Trends Biomater. Artif. Organs, Vol 18 (1), pp 18-23 (2004) *http://www.sbaoi.org*

Chitosan and Alginate Wound Dressings: A Short Review

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Introduction

The skin is considered the largest organ of the body and has many different functions. The epidermis or outer layer is made of mostly dead cells with a protein called keratin. This makes the layer waterproof and is responsible for protection against the environment. The dermis or middle layer is made up of living cells. It also has blood vessels and nerves that run through it and is primarily responsible for structure and support. The subcutaneous fat layer is primarily responsible for insulation and shock absorbency. Cells on the surface of the skin are constantly being replaced by regeneration from below with the top layers sloughing off. The repair of an epithelial wound is merely a scaling up of this normal process. Science of wound healing is recorded as "three healing gestures" on a clay tablet, one of the oldest medical texts dated 2200 BC. It describes the three gestures as; Washing the wound; Making plasters; and Bandaging the wound. Although there had been a significant advancement in today's science of wound healing the basic theme seems to be similar. The work of Joseph Lister and Louis Pasteur established a sound basis for the management of infection by identifying the cause and developing methods for preventing it (1). Louis Pasteur proved that bacteria did not spontaneously generate but were introduced into wounds from a foreign source. These findings encouraged Lister's advocacy of frequent washing with soap and water and fueled his search for ways to kill bacteria, or the "antiseptic technique" — a major advance in the field of wound healing. The antiseptic technique was followed shortly by the "aseptic technique," in which a sterile environment was used to prevent the onset of infection.

Wounds are generally classified as, wounds without tissue loss (e.g. in surgery), and wounds with tissue loss, such as burn wounds, wounds caused as a result of trauma, abrasions or as secondary events in chronic ailments eg: venous stasis, diabetic ulcers or pressure sores and iatrogenic wounds such as skin graft donor sites and dermabrasions. Wounds are also classified by the layers involved, superficial wounds involve only the epidermis, partial thickness wounds involve only epidermis and dermis, and full thickness wounds involve the subcutaneous fat or deeper tissue. Although restoration of tissue continuity after injury is a natural phenomenon, infection, quality of healing, speed of healing, fluid loss and other complications that enhance the healing time represents a major clinical challenge. Majority of wounds heal without any complication. However, chronic non-healing wounds involving progressively more tissue loss give rise to the biggest challenge to wound-care product researchers. Unlike surgical incisions where there is very little tissue loss and easy to heal, chronic wounds disrupts normal process of healing and is often not sufficient in itself to effect repair. Delayed healing is generally a result of

compromised wound physiology (2) and typically occurs with venous stasis, diabetes, or prolonged local pressure. Second major challenge is the prevention of scarring, keloid formation or contractures and a cosmetically acceptable healing.

Global Wound Market

In the year 2001 the global wound care market was estimated at US$ 13156 million with an annual growth rate of 15% (3). This projection was for 40-45 million surgical procedures, and other chronic wounds like 8-10 million leg ulcers, 7-8 million pressure sores and an equal number of burn wounds. The use of growth factors to accelerate the healing of wounds offers tremendous promise as a therapeutic approach in treating chronic wounds. Including this, the anticipated market share for wound care products in 2006 is expected to reach approximately US $ 25000 million. Clinicians are unable to recommend the use of advanced dressing although they are more conducive to healing due to its high cost. However, it requires fewer dressing changes with less care, and because of its faster healing it reduces the resources required. The analysis of wound care market indicates the gradual shift toward the advanced wound dressing.

Biochemical Process in Wound Healing

Wound healing process may be divided into four continuous phases, namely haemostasis, inflammation, proliferation and maturation or remodeling (4).

The platelets present in the exposed blood aggregates and a temporary plug is formed reducing bleeding. The phagocytes act to clear debris and destroy the ingested material. New vessels are formed and carry oxygenated blood to the wound bed. The fibroblast cells lay down a network of collagen fibres surrounding the neovasculature of the wound. Finally the process of remodeling of the collagen fibres laid down in the proliferation phase occurs which may take years.

Moist wound healing theory

The most significant advancement in wound care came with Winter's (2,5) study in 60's, which showed that occluded wounds healed much faster than dry wounds and moist wound healing environment optimized the healing rates. He demonstrated that when wounds on pigs are kept moist, epithelialisation is twice as rapid as on wounds allowed to dry by exposure to air. Later Hinman and Maibach (6) confirmed Winter's work on human beings in 1963. An open wound, which is directly exposed to air, will dehydrate and a scab or escar is formed. This forms a mechanical barrier to migrating epidermal cells and are then forced to move in a deeper level of tissue, which prolongs the healing process. Moist healing prevents the formation of scab as the dressing absorbs wound exudate secreted from the ulcer.

Classification of wound dressing products

Wound dressings are generally classified as 1. Passive products, 2. Interactive products and 3. Bioactive products, based on its nature of action. Traditional dressings like gauze and tulle dressings that account for the largest market segment are passive products. Interactive products comprise of polymeric films and forms, which are mostly transparent, permeable to water vapor and oxygen but impermeable to bacteria. These films are recommended for low exuding wounds. Bioactive dressing is which delivers substances active in wound healing; either by delivery of bioactive compounds or dressings is constructed from material having endogenous activity. These materials include proteoglycans, collagen, non-collagenous proteins, alginates or chitosan. In November 1999, Food and Drug Administration of the United States of America (FDA) reclassified the dressing categories as, 1. Non-resorbable gauze/sponge dressing for external use, 2. Hydrophilic wound dressing, 3. Occlusive wound dressing, 4. Hydrogel wound and burn dressing and 5. Interactive wound and burn dressings.

Alginate and chitosan

Wound dressing based on alginic material is well known, in literature as well as from commercial point of view, in wound management (7-10). Calcium alginate being a natural haemostat, alginate based dressings are indicated for bleeding wounds. The gel forming property of alginate helps in removing the dressing without much trauma, and reduces the pain experienced by the patient during dressing changes (11). It provides a moist environment that leads to rapid granulation and reepithelialization. In a controlled clinical trial, significant number of patients dressed with calcium alginate was completely healed at day 10 compared with the members of the paraffin gauze group. Calcium alginate dressings provide a significant improvement in healing split skin graft donor sites (12). In another study with burn patients, calcium alginate significantly reduced the pain severity and was favored by the nursing personnel because of its ease of care. The combined use of calcium sodium alginate and a bio-occlusive membrane dressing in the management of split-thickness skin graft donor sites eliminated the pain and the problem of seroma formation and leakage seen routinely with the use of a bio-occlusive dressing alone (13).

Table 1: Alginate-based wound dressings commercially available in the market

Product	Manufacturer
AlgiDERM	Bard
AlgiSite	Smith & Nephew, Inc.
Algosteril	Johnson & Johnson
CarraSorb H	Carrington
CURASORB	Kendall
CURASORB Zinc	
Dermacea	Sherwood-Davis & Geck
FyBron	B. Braun
Gentell	Gentell
Hyperion Advanced Alginate Dressing	Hyperion Medical, Inc.
KALTOSTAT	ConvaTec
KALGINATE	DeRoyal
Maxorb	Medline
PolyMem	Ferris Mfg.
Restore	Hollister
SORBSAN	Dow Hickam
SeaSorb	Coloplast Sween Corp.
Tegagen HG	3M Health Care
Tegagen HI	

As an alternative to standard alginate dressing, new alginate dressings have also been experimented which claims superior properties (14-16). Different alginate wound dressing materials have been commercially utilized as shown in table 1, and have been reviewed widely in literature.

Chitosan is a natural biopolymer that is derived from chitin, a major component of crustacean outer skeletons. This material is known in the wound management field for its haemostatic properties. Further, it also possesses other biological activities and affect macrophage function that helps in faster wound healing (17). It also has an aptitude to stimulate cell proliferation and histoarchitectural tissue organisation (18). The biological properties including bacteriostatic and fungistatic properties are particularly useful for wound treatment. Like alginate material, there is also number of references on chitosan in wound treatment (19-22). Flexible, thin, transparent, novel chitosan–alginate polyelectrolyte complex (PEC) membranes caused an accelerated healing of incision wounds in a rat model compared with conventional gauze dressing. Closure rate and appearance of PEC membrane treated wounds were comparable with Opsite1-treated wounds (23). Application of the photo-cross-linkable chitosan hydrogel on full-thickness skin incisions made on the backs of mice significantly induced wound contraction and accelerated wound closure and healing compared with the untreated controls (24-26). Healing at split skin graft donor sites was studied with chitosan by dressing half with chitosan and half with a conventional dressing. It showed that chitosan facilitated rapid wound re-epithelialization and the regeneration of nerves within a vascular dermis. Early returns to normal skin color at chitosan-treated areas were demonstrated (27). Treatment with chitin and chitosan demonstrated a substantial decrease in treatment time with minimum scar formation on various animals (28). Biochemistry and histology of chitosan in wound healing has been reviewed by Muzzarelli et al. (29) and Feofilova et al. (30). The silver sulfadiazine-

incorporated bilayer chitosan wound dressing showed excellent oxygen permeability, controlled water vapor transmission rate, and water-uptake capability. It exhibited excellent antibacterial activity in in vitro culture for 1 week (31). Chitosan has been studied widely as a wound dressing material, (32,33) however, a wound-dressing product based on chitosan is yet to be commercialized.

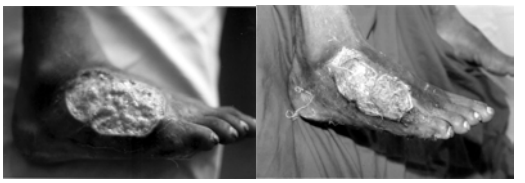

Figure 1: Healing of chronic ulcer wound on first patient with the application of chitosan based wound dressing

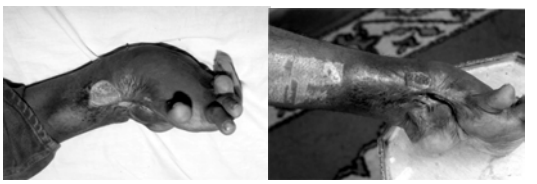

Figure 2: Healing of chronic ulcer wound on second patient with the application of chitosan based wound dressing

Faster wound healing was observed when a variety of chitosan-based skin graft material was tested in Guinea pigs and rabbits in our laboratory (34). A dressing with an optimal combination of chitosan, alginate and poly ethylene glycol containing a synergistic combination of an antibiotic and an analgesic was studied on human subjects with chronic non-healing ulcers. It was observed that this material made the ulcer cleaner and had beneficial effect in the control of infection (35). A patient with chronic ulcer on the right foot, which was non-healing for one year, was applied with the chitosan based dressing. After one week the wound became sterile and clean and the graft was applied. The wound healed in another one week (figure 1). The donor site also healed well with no pain with the application of the same dressing. Another patient with chronic unstable ulcer foot, one-and-a-half month duration, was applied with chitosan dressing for three days. The wound became very clean and graft was applied. Graft take was good and donor site healing was uneventful (figure 2). Application of chitosan wound dressing made the chronic ulcers heal faster and also the ulcers became sterile than usually by take of local applications. The graft take was excellent and the re-epithelialization process was faster. Application of this dressing was extremely satisfactory particularly at donor site with painless healing. This wound dressing is now under multicentric clinical trial at various centers and is expected to be commercialized soon. A comparative study of this wound dressing has been done with the commercially available wound dressings of the same class, with respect to economics (table 2). It seems that compared to other bioactive dressings chitosan based dressing is economical.

Chitosan provides a non-protein matrix for 3D tissue growth and activates macrophages for tumoricidal activity. It stimulates cell proliferation and histoarchitectural tissue organization. Chitosan is a hemostat, which helps in natural blood clotting and blocks nerve endings reducing pain (figure 3). Chitosan will gradually depolymerize to release N-acetyl-b-D-glucosamine, which initiates fibroblast proliferation and helps in ordered collagen deposition and stimulates increased level of natural hyaluronic acid synthesis at the wound site. It helps in faster wound healing and scar prevention.

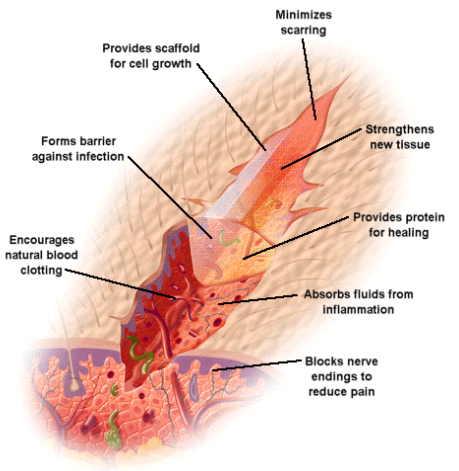

Figure 3: Schematic representation of the benefits of chitosan wound dressing (36)

Conclusion

Wound healing is a complex process that can be compromised by a number of factors. Although with proper care, some wounds fail to heal in an appropriate fashion and may become chronic. From the different studies reported in literature chitosan seems to be an excellent candidate dressing material for the wound healing applications. An optimum combination developed from alginate and chitosan, which has been clinically tested for the treatment of chronic ulcers, now can be commercially utilized for the same purpose. This will help millions of patients with non-healing chronic ulcers.

Acknowledgement

We are grateful to Prof. K. Mohandas, Director, and Dr. G.S. Bhuvaneshwar, Head BMT Wing of Sree Chitra Tirunal Institute for Medical Sciences & Technology for providing facilities for the completion of this review. We are thankful to Dr. Ramakrishnan Nair, Plastic Surgeon for the clinical evaluation of our wound dressing samples and the laboratory staff and library staff for their assistance. The data given in the table 2 are taken from the official website of the respective company and is acknowledged.

Table 2: A comparative chart of some commercial dressing material (Interactive and bioactive products).

Dressing	Type	Company	Material	Price Rs / cm^2
Bioclusive®	Film	Johnson & Johnson	Polyurethane	0.75
Mitraflex®	"	BritCair	Polyurethane	-
Omiderm®	"	Iatro Medical	Polyurethane	-
Opsite®	"	Smith & Nephew	-	0.70
Spyrosorb®	"	PolyMedica	Polyurethane	1.40
Tegaderm®	"	3M Health Care	-	0.60
Lyoform®	Form	Seton	Polyurethane	0.75
Allevyn®	"	Smith & Nephew	Polyurethane	0.95
Tielle®	"	Johnson & Johnson	Polyurethane	1.20
Actisorb plus®	Deodorising	Johnson & Johnson	Activated charcoal cloth with silver	1.50
Carbonet®	"	Smith & Nephew	Activated charcoal cloth	-
Kaltocarb®	"	BritCair	Activated charcoal cloth with alginate	-
Comfeel Contour®	Bioactive	Coloplast AS	Hydrocolloid	2.50
Granuflex®	"	ConvaTec	"	1.80
Tegasorb®	"	3M Health Care	"	1.70
Duoderm®	"	ConvaTec	"	0.70
Granugel®	Bioactive	ConvaTec	Hydrogel	8.30
Intrasite Gel®	"	Smith & Nephew	"	12.00
Nu-Gel®	"	Johnson & Johnson	"	8.20
Sterigel®	"	Seton	"	8.30
Algisite®	Bioactive	Smith & Nephew	Alginates	2.10
Kaltostat®	"	ConvaTec	"	2.05
Tegagel®	"	3M Health Care	"	2.05
Comfeel SeaSorb®	"	Coloplast AS	"	2.10
Mepore®@	Traditional	Mölnlycke	non-woven polyester fabric	0.15
Experimental Wound Dressing#	Chitosan Bioactive	SCTIMST	Chitosan/Alginate combination	0.55

@ Traditional dressing for comparison. # Currently under clinical trial. Estimated price including infrastructure and staff salary of the project.

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