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REVIEW ARTICLE

Novel techniques to enhance wound healing

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Abstract

Wound healing is a complex, dynamic and multifaceted biological process. Wound repair is mainly similar at all anatomical sites and can be divided into four major phases including hemostatic phase, inflammatory phase, proliferative phase and remodeling phase. Interrupted or failure during healing process can lead to chronic wound healing. Chronic wound healing is the most common complication in veterinary practice. This condition leads to painful, uncomfortable and later consequently died, as well as leads time consuming and cost of treatment. Currently, physical therapy modalities in the wound healing process have been developed and widely used for adjunctive therapy in veterinary medicine, including electrical stimulation, shockwave therapy, ultrasound therapy and low intensity laser therapy to enhance wound healing. The biological effects of electrical stimulation are result of exogenous electrical signals and are amplifying the biological signal into target tissue. The mechanism of shockwave therapy and ultrasound therapy are the consequence of cavitation phenomenon, activated cellular activity, and increase tissue perfusion. Meanwhile, mean mechanism of low intensity laser therapy is known to supply direct biostimulative light energy to target cells, and to initiate cellular processes. These modalities deliver physical energy to produce therapeutic biological effect, especially inflammatory phase and proliferative phase. Importantly, the biological effects produced by these modalities are including supported the proper environment for healing process, increasing phagocytosis by macrophages, leukocyte adhesion, growth factor production, angiogenesis, collagen synthesis, fibroblast synthesis and granulation tissue formation. In additions, physical energy may affect into the remodeling stage by increasing wound breaking strength.

Keywords: electrical stimulation, low intensity laser therapy, shockwave therapy, ultrasound therapy, wound healing

Introduction

One of the most common complications of skin wound in public health and veterinary medicine is chronic wound healing, described by delayed cellular infiltration, delayed granulation tissue formation, decreased collagen deposition and decreased blood flow into the wound site (Zins et al., 2010). Chronic wound healing may be caused by wound contamination, infection, ischemia, hypoxia, malnutrition, immunodeficiency or some medications. These conditions can lead to pain, reluctance to movement, discomfort and eventually causing death (Demir et al., 2004), as well as time consuming and cost of treatment for the patient or animal. The treatment goal for wound healing is rapid closure and is returning fully recovery to the normal function. In small animal practice, there are many cases of chronic wounds where the normal wound healing process has not been adequate. Therefore, various medical approaches and alternative modalities to enhance wound healing in small animals have been developed and could be used in practice. This review describes the basic wound healing process and alternative, noninvasive physical energy modalities to improve wound healing, including electrostimulation, shock wave therapy, ultrasound therapy and low intensity laser therapy.

Wound and wound healing

Wound is defined as a breakdown in the protective function of skin or loss of continuity of the epithelium, with or without loss of underlying connective tissue. Wound healing is a dynamic, interactive process involving solution mediators, blood cells, extracellular matrix, and parenchymal cells (Singer and Clark, 1999; Schreml et al., 2010; Sinno and Prakash, 2013). The wound repair is mainly similar at all anatomical site and can be divided into four major phases (Table 1): hemostatic phase, inflammatory phase, proliferative phase and remodeling phase (Baum and Arpey, 2005; Janis and Harrison, 2016). In practice, there is an overlapping of these phases. In general, each phase occurs in a precise and carefully regulated manner. Interruptions or failure of one or more processes can lead to chronic wound healing, impaired healing or non-healing. Thus, an understanding of the normal wound healing process is essential to investigate and to apply novel techniques to improve wound healing.

The first stage of wound healing is hemostatic phase that starts immediately after tissue injury. Tissue injury is characterized by vascular injuries and extravasation of blood at the wound site. This condition leads to vasoconstriction, instant activation of the clotting cascade, platelet aggregation at the wound zone and stoppage of bleeding. The blood clot reestablishes hemostasis and provides a basic extracellular matrix for cell migration, such as, chemokines and platelet-derived growth factor, that helps stabilize the wound through clot formation, and also activates macrophages and fibroblasts that are important in normal inflammatory response (Singer and Clark, 1999; Sinno and Prakash, 2013).

The second stage is inflammatory phase that occurs in 1-3 day after wounding (Enoch and Leaper, 2005). This stage is characterized by inflammation, which is marked by the sequential infiltration of neutrophils, macrophage and lymphocytes (Broughton et al., 2006; Guo and Dipietro, 2010). Neutrophils are recruited into the wound site to remove invading bacteria, foreign material, and cellular debris (Diegelmann and Evans, 2004; Broughton et al., 2006). After that, macrophages appear and continue the process of phagocytosis and also secrete additional cytokines, chemokines, and growth factors that promote fibroblast synthesis and support angiogenesis (Broughton et al., 2006; Reinke and Sorg, 2012; Janis and Harrison, 2016).

The third stage is proliferative (reparative or fibroblastic) phase which occurs in 2-10 days (Rosinczuk et al., 2016). The wound is markedly filled by re-epithelization, angiogenesis, granulation tissue formation and collagen deposition. Activated platelets and macrophages stimulate epithelial proliferation on the wound edge (Janis and Harrison, 2016) and subsequently, a protective barrier against fluid loss and microbial invasion is reestablished (Broughton et al., 2006). The fibroblast is attached significantly cytokines and chemokines triggering stimulation of new blood vessels into the wound (Schreml et al., 2010). Additionally, the process later synthesizes and secretes collagen and ground substances which represents the basis for a new matrix of connective tissue - serving as substances filling the wound gaps (Reinke and Sorg, 2012) and increasing the tensile strength of the tissue (Chester and Brown, 2017). Subsequently, the proliferative phase builds granulation and collagen tissues onto the wound forming the bulk of the mature scar.

Lastly, the final stage of wound healing is remod-

Table 1. The normal wound healing process (modified from: Guo and DiPietro, 2010. Factors affecting wound healing)

Wound healing phase	Biophysiologic event
Hemostatic phase	1. vasoconstriction 2. clotting cascade, platelet aggregation, blood cloth 3. extracellular matrix migration (chemokines and platelet-derived growth factor)
Inflammatory phase	1. neutrophils infiltration 2. macrophage infiltration 3. lymphocytes infiltration
Proliferative phase	1. re-epithelization 2. angiogenesis 3. granulation tissue formation 4. collagen deposition
Remodeling phase	1. wound contraction

eling that occurs within one to several weeks (Enoch and Leaper, 2005) and continues for a year or longer time, depending on the wound size. Wound contraction occurs through the interactions between fibroblasts and the surrounding extracellular matrix and is influenced by a number of cytokines, including platelet-derived growth factor, transforming growth factor-ß and basic fibroblast growth factor. Finally, the wound, healed with maximum of 75-80% strength of original tissue, can be achieved (Sadava et al., 2014; Chester and Brown, 2017).

Novel techniques enhancing wound healing

1. Electrical stimulation

Electrical stimulation is defined as the application of exogenous electrical signals into the target tissue or on the wound (Ennis et al., 2016). It is believed to restart or to improve the wound healing by mimicing the natural bioelectrical response to injured tissue (Broughton et al., 2006) and to amplify the biological signals (Kloth, 2014). Electrical stimulation has been suggested to reduce inflammation and pain, to improve immunity response, to increase blood perfusion and to improve wound healing (Thakral et al., 2013). Recently, a clinical review has been described electrical stimulation can be manipulated to increase the migration of cells, including neutrophils, macrophages and fibroblasts, increasing release of growth factors, angiogenesis, DNA and protein synthesis and collagen synthesis (Ennis et al., 2016) which has been supported of inflammatory and proliferative phases of the wound healing. Previous study has investigated the use of electrostimulation resulting in the increased production of collagen, improved vasculature and also increased tensile strength in remodeling phase (Broughton et al., 2006). Several clinical studies of electrical stimulation have been reported significant effective treatment the wound in many species by increased wound breaking strength and fibroblast number, significantly reducing the wound surface area, and significantly reduced in wound volume (Demir et al., 2004; Talebi et al, 2015; Ud-Din et al., 2015) as shown in the Table 2.

2. Shockwave therapy

Shockwave therapy or extracorporeal shockwave therapy are defined as pressure wave or transient pressure oscillations or pulsed oscillations. A shockwave is the result of quickly release of chemical, electrical, nuclear, or mechanical energy (McClure and Dorfmuller, 2003). Compressive and tensile force cause cavitation and mechanical microstress in cells and tissues. The mechanism of action of shockwaves is known as the cavitation phenomenon, and relates to an increase in cellular activity and tissue perfusion (Kuo et al., 2009). The first application of shockwaves was used for disintegrating urinary stones in humans (Chaussy et al., 2002). It was later applied for treatment in orthopedic conditions (McClure and Dorfmuller, 2003), in soft tissue, and in chronic wounds (Mittermayr et al., 2012). In addition, shockwaves can be applied without anesthesia which are safe and cause minimal drug interaction

Table 2. The study of physical modalities for wound treatment.

Author and year	Treatment modality	Parameter	Model	Result (Control)
Demir et al. (Demir et al., 2004)	Electrical stimulation	300 µA, 30 min/days/7days day 1-3: negative polarity day 4-10: positive polarity	Swiss-albino rats	Fibroblast on 10th days: 115.2±1.9 (Control: 51.8±1.9) Breaking strength: 7.7±1.4 (Control: 2.38±0.77)
Ud-Din et al. (Ud-Din et al., 2015)	Electrical stimulation	0.004 mA, 60 Hz and impulses x 600 second	Human	Wound healed: 21.6% on days 10 and 41.7% on days 14
Talebi et al. (Talebi et al., 2008)	Electrical stimulation	600 A, 60 min/days, three time a day x 3 weeks	Guinea pigs	Wound healed: Anodal= 84.4±10.5% Cathodal= 82.8±11.4% Control= 74.9±11.1%
Omar et al. (Omar et al., 2014)	Shockwave therapy	100 pulse/cm^2, 0.11 mJ/cm^2	Human	Wound healed: 33.3% (Control= 14.28%) on weeks 8
Hayashi et al., 2012 (Hayashi et al., 2012)	Shockwave therapy	25 mJ/mm^2, 4 Hz	Mice	Wound healed: 88.2±14.5% (Control = 71.1±13.6%) on days 10
Kuo et al. (Kuo et al., 2009)	Shockwave therapy	800 impulse at 10 kV, 0.09 mJ/cm^2 at days 3 and 7	Rat	Healing time: 5.7±0.6 weeks (Control= 9.83±0.31 weeks)
Maan et al. (Maan et al., 2014)	Ultrasound therapy	40 kHz, 3 min, 3 time/week	Mice	Healing time: 17.3±1.5 days (Control= 24±10 d)
Kavros et al. (Kavros et al., 2008)	Ultrasound therapy	0.1-0.8 W/cm^2, low-frequency 40 kHz, treatment time= 4x4 cm with 4 min	Human	Wound healed: 53% (Control= 32%)
Demir et al. (Demir et al., 2004)	LILT	904 nm, 6 mW, 1 J/cm^2, 10 min/ days/10 days	Swiss-albino rats	Fibroblast on 10th days: 113.2±4.1 (Control: 53.0±2.8) Breaking strength = 6.8±1.3 (Control: 1.84±0.61)
Shalaby et al. (Shalaby, 2013)	LILT	650 nm diode laser, 1.8, 3.6, 5.5 J/cm^2 for 5 days a week	Mice	Healing time: 15 days (Control = 21 days)
Gupta et al. (Gupta et al., 2015)	LILT	904 nm, 200 ns pulse width, 100 Hz, 0.7 mW	Rats	Wound healed: 50% (Control= 18%) on days 8

(Schaden et al., 2007). Other possible advantages of shockwaves are pain reduction (Krukowska et al., 2016).

Shockwaves can be applied in chronic wound conditions by using convergent waves, a weak pressure surface with intensified energy (McClure and Dorfmuller, 2003). A study in rats has demonstrated that extracorporeal shockwave could improve blood flow and tissue oxygen saturation after first application and fractionated repetitive treatment boosted and prolonged the effect on microcirculation (Kisch et al., 2015). Furthermore, several studies have indicated that using of low-energy extracorporated shockwaves for accelerate wound healing (Dumfarth et al, 2008; Hayashi et al., 2012). Hayashi et al. (2012) has been reported using of shockwaves therapy of 25 mJ/cm^2 which can increase the expression of endothelial nitric oxide synthase (eNOS), vascular endothelial growth factor (VEGF) and angiogenesis in proliferative phase, the treated wound became significantly healed on days 10 (Table 2). Another

Table 3. The comparisons of various modalities for chronic wound treatment.

Comparisons/ Modalities	Electrical stimulation	Shockwave therapy	Ultrasound therapy	Low intensity laser therapy
Wound healing	Positive effect	Positive effect	Positive effect	Positive effect
Biological mechanism on wound healing	Increased electrical signals into target tissue	Increase cellular activity and blood perfusion	Increase cellular activity, blood perfusion and thermal effect	Increase cellular energy
Anesthesia required	No	No	No	No
Animal contact	Contact	Contact	Contact	Available for non-contact and contact
Tissue reaction	Muscle spasm	Exacerbated (multiple dose)	Thermal effect	No harmful

study on induced-diabetic rats has demonstrated that the shockwaves can be used to increase collagen and fibroblast synthesis, to improve wound breaking strength and to enhance the wound healing in remodeling phase (Yang et al., 2011). Moreover, using of shockwaves therapy with difference dosages have been showed improve wound healing (Kuo et al., 2009; Omar et al., 2014) by reducing wound healing time significantly (Table 2).

3. Ultrasound therapy

Ultrasound energy is a continuous oscillating sound pressure waves producing electrical energy. Ultrasound therapy increases blood flow and relaxes muscle tone and also affects inflammatory response by thermal effects. Non-thermal effects are the main mechanism of ultrasound therapy by the process of cavitation, producing and vibrating micro-bubbles in the tissue (Speed, 2001). Furthermore, movement of fluids along the acoustical boundaries, called microstreaming, is produced by the mechanical pressure. The movement and compression of micro-bubbles causes activated cellular activity (Ennis et al., 2016). Thereby, therapeutic ultrasound effect relies on both thermal and non-thermal effects (Khan and Arany, 2015).

Ultrasound therapy has been shown to be gentle, painless and able to stimulate cells at the wound (Fantinati et al., 2016). Moreover, several studies have suggested wound healing by using ultrasound therapy, modulating vasoconstriction, reducing inflammation, and increasing phagocytosis (Broughton et al., 2006; Maan et al., 2014; Fantinati et al., 2016). In addition, ultrasound therapy has been effective during the inflammatory phase by decreasing necrotic tissue, in proliferative phase by increasing collagen and granulation tissue synthesis (Fantinati et al., 2016). In clinical study with a diabetic mice model it has been demonstrated with ultrasound therapy that the effect of ultrasound treatment became significantly improved by decreased mean wound area relative to original size by day nine after wounding, and also visibly the wound closed faster than control group (17.3±1.5 days versus 24±1.0 days) (Maan et al., 2014). Moreover, a study of ultrasound therapy with 0.1-0.8 W/cm^2 in human has been showed significant decreased area of chronic lower-extremity wounds (Kavros et al., 2008) (Table 2).

4. Low intensity laser therapy

Low Intensity Laser Therapy (LILT), also called low level laser therapy or photobiomodulation, is known to supply direct biostimulative light energy to body cells (Karu, 1989). However, the therapeutic effects of photobiomodulation have not been proven, but previous study suggests that LILT improves wound healing and reduces painful (Bjordal et al., 2006). When employed with appropriate parameters, the light is able to penetrate and to absorb into target tissue sufficiency to initiate cellular processes (Zecha et al., 2016). The absorbed laser energy stimulates molecules and atoms of cells, but it does not significantly increase in tissue temperature (Ebrahimi et al., 2012; Feitosa et al., 2015; Mizutani et al., 2016) and has no remarkable side effects (Marinho et al., 2013). The mechanism for enhanced wound healing is assumed as through stimulation of photoreceptor in the mitochondrial respiratory chain (Karu, 1989). Cytochrome c oxidase is considered as the photoreceptor (Karu, 2008) and function of

cytochrome c oxidase as a generated signal and can lead to quickening of electron transfer reaction, as a result changes in cellular adenosine triphosphate (ATP) or cyclic adenosine monophosphate (AMP) levels, and cell membrane stabilization (Karu, 1989; Broughton et al., 2006).

Various biostimulatory effects of LILT have been reported on wound repair influencing different stages, including immune cells migrate to the wound site in inflammatory phase (Zecha et al., 2016). Hoffman and Monroe (2012) has reported that LILT could increase the mitochondrial membrane potential and could enhance the binding of coagulation factors to activated platelets, increasing fibroblast proliferation and increasing fibroblast growth factor synthesis (Zecha et al., 2016), increasing collagen synthesis (Mester et al., 1985), increasing DNA and collagen synthesis (Ebrahimi et al., 2012), increasing protein synthesis and stimulating cell proliferation and granulation tissue formation in proliferative phase (Evans and Abrahamse, 2008). Using of 904 nm LILT with difference dosages were significantly accelerated wound healing by increasing wound breaking strength and reduced healing time (Demir et al., 2004; Gupta et al., 2015) (Table 2). Additionally, a study of 650 nm diode laser in diabetic induced mice with insulin has been shown markedly faster healing (15 days versus 21 days) (Shalaby et al, 2013).

In the past decade, LILT began to be used for adjunctive treatment in small animal practice, because, there are friendly used, low cost, non-invasive and no harmful side effects, even in patients with negative treatment outcomes. However, Information or knowledge of using LILT in small animals are limited and are no standardized ideal dosage for stimulating tissue healing has been proposed. Therefore, the potential benefits of LILT in small animals need to be further investigated.

Conclusions

In summary, chronic wound healing is commonly present in veterinary practice. The chronic wound may cause due to the interruption or failure of one or more processes of wound healing. The goal of chronic wound management is to accelerate wound healing and recovery to the normal function. Various modalities can be used for adjunctive therapy to enhance wound healing, including electrical stimulation, shockwave therapy, ultrasound therapy and low intensity laser therapy. These modalities have been shown significantly promise in stimulating wound healing in human and animals by deliver physical energy to produce therapeutic biological effects and to support the inflammatory, proliferative and remodeling phase of wound healing. However, low intensity laser therapy has been shown more remarkable than other modalities by accelerated wound healing without side effects to the tissue, including muscle spasm, exacerbated or heat from treatment.

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