proteins which fix the cell to the underlying surface.

**Maturation**

The newly-healed wound may be covered in epithelial tissue but the disorganised collagen lacks strength. During this final stage of healing, the type III collagen that is prevalent during proliferation is gradually replaced by stronger type I collagen (Dealey, 1999). Collagen fibres are realigned along tension lines and cross-linked through a process of collagen synthesis and lysis (Lorenz and Longaker, 2003).

Redundant fibroblasts and superfluous capillaries are removed by a process of apoptosis. This stage can take up to two years to complete and generally results in a mature scar, which has up to 80% of the tensile strength seen in the pre-damaged tissues (Mercandetti and Cohen, 2005).

**Overgranulation**

The formation of granulation tissue is central to the proliferative phase of wound healing (Romo et al, 2008). However, in some cases the formation of granulation tissue continues without the migration of epithelial cells across the wound bed. As this occurs, the granular tissue increases to a level higher than the surrounding healthy tissues. This forms areas of friable, irregular heaped tissues referred to as hypergranulation, overgranulation, hypertrophic granulation, hyperplasia of granulation tissue or proud flesh (Harris and Rolstad, 1994; Young, 1995).

This tissue is highly vascular with a dense network of blood vessels and capillaries. This means that it is often dark in colour, ranging from dark red to bluish purple (Harris and Rolstad, 1994; Johnson, 2007). Biopsy of the tissues usually reveals an overgrowth of fibroblasts and endothelial cells, with a similar structure to healthy granulation tissue but in excess of that normally seen (Dunford, 1999; Semchyshyn, 2009). Generally, overgranulation tissue is not painful as it contains little nerve tissue, however, if left untreated, innervation can occur which will increase sensation.

**Effects of overgranulation**

Although relatively minor in both prevalence and size, overgranulation can have a profound impact on healing and patient well-being, as well as resulting in frustration for clinicians.

Granulation tissue is highly vascularised but lacks a protective epithelial layer — it therefore tends to remain moist and is unable to withstand even minor trauma. In an affected wound, overgranulation tissue will be proud of the surrounding epithelium, making it prone to damage from contact (i.e. rubbing) with dressings and clothing. Similarly, leakage of haemorrhagic exudate can lead to painful periwound maceration and soiling and can require the prolonged use of protective and absorbent dressings.

The moist wound surface of granulation tissue, combined with the excellent vascularisation that provides oxygen and nutrients to the tissues, provide an ideal environment to support the growth and migration of keratinocytes. However, this environment is also ideal for bacterial colonisation and the formation of biofilms. The presence of bacteria within tissue further adds to exudate production and can cause offensive odour, infection and delays in healing.

Wounds exhibiting overgranulation have been found to be slower in healing. This chronicity makes them more prone to infection (Nelsen, 1999) and subsequent wound deterioration. In addition, the presence of bacteria may contribute to further abnormal granulation. It has also been suggested that by forcing regenerating wound borders apart, the overgranulation tissue may increase the risk of scar tissue (Dunford, 1999).

If overgranulation occurs in wounds around or near devices, the presence of raised tissue can offer a physical barrier to device placement. For example, overgranulation around stoma wounds can prevent the close fitting of stoma flanges, gastrostomy tubes and tracheostomy tubes. This further complicates management, as exudate and effluent is able to come into intimate contact with the peristomal skin leading to breakdown.

Rollins (2000) reports that many patients feel that clinicians trivialise the impact of overgranulation.

**Causes of overgranulation**

The exact mechanism of overgranulation is unknown. However, there may be a number of contributing mechanisms, which either in isolation or together; provide an environment in which the production of excessive granulation tissue is likely to occur. The low prevalence of overgranulation makes it difficult to perform meaningful studies (in terms of patient population) from which to draw conclusive evidence on its cause and treatment (Nelsen, 1999). Perhaps because of this, although it can delay healing, overgranulation occupies a lower ranking in research priorities than many other wound-related issues (Vuolo, 2010).

The overwhelming opinion is that overgranulation is precipitated by an aberrant inflammatory response, although the precipitating mechanisms...
for this may be diverse and are highly patient-dependent.

There appear to be a number of factors that could initiate a overgranulation response:

- Infection/high bioburden
- Reaction to foreign bodies
- Mechanical/trauma
- Allergy/hypersensitivity

**Infection/high bioburden**

Critical colonisation and localised, subclinical infection have also been recognised as significant factors in prolonged wound healing (Edwards and Harding, 2004; Warriner and Burrell, 2005). This is frequently seen in chronic, hard-to-heal wounds where a cyclical process is found in which the bacterial load and interaction with the host defences stimulate an immune response, leading to increased levels of proteases. These proteases interfere with normal wound healing leading to wound chronicity.

However, the failure of a wound to heal also results in an increased opportunity for organisms to colonise it, further extending healing times. High levels of bacteria in the wound compete for nutrition and oxygen with the host tissues, and bacterially-produced proteases are released which interfere with normal repair processes. If the numbers of bacteria reach high enough levels, or the host defences are compromised, local and systemic infection can occur.

**Reaction to foreign bodies**

The presence of foreign material within a wound can lead to prolonged inflammation as the body seeks to overcome a perceived threat to tissue integrity. The decline of cotton wool as a cleansing material has seen a reduction in fibres acting as a focus of inflammation in the wound. However, many less-informed patients and informal carers continue to use shedding material as a method of coping with high levels of exudate. This can result in significant amounts of debris being left in the wound margins. Unless removed, this will act as a focus for a prolonged inflammatory response.

**Allergy/hypersensitivity**

A number of wound products, such as adhesives and some antimicrobial agents, have the potential to trigger an immune reaction in some susceptible individuals. This immune response acts as a focus of continued inflammation until the causative ingredient is removed.

**Mechanical trauma**

In some circumstances it is necessary to leave a foreign material such as a gastrostomy tube, flange or metal orthopaedic pin in a wound to encourage the formation of an artificial epithelialised track. Older, biological materials such as latex are associated with adverse reactions and an increased risk of high bacterial colonisation. This is supported by Hanlon and Heximer (1994) who reported a higher incidence of overgranulation in areas surrounding latex tubes than with other materials such as silicone. Therefore, more biocompatible tube materials, such as polyurethane and silicone, are recommended (Huddleston et al, 1989).

However, even when newer products are used, repeated trauma through friction and traction on the wound can still lead to inflammatory reactions (Hanlon and Heximer, 1994). Such irritation can be commonplace in gastrostomy and tracheostomy site wounds and may account for the frequency with which overgranulation is seen in these wounds. Vuolo (2010) suggests that mechanical irritation and the development of subsequent inflammation may also be the cause of overgranulation in other wounds as dressings rub on the wound interface.

The overwhelming opinion is that overgranulation is precipitated by an aberrant inflammatory response, although the precipitating mechanisms for this may be diverse and are highly patient-dependent.

**The result of prolonged inflammation, whatever the cause, may be the formation of non-cellular extracellular matrix and fibres in excess of what is required for wound healing (Dunford, 1999). In addition, the increased permeability of the capillary network leads to the formation of wound oedema. This may be amplified by the use of occlusive dressings, which prevent the evaporation of excess moisture (Hampton, 2007). Falanga (1988) suggests that there may be links between the use of occlusive dressings (such as hydrocolloids) and the development of overgranulation. This appears to be supported by Vandeputte and Hoekstra (2006), who suggest that it is the fluid within the overgranulated tissue which is the principle cause of the problem.

There may also be a relationship between the proteolytic enzymes, matrix metalloproteinases and the development of overgranulation. Sussman and Bates-Jensen (2006) suggest that an imbalance of the normal collagen synthesis and lysis previously mentioned could result in the unchecked proliferation of collagen leading to hypergranulation formation.

**Treatment options**

Little research has been carried out into the treatment of overgranulation and, thus, management regimens tend to develop out of clinicians’ anecdotal experience, which obviously varies considerably. To date, there is no consensus on the best way to manage these wounds. However, as with all wound issues, the implementation of any management regimen should be preceded by a thorough and holistic assessment of the patient and the presenting problems. Where possible, the causative factors should be eliminated, or their impact on the wound healing cascade minimised. For example, if localised inflammation is precipitated by repeated mechanical trauma from dressings and appliances, it is important to ensure that these are correctly secured (Vuolo, 2010).

Similarly, if the principle cause of overgranulation is poor moisture...
control and oedema, steps should be taken to manage this. The use of higher absorbency or less occlusive dressings enable improved exudate management, thereby preventing tissues becoming saturated with fluid (Dunford, 1999). The application of local pressure may also assist in forcing fluid out of the tissues and so ‘flattening’ any raised areas (Harris and Rolstead, 1994; Williams 1999; Rolins, 2000). This effect may, in part, account for the success of foam-based dressing materials, however, in certain situations (for instance in wounds around stoma sites), this may be difficult to achieve.

**Antimicrobial agents**

If the precipitating factor is the presence of high bacterial burden, either as critical colonisation or local, sub-clinical wound infection, there is a need to redress the bacterial balance. Systemic antibiotics are effective in reducing bacterial load but may be associated with systemic complications and are not indicated for the treatment of colonisation and localised wound infection (World Union of Wound Healing Societies [WUWHS], 2008; Best Practice Statement, 2010).

Topical antimicrobial products have a more localised effect and may be effective at reducing bacterial burden without affecting systemic flora. This makes them an effective tool in wound care, however; their use should be limited to a 10–14-day period (WUWHS, 2008; Best Practice Statement, 2010). In the management of overgranulation, topical antimicrobial products include povidone-iodine, cadexomer-iodine, silver and honey-based dressings (Leak, 2002; Hampton, 2007).

**Caustic preparations**

Historically, caustic preparations have been used to ‘burn back’ overgranulation tissue. The principle products used are silver nitrate sticks but these have a number of disadvantages, including damage to the surrounding skin and pain (Harris and Rolstad, 1999). They can also promote tissue necrosis, which represents a further site of potential inflammation (Nelson, 1999) and infection, and can cause systemic effects if used over a wide area (Rolins, 2000; Dealey, 2005). Caustic preparations are no longer recommended by many clinicians and only tend to be used as a last resort when all other options have failed (Griffiths et al. 2001; Hampton, 2007).

**Steroids**

In the absence of infection, the use of topical steroids should be considered (Vuolo, 2010). These can effectively dampen the inflammatory response and reduce the production of overgranulation tissue (National Institute for Health and Clinical Excellence [NICE], 2004). Corticosteroids modify the functions of the epidermal and dermal cells and leukocytes that participate in proliferative and inflammatory skin diseases. After passage through the cell membrane, corticosteroids react with receptor proteins in the cytoplasm to form a steroid-receptor complex. This complex moves into the nucleus, where it binds to the cell's deoxyribonucleic acid (DNA). DNA forms the ‘blue-print’ for the cell and so determines its activity and function. However, DNA is locked within the cell nucleus. The cell therefore requires a messenger which can take the code from the nucleus to the various organelles of the cell. This function is undertaken by messenger ribonucleic acid (mRNA). The binding of the steroid-receptor complex to DNA changes the replication of mRNA, (a process called ‘transcription’), altering the message given to the organelles of the cell.

As mRNA acts as a template for protein synthesis, corticosteroids can either stimulate or inhibit the synthesis of specific proteins. For example, corticosteroids are known to stimulate the production of lipocortin, which inhibits the activity of phospholipase A2 (an enzyme that mediates the inflammatory response), and inhibits mRNA responsible for interleukin-1 (IL-1) formation. IL-1 is a cytokine which possesses a wide spectrum of metabolic, and physiological activities, and plays one of the central roles in the regulation of the immune responses. Of particular relevance in the formation of overgranulation tissue, in vitro and in vivo studies of IL-1 have shown it to induce proliferation of fibroblasts, procollagen type I and III synthesis and induce collagenase secretion.

These actions produce anti-inflammatory and immunosuppressive effects and inhibit cell proliferation (Kragballe, 1989). However, they may also impede healing, and products are often contraindicated for use on open wounds (Young, 1995). Licensed usage should always be checked.

**Haelan® Tape**

One product that may be of benefit due to its clinical effect, ease of use and suitability for many overgranulated wounds, is Haelan® Tape (Typharm). Haelan Tape is a protective, waterproof, self-adhesive polythene tape impregnated with 4ug/cm² fluoroxy cortide (flurandrenolone) (British Medical Association [BMA], Royal Pharmaceutical Society of Great Britain, 2010). Fluoroxy cortide is a fluorinated, synthetic, moderately potent corticosteroid. The product is recommended for the treatment of recalcitrant dermatoses. Examples of this type of lesion include hypertrophic scarring, pyoderma gangrenosum and overgranulation tissue around stoma sites.

The tape is designed to allow the diffusion of the steroid to the affected area over a prolonged period of time. By occluding the treated area, penetration of the steroid is enhanced, increasing its local effect. It is also possible that the pressure exerted by the tape while in situ has a positive effect on reducing overgranulation tissue (Johnson, 2007). As with other topical steroids, the therapeutic effect of the product is primarily the result of its anti-inflammatory activity.

The fluoroxy cortide contained in the tape binds to the glucocorticoid receptors found in the cytoplasm of the cell, inhibiting prostaglandins and leukotrienes, and stimulating lipocortin-1 to escape to the extracellular space. Lipocortin-1 binds to the leukocyte membrane...
receptors and inhibits various inflammatory events initiated by neutrophils, macrophages and mastocytes (such as epithelial adhesion, emigration, chemotaxis, phagocytosis, respiratory burst and the release of various inflammatory mediators). Additionally, the immune system is suppressed by a decrease in the function of the lymphatic system, a reduction in immunoglobulin and complement protein concentrations, the precipitation of lymphocytopenia, and interference with antigen-antibody binding (Reynolds and Parfitt, 1993).

Although the use of topical steroid creams and ointments to manage overgranulation has been alluded to by a number of authors (Dunford, 1999; Rollins, 2000), this can prove difficult in the clinical environment due to the additional moisture these products add to the wound bed. However, because Haelan Tape is steroid-impregnated, it is possible to cut it to fit the precise shape of the lesion and place it around devices such as tubes and stoma sites. This offers flexibility in practice (Layton, 2004).

Before application, Haelan Tape should be cut into a size that is 5mm larger than the treatment area itself. Clinicians should ensure the treatment area is dry and free from hair. The corners of the tape should be trimmed off to minimise the risk of accidental removal and the backing must be removed. Multiple strips of tape may be used to enable coverage of the entire area.

As with all steroid use, Haelan Tape should not be used for long-term treatment. Depending on the nature of the lesion being treated, the tape can remain in situ for 12–24 hours, or longer if clinical conditions dictate. If used on the face or in children, courses should be limited to five days. Cosmetics may be applied over the tape. If irritation or infection develops, the tape should be discontinued and an alternative therapy initiated. If there is no improvement observed within seven days of use, treatment with Haelan Tape should be discontinued.

Case report
Ms X was an 81-year-old woman who was referred to the complex wound clinic in May, 2008. She had a non-healing wound to her forearm following a fall over 20 weeks previously. She had initially been treated by her GP and the practice nurse, but despite the use of non-adherent impregnated povidone-iodine and foam dressings, the wound had failed to progress to re-epithelialisation. Referral to the plastic surgery department was also being considered, however, Ms X’s advanced age made this option less appealing to both the patient and the care team.

Ms X’s wound was found to be painful. There was exuberant granulation tissue present, which was bright red, soft and oedematous with a shiny appearance (Figure 1). There was no evidence of infection but the wound displayed signs of overgranulation and it was considered that control of this tissue was necessary to enable epithelial cover.

It was decided to use Haelan® Tape as this would achieve the wound care goals and be easy to administer. As well as providing the therapeutic effect of the steroid in the tape-covered area, the clinic thought that the exertion by the tape while in situ would have a positive effect on the reduction of the overgranulation tissue. In addition, the tape would protect the wound area, thus preventing damage from scratching and other irritation. The tape was cut to the desired shape and size to cover the wound and reapplied twice a week in clinic as, due to the location of the wound, Ms X was unable to apply the product herself. Over a four-week period, eight applications were administered.

The use of Haelan tape produced an excellent clinical result (Figure 2). As well as eliminating pain, the protruding oedematous granular tissue resolved and epithelial migration from the wound borders produced a closed wound. This had an immediate positive impact on Ms X’s wellbeing and surgical intervention (with all its potential risks and associated costs) was avoided.

Figure 1. Wound with granulation tissue present.

Figure 2. After treatment with Haelan Tape the wound achieved full closure.

Conclusion
An intricate balance exists within the healing wound with many processes being modulated by interconnected chemical messengers. Therefore, it is not surprising that these processes can become disrupted, leading to wound healing anomalies, including the production of overgranulation. While overgranulation is not life-threatening or life-limiting, it can seriously delay healing and result in distress for the patient.

To date, there is no consensus on the best way to treat this condition. However, in the author’s opinion, the use of an easy-to-apply steroid-impregnated tape does appear to offer clinicians a treatment that is effective and well-tolerated.

References


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