Tissue Engineering Products and Biomaterials in Wound Healing in Veterinary Medicine

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Abstract: Current practice of regenerative medicine successfully takes the advantages of tissue engineering products and biomaterials consisted of scaffolds, cells and biologically active molecules. With the help of these products, restoration, maintenance 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.

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, pneumphigus 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 fibres formate cross links ensuring tissue firmness and integrity (Zbigniew and Schwartz, 2000). Healing process starts just after laceration and follows a specific 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 (Kurtoglu and Karaş, 2009; Maria et al., 1997; Robson et al., 2001). Various systemic and local factors affect the healing process. Local factors include infection, insufficient circulation, hypoxia, necrosis, foreign particles, 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 absorption 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 pharmacetic 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).

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

**Forms of Wound Dressings**

**Foams:** Foam dressings are flexible, soft and pored materials with high absorption 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, polyurethan 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 for stem cells. Ijima et al. (1998), developed a practical hybrid artificial live support system by producing monkey kidney cells (Vero), human embryonic kidney cells, human liver cells (PLC/PRF/S), 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 comfort without limiting function. They are well functioning barriers against bacteria. They also prevent bleeding and therefore the most suitable utilizing area are gret 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, elastomers and adhesives. When contact with wound exudate, hydroactive pieces present 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).

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

Hydrogels: Hydrogels are three dimensional networks of high water including hydrophilic polymers. These dressings have high absorption capacity and do not adhere to wound surfaces. They also have an anealgesic and thermoregulating effect nearby forming a damp wound atmosphere, easily shaping and readily cleaning features. Also they enable topical applications (Boateng et al., 2007). Amorph hydogaels, increases the humidity and collagenase production of bruise tissues, enabling autolytic debridement of infected and damaged tissues (Harding et al., 2000; Kurtöglu and Karataş, 2009). Ribeiro et al. (2009), demonstrated the effect of hydrogels 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.

Alginate dressings: Alginate 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.
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).

<table>
<thead>
<tr>
<th>Type</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metal</td>
<td>Silver, MgF2, Cerium oxide, Copper, Iron oxide, Gold</td>
</tr>
<tr>
<td>Antibiotic carriers</td>
<td>Polycrylate, Poly (butyl acrylate–styrene), Chitosan, gelatin, and epipallocatechin gallate, Folic acid–tagged chitosan</td>
</tr>
<tr>
<td>Nitric oxide excreting</td>
<td>Tetramethyloisilicate, PEG, and chitosan, Silica</td>
</tr>
<tr>
<td>Natural products</td>
<td>Genipin, chitosan, PEG, and silver</td>
</tr>
<tr>
<td>Lipid based</td>
<td>Proteoliposomes in alginate hydrogel, Solid lipid nanoparticles, Exosomes</td>
</tr>
<tr>
<td>Polymer based</td>
<td>Chitosan, pectin, and titanium dioxide, Hyaluronan</td>
</tr>
</tbody>
</table>

Active ingredient content

Antibacterial containing dressings: They are very efficient in wounds with high infection risk such as diabetic ulcers, traumatic or accidental wounds (Harirara et al., 2006). Antibiotics are absorbed in dressings, for example povidone iode is absorbed in textile material dressings and silver is observed 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 (Senela 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).

Greffsandgreft 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 and hepatitis (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 cultivation 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. Extracelluar matrices are produced from synthetic collagen like IntegraTM and hyaluronic acid components. Cellular matrices are produced from structurally kept natural dermis like AlloDermTM. Cell transporter tissue engineering products may include biologically disintegratible films made up of collagen and Apligraf TM glycoaminoglycan 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 (Dalğın 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 the increase in the consideration of them will significantly augment the therapeutic success in severe wounds in veterinary medicine, also saving cost, but most important decreasing patient suffer.

References


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