How to...
Top Q&As on the use of collagen oxidised regenerated cellulose dressings in stalled wounds

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The stalled wound can be described as one that is in a non-healing state. This usually occurs at the inflammatory stage of healing and is associated with high levels of proteases in the wound. The tell-tale signs that a wound is stalled in the inflammatory stage include a lack of size reduction and lack of granulating tissue, which is followed by a degeneration of the wound bed colour and increase in exudate, malodour and erythema in the periwound region[1].

Although this description might overlap with that of a chronic wound, a stalled wound may be an acute wound that, at a point, stops healing without any obvious cause, even though it is being managed appropriately (i.e. control of bioburden, correct moisture balance, appropriate dressing selection, offloading where necessary, proper dressing technique, good patient nutrition, control of comorbidities, and control of oedema)[1].

It has been suggested that activated neutrophils are present in the wound bed of stalled wounds, which results in the stimulation of matrix metalloproteinases (MMPs). In turn, MMPs contribute to extracellular matrix damage that delays or stalls healing[2,3]. MMPs preferentially break down the proteins which form the extracellular matrix of tissues.

In normal wound healing, the proteases assist in the removal of damaged tissue, especially the extracellular matrix. MMPs are produced by inflammatory cells (macrophages and neutrophils) and wound cells (epithelial cells, fibroblasts and vascular endothelial cells). When first synthesised, MMPs are latent. Once activated by other proteases, the MMP binds to its protein substrate(s). Tissue inhibitors of metalloproteinases (TIMPs) inhibit activated MMPs and block the activation of pro-MMPs; in normal healing, TIMPs dampen down the activity of proteases once the required amount of damaged tissue has been removed[4].

Different proteases in the wound exudate of stalled wounds act in tandem in the degeneration of soft connective tissue constituents. Therefore, it might be deduced that wound exudate containing these proteases directly contributes to stalling the wound healing progress[5]. In this situation, in order to achieve therapeutic efficacy, the clinician's goal is to modify the wound environment to readdress the protease imbalance[6].

There are now dressings available that can modulate protease activity in the wound. However, they do not all work in the same way, so it is important that the clinician understands the differences between them. Some classes of protease-modulating dressings directly interact with the wound and bind to and inactivate MMPs, while others target exudate, removing proteases through sequestration.

Collagen and oxidised regenerated cellulose (ORC) dressings have been portrayed as having the ability to 'mop up' excess MMPs and significantly reduce the activities of neutrophil-derived elastase, plasmin, and MMPs[6,7].

Promogran™ is a collagen/ORC dressing that binds and inactivates proteases (in particular MMP 2 and 9, in addition to elastase) and absorbs oxygen free radicals and excess metal ions. When the collagen/ORC matrix comes into contact with fluid/exudate in the wound, it absorbs the liquid to form a soft gel. This allows the dressing to conform to the wound shape and come into contact with all areas of the wound. The gel physically binds to and inactivates damaging proteases present within the wound. In addition, it binds with naturally occurring growth factors and prevents them from being broken down by damaging proteases. As the matrix slowly breaks down, the growth factors are released back into the wound in an active form, while the damaging proteases remain inactive. Promogran Prisma™ is a version of Promogran that includes silver.

TOP Q&As ON THE USE OF COLLAGEN OXIDISED REGENERATED CELLULOSE DRESSINGS IN STALLED WOUNDS

What is the evidence for using this product?

Collagen/ORC dressings have been evaluated

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in several randomised controlled clinical trials to examine their performance in diabetic foot ulcers, pressure ulcers and venous leg ulcers.

Diabetic foot ulcers

A systematic review of collagen-based wound dressings for the treatment of diabetic foot ulcers was conducted by Holmes et al, who reported the following studies on collagen/ORC[8].

Lobmann et al undertook a randomised, controlled trial involving 33 patients with chronic diabetic foot ulcers who were either treated with a collagen/ORC dressing (Promogran; *n*=18) or received standard wound care (*n*=15) for 8 days. A significant reduction in the ratio of MMP-9 to TIMP-2 was seen in the treatment group, and wounds reduced in size to a greater extent than in the control group (16% vs 1.65%)[9].

In a randomised control trial undertaken by Motzkau et al, 19 patients with chronic diabetic foot ulcers were treated with a collagen/ORC dressing changed daily (*n*=13) or standard wound care (*n*=6). After 5 days, MMP-2 levels were significantly lower in the collagen/ORC group (*P*=0.043), and there was a significant reduction of the wound area in this group (P=0.003); 68% of patients in the collagen/ORC cohort showed wound healing within 28 days while there were none in the control cohort[10]. The authors concluded their data supported the potential role of collagen/ORC as a wound dressing and that modulation of MMPs appeared to be beneficial in the treatment of chronic diabetic wounds.

In another randomised prospective controlled multicentre clinical trial, Veves et al treated 276 patients with diabetic foot ulcers with either collagen/ORC (Promogran; *n*=138) or standard treatment (saline moistened gauze; *n*=138) and a secondary dressing. More wounds achieved complete healing with Promogran treatment, especially in wounds of less than 6 months duration (45% vs 33%; *P*=0.056). In those with wounds of at least 6 months duration, similar numbers of patients healed in the Promogran and control groups. Patients and clinicians expressed preference for Promogran compared to standard treatment[11].

In Holmes et al's[8] systematic review, the authors concluded that although 'there is no evidence to support that collagen products should replace the gold standard of diabetic wound management … wound dressings containing collagen do appear to have some benefit in the treatment of diabetic foot ulcers and should be carefully considered by clinicians that manage wounds.'

Further studies have been conducted on use of collagen/ORC dressings in diabetic foot ulcers. A randomised, prospective, controlled, clinical trial was conducted in 40 patients with a neuropathic diabetic foot ulcer of at least 6 weeks duration. One group (*n*=20) received treatment with a protease-modulating dressing (Promogran); while the control (*n*=20) received standard treatment. Patients were followed up for 6 weeks. A significant number of wounds achieved complete healing with Promogran (63% vs 15%; *P*<0.03) and healing time was shorter (23.3 vs 40 days; *P*<0.01) in comparison to moist wound healing[12].

Another randomised, prospective, clinical study examined 51 patients with chronic diabetic foot ulcers ≥2.5cm who had previously been treated only with moist gauze. Patients were randomly split into three groups. One group was treated with collagen/ORC (Promogran), one with autologous growth factors and the third group with a combination. Collagen/ORC was more effective at reducing ulcer size than autologous growth factors, although this difference was not statistically significant. However, the combination of both these products was significantly better than either alone (*P*<0.001)[13]. The authors concluded that protease-modulating dressings act synergistically with autologous growth factors and enhance their efficacy in diabetic foot ulcers.

Venous leg ulcers

Three studies have been conducted on use of these dressings in venous leg ulcers. In a randomised, prospective, controlled, multicentre, clinical trial (*n*=73) by Vin et al, 37 patients with stagnating venous leg ulcers were allocated to collagen/ORC (Promogran) and 36 to a non-adherent dressing (Adaptic), with a secondary dressing of gauze followed by short-stretch (inelastic) compression, and followed up for 12 weeks. More leg ulcers were considered to be healed or improved in the collagen/ORC cohort (62% vs 42%; *P*=0.079), while a significant reduction in wound area was achieved with Promogran over the Adaptic group (*P*<0.0001)[14].

A randomised prospective controlled clinical trial into short-term healing involving two cohorts with chronic venous leg ulcers (*n*=30; *n*=10) compared collagen/ORC (Promogran) with moist wound healing for 2 weeks. The authors concluded that the collagen/ORC cohort showed a significant improvement in quality of healing and pain levels[15].

Smeets et al measured the effect of a collagen/ORC dressing (Promogran) on proteases. The study population was divided into two cohorts who received either a hydrocolloid dressing alone (n=10) or ORC/collagen plus a hydrocolloid dressing (n=17).

In wounds treated with collagen/ORC, a significant decrease in elastase and gelatinases was shown in comparison to the control (P<0.05). There was no significant difference in MMP-2 concentrations between the two groups[16].

Pressure ulcers

In a randomised prospective controlled clinical trial (n=80) of pressure ulcers, patients were randomised to ORC/collagen (Promogran) or conventional dressings. More wounds achieved complete healing when treated with collagen/ORC (90% vs 70%), within shorter healing times, than the control [17]. The cost-effectiveness balance was found to be more advantageous in the treated group.

Cost-effectiveness

A study conducted across four European countries investigated whether using 'good wound care' and collagen/ORC dressing (Promogran) would be more cost-effective than good wound care alone in treating non-superficial diabetic foot ulcers. Country-specific treatment costs were used to estimate the incremental cost per ulcer-free day gained over 12 months.

Within the first three months of treatment, 26% of ulcers in the Promogran cohort healed compared with 20.7% in the good wound care cohort. The authors concluded that the dressing was found to be cost-effective for the treatment of neuropathic foot ulcers in all four countries[18].

Limitations

The limitations of these studies (e.g. population size, industry funding, etc.) should be weighed against the results prior to reaching any conclusions, or implementing or changing any protocols in clinical practice.

The manufacturer's website (http://www.systagenix.ae/our-products/lets-promote/promogran-263/evidence) lists five level one evidence papers, while the International Network of Agencies for Health Technology Assessment (2011) suggests that 'more clinical research is warranted to provide further additional evidence'[19].

A validated tool, such as the Critical Appraisal Skills Programme (http://www.casp-uk.net/), can aid the clinician in assessing the value of such evidence.

When should I use the product?

Collagen/ORC is indicated in stalled and chronic wounds that are free from necrotic tissue and any signs of clinical infection[20]. These dressings can be used for the treatment of exuding wounds including diabetic foot ulcers, venous leg ulcers and pressure ulcers. In practical terms, if a patient presents with a wound that has shown little change in the appearance of the wound bed or edges, and the size has remained the same, collagen/ORC dressings should be considered. The aim of the treatment is to kick start healing in a stalled wound.

Collagen/ORC dressings modify the wound environment by reducing factors that have been shown to be of detriment to wound healing. The dressings remove excess proteases and oxygen free metal ions, and also protect positive substances in the wound, such as growth factors[21]. The dressing turns into a biodegradable gel when in contact with wound exudate, which in turn binds and inactivates excess MMPs[7].

Where there are signs of local or low-grade infection, or a history of recurrent local infection, a collagen/ORC dressing that contains 1% silver and an increased amount of collagen/ORC is recommended (such as Promogran Prisma)[22].

It may also be appropriate to use a silver collagen/ORC dressing if there has been a history of recurrent local infection, when the dressing can be used as a preventative measure.

Clinicians must make their own judgment regarding whether or not a wound is stalled and, if it is, decide whether the wound is stalled due to excess MMPs — which is very difficult to accurately predict[23]. Although some laboratory tests are able to assess protease levels, these are not widely available to the majority of wound care clinicians[24].

The expert working group that devised the 2011 international consensus document *The Role of Proteases in Wound Diagnostics* suggests that a point-of-care protease test would be the optimum solution to lead to 'informed, cost-effective decisions about which treatment is or is not appropriate'[24].Clinicians would then have the option to utilise such a test to assist them in more accurate wound assessment and targeted use of collagen/ORC dressings[25].

In many facilities, collagen/ORC dressings are not available on the wound care formulary, often due to their higher per unit cost and the

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concern that such modalities might be used inappropriately.

However, when used appropriately, that is when applied to stalled wounds, case studies have shown this modality as being cost effective by increasing healing rates[11,12,14,15]. Furthermore, the cost-effectiveness of utilising this dressing can be enhanced by ensuring that it is used appropriately, that is, in the presence of elevated protease activity. This is facilitated by utilising a point-of-care test that establishes if actual elevated protease levels are in the wound without leaving the decision up to guesswork[26].

A case for using these products can be made if they can be shown to accelerate healing and reduce the number of dressing changes. This may be supported by evidence from clinical trials. In addition, it is important to consider quality of life factors, such as pain reduction and psychological effects of chronic wounds.

Clinicians in lead roles in wound management should ensure that such dressings are used only where indicated, based on proper expert assessment.

The UAE is ranked 15th worldwide for diabetes prevalence, with 18.98% of the population living with type 2 diabetes[27]. Due to this high incidence of diabetes, chronic and stalled wounds are often seen in our clinics in the Middle East. Collagen/ORC has been utilised in our facilities with encouraging results and, in my own experience, when utilised appropriately it allows the clinician to jump-start a stalled wound. The point-of-care test to detect elevated protease levels means it is now possible to utilise these dressings when really appropriate.

It has been shown that using collagen/ORC in conjunction with other therapies does provide for better results, such as a reduction in wound area of leg ulcers treated with collagen/ORC in conjunction with compression therapy[28].

Are there any contraindications?

Collagen/ORC dressings are not indicated if there are any active signs of vasculitis, full-thickness burn injuries, or in individuals with known sensitivity to either collagen or ORC[29]. Promogran is safe to be used under compression therapy.

Making the case for collagen/ORC

Cost-effectiveness is a strong argument to present to decision makers when introducing collagen/ORC dressing on your formulary. Ghatnekar et al conducted a study in four European countries (France, Germany, Switzerland and UK) into the early stages of establishment of collagen/ORC as an effective dressing. It was shown that the treatment was found to be cost-effective in all four countries, with further suggestions that it could even be cost saving[18].

With the introduction of the point-of-care test for elevated protease levels, guesswork has been eliminated. Clinicians now have a definitive test allowing them to properly utilise collagen ORC dressings, which provides for better results and a shorter healing time[30].

More recently, Cullen et al have provided evidence that 'early treatment of chronic wounds with collagen/ORC or collagen/ORC/silver leads to increased rates of healing. In the first 6 months of a wound, its ability to heal is greatest with the healing rate with advanced treatments such as collagen/ORC or collagen/ORC/silver as high as 70%[31].'

How should the dressing be applied?

Wound bed preparation is essential in any wound management protocol. Clinicians should follow local policy in wound bed preparation prior to applying a collagen/ORC dressing. However, if signs and symptoms of infection are present then it is suggested to treat this appropriately or use a silver collagen/ORC dressing.

The tray that the dressing is supplied in can be used to premoisten the dressing if the wound exudate level is low, for initial breakdown of the dressing. The dressing should be applied in direct contact with the wound bed. Multiple layers may be applied for deeper wounds.

The manufacturer suggests that the dressing should be changed every 72 hours, but it should be changed more frequently if exudate levels are high. It is suggested the dressing be left in place if it has not yet gelled and biodegraded. When the dressing is fully biodegraded there is no residue left on the wound bed and/or secondary dressing.

If the dressing is effective, the clinician should note a healthier wound bed colour together with reduction of exudate levels and/or slough. If the wound is progressing, the same wound management should be continued, however, the use of a non-adherent dressing may be adopted once the wound starts epithelialising.

How can we best use collagen/ORC dressings in our practice?

Any use of wound care products should be treated as any other medication or device;

collagen/ORC dressings are no exception. Clinical practice guidelines – whether local, national, or international – when based on robust clinical evidence, provide effective and appropriate recommendations. The use of collagen/ORC dressings should be governed by evidence-based practice guidelines to ensure that these dressings are used as indicated for the best outcomes with best benefit for our patients in the most cost-effective manner.

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