.

A Review on Hemostatic Wound Dressings

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ABSTRACT

Traumatic injuries leading to uncontrollable hemorrhage is one of the major causes of loss of life in the present era. Existing strategies to control bleeding are not efficient in the cases of emergency. Therefore, development of hemostatic wound dressings is one of the requirement of the current wound care technology. Presently wound dressings are classified as passive, interactive and active dressings. Active wound dressings are designed to manipulate to the wound site mechanism and provide functional support. Many commercially available dressings are made up of hydrogels and nanofibers and their composites fabricated from polysaccharides or plant based or animal based natural degradable biopolymers. Polymers used for devising hemostatic dressings are collagen, chitosan, micro- fibrillar collagen, oxidized regenerated cellulose and gelatin. The intrinsic properties of these materials play a major role in bringing upon hemostasis. However, acid soluble based natural polymers are found cause burns to the patients using it. Also, an acidic odor is found at the wound site. The properties can be improved by incorporating substances which can further aid in blood clotting. Apart from the biochemical properties of the material, scaffold design and architecture also help in bringing upon the desired action. High swelling capacity of the hydrogels have found to play an important role in aggregating blood components and hence faster hemostasis. Cryogels can bring upon faster hemostasis due to their high swelling capacities owing to their interconnected and macro- porosity. The macro porous nature helps in faster diffusion of water and blood components and faster hemostasis.

Keyword: - *Wound dressing, Hemostasis, Collagen, Chitosan and Hydrogel*

1. INTRODUCTION

The present generation encounters a wide variety of traumatic injuries with each new wound posing a different challenge for the health care providers. So is the challenge for biologists, pharmacists, engineers and caregivers in the field of science, engineering and health care to bring about advances in wound care technologies, which address the complexities of different types of wounds arising from traumatic injuries or chronic illnesses with expertise and minimum discomfort to the user. In a separate study by Baker et al. in 1977[1], a trimodal distribution on the study of deaths due to traumatic injury in a course of one year was made on the basis of deaths in the early stage or pre-hospitalization deaths, due to severe blood loss or exsanguination, medial stage where deaths occurred within a short period of hospitalization due to similar reasons and the third stage where deaths occurred at later periods while in the hospital or post discharge due to possible organ failures, with 51% deaths occurring at the pre- hospitalization stage itself. A recent study showed 66% deaths in comparison to the 55% deaths recorded earlier at the pre-hospitalization death or death at the Emergency Department (ED) due to similar reasons [2]. Also, major deaths in military settings were found to be due haemorrhage from incompressible wounds [3].

1.1 Wound Healing

A wound can be defined as a break in the integrity of the skin, tissue or biological membrane by means of physical, chemical or biological trauma [5]. A wound can be classified into various categories depending on the nature of the force causing the wound, the duration the wound takes to heal and the level of damage to the tissue or organ. According to Nicholas J Percival[6] wounds can be classified intro three categories, one; the nature of injury causing agency as clean, incised, contaminated, crushing or burns, second; the time to heal as acute or chronic, and third the depth of the injury as superficial, dermal or full tissue injury. Open wounds and traumatic amputations observe minimal to alarming levels of haemorrhage ranging from level I to IV haemorrhagic shock consequently incurring loss of life in majority of the cases, where level I haemorrhage can be classified as a non- shock stage and level IV marks to a pre- terminal event [7]. The process of wound healing follows a complex process consisting of various biological, physical and chemical factors. Wound healing, though being a continuous overlapping process can be differentiated into various stages as follows: (i) Haemostasis, (ii) Inflammation, (iii) Proliferation, (iv) Remodelling and formation of scar tissue. Bleeding occurs immediately following damage to the tissue.

1.2 Hemostasis

Haemostasis involves various biological, chemical and physical factors, efficient understanding and application of which may help design artificial haemostatic dressings, usable when the body's own haemostatic mechanism struggles to bring upon the efficient clotting to control the level of haemorrhage. The initiation of the blood coagulation process occurs with vasoconstriction to limit the blood loss from the vasculature, followed by platelet plug and clot formation. Platelets are the chief cells responsible for blood clotting. Apart from this, platelets also play an important role in other stages of wound healing. The fibrin clot formed serves as a scaffold aiding migration of WBCs, keratinocytes, fibroblasts, and endothelial cells serving as a reservoir of important growth factors. Therefore, the process down to efficient remodelling and reconstruction of skin/ complete healing of wound starts with the very first stage; Haemostasis[8]. Following break in the integrity of the blood vasculature, vascular spasm or vasoconstriction which is the result of contraction of smooth muscles stimulated by nervous reflexes associated with the injury site, is marked by narrowing of the blood vessels, which eventually aids in reducing the level of haemorrhage. The chemicals released by platelets such as thromboxane act as local vasoconstrictors. Blood coagulation can also be observed as a result of cascading events of chemical reactions of plasma proteins or clotting factors. These factors normally found circulating in inactive form get activated on surface contact or enzymatic cleavage. The extrinsic pathway is a type of coagulation cascade that begins with trauma to blood vessels and surrounding tissues. Tissue trauma releases tissue thromboplastin, which is a collection of phospholipids and several factors. Tissue thromboplastin combines with factor VII and activates it, this complex further activates through enzymatic actions factor X. The factor Xa binds with phospholipids and factor V to form prothrombin activator in the presence of calcium ions. The prothrombin activator activates prothrombin and in the presence of divalent calcium ions produces thrombin eventually leading to the formation of fibrin mesh. The intrinsic pathway is one similar cascade initiated by exposure of the blood to foreign surfaces or with trauma to platelets within the blood. Factor XII binds to foreign surface and gets activated. Platelets adhering to the surface release platelet factor 3 and phospholipids. This mechanism joins the extrinsic pathway at two points; during the activation of factor X and during the formation of prothrombin activator. The events down the formation of prothrombin activator are same for both the coagulation pathways hence termed common pathway. These pathways can be viewed as important feedback and feed- forward loops of an engineering control system. Identification of necessary control points in the system may help devising artificial systems for blood coagulation by manipulation or mimicking of natural coagulation cascades. One of the major controlling points in the system is the indulgence of calcium divalent ions (Ca^{2+}) without which blood coagulation cannot occur. Limiting or enhancing the availability and activity of Thrombin may also allow control of the clotting process. Platelets and platelet derived factors and enzymes are the chief cells and chemicals participating in blood coagulation. Understanding the adherence mechanisms of platelet may be useful in the making of biomedical devices that aid blood coagulation or vice versa when implants are considered. Also, the formation of factor Xa is essential for concluding the coagulation cascade by the formation of thrombin and fibrin. Controlling the availability and activation of the factors also play a major role. The manipulation of these control points and pathways to bring about artificial coagulation is itself a challenge. However, these natural mechanisms to bring about blood coagulation fail to deliver the optimum outcomes when the wounds are deeper for example resulting from incisive type of wounds; penetrating type or incompressible as observed in ballistic trauma, involving injury to major blood vessels or present at locations not easily accessible. Also, the age, condition (patients with bleeding disorders like haemophilia, patients lacking important coagulation

factors, etc.), duration between the traumatic impact and beginning of emergency medical care play a major role in bringing about haemostasis.

2. WOUND DRESSINGS

A wound dressing can be defined as a protective barrier applied in direct contact with the wound to prevent further damage to the wound and promote natural healing of the wound. The modern classification of wound dressing, identifies wound dressings into three categories: a) Passive Wound dressings, b) Interactive wound dressings, and c) Active wound dressings[9]. Passive wound dressings are ordinary 'gauze- like' materials and products that are simply used to cover the wound site. These dressings have very low fluid absorbing capabilities and they neither promote nor hinder the natural wound healing process. Interactive wound dressings originated in the later 1980s. Interactive dressings provide an environment to the wound such as moist warm environment which eventually promotes wound healing. These are essentially semi- permeable film membranes aiding oxygen and water vapour exchange and inhibiting transport of fluid and bacteria made up of polyurethane for example, hydrocolloid dressings[10] which retain moisture providing a moist environment to the granulating tissue with minimal exudate absorbing capacity, foams and non-adherent wound contact materials. Active wound dressings are modern dressing materials essentially made from biomaterials incorporated with bioactive agents that promote, re- stimulate or initiate the wound healing processes at required stages by manipulation of wound healing mechanisms. Antimicrobial drug carrying dressings[11],[12], collagen dressings[13], bioengineered skin substitutes etc. are general examples of active wound dressings.

2.1 Hemostatic Hydrogel based Dressings

Hydrogels are one such class of polymeric 3D scaffolds which due to its desirable properties such as high swelling capacities, fluid retention, biodegradability, excellent permeability and highly porous nature are the chief candidates for tissue engineering scaffolds[14],[15]. Hydrogels are three dimensional, high swelling crosslinked polymeric networks which can hold high amount of water or fluid yet not dissolve in it [16]. This insoluble polymeric network serves as a seat for effective encapsulation of bioactive agents and molecules [17]. Hydrogels can be broadly classified into chemical or permanent gels or physical or reversible gels. Hydrogels can also be categorized on the basis of their ionic charge into neutral, cationic, anionic and ampholytic hydrogels [18]. The hydrophilic groups of the hydrogel are first to get hydrated on coming in contact with an aqueous environment to form the primary bound water. The hydrophobic groups get exposed on initial swelling of the hydrophilic part and second type of water is bound to hydrophobic groups as bound water or secondary water. The additionally absorbed water due to osmotic and diffusive exchange into the pores of the hydrogel is called free water. This additional uptake of water is opposed by the cross linkages of the hydrogel and a state of equilibrium is reached.

2.2 Hemostatic Dressings

Bringing upon artificial hemostasis is the chief aim in the cases where conventional gauze- like wound dressings and person's own hemostatic mechanisms fail. Jesty et al classified hemostatic dressings into three categories on the basis of mode of action as i) coagulation inducing, ii) platelet aggregating and iii) other mechanism based hemostatic active dressings[19]. Coagulant active dressings such as Dry Fibrin Selant Dressings DFSD included agents which directly could form fibrin meshes containing active thrombin, calcium and fibrinogen on glycan backing [20]. Platelet aggregating dressings were essentially collagen and chitosan based hemostatic dressings. Other sources of hemostasis included rapid and high fluid absorption type gauzes such as zeolite based QuikClot® (Z-medica) and chitosan doped perfluorocarbons as oxygen carriers (ChitO2- clot)[21] Biomaterial science has observed the hemostatic effects of collagen, chitosan, kaolin clays, and fibrin scaffolds which make them the chief candidates of hemostatic wound dressings. Gelatin has also found application as hemostatic sponges [22], [23]. Gelatin soaked in thrombin are also used as hemostats for low pressure bleeding [24]. Oxidized Regenerated cellulose (ORC) also found application in hemostatic gauzes for surgical trauma [25]. It has been used for controlling bleeding from broad surfaces, small brain vessels and osteoplastic flaps [26]. Surgicel®, a commercial dressing of this category finds application in venous bleeding from tumor surfaces [27] Collagen appears in 25 different types. They make up, up -to 40 % of the total available protein of the blood vessel wall [28]. Following trauma to the blood vessels, the blood gets exposed to the sub endothelial connective tissue matrix which consists of collagen as matrix protein. Platelets adhere to the sub endothelial collagen and become activated and form platelet aggregates [29]. The formation of thrombin is regulated by collagen indirectly because negatively charged

phospholipids are exposed on the surface of the platelets and form catalytic seat for thrombin generation after the platelets' activation following contact with collagen [30].

3. CHITOSAN BASED DRESSINGS

Chitosan is a linear polymer polysaccharide consisting of D- glucosamine and N- acetyl D- glucosamine units [31]. It is obtained from chitin on deacetylation. Chitin is a natural second most abundant biopolymer after cellulose derived from invertebrates as shrimp shells and crustacean shells [32], [33]. The degree of deacetylation of chitosan varies from 60 to 100% with the molecular masses ranging from 300 to 1000kDa. The presence of amino group on D- glucosamine residues differentiates chitosan from chitin and also is the reason for most of its peculiar properties. The hemostatic activity of chitosan is due to the presence of these protonable amine groups or positively charged amine terminals as they successfully attract negatively charged RBC membranes bringing about aggregation of RBCs and blood components [34]. Addition of hemostatic agents can further increase the hemostatic potential of the chitosan based dressings. In a recent study, Polyphosphate added chitosan dressings showed improved hemostatic and antimicrobial property by formation of Poly electrolytic complexes [35]. Platelet adhesion to chitosan was also found to increase due to plasma and extra cellular matrix protein adsorption where preferential adsorption of fibrinogen increased hemostatic activity, however collagen coated sponge showed non- significant changes in hemostatic activity [36]. In another study, polyacrylate based synthetic polymers were found to show platelet binding as a potential hemostatic agent [37]. Apart from material interactions, high swelling capacities and faster fluid absorption were also found to be one of the major factors in achieving hemostasis [38]. Freeze dried, chitosan and zinc oxide gels showed improved hemostatic property over natural chitosan with high swelling capacitates [39] Such effects apart from ionic interactions were also observed for graphene sponges [40]. With increasing swelling capacities and rapid fluid absorption rates, high hydrophilicity aided adhesion of platelets [41]. Antifibrinolytic drug loaded hemostatic dressings also showed reduction in bleeding post operatively [42], [43]. Among the major short comings of commercially available wound dressings are lack of mechanical strength under compression, release of acidic constituents to the wound bed and burns as observed in the case of HemCon®, a chitosan acetate sponge and QuikClot® hemostatic sponges [44]. Kang, Pei-Leun, et al evaluated sodium hydroxide and sodium tripolyphosphate treated chitosan dressings for hemostasis purpose to improve upon the properties of acetic acid treated chitosan dressings in terms of odor and mechanical strength of commercially available dressings Clo-Sur PAD® (Scion Cardio-Vascular, Inc., FL, U.S.A.) and Instant Clot Pad® (Cosmo Medical Inc., Taiwan). The study showed improved hemostatic performance with elimination of odor and increase in mechanical strength and shape retention under compression.

4. CONCLUSIONS

It follows from the literature study that artificial hemostatic effects could be obtained by mimicking the natural phenomenon of blood coagulation in 3D micro- environments. The creation of micro- environment included fabrication of macro- porous, high swelling capacity scaffolds with biopolymers having possible ionic or biochemical interactions with the blood constituents which could eventually lead to artificial blood coagulation by either inducing or initiating the blood coagulation cascade or by aiding and promoting the natural blood clotting mechanism with consequently leading to the formation of potential hemostatic wound dressing materials addressing different levels of hemorrhage.

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