Tissue Enginnering Products and Biomaterials in Wound Healing in Veterinary Medicine

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Geliş Tarihi: 28.03.2017 Kabul Tarihi: 02.06.2017

Abstract: Current practice of regenerative medicine succesfully takes the advantages of tissue engineering products and biomaterials consisted of scaffolds, cells and biologically active molecules. With the help of these products, restoration, maintainance and healing of damaged tissues became faster, cost effective and the most important provides patient comfort with considerably less suffering. These materials are also introduced to veterinary practice, but unfortunately has not been benefited sufficiently yet. This review overviews the features, efficiencies and areas of utilization in wound healing in veterinary practice, of these commercially available and efficient materials.
Keywords: *Wound, Biomaterial, Tissue engineering.*

Veteriner Hekimlikte Yara İyileşmesinde Biyomateryaller ve Doku Mühendisliği Ürünleri

Özet: Günümüzde, doku iskeleleri, hücreler ve biyolojik olarak aktif moleküllerin kullanılarak geliştirildiği doku mühendisliği ürünleri ve biyomateryaller rejeneratif tedavi alanında başarıyla kullanılmaktadır. Bu ürünler yardımıyla, hasarlı dokuların restorasyon, idame ve iyileşme süreçleri daha hızlı ve daha az maliyetli hale gelmiş olup, daha önemlisi, hasta konforu açısından çok katkı sağlamıştır. Bu materyaller, veteriner hekimliğin de hizmetine sunulmuş olmakla birlikte, maalesef uygulamada henüz yeterince faydalanılamamaktadır. Bu derlemede, ticari olarak kolayca ulaşılabilen bu malzemelerin özellikleri, veteriner sahada yara iyileşmesinde kullanım alanları ve etkinlikleri özetlenmiştir.
Anahtar Kelimeler: *Yara, Biyomateryal, Doku mühendisliği.*

Introduction

Skin wounds are the most frequent type of wounds refer in clinical practice. Skin is the largest organ of the body which constitutes 24% of live weight in puppies and 12% in adult dogs (Pavletic, 1999**)**. The major function of the skin is to create a posture and defense the body against exterior threats, nearby other functions such as secretion, excretion, sense, thermoregulation, vitamin synthesis. Skin is subjected to wound risks because it is the organ most exposed to external environment. Systemic or immune diseases (diabetes, pomphigus vulgaris) also causes skin wounds.These wounds sometimes are resistant to medications and courses to large tissue losses (Amaral et al., 2016**)**.

Natural response of the organism is to regenerate the wounded tissues. Healing process includes a complex of biochemical, cellular and dynamic issues. The major component of healing is cell proliferation. These cells migrate to wounded areas. Collagen synthesis plays a key role in healing. Synthesized collagen fibriles formate cross links ensuring tissue firmness and integrity (Zbigniew and Schwartz, 2000). Healing process starts just after laceration and follows a spesific order named as natural healing process. Secretions from the wound edges starts exchange processes between blood and cells, controls bleeding, inhibits infections and expedites healing. These haemostasis, inflammation, proliferation and renewing phases actualize in order (Kurtoğlu and Karataş, 2009; Maria et al., 1997; Robson et al., 2001). Various systemic and local factors effect the healing process. Local factors include infection, insufficient circulation, hypoxia, necrosis, foreign particules, repetitive traumas and mobility of the region. Systemic factors include malnutrition, diabetes, chronic renal insufficiency, immune disorders, corticosteroids, age and genetic factors. Many wounds heal naturally, but in some wounds healing may delay revealing impediment in the process resulting with chronic wounds (Moore et al., 2006; Robson et al., 2001). Both conditions and wound characteristics vary, therefore each wound must be considered privately (Kumar et al., 2004). Significant similarities with humans in wound healing were observed in animal models including mouse (Wong et al., 2011), rat (Dorsett-Martin and Wysocki, 2008), rabbit (Chien, 2007), and swine (Sullivan et al., 2001**)**.However, small mammals like mouse, rat and rabbit may not be a preferable model for humans due to the thin structure and differences in collagen characteristics of the skin, therefore swine is accepted as the best model for wound healing in humans (Subhamoy and Aaron, 2016).

Wound Dressings: Interestingly, wound therapy with biomaterials were determined in ancient Egypt tablets with honey, various oils and plant fibers (Subhamoy and Aaron, 2016**)**. In near future, natural and synthetic bandages, hydrophil cotton and gauze bandage were used with different absorbtion characteristics (Boateng et al., 2007). However today the role of cytokines, growth factors and extracellular matrix in wound healing are discovered (Christgau et al., 2007; Kapoor et al., 2006), regarding the necessity of new dressings. Different dressings with various shapes, forms and mechanisms are tested with pharmaceutic and clinical trials (Table 1, 2, 3) (Horch et al., 2010).

Table 1. Biomaterial based modern wound dressings (Altay and Basal, 2010; Harding et al., 2000; Kumar et al., 2004; Subhamoy and Aaron, 2016).

Type	Structure
Independents	Syloxylane Dextran Urethane Collagen Synthetic
With bioactive components	Fibrine Hyaluronic acid
Cell encapsulating	Poly β amino ester Fibrine and PEG PEG + RGD
Nucleic acid delivering	Collagen Hyaluronic acid Polyurethane Chitosan, dextran sulfate, and poly 2
Animal derived	Small intestine submucosa Amniotic membrane Fibrin Marine collagen
Drug or antibiotic carriers	Chitosan and PEG Carrageenan, polyox, HPMC Polyurethane and dextran PEG and chitosan PEG

Forms of Wound Dressings

Foams: Foam dressings are flexible, soft and pored materials with high absorbtion capacity and high endurance. They may be polyurethan or silicon based, manufactured from hydrophobic or hydrophilic monomers resulting with different porosity and fluid containment capacity. They may be used as the first dressing in contact with the wound or as the second dressings. When placed on wet wound surface, wound fluid is absorbed inside the foam with capillary effect and when placed on dry wound surface, poliurethan support layer minimizes the moisture loss and prevents surface drying (Hanna and Giacopelli, 1997). Foam dressings are hydrophilic structures in order to prevent wound fluid leakage and inhibit bacterial penetration to limited extent, permitting gas permeability and do not stick. They accord in the wound cavity and enlarge with time. This enlargement decreases the oedema and speeds granulation formation. They are beneficial in necrotic and wounds with moderate exudate. They are not suitable for dry and crusted wounds (Boateng et al., 2007; Kurtoğlu and Karataş, 2009). Foams are also used as a medium forstem cells. Ijima et al. (1998), developed a practical hybrid artificial live support system by producing monkey kidney cells (Vero), human embriyonic kidney cells, human liver cells (PLC/PRF/5), rat, dog and swine hepatocytes in polyurethan foam and transplanted this tissue to rats with hepatic failure achieving 80% recovery.

Transparent films: Also named as semi-permeable films with an acrylic adhesive face and a polyurethan membrane face. These synthetic adhesive films are very elastic, providing patient confort without limiting function. They are well functioning barriers against bacteria. They also prevent bleeding and therefore the most suitable utilizing area are greft obtained zones. They are water proof, but permeable for oxygen, carbondioxide and vapor which are crucial for the healing process. Permeability varies with the product type. Transparency provides monitoring of the wound beneath and also has the advantage of slimness. Disadvantages include the possibility of exudate accumulation and maceration due to lack of absorbant feature, frequent changing requirement and necessity of surrounding healthy tissue for adhesiveness (Harding et al., 2000; Kurtoğlu and Karataş, 2009.

Basic materials of wound dressings

Hydrocolloids: Hydrocolloid dressings are produced from gel forming agents, elastomersand adhesives. When contact with wound exudate, hydroactive piecespresent homogeniously in their structure forming a hydrocolloid matrix absorbs the fluid and forms a gel structure. Thus the wound is covered with a moisture transmissive layer, easing healing process. Hydrocolloids also augments epithelisation speed and collagen production. Advantages include application facility because of solo competence, anealgesic effect, interception to foreign matters, keeping away microorganisms and therefore forming a barrier for bacteria, providing ideal humidity and gas permeability, relatively infrequent changing necessity, stimulating angiogenesis. They are suitable for mild-moderate exudated, partial or complete wounds, but not suitable for infected wounds. Delay in changing these dressings may weaken the skin (Harding et al., 2000; Kurtoğlu and Karataş, 2009). Several trademarks are newly introduced to veterinary practice (Derma GeL®).

Table 2. Clinical endication profiles of biomaterial based wound dressings (Altay and Basal, 2010; Harding et al., 2000; Kumar et al., 2004; Subhamoy and Aaron, 2016).

Type	Structure	Examples	Endications
Films	Polyurethan	Tegaderm, Blisterfilm, ClearSite, Comfeel film, Suresite, Procyte, OpSite, Dermaview	Small wounds, pressure, donour, postoperative wounds, erosions, lacerations
Hydrogels	Glycerine	BIolex, elastogel, Curasol gel, Elasto-Gel, flexigel, IntraSite gel, Restore Gel, Hypergel, tenderwet, SoloSite, Vigilon	Necrotic and dry ulcers
Wafers	Hydrocolloids	DuoDERM, Restore plus, RepliCare, Exuderm, Tegasorb, DuoFilm, Cutinova Hydro, nuderm	Ulcers with moderate exudation
Foams	Polyurethans	Lyofoam, PolyMem, COPA, Optifoam, Gentleheal, Allevyn	Ulcers with severe exudation, granulation and pain.
Hidrogels	Alginate	Calcicare, nuderm, SeaSorb, Sorbsan, alginate, Kaltostat, Maxorb, Mesalt comes with sodium chloride, Medi-honey with honey	Ulcers with severe exudation or bleeding ulcers
Haemostaticsr	Collagen	Cellerate, Fibracol, Prisma, Promogran, puracoll	Traumatic wounds, bleeding ulcers
Hydrofibers	Cellulose	Silvercel, Prisma, Aquacel, Promogran, Tegaderm matrix, Dermafill Xylinum Cellulose, Xcell (bacterial cellulose)	Ulcers with severe exudation and infected wounds
Chelants	Dimethicone	Benzoin, Cavilon Barrier Film, Skin-prep, No sting barrier	Organ wounds, fistulated wounds
Composite	Multiple types	CombiDERM, Island, Telfa Island, Covaderm plus, Alldress, Dermadress, Adaptic, Adaptic touch, wound veil, Restore, Mepilex, Telfa, CarboFlex, Melolin, Clinisorb, Versiva, Mepitel	Complex wounds

Hydrogels: Hydrogels are three dimensional networks of high water including hydrophilic polymers. These dressings have high absorbtion capacity and do not adhese to wound surfaces. They also have an anealgesic and thermoregulating effect nearby forming a damp wound athmosphere, easily shaping and readily cleaning features. Also they enable topical applications (Boateng et al., 2007). Amorph hydogels, increases the humidity and collagenase production of bruise tissues, enabling autolytic debridement of infected and damaged tissues (Harding et al., 2000; Kurtoğlu and Karataş, 2009). Ribeiro et al. (2009), demonstrated the effect of hydrogells in the therapeutic level and also combining with chitosan as a carrier. The disadvantages include the necessity for a second dressing due to lack of bacterial defense (Harding et al., 2000). Hidrogels are widely used in veterinary medicine in the world.

Alginatedressings: Alginates has high absorbant capacity, therefore forms a fortified hydrophilic gel when in contact with the wound exudate. Formed gel provides ideal humidity and temperature for the lesion together with calcium ions and are one of the ideal materials for the moist curative dressings

(Altay and Basal, 2010). Addition of zinc increases antibleeding activity. Although they lack antibacterial feature, they pen up bacteria in the gel passively and changing the dressing remove away the agents (Kurtoğlu and Karataş, 2009; Stashak et al., 2009).

Table 3. Nano-particul based wound dressings (Altay and Basal, 2010; Harding et al., 2000; Kumar et al., 2004; Subhamoy and Aaron, 2016).

Type	Structure
Metal	Silver MgF2 Cerium oxide Copper Iron oxide Gold
Antibiotic carriers	Polyacrylate Poly (butyl acrylate–styrene) Chitosan, gelatin, and epigallocatechin gallate Folic acid-tagged chitosan
Nitric oxide excretings	Tetramethylorthosilicate, PEG, and chitosan Silica
Natural products	Genipin, chitosan, PEG, and silver
Lipid based	Proteoliposomes in alginate hydrogel Solid lipid nanoparticles Exosomes
Polymer based	Chitosan, pectin, and titanium dioxide Hyaluronan

Active ingredient content

Antibacterialcontaining dressings: They are very efficient in wounds with high infection risk such as diabetic ulcers, traumatic or accidental wounds (Harihara et al., 2006). Antibiotics are absorbed in dressings, for example povidone iode is absorbed in textile material dressings and silver is obserbed in modern dressings (Lee-Min Mai et al., 2003). Local applications inhibit organ accumulation of antibiotics (Chu et al., 2006) and also provides a more effective healing (Kurtoğlu and Karataş, 2009).

Growth factor containing dressings: Growth factors are efficient in cell proliferation, migration and differentiation, stimulating angiogenesis and cell propagation therefore have a major role in healing (Steenfos, 1994). Mann et al. (2006), demonstrated the beneficial activity of Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF) in wound healing in transgenic rats. Growth factor application has promising results in wound healings (Khan and Davies, 2006).

Modern dressings

Bioactivedressings: These products usually keep together polymers such as elastine, collagen, chitosan, hyaluronic acid and alginates. Biomaterials has advantages of containing natural extracellular matrix components, biological disruption, active role in healing, being nontoxic and biofit (Lazovic et al., 2005). In some applications, antimicrobials and growth factors are replaced in them (Tyrone et al., 2000; Yan et al., 2010). Collagen is the natural and major component of connective tissue and all tissues, and has a very important function in all stages of wound healing (Purner and Babu, 2000). Hyaluronic acid is one of the most important components of extracellular matrix with hydrophilic ability, stimulating cytokin production by macrophages and hence angiogenesis (Adhirajan et al., 2009). Hydrogel films produced from cross linked hyaluronic acid were evaluated as drug carrier biomaterials with successfull results (Luo et al., 2000). Hyaluronic acid based dressing “Hyaff®” is manufactured commercially. Chitosan is another bioactive polymer effective in wound healing by accelerating granulation tissue formation (Şenela and McClure, 2004). Chitosan is well studied in veterinary medicine; in tendon healing of sheep (Okamoto et al., 1995), in wound healing of various animals (Minami et al., 1999), in bone healing of rabbits (Muzzarelli et al., 1993; Wang et al., 2002), in wound (Kosaka et al., 1996; Okamoto et al., 1995; Ueno et al., 2001) and bone healing of dogs (Khanal et al., 2000).

Greftsandgreft equivalents: Are usually benefited in second degree burns and provides significant recovery at the underlying epithelium nearby functioning a transient dressing until autogreft procedure. Most frequent useds are homogrefts, allogreft (fresh or frozen), amniotic membranes (fresh or frozen) and xenogreft (fresh, frozen or lyofilized) (Zhong et al., 2010). Xenogrefts from swine or allgrefts from cadaver are successully used (Marcia and Castro, 2002). These products are rejected and eliminated by the immune mechanisms in time. Disadvantages include transmitting diseases such as AIDS andhepatitis (Kurtoğlu and Karataş, 2009).

Tissue engineering products: Conventional and modern wound dressings are promise successfull healing processes, but they lack fulfilling the lossy wounds. Development of biomaterials together with culturation of skin cells gave chance to new alternatives that act as scaffolds designed for tissues that may imitate physiologic actions (Whitaker et al., 2001). Two matrixes are used in tissue engineering; extracellular and intracellular. Extracellular matrixes are produced from synthetic collagen like IntegraTM and hyaluronic acid components. Cellular matrixes are produced from structurelly kept natural dermis like AllodermTM. Cell transporter tissue engineering products may include biologically disintegretable films made up of collagen and Apligraf TM glycozaminoglycan scaffolds. They disintegrate in time leaving a suitable connective tissue matrix in time They disintegrate in time leaving a suitable connective tissue matrix (Boateng et al., 2007). Scaffolds also provide the chance to leave growth factors and stem cells to the wound (Storie and Money, 2006).

Conclusion

Regenerative medicine advances rapidly. Our own practice resulted efficient therapies using platelet rich plasma therapy, whey protein, biomaterials and tissue engineering products (Dalgın and Meral, 2016; Dalğın et al, 2017a;Dalğın et al, 2017b).

In conclusion, current practice provides various alternatives for the management of different types and characteristics of wounds. Furthermore, they are commercially available and most are cost effective. Nevertheless, the poor utilization of these amazing products seems amazing. We hope that increase in the concideration of them will significantly augment the therapeutic success in severe wounds in veterinary medicine, also saving cost, but most important decreasing patient suffer.

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