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ALGINATE DRESSINGS
Do they influence wound healing?

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Alginate dressings in surgery and wound management – part 1

This first article in a series of three looks at the history and use of seaweed-derived dressings

Alginates; Dressings; Literature review; Production techniques

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Alginic acid and its salts were first described and partially characterised in 1883 by Stanford,[1] a British chemist who spent many years seeking a use for the large quantities of seaweed thrown up onto the Atlantic coast of the British Isles. He had observed that the long flat fronds of one species, *Laminaria*, contained sacs of a near colourless solution which, on partial drying, formed a jelly-like substance that could be drawn out in long tenacious strings. This substance, which he called 'algin', was freely soluble in alkali but is coagulated by alcohol or mineral acids.[1] In 1881, he patented a process to extract this material for commercial use.

The viscous nature of purified alginate solutions eventually led to their widespread use as thickening and stabilising agents in the food and brewing industry – in products as diverse as ice cream and beer. A significant quantity of alginate is also used by the pharmaceutical industry in the production of controlled-release agents, bio-adhesive systems, tablet disintegrants, suspending agents and implants. It is estimated that, throughout the world, in excess of 20,000 tons of alginate are used annually for these and other purposes.

According to Gacesa,[2] most alginate is obtained commercially from three of the 265 reported genera of the marine brown algae, *Phaeophyceae*. The majority is extracted from members of the genus Macrocystis that includes the giant kelp (*Macrocystis pyrifera*) harvested off the west coast of the USA. In northern Europe alginates are extracted from horsetail kelp (*Laminaria digitata*) and sugar kelp (*L. saccharina*) collected from waters off the Outer Hebrides and the west coast of Ireland.

Although the extraction of alginates is a relatively recent invention, seaweed has been used for centuries for a variety of purposes.

Some reports suggest that it was used in China as early as 2700BC.[3] In Greek and Roman times, seaweed was used as fodder and for the production of herbal medicine. In Ireland it is known to have been exploited since at least the 12th century and from the early 1700s ash made from seaweed heated in kelp kilns was used to manufacture soap and glass as well as a fertiliser and source of iodine.

The function of alginates within the algae is thought to be primarily skeletal,[4] with the gel conferring the strength and flexibility required to withstand tidal activity in the water in which the seaweed grows.

Certain species of bacteria – including *Azobacter vinelandii* and *Pseudomonas aeruginosa* – are known to produce alginates which form a protective coating around the organism but these are not used commercially.

Chemistry of alginates

Alginates occur naturally as mixed salts of alginic acid and are found primarily as the sodium form. The yield varies with the species but is typically in the order of 20-25%.

Alginates consist of a three-dimensional network of long-chain molecules held together at junctional sites. As no evidence of branching has been detected, the molecule is thought to be essentially linear.[2]

The alginate molecule is a polysaccharide formed from homopolymeric

ABSTRACT

Large quantities of alginate dressings are used each year to treat exuding wounds, such as leg ulcers, pressure sores and infected surgical wounds. Originally these dressings were a loose fleece formed primarily from fibres of calcium alginate. More recently they have been developed so that the fibres have been entangled to form a product with more cohesive structure, which increases the fabric's strength when it is soaked with exudate or blood. Some products also contain a significant proportion of sodium alginate to improve the gelling properties of the dressing in use. Other dressings have been produced from freeze-dried alginate.

Once in contact with an exuding wound, an ion-exchange reaction takes place between the calcium ions in the dressing and sodium ions in serum or wound fluid. When a significant proportion of the calcium ions on the fibre have been replaced by sodium, the fibre swells and partially dissolves forming a gel-like mass. The degree of swelling is determined principally by the chemical composition of the alginate, which depends on its botanical source.

Although it is recognised that the differences between the various brands of dressings may influence their handling characteristics – particularly when wet – it is generally assumed that these differences are of limited relevance to the dressing's performance clinically or at a cellular level. There is some evidence to suggest, however, that these assumptions may be wrong and that alginates may influence wound healing in a number of ways not yet fully understood.

This three-part review of the literature

regions of (-D-mannuronic, (M) and (-L-guluronic, (G) acid called M-blocks and G-blocks interspersed with regions of mixed sequence, MG-blocks. Methods for characterising the structure and molecular weight of alginates were published by Johnson et al,[4] who examined five different samples of alginate and found that their MG ratios ranged from 42% to 63.6% with molecular weights from 12,000 to 180,000.

The relative proportions and arrangement of the M, G and MG blocks have a marked effect on the chemical and physical characteristics of the alginate and therefore any fibre made from it. These properties are determined by the seaweed's botanical source. Even within species, some seasonal variations have been reported, particularly in Laminaria, where alginates were found to have a higher proportion of mannuronic acid in the summer.[4]

Regions in which the M-blocks predominate form an extended ribbon-like molecule, analagous to cellulose, whereas regions rich in G-blocks form a 'buckled chain'.[2] All the block structures are capable of forming ionic bonds with di- or multivalent cations, but regions containing G-blocks are also able to chelate the metal ions, because of the spatial arrangement of the ring and the hydroxyl oxygen atoms, thus forming a much stronger interaction.

It is this interaction between the polyguluronic acid blocks that is responsible for the nature and strength of the gel that is formed when solutions of sodium alginate come into contact with divalent metal ions such as calcium. The calcium ions cross-link the polymeric chains producing an eggbox-like structure in which the calcium ions represent the eggs within the convoluted polysaccharide chain.[5] The higher the content of guluronic acid in the alginate, the greater the interaction and the more stable and harder the resultant gel.

The calcium ions present in high-M alginates are less firmly attached to the molecule so are more easily replaced by sodium ions, resulting in increased fluid uptake and fibre swelling and faster gel formation. Therefore, high-M alginates are more absorbent on a gram for gram basis and form softer gels than those rich in high-G. They are also more readily soluble in saline solution.

Alginate dressings function by interacting with exudate to form a gel on the wound surface. In this way they produce the moist wound healing conditions that Winter showed were able to reduce healing times of wounds in his animal model.[6]

The differences in gel structure and rheology caused by the differences in chemical structure have important implications for the product's clinical use.

The soft gel residues from products made from high-M alginates can be washed out of the wound or irrigated out of sinuses or cavities with a jet of saline, but the fibres in dressings made from high-G alginates swell only slightly in the presence of wound fluid and may appear relatively unchanged even after an extended period. Such dressings are therefore usually removed in one piece using a forceps or gloved hand.

By carefully controlling the manufacturing process, it is possible to produce alginates in which some of the calcium ions are replaced by sodium in order to accelerate the gel-forming process. These are known as calcium/sodium alginate,[5] and can be produced both from alginates with a high guluronic acid content, such as Kaltostat, and high mannuronic acid content, such as Kaltogel.

Production of alginate dressings

Alginate is extracted from washed, milled seaweed using an aqueous alkali solution, which results in the formation of alginate 'dope', a crude viscous colloidal solution of sodium alginate. This is clarified by filtration and the alginate subsequently precipitated by the addition of calcium chloride. The resultant gel is washed with acid before being redissolved in sodium carbonate solution from which sodium alginate is obtained by a drying and milling process.[5]

If a solution of sodium alginate is extruded under pressure through a fine orifice into a bath containing calcium ions, an ion-exchange reaction takes place resulting in the formation of fibres of insoluble calcium alginate. Although a

METHODOLOGY FOR ALGINATE DRESSINGS LITERATURE REVIEW

For the purpose of this review, information on alginates was gathered from numerous sources. These included the internet and various electronic databases, particularly Medline and Bids, using free-text searching for references containing the words alginate, alginic acid, or proprietary names of known alginate dressings. This resulted in hundreds of references, most of which were not relevant to the current project. Combining these search terms with secondary terms such as wound, healing and ulcer, reduced the number of hits to manageable proportions. These were then downloaded and inserted into a reference management system, Endnote (Niles Software), for further examination.

In addition to the electronic sources, some references were obtained from manufacturers of alginate dressings and many more were obtained by examination of the existing literature and citations in papers already collected. References in languages other than English were generally, but not always, excluded.

While every effort has been made to make the reference list as comprehensive as possible, it is accepted that some potentially important publications may well have been overlooked.

In an attempt to keep the citations to a reasonable number, in the section on the possible biochemical activity of alginates, general references on TNF, interleukins, etc have not been included as they are not directly relevant to the subject area. However, papers that describe the possible stimulatory activity of alginates have been fully referenced.

encompasses the history, origin, structure, chemistry and clinical applications of alginates and alginate dressings.

This review reveals that, despite their widespread use, alginates have been the subject of very few well-controlled clinical studies. There is fairly convincing evidence, however, that they do offer advantages over more traditional dressings for at least some clinical indications. It has also become obvious that there is a general lack of understanding about the importance of secondary dressing systems that must be used in with alginate dressings.

Careful examination of the design and outcomes of the published studies suggests that the choice of both the primary alginate dressing and the secondary dressing can play a major role in determining treatment outcomes.

In 1995, the *British Pharmacopoeia* (BP) published monographs for alginate fibre[14] and alginate dressings.[15,16] These include simplified methods for assessing gelling, wet integrity and fluid handling properties. It is anticipated that these test methods will shortly form part of a new European Standard for these materials.

The BP monograph classifies alginate dressings both in terms of their absorbency and their ability to maintain structural integrity when wet. Flat dressings are described as high absorbency if they retain more than 12g of Solution A per 100 cm^2. For cavity wound dressings the limit is 6g/g.

The absorbency values quoted for flat dressings are expressed as g/unit area rather than g/g because dressings are used as individual pieces of standard size as supplied by the manufacturer regardless of their weight. This is a more clinically relevant than the figures quoted previously.[11]

Previously unpublished values for the absorbency of alginate dressings together with results of the dispersion test, determined by the BP methods, are shown in Table 1. This table also includes results for two other fibrous absorbents that are used for similar clinical indications and are therefore included for comparison purposes. In normal use, those products that maintain their integrity are removed from a wound in one piece, those products that do not can be irrigated away with saline.

The results shown in this table are typical of those obtained with a dressing sample not subjected to any form of pressure. In the clinical situation, however, the use of compression bandages may substantially reduce the absorbent capacity of the individual products.

High-G alginates generally form wet integral or non-dispersible dressings, and high-M alginates dispersible dressings. The situation has been made a little more complicated, however, by the production of high-M alginates, for example Tegagen, that are subjected to a fibre entanglement process that limits the ability of the fibres to swell and thus disperse during the integrity test.

Early use of alginate wound dressings

Although the literature contains isolated historical allusions to the early use by sailors and others of seaweed as a dressing,[17-19] these are generally not well referenced and no authoritative medical texts have been found that confirm its use in this way. Given the range of materials that have been used in wound management, however, it would be surprising if seaweed had not been used.

The first person in modern times to recognise the potential value of alginates in surgery and wound management was George Blaine, a major in the Royal Army Medical Corps. He showed them to be absorbable in tissue, sterilisable by heat, and compatible with penicillin.[20] He also described how he had used alginate films clotted *in situ* for the treatment of wounds and burns in troopship hospitals in the Far East and described the use of alginate, sometimes in combination with plasma as an alginate-plasma film, as 'puncture patches' over scleral defects.

During a subsequent assessment of the use of alginates as haemostats and wound dressings, Blaine reported their apparent lack of toxicity following a series of animal studies in which fibres were implanted into animal tissues, and gels made from alginates were used to treat experimentally produced burns.[21] Clinical studies followed, and the successful use of alginate-derived materials in aural surgery and neurosurgery was reported by Passe and Blaine[22] and Oliver and Blaine[23] respectively.

Other, more general, applications were described in 1948, when the results of a three-month trial into the use of alginate in the casualty department of Croydon Hospital were reported by Bray et al.[24] In this study, alginates – in the form of films, wool, gauzes, and clots (formed *in situ* by mixing sterile solutions of calcium chloride and sodium alginate) – were applied to a wide range of wounds, including burns, lacerations, ulcers and amputations. In all cases, healing was rapid and uneventful.

According to the results of a survey carried out by Stansfield and reported by Blaine,[25] in the late 1940s and early 1950s, alginates were being used in some 70 hospitals over a range of surgical specialties.

Overall, they were found to be highly satisfactory in use. Where criticisms were recorded, they were directed mainly at the poor absorption properties of the material and its consequent tendency to induce fistula formation. It was noted that most of these criticisms related to cases in which the product had been used as packing for large cavities or dead spaces, a function for which it was never originally intended.

Following the early work of Blaine and others, a number of commercial medical alginate products were produced, including an absorbable swab called Calgitex. When the large-scale manufacture of alginate fibre ceased in the early 1970s, for reasons described previously, this product was discontinued owing to the high cost of production.

The first clinical reports recording the use of Sorbsan were published in 1983 when Fraser and Gilchrist[26] and Gilchrist and Martin[18] described their experiences with the dressing in the management of foot disorders and a variety of skin lesions, following a clinical evaluation in a group of hospitals in the Sunderland area.

The results of these studies were very positive and supported the findings of Blaine some 40 years earlier. Further papers described the use of Sorbsan in the management of problem wounds including infected traumatic wounds and leg ulcers.[27,28] In 1986, a second product, Kaltostat, was launched and in 1988 alginate dressings finally gained widespread clinical acceptance when Sorbsan was included in the Drug Tariff.

Current use of alginate wound dressings

Several reviews have been published on alginates[2] and alginate dressings[29-32] and the literature also contains numerous references to their use.[19,27,33-40] Imamura et al[41] described how a calcium/sodium alginate dressing was successfully applied to extensive areas of skin loss caused by toxic epidermal necrolysis that had spread from the scalp to the lower extremities and suggested that the dressing could be used to treat other disorders with widespread detached epidermis such as auto-immune blistering diseases.

Cannavo et al[42] compared the performance of three different dressings in the management of 36 dehisced surgical abdominal wounds. These were a standard alginate; a gauze moistened with sodium hypochlorite (0.05%); and a combined dressing pad. The latter consists of an absorbent pad to which is added a semi-permeable film dressing.

No statistically significant differences in healing rates between the three treatment groups were detected but there was a trend for the combined dressing pad protocol to produce a greater reduction in wound area. Maximum pain was sig-

method of manufacturing calcium alginate fibre was first disclosed in a patent in 1898, production of the material on a commercial scale only became possible after the publication of a further series of patents in the 1930s.

The fibre produced at that time was used principally in the textile industry as a soluble yarn, that would dissolve in a scouring process. It was used as a support during the manufacture of fine lace, or as draw threads in the production of hosiery.[7] Fabrics made from alginate fibre were also once produced commercially for their fire-resistant properties, a feature of their high metallic content,[5] and for the manufacture of bags used to transport soiled hospital linen that were designed to dissolve in the wash. By the 1970s, they were replaced for these applications by cheaper non-flammable and water soluble fibres.

At that time, the amount of alginate fibre that was used in surgery and wound management represented only some 10% of annual production. It therefore became uneconomic to continue to produce the relatively small quantity of fibre required for medical applications. Some years later, technological advances and improvements in production techniques in the textile industry, together with an increased understanding of the mechanisms of wound healing, reawakened interest in the potential value of alginate which enjoyed a renaissance in the early 1980s.

The first of the new generation of alginate dressings was Sorbsan,[7] which was launched in 1983. It consisted of a loose fibrous fleece of calcium alginate fibres with a high mannuronic acid content.

This was soon followed by other products that differed both in their chemical composition and method of construction. The first was Kaltostat, a fibrous high-G calcium alginate. When it was introduced to the market place in 1986, Kaltostat contained traces of a quaternary ammonium compound, arquad, which was used to aid fibre handling during the manufacturing process. This was found to impart pronounced cytotoxic properties to the dressing when tested by a cell culture method. Following correspondence in the pharmaceutical press,[8-10] the manufacturing process was modified to ensure that the arquad was reduced to sub-toxic levels. Around 1988 Kaltostat was further modified to consist of a mixture of calcium and sodium alginate in the ratio of 80:20. This was done to improve the gel-forming ability of the fibres.

TABLE 1. ABSORBENCY AND DISPERSIBILITY OF DRESSINGS

Dressing	Manufacturer	Absorbency g/100cm²	Dispersion
Algisite M	Smith and Nephew Medical	18.3 (0.7)	Non-dispersible
Aquacel*	Convatec	18.5 (1.0)	Non-dispersible
Kaltostat	Convatec	21.7 (1.9)	Non-dispersible
Kaltogel	Convatec	17.9 (2.3)	Dispersible
Comfeel Seasorb	Coloplast	21.2 (2.1)	Non-dispersible
Sorbsan	Maersk Medical	16.2 (0.8)	Dispersible
Sorbalgon	Hartmann	19.90 (1.4)	Dispersible
Tegagen	3M Healthcare	24.7 (1.9)	Non-dispersible
Urgosorb**	Urgo	26.6 (3.0)	Non-dispersible

* Carboxymethylcellulose fibre **Carboxymethylcellulose/alginate blend

High-G alginates generally form wet integral or non-dispersible dressings and high-M alginates dispersible dressings. The situation has been made a little more complicated, however, by the production of high-M alginates, for example, Tegagen, that are subjected to a fibre entanglement process that limits the ability of the fibres to swell and thus disperse during the integrity test.

Alginate dressings are produced as flat sheets – used to cover superficial wounds – and as cavity fillers – usually in the form of ribbon or rope. The flat dressings are normally made in a non-woven fabric process in which the fibres are carded to form a web that is then cross-lapped to form a felt. In some products, the felt is then needled or entangled by means of high-pressure water jets to give the dressing a coherent structure.

Comfeel Seasorb (Coloplast) is somewhat different in that it is manufactured from a high M calcium/sodium alginate produced in a freeze-dried form carried on a high density polyethylene net so that the dressing superficially resembles a fine soft foam sheet.

Fibracol (Johnson and Johnson Medical), which is now discontinued, was a composite dressing manufactured from collagen and calcium alginate, also in a freeze-dried form. The rationale for the combined use of these two agents was that the alginate provided a moist wound healing environment and the collagen provide a scaffold for the newly developing tissue.

Most alginate cavity fillers are made by forming the carded web into a sliver that is then cut to length to form a loose rope or ribbon.[5]

Comparison of alginate products

The rapid proliferation of alginate dressings has made it necessary for manufacturers to seek a marketing advantage for their individual products. This is often related to an aspect of the fluid-handling properties or absorbency of their particular brand. When examining the marketing claims made by different companies, it is particularly important to take note of the fluid used during any laboratory-testing procedures.

A laboratory study published in 1992[11] compared the weight of fluid retained by different alginate dressings using water, sodium chloride solution 0.9% and Solution A, a mixture of sodium and calcium chloride containing 142mmol of sodium ions and 2.5mmol of calcium. This ionic composition was chosen because it approximates to that of blood or serum and therefore probably provides the most clinically relevant data.

Under the conditions of test, the weight of each fluid absorbed by 1g of Sorbsan was 8g, 21g and 14g respectively. With Kaltostat the results were somewhat different, 15g, 14g and 13g respectively. These variations were due to differences in the gelling characteristics of the alginate fibres, largely a function of the M:G ratio described previously.

It is also possible to prepare alginate dressings from mixtures of fibres from different types of alginates. Melgisorb (Mölnlycke), for example, consists of a blend of 60% high-M and 40% high-G alginate which is predominantly (96%) in the calcium form.

The absorbency and tensile properties of eight alginate dressings were compared in a laboratory study published by Johnson and Simpson,[12] and Ichioka et al[13] compared the gelling and fluid handling characteristics of alginates and hydrocolloid dressings using a method similar to that published previously.[11]

nificantly greater (p = 0.011) and satisfaction significantly lower among patients who received the sodium hypochlorite treatment. The associated treatment costs were also substantially higher for this group of patients. The authors concluded that the use of sodium hypochlorite soaked dressings for surgical wounds should be abandoned.[42]

Berry[43] compared Kaltostat with a polyurethane foam dressing (Allevyn, Smith and Nephew) in the management of patients with non-infected cavity wounds. Both dressing regimens were found to be easy to use, effective and acceptable to patients and clinicians.

Patients with gaping abdominal wounds following caesarean section[44] and radical vulvectomy[45] were also managed successfully with alginate dressings. A patient with a 10-year history of heroin abuse and multiple ulcerations to his upper arm had his wounds dressed with a calcium alginate rope and covered with a four-layer bandage. Dressings were changed weekly and during treatment the patient remained heroin free. Complete healing was achieved in 42 days.[46]

It has been suggested that alginates have a role in accident and emergency departments as an alternative to paraffin tulle dressings.[47]

In the treatment of 'road rash' and other similar abrasions, following surgical toilet they have been applied moistened with a solution of bupivacaine with adrenaline (20 ml 0.05% with 1:200 000) to provide initial pain relief and reduce bleeding.[48] When covered with paraffin gauze, Gamgee tissue and a bandage, the dressing may be left undisturbed for up to 10 days.

Composite dressings containing alginate have been developed in a variety of forms that include simple adhesive island dressings (Kaltoclude) to absorbent pads with an alginate wound contact layer (Sorbsan Plus). An alginate-faced dressing containing activated charcoal for use in the management of malodorous wounds has also been developed and the results of a laboratory-based evaluation to compare the performance of this dressing with other charcoal dressings has been described in the literature.[49]

The results of a small study to assess the performance of an alginate/film combination, Kaltoclude (now discontinued), were published by Moody,[50] who concluded that although the dressing is not suitable for wounds that produce copious amounts of exudate, it was satisfactory for moist chronic wounds that produce low to moderate levels of exudate. ■

■ *Part two of this review on 'The use of alginate dressings in specific types of wounds' appears in next month's issue.*

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Alginate dressings in surgery and wound management: part 3

This final article in the series looks at the functioning of seaweed-derived dressings at a cellular level, as well as the importance of choosing appropriate secondary dressings

Alginates; Biocompatibility; Dressings; Literature review;Toxicity

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Alginate dressings offer advantages over more traditional dressings, at least for some clinical indications. However, there have been relatively few well-controlled clinical studies investigating their biocompatibility with wound tissue, and the effects of secondary dressings in determining treatment outcomes. These key areas are addressed in this third and final article in the series.

Biocompatibility

In a comparative study of the properties of three modern haemostatic agents used in current surgical practice, Blair[1] found Kaltostat to be more effective than either oxidised cellulose or porcine collagen in controlling bleeding from a surgically inflicted wound in rabbit liver. In addition, the alginate showed no tendency to cause intestinal obstruction when implanted into mesentery. By contrast, rabbits receiving porcine collagen had to be sacrificed. After six weeks, the oxidised cellulose had completely dissolved, but histological examination of the wound sites treated with alginate showed some evidence of calcium deposition and some fibrous reaction. It is possible that the fibrous reaction was due, in part, to the presence of Arquad, a quaternary ammonium compound added to the fibres to assist in the manufacturing process.

In another animal study, Lansdown[2] implanted samples of Kaltostat subcutaneously in rats to evaluate their biodegradability and ability to evoke local tissue reactions. Implant sites were evaluated after 24 hours, seven days, 28 days and 12 weeks. Histological sections showed no noticeable degradation of the alginate within the three-month observation period.

Although there was an initial modest foreign body reaction, after this had subsided the implants became embedded in thin fibrous sheaths, which were infiltrated with vascular channels and fibroblasts. The authors concluded that Kaltostat fibres in the rat model presented no obvious toxic risk or contraindication to their use as wound dressings or as haemostatic agents in general surgery.

A novel freeze-dried alginate gel dressing (AGA-100) was compared with extracts prepared from Kaltostat and the latter was found to induce cytopathic effects when tested *in vitro* on L929 cells (mouse fibroblasts).[3] In a second *in vivo* study, samples of both alginates— together with cotton gauze — were applied to circular full-thickness wounds on the backs of pigs. Wound tissue was harvested on day 18 for histological examination. The wounds dressed with AGA-100 showed rapid wound closure compared with the control wounds, dressed with Kaltostat and cotton gauze. Foreign-body reaction was marked in Kaltostat and gauze-treated wounds, but not in the wounds dressed with AGA-100. Based on these data, the authors conclude that use of AGA-100 could reduce cytotoxicity to fibroblasts and foreign body reactions that have been observed with currently available calcium alginate.

Cellular effects

It has been observed that alginate-based microcapsules containing islets of Langerhans used as a bioartificial pancreas produce a foreign body reaction with fibrosis in an animal model. Pueyo et al[4] demonstrated that macrophage cells involved in this process could be produced from monocytes activated by alginate-polylysine microcapsules *in vitro*.

Otterlei et al[5] compared the ability of alginates to stimulate human monocytes to produce three important cytokines – tumour necrosis factor-a (TNF-a), interleukin-1 and interleukin-6. They reported that high-M alginates (high in mannuronic acid) were approximately 10 times more potent in inducing cytokine production than high-G alginates (high in guluronic acid) and therefore proposed that mannuronic acid residues are the active cytokine-inducers in alginates.

Other authors have also produced evidence to suggest that it is the b(1→4) glycosidic linkage (M blocks) rather than the a(1→4) linkage (G blocks) that is responsible for cytokine stimulation and anti-tumour activity. These b(1→4) bonds are found linking D-glucuronic acid in C-6-oxidised cellulose, which also has demonstrable TNF-a-stimulating activity, although this is limited compared with that of alginate rich in mannuronic acid.[6] Unpublished data from Shalby et al, cited in a review by

Skjak-Braek and Espevik,[7] records that b(1→4)-linked uronic-acid polymers such as poly M are potent cytokine inducers *in vivo*, able to protect mice against lethal infections with *Staphylococcus aureus* or *Escherichia coli*. It is also stated that they can provide a marked degree of protection against lethal irradiation by increasing the production of myeloid blood cells as a result of stimulating haematopoietic cells in the bone marrow. Further evidence for the importance of high concentrations of M blocks comes from the finding that treatment of alginate with a high mannuronic acid content with C-5 epimerase (which converts b-D-mannuronic acid into a-L-guluronic acid) results in a loss of TNF-inducing ability.[7]

Zimmerman et al[8] and Klock et al[9] disputed the difference in activity of M and G alginates following studies in which they tested different types of alginates for mitogenic activity both *in vivo* and *in vitro* before and after purification by free-flow electrophoresis and dialysis. They found that material treated in this way lost all its mitogenic properties regardless of the M/G ratio of the raw material, and suggested that this activity could be partly due to oligomers of mannuronic or guluronic acids. They also identified positively-charged fractions with strong mitogenic activity that they proposed was related to lipopolysaccharide (LPS) molecules, but this observation is not in accord with the earlier work by Otterlei et al,[6] who demonstrated that mitogenic activity in alginates was not inhibited by the addition of Polymixin B, which they showed was able to inhibit LPS-induced cytokine production.

LPS consists of a lipid A, a core oligosaccharide and a polysaccharide part of varying size and complexity. In their review Skjak-Braek and Espevik[7] state that LPS and poly M alginate share a common binding site on the macrophage, reacting with the membrane protein CD-14, which is believed to have a broad specificity for compounds rich in various types of sugar residues. They also report that the binding of poly M and LPS to monocytes can be inhibited by addition of G-blocks. Unlike LPS, which can stimulate cells that do not express membrane CD-14, poly M is unable to stimulate cell types that lack this membrane protein. Skjak-Braek and Espevik suggest that poly M could activate the non-specific immune system, thus increasing protection against various types of infections.

The effect of calcium alginate dressings on other cell types was investigated by Doyle et al,[10] who showed that low concentrations of an extract of one alginate dressing (Sorbsan) stimulated human fibroblasts on extended contact but decreased the proliferation of human microvascular endothelial cells and keratinocytes. They proposed that this activity could be due to calcium ions released from the dressing during the gelling process.

Assessment of alginates

Despite the substantial number of alginate dressings now being used, this three-part review has identified relatively few publications that provide robust statistically convincing evidence to justify their use in any particular type of wound. The randomised trials that have been performed have often provided conflicting results, or are of limited value for other reasons (e.g., the comparator dressing is not widely used in clinical practice in the UK, or the way in which dressings were applied adversely affected their performance).

Any evaluation of the use of alginates in wound care is made particularly difficult because there is no such thing as a 'standard' alginate dressing. Alginates, even those derived from a single species of seaweed, are subject to minor variations in composition and structure; this variation can be considerable when products from different species are compared.

Variations in the M:G ratio will influence the nature of the gel formed when the dressing is applied to an exuding wound. A high-M product, particularly if it contains a proportion of sodium alginate, will form a thick, soft gel as the fibres take up liquid and swell. A high-G alginate, particularly one composed entirely of calcium alginate, will change very little as it absorbs exudate, as the degree of swelling of the individual fibres is very limited.

It is tempting to speculate that as the high-M alginate fibres swell they could absorb agents in wound fluid, such as bacteria, proteolytic enzymes and toxins, that have a deleterious effect on the healing process. This effect would occur to a much lesser extent with fibres that swell only slightly.

It is also not unreasonable to suppose that a fibre that gels readily and dissolves more easily in biological fluids would be eliminated from tissue more quickly than one which resisted the dissolution process. In 1949, Rumble[11] recognised the importance of selecting the right type of alginate for treating haemorrhage following tooth extraction to ensure rapid absorption of the fibre. Few, if any, authors of the more recent clinical papers appear to be so aware of the differing characteristics of alginates, or to recognise their importance.

It is interesting that most implantation studies involving alginates have been conducted using a high-G alginate. The fluid-handling properties of alginate dressings have been discussed in some detail, particularly the importance given to the absorbency values determined experimentally. It is not uncommon to read that alginates are suitable for the management of heavily exuding wounds because they absorb up to 20 times their own weight of fluid. While it is true that they are capable of taking up many times their own weight of fluid, a standard 10x10cm alginate dressing only weighs about 1g, therefore the total amount of fluid that it can absorb will be limited.

To put this into context, leg ulcers have been found to produce up to 0.5ml of exudate/cm^2/24 hours (h) – in the presence of infection this may double. For a 20cm^2 wound dressed with a single piece of alginate dressing measuring 10x10cm, this equates to the production of 10–20ml of fluid a day.

The fluid-handling capacity of alginate dressings ranges from about 15–25g/100cm^2 (*not* grams per gram). Under a compression bandage this may be reduced to 5–10ml. Therefore, a standard 10x10cm dressing would not be able to cope with the exudate produced from a 20cm^2 wound for more than about 12 hours. A standard film dressing, which has a maximum moisture-vapour transmission rate (MVTR) of approximately 1,000g/m^2/24h[12], applied over an alginate sheet, allows for the loss of another 5g of fluid in 24 hours. This makes a total fluid-handling capacity for an alginate/film dressing combination of 10–15ml in the first

day, which is still less than the volume of fluid produced by a heavily exuding leg ulcer or donor site. On the second day, however, the alginate dressing, being fully saturated, would be unable to absorb any more exudate so fluid would rapidly accumulate beneath the dressing, resulting in leakage and/or maceration of the surrounding skin.[13]

The application of an 'intelligent' film dressing over a sheet of alginate might partially resolve such problems. In the presence of liquid, such films have an MVTR of 5,000–10,000g/m^2/24h, which greatly enhances their ability to cope with exudate production. As the wound begins to dry, the MVTR of the film would decrease and thus help to preserve moisture in the alginate fibre. Such a combination could prove particularly valuable in the treatment of donor sites.

The main advantage of alginate dressings lie in their ability to form a moist environment on the wound surface that facilitates optimal wound healing and permits pain- and trauma-free removal. Therefore, they should be regarded as low-adherent, gel-forming interface layers, rather than as absorbent dressings in their own right. This description emphasises the importance of an appropriate secondary dressing to control moisture-vapour loss and provide a bacterial barrier function.

One of the common criticisms levelled at alginate dressings – like many other types of 'modern' wound dressings – is that of price. Many modern materials are significantly more expensive on a unit cost basis than traditional dressings. However, such simple cost comparisons are artificial, as they take no account of effectiveness. The method of comparison is particularly important when calculating the total cost of managing chronic wounds. Leg ulcers claimed to be of up to 30 years' duration are still encountered; any dressing or treatment that can facilitate healing in such wounds in a reasonable time, regardless of unit cost, must be worthy of serious consideration.

Most financial arguments relating to the cost-effectiveness of dressings, particularly in the community, revolve around the nursing costs associated with dressing changes. Reducing the frequency of dressing changes can result in significant savings in nurse time and travelling costs.[14] A detailed costing system which took account of treatment failure as well as success has been described previously.[15]

Infected wounds

The differences between the various types of alginates described within this review may not be limited to their physical properties. In 1992, a survey was conducted into the management of fungating wounds and radiation-damaged skin by specialist centres throughout the UK.[16] Although the 114 respondents rated Sorbsan and Kaltostat as equivalent in terms of fluid-handling properties, Sorbsan was considered to be much superior to Kaltostat in the treatment of malodorous, necrotic or infected wounds. It even scored higher than some products containing activated charcoal or recognised antimicrobial agents.

These subjective opinions may have some scientific basis, for the review has identified numerous references that suggest the relatively small differences in the structure of the alginate dressings may have important implications for the way in which they perform at a cellular level within the wound.

Many of these references consider the interaction between the alginate molecule and macrophage cells that play a key role in many physiological and pathophysiological processes by synthesising various biologically-active molecules called cytokines.

A major cytokine secreted by macrophages is TNF-a, also known as cachectin, which is produced when the cells are exposed to endotoxins (LPS molecules derived from bacterial cell walls). It was first described as a tumour cytotoxic agent, having cytotoxic properties against both tumour cells and normal cells infected with intracellular pathogens. It is also a very important inflammatory mediator, which modulates many physiological and immunological functions and has been implicated in inflammatory conditions, such as rheumatoid arthritis, Crohn's disease, multiple sclerosis and the cachexia associated with cancer or human immunodeficiency virus infection.

Experimentally it has been shown that the production of endotoxin-induced TNF-a inhibits the effect of growth factors in the area of a wound, resulting in decreased collagen production and eventually to impairment of the healing process.[17] A reduction in collagen production has similarly been shown to result from the direct application of TNF-a to human and animal fibroblasts *in vitro*.[18] Paradoxically, however, it has been suggested that the ability of TNF-a to inhibit collagen formation may be beneficial in foetal wounds, where it will limit fibroplasia and thus reduce scarring.[19]

The ability of a macrophage to function in this way depends on the successful completion of the differentiation pathway of immature precursor cells to the mature macrophage. Circulating blood monocytes emigrate into extravascular tissue either to become resident organ-specific mature macrophages or to be recruited as immune effector cells at sites of inflammation, injury, allograft or tumour rejection. Macrophages are the main cell type that regulates the wound-healing cascade, and their deactivation halts the healing process. Wound macrophages can be stimulated (activated) by both endogenous and exogenous factors including alginates. It is interesting to speculate if this activity could be the reason for the preferred use of a high-M alginate in the treatment of infected or malodorous wounds as highlighted in the survey described above.[16]

Conclusions

Differences in structure of calcium-alginate dressings influence their gelling and fluid-handling properties, and thus have important implications for their absorbency and usage, particularly the method of removal from the wound. The possibility that these differences may have implications for healing and infection rates of wounds has not yet been seriously investigated.

It is clear that alginates require the application of an appropriate secondary dressing in order to function optimally. An absorbent pad is usually necessary for heavily exuding wounds, but for more lightly exuding wounds or those that are approaching the end of the healing process, a semipermeable film or foam may be more appropriate to prevent desiccation of the primary dressing. The choice of secondary dressing is critical, as it can have a major effect on treatment outcomes, and should be considered when designing or undertak-

ing studies with alginate dressings.

There is convincing evidence that alginate dressings are superior to paraffin gauze in the management of donor sites, reducing healing times and pain and trauma associated with dressing changes. Moistening the alginate with a suitable local anaesthetic may provide further pain relief.

Results of studies that suggest that scarlet red ointment dressing is superior to alginates[20] should be regarded with some caution in the light of the extended healing times recorded with both products. It is likely that these are due to the use of inappropriate secondary dressings.

There is also evidence to suggest that alginates may be superior to paraffin gauze in the treatment of leg ulcers. However, the influence of the primary dressing is minimal compared with that of external graduated compression in the treatment of venous ulcers.

Alginate dressings also appear to a have a role in the treatment of different types of wounds that are left to heal by secondary intention surgery. The literature on their use as haemostatic agents is confusing; there is little doubt that the material is an effective haemostatic agent, however, a number of papers, as discussed in the part two of this series[21], suggest that if left *in situ*, it may cause a foreign-body reaction and impede wound healing. Other authors have reported, however, that alginate is completely absorbed with no adverse effects.[21]

From this review it seems likely that three factors need to be considered:

- The chemical nature of the alginate
- The amount of fibre implanted
- The vascularity of the tissue at the site of implantation.

The evidence suggests that small quantities of a fast-gelling alginate implanted into a very vascular area will be eliminated rapidly, but large amounts of fibres of a slow-gelling material tightly packed into a relatively poorly vascularised area will remain in place for an extended period. Further research is needed in this area.

Research has indicated that alginate dressings may have an effect on wound healing at the cellular level. It has been suggested that they can stimulate the production of cytokines and other biologically active molecules from key cells involved in the healing process. There is also some evidence that this effect is greatest in alginates that are rich in mannuronic acid, although some authors dispute this, claiming that the activity is related to the presence of a contaminant or breakdown product, and is lost if the material is highly purified.[8,9]

Alginate dressings represent a valuable and, in some ways, unique family of wound management materials that remain poorly understood by most users. Further work is required to investigate the effects of the various types upon the cellular process involved in wound healing and their reported ability to combat wound odour and infection. ■

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