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Wound Dressings in Veterinary Small Animal Medicine - A systematic review

Diplomarbeit

Veterinärmedizinische Universität Wien

vorgelegt von

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Table of Contents

1. Introduction:

This diploma thesis is about wound dressings and their use in veterinary medicine. In small animal medicine, wounds are a part of everyday life and are a result of many different causes. Because of the diversity of wounds, treatment is complex and veterinary practitioners must decide which wound dressing would best treat a wound, taking into account the contamination, the status of the healing process, as well as many other factors.

In human medicine, there is an immense variety of wound dressings whose effectiveness is confirmed by randomized, double-blind trials. The use of wound dressings in human medicine is mostly in chronic wounds like diabetic or decubital ulcers (Sen et al. 2009) and therefore, a great amount of specialized wound dressings is available to promote the healing of these types of wounds. However, most wounds that a veterinary practitioner faces, are acute and come with numerous origins. Wound dressings, that are used in veterinary medicine, are derived from human medicine, so the effectiveness of these dressings is not explicitly being tested in order to improve wound healing. To adequately treat a wound in small animal medicine, it must first be evaluated and classified. Based on this assessment, a wound dressing that best matches the specific wound environment should be used.

A systematic review is a work that gives an overview about current scientific findings and their benefit for different communities. Every systematic review tries to answer a question and therefore, all publications that match certain criteria are screened and evaluated based on specific guidelines. There are different organizations that are addressing this topic like the Cochrane Musculoskeletal Group (CMG) or The Grading of Recommendations Assessment, Development and Evaluation working group (GRADE). These organizations give scientists a platform to get access to high quality evidence. The guidelines, which are individually defined by each organization, are based on the evidence pyramid.

The evidence pyramid is a visualization of the different levels of evidence. It is well known in many professional groups that a hierarchy of evidence exists and therefore, different versions of the evidence pyramid have been described. Most of these versions show weak study designs like case-reports on the bottom, followed by case-controlled trials. The higher levels of the pyramid are randomized, blind trials and randomized double-

blind trials. At the top of the pyramid are systematic reviews and meta-analysis (Murat et al. 2016). Some of the working groups define their evidence into levels (e.g. CMG) or classify them based on a checklist (e.g. GRADE or PRISMA Fig. 1).

The aim of this study is to evaluate studies about wound dressings and their use in small animal medicine, particularly in dogs and cats, using the guidelines from the Cochrane Musculoskeletal Group and the evidence levels defined by Santesso et al. (2006).

The hypothesis is that currently less than 30% of all trials are high quality studies with an evidence level of gold or higher.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Fig. 1 PRISMA Checklist for Systematic Reviews (Moher et al. 2009)

2. Literature Review

2.1 Integumentum Commune and Wound Healing

2.1.1 Integumentum Commune

Making up 12% of the weight of an adult dog, the Integumentum commune is the body´s largest organ (Pavletic 2018). In addition to its multiple functions such as thermoregulation, synthesis of Vitamin D, and water storage, the skin is also the first defence against all physical and mechanical influences such as trauma and infection. The Integument is composed of the epidermis, which is ectodermal in origin, the dermis as the underlying layer, which is derived from the mesenchyme, and the deepest layer, the subcutis (Fossum et al. 2018).

The epidermis consists of three major layers: the profound Stratum basale and the Stratum spinosum, which together form in combination, the mitotically active Stratum germinativum. The outermost Stratum corneum, which is in contact with the environment and, is derived of multiple layers of horny cells (Baumgärtner 2012). In some areas of the body such as the footpad, the epidermis is thicker than in areas where dense hair growth is present (Fossum et al. 2018). In these areas, the Stratum lucidum and the Stratum granulosum can be found. In abrasions that penetrate the skin, the Stratum germinativum along the intact skin margins are the source of epithelial cells that cover the exposed defect (Fossum et al. 2018). It must be noted, that the epidermis is an avascular tissue that gets nourished by deeper layers through fluid penetration (Pavletic 2018).

The deeper dermis (corium) is a layer of collagenous, elastic and reticular fibers. Next to those fibers, the dermis contains, inter alia, the capillary network, the arrector muscles for the pili, and neural components. This layer is divided into the superficial Stratum papillare, which attaches to the Stratum basale of the epidermis, and the profound Stratum reticulare (Fig. 1). Those layers of the skin can have various thicknesses in different parts of the body (Baumgärtner 2012).

This varied structure of the Integument of the body must be considered in wound management. For example, the thickest skin is located on the dorsum, the neck, and the head. The thinnest skin is along the ventral aspect of the body and on the medial side of the

extremities (Pavletic 2018). Along with several characteristics, such as the host factors and others, this knowledge is an important requirement in the wound healing process.

The deepest layer is the subcutis (hypodermis), which is composed mostly of fat and, like the more superficial layers, it varies in thickness across the body. The hypodermis is divided primarily into two layers: the Stratum adiposum subcutis and the Stratum fibrosum subcutis. The subdermal plexus is also located in this layer (Fossum et al. 2018). The function of the Stratum adiposum subcutis is to isolate the body from external temperature fluctuation, protect against mechanical influences, and serve as a potential storage of energy.

In humans, blood supply comes from musculocutaneous vessels, which are absent in loose-skinned animals such as dogs and cats. Instead, bloody supply comes from direct cutaneous vessels running parallel to the skin, so some special reconstructive techniques from human medicine cannot be transferred to veterinary medicine (Fossum et al. 2018).

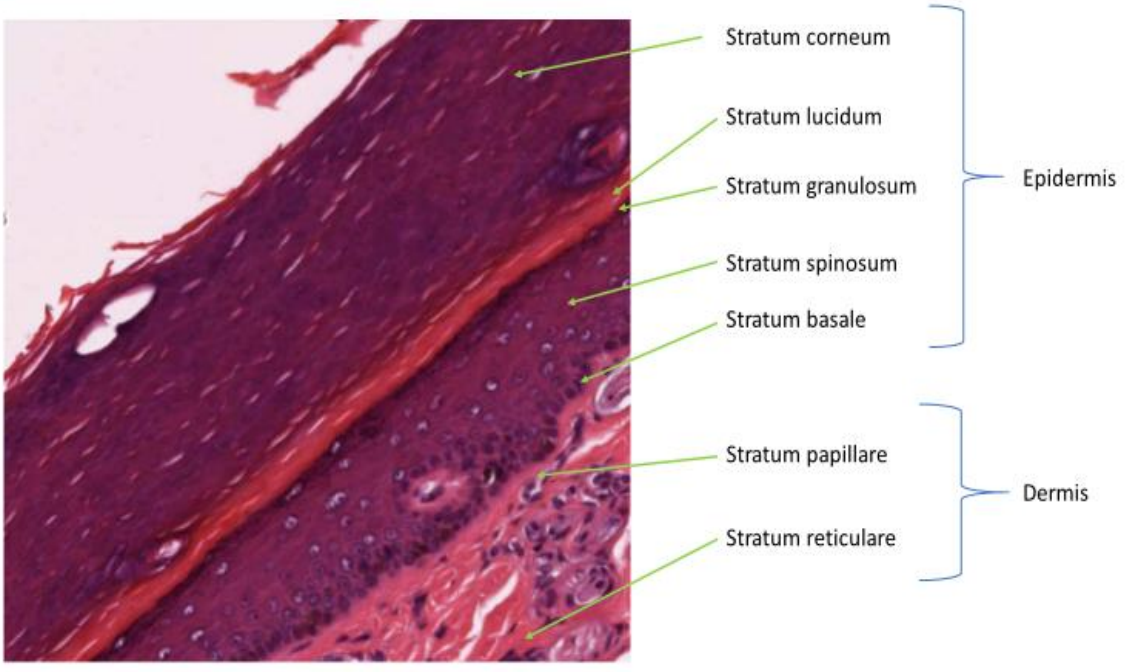

Fig. 2 Präparate Trainer vetucation Schnitt 77b „Sohlenballen Katze“, Veterinärmedizinische Universität Wien, Access: 08.05.2019)

2.1.2 Wound Healing

2.1.2.1 Introduction

“By definition, a wound is a break or loss of cellular and anatomic continuity, with impairment of the tissue’s protective or physiological functions. Trauma, by definition, is a physical injury or wound caused by external force or violence. In common usage, trauma is used to indicate the general aspects of a physical injury, whereas wound is used to describe a more specific lesion” (Pavletic 2018). Wound healing is the process of restoring the continuity of tissue after an injury through a combination of different processes including chemical and physical events that restore the skin or replace the former tissue with collagen. Full-thickness or partial-thickness wounds are the most common abrasions an animal is treated for at the small animal clinic at the University of Veterinary Medicine Vienna. A partial- thickness wound is a wound, that penetrates the upper two layers of the skin: the epidermis and the dermis, whereas a full thickness wound also affects the deeper layers such as the subcutis or even the underlying tendons or bones (Washmut 2017).

Wound healing can be staggered into three phases: inflammation, proliferation and reparation. These phases may occur simultaneously because wound healing is a dynamic process. To initiate the healing process, the damaged cells secrete cytokines, that attract inflammatory cells like macrophages and others to the injured tissue (Fig. 2).

Cytokines play an important role in wound healing, acting as mediators to direct cells to produce proteins, enzymes, and many other components that are necessary in the repair of damaged tissue (Dyson 1997, Gonzales et al. 2015). Growth factors are cytokines that bind to receptors on the cell surface and regulate cell growth and function (Pavletic 2018). They are secreted by various cells and have many effects on wound healing, such as chemotaxis or cellular stimulation. The following chart gives an overview of the most important growth factors (Tab. 1).

Tab. 1 Important growth factors in wound healing (Pavletic 2018)

Abbreviation	Factor	Producing Cells
CTGF	Connective tissue growth factor	Endothelial cells, fibroblasts
EGF	Epidermal growth factor	Platelets, macrophages
FGF-2	Fibroblast growth factor - 2	Macrophages, mast cells, T-lymphocytes, endothelial cells, fibroblasts etc.
GM-CSF	Granulocyte/Macrophage colony stimulation factor	Multiple cells
HB-EGF	Heparin-binding epidermal growth factor	Macrophages
IGF-1	Insulin-like growth factor -1	Macrophages, fibroblasts, epidermal cells, lymphocytes etc.
KGF	Keratinocyte growth factor	Fibroblasts
NGF	Nerve growth factor	Neural cells, glial cells
PDGF	Platelet derived growth factor	Platelets, macrophages, endothelial cells, epidermal cells, smooth muscle cells etc.
TGF-α/β	Transforming growth factor - beta	T -lymphocytes, macrophages, epidermal cells, endothelial cells, fibroblasts, smooth muscle cells
VEGF	Vascular endothelial growth factor	Epidermal cells

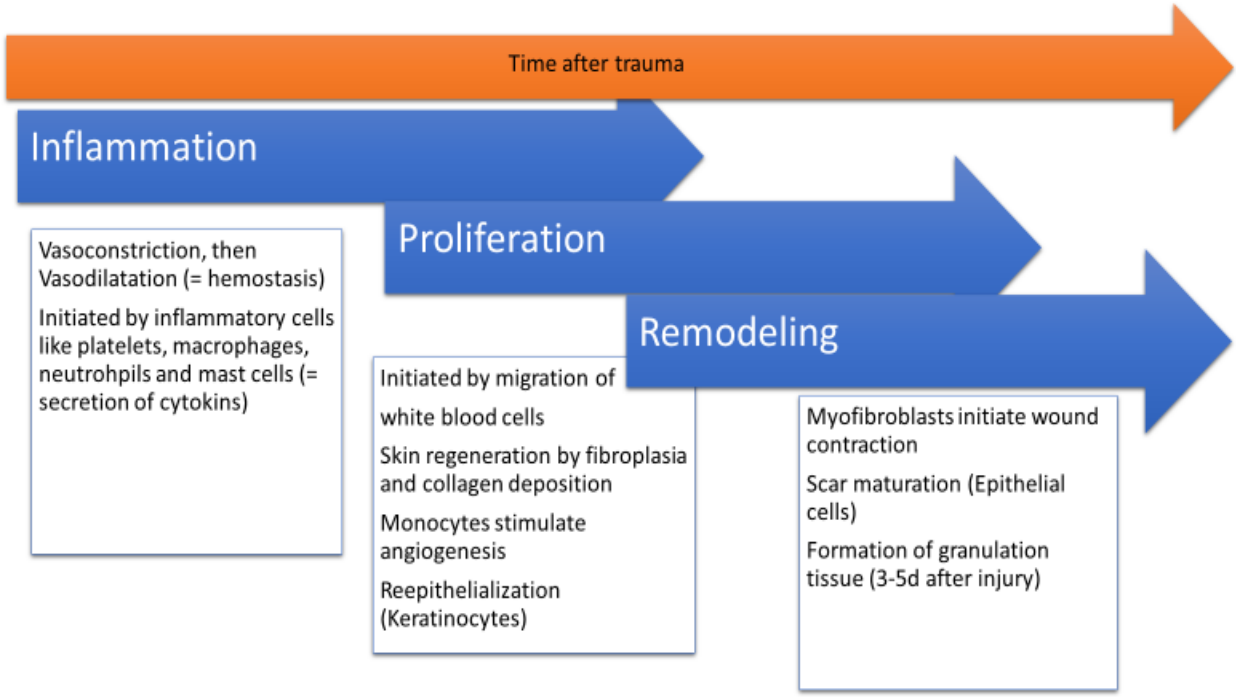

Fig. 3 Stages of Wound Healing

2.1.2.2. Inflammatory Phase:

The inflammatory phase of the wound healing process begins immediately after trauma. During the inflammatory response, the local vascular system contracts for five to ten minutes in order to minimize blood loss. After the initial trauma, it is followed by vasodilatation to allow blood cells such as leucocytes to migrate to the exposed tissue. This process ends in the formation of a clot, to prevent further blood loss. Coagulation is a complex system of mediators leading to an aggregation of thrombocytes and formation of a fibrin network. The building of this extravascular clot is facilitated by platelets and will serve as a matrix for cellular migration. Platelets also secrete several chemotactic factors to recruit leucocytes and vasoactive substances. This first response after an injury is essential to maintain the skins integrity and to secure its function as a barrier against microorganisms by forming a provisional matrix (Pavletic 2018, Gonzales et al. 2015).

The first stage of the wound healing process is characterised by the migration of white blood cells, as well as signs of inflammation such as tumor, rubor, calor, dolor, and functio laesa. Within 30 to 60 minutes after the injury, the leucocytes adhere to the endothelium. The increased permeability of the endothelium in this stage of wound healing allows the leucocytes, along with other components, to migrate into the lesion. The increased permeability is initiated by histamine, serotonin and kinins which are released by mast cells, acting on the venous side of the capillary loop (Pavletic 2018). The first leucocytes emigrating to the wound are neutrophils, which appear in a significantly higher number due to their abundance in circulation, and monocytes, which instantly become activated and transform into macrophages. Both of those cell types continue to secrete cytokines to recruit more inflammatory cells and to activate several processes in wound healing. While monocytes are essential to the healing, neutrophils are not, and their number decreases significantly in the absence of an infection, allowing monocytes to become the dominant population of cells. Neutrophils secrete antibacterial agents, as well as proteinases to degrade necrotic tissue and to attract further neutrophils. Macrophages serve as the wound´s digestive system, consuming foreign material, bacterial components, and produce proteases. The combination of these effects lead to a decrease in necrotic tissue and an increase in wound healing, which can be supported by debridement and lavage, which also plays a role in preventing infections (Fossum et al. 2018, Pavletic 2018).

Normally, the inflammation phase lasts for five days in experimental wounds. However, there is a significant difference between acute and chronic wounds. The first phase of the wound healing process occurs in a short time in acute wounds and is prolonged in chronic wounds (Pavletic 2018). This is an important consideration in the treatment of such wounds.

2.1.2.3 Proliferative Phase

The proliferative phase begins within 48h (hours) after the initial trauma. The purpose of the proliferative phase is to reduce the exposed tissue area by contraction and fibroplasia (Gonzales et al. 2015). In this phase, granulation tissue appears, which is characterised by its bright red colour and its unique surface. Granulation tissue is formed within the first four days after the lesion. The proliferative phase also includes angiogenesis and reepithelialization (Gonzales et al. 2015). Neovascularization is essential to wound healing because it allows for inflammatory cells to migrate and nourish the newly formed stroma with

oxygen and nutrients. This process includes two mechanisms to form vein collaterals: germination and cell division (Gonçalves et al. 2010). The new vascular tissue then differentiates into smaller and larger vessels (Gonzales et al. 2015). The endothelial cells from the damaged vessels can detach from the endothelial wall under the influence of cytokines and migrate into the provisional matrix. They build a vascular loop when in contact with other endothelial cells and sustain the nourishment of the newly formed matrix. Along with low oxygen levels, the wound environment potentiates the neovascularization. Another essential part of the wound healing process is fibroplasia and collagen deposition. Fibroblasts appear in the wound within the first 72h after the trauma. They can attach on fibrin and move along the fibrin fibers. After they arrive at the lesion, they switch to protein synthesis which results in a loose fibronectin matrix, followed by a collagenous matrix (Pavletic 2018). Tropocollagen is found in the extracellular matrix and is arranged in three chains forming a helix. Its components are mostly glycine, proline, and other amino acids (Holzfäller 2003).

Those molecules form fibrils, which are responsible for the strength in the collagen fibre. The first type of collagen occurring in the wound is collagen type III which is converted by collagenases to the stronger collagen type I. Pavletic (2018) also noticed, that this newly formed collagen has a greater tensile strength due to its basket-weave design, but the quantity of collagen is less compared to the original tissue. Furthermore, Pavletic (2018) revealed that the fourth and fifth day after the injury are the most critical times in which dehiscence can occur, because fibroplasia and collagen deposition are prominently noted. After these two days strength of the newly formed tissue increases. Since collagen is responsible for the strength of tissue, its presence is essential to wound healing which could otherwise lead to the mentioned dehiscence. The proliferative phase is also the phase of wound healing in which contraction of the wound edges occurs. This process is initiated by fibroblasts which contain a high amount of actin. These special cells are called myofibroblasts and by accumulating in the wound margins and contracting, they pull the edges toward each other. Reepithelialization occurs simultaneously to the mentioned processes. By the action of specific cytokines, the epithelial coating cells begin to close the wound´s surface (Gonzales et al. 2015). These cells are keratinocytes and their reservoir are epidermal germ cells in the hair follicle (Li et al. 2007). At first, this epithelial layer is only one cell layer thick but becomes thicker as soon as additional cell layers begin to form. In sutured wounds with no gap between the margins, the epithelial layer can close the incision within

48h. Depending on the severity of the defect, the remaining scar tissue after the healing process is different in its shape. In superficial wounds, the healing may occur with good cosmetic results unlike in partial or full thickness wounds where the reepithelialization is not always completely covering and hair growth is less than in superficial wounds. With the decreasing number of capillaries and fibroblasts and a higher rate of collagen, this phase ends (Pavletic 2018). There are several drugs that can affect the normal healing process such as steroids (prednisolone) or anti-inflammatory drugs (non-steroidal, anti-inflammatory drugs, also known as NSAIDs). With these drugs, the process can be delayed, prolonged or even absent (Kunt 1980). Furthermore, different diseases like diabetes, autoimmune diseases or (passive) smoking can lead to a persistent wound or a prolonged healing phase (Gonzales et al. 2015). Another complication, especially in wound contraction, is contracture, or the loss of function or immobility after excessive scar tissue growth or muscle atrophy (Pavletic 2018). In a comparative study on wound healing in cats versus dogs, it was shown by Bohling et al. (2004), that epithelialization in dogs is significantly higher than it is in cats on the same measurement day, which led to the conclusion that wound healing is slower in cats due to the lack of great subcutaneous fat and therefore a lower number of subcutaneous vessels (Bohling et al. 2004). This difference must be considered in the individual treatment of wounds in veterinary practice.

2.1.2.4 Remodeling Phase

The final phase of wound healing begins 20d after an injury and can last up to one year. This phase occurs simultaneously to the second phase of wound healing. Granulation tissue becomes scar tissue, and scar maturation occurs, which is achieved through remodeling and resynthesis of the extracellular matrix to maintain the tensile strength. In this stage, the number of inflammatory cells, blood vessels and fibroblasts decrease due to apoptosis, emigration and other processes which leads to formation of scar tissue with a reduced number of cells (Gonzales et al. 2015). In this phase, the tensile strength of the scar increases to between 70% and 80% of the initial strength of the skin (Pavletic 2018). In a comparative trial between cats and dogs, Bohling et al. (2004) revealed that experimentally induced wounds in dogs have a higher healing rate than the same wounds in cats. The contraction and epithelialization were less in cats than in dogs. Also, granulation tissue started appearing significantly earlier in dogs than in cats (Bohling et al. 2004). These outcomes may lead to the assumption that due to the lack of great subcutis tissue, wounds

occurring in cats heal slower than in dogs as this layer contains the nourishing vessels which are essential to wound healing. An additional point of consideration is the difference in various dog breeds. Breeds with thin skin or a thinner subcutis may have a prolonged wound healing phase, similar to cats.

2.2 Wound Classifications

All the phases mentioned above need special treatment and extensive consideration should be used, when deciding which wound dressing to use. The first step in determining which wound dressing is the best, is to classify the wound. The determining factors are the species of the animal, the origin of the lesion, the affected body area, the extent of the traumatised tissue, the duration of time since trauma occurred, and the contamination of the wound. By conducting a physical exam and a careful anamnesis, most of the criteria mentioned above can be set. In general, all species undergo the same phases of wound healing mentioned above, but there is a noticeable difference between feline and canine patients due to the different structure of the skin components. In loose-skinned animals, a wound heals mostly through contraction (Tobias et al. 2017).

In general, there are two classes of wounds: open and closed wounds. By definition, a closed wound is an injury without loss of the integrity of the skin. In contrast, an open wound is a lesion that penetrates the skin with a specific depth (please refer to the definition of partial and full thickness wounds p.4f) and can be classified into different types, based on their origin:

Abrasion: Skin damage with a loss of epidermis and a portion of the dermis (partial-thickness wounds, e.g. (exempli gratia) first to second degree burn injuries)

Avulsion: Tearing of tissue from its attachments (e.g. car accidents)

Incision: Wound created by a sharp tool, resulting in wound edges with minimal tissue trauma (e.g. surgeries)

Laceration: Irregular wound caused by tearing, which produces superficial and underlying tissue damage (e.g. staking injuries)

Puncture: Penetrating wound caused by a sharp object; punctures cause minimal skin damage, but underlying tissue damage may be severe, resulting in a higher risk of subsequent infection by contamination introduced at time of puncture (e.g. bite wounds, open fractures)

Contusion - Blunt-force trauma that doesn't break the skin but causes damage to the skin and underlying tissue (closed wound, e.g. window- cat syndrome, closed fractures)

Crushing Injury - Force applied to an area of the body over a period (closed wound, e.g. bite wounds)

(Terminology: Bosco 2012)

Additionally, a veterinarian must determine the contamination status of a wound in order to assess the risk of infection. To evaluate this parameter, the veterinarian must know the exact duration of a lesion, as the bacterial colonisation rapidly increases over time and early intervention can reduce the risk of an infection drastically. Clinical research has indicated that bacteria can proliferate from 100/g tissue to 100000/g tissue within six hours (Pavletic 2018). Therefore, four classes of wound classification exist based on the criteria mentioned above:

Clean – Wounds created under aseptic/sterile conditions (nontraumatic, uninfected), those wounds are normally closed by primary intention and do not involve the hollow organs such as the alimentary tract or the respiratory tract

Clean-contaminated – Surgical wounds that involve the alimentary or respiratory tract, wounds that are macroscopically minimal contaminated, duration is from 0h to 6h

Contaminated – Incisions made near inflamed/ infected areas, surgical wounds that involve the colon and traumatic wounds with significant macroscopical visible contamination, duration from 6h to 12h

Dirty and infected – Wounds that involve infected viscera or clinical infection, old traumatic wounds with gross contamination and a duration more than 12h, here the bacterial colonization is 100000/g tissue while in the other classifications the colonization the limit is 10000/g tissue

(Classifications modified from Pavletic 2018, Bosco 2012)

The classification of acute vs. chronic wounds will help the practitioner decide which individual wound dressing shall be used, as a wound with a duration of less than six hours has a reduced chance of evolving into an infection than a wound that is older. Also, trauma of the skin that happened recently needs a completely different treatment than a chronic wound where the wound healing process is noticeably prolonged due to several healing failures. Based on the gross assessment of contamination and the wound duration, the classification

is not always clear. When the practitioner is in doubt, Pavletic (2018) recommends downgrading the wound and treating it accordingly to minimize the risk of complications. To classify a wound correctly, the severity of the damaged tissue and the depth of the wound must be evaluated. Most practitioners use a bulb-headed probe to measure the depth of a wound, the extent of the wound cavity, and a possible perforated body cavity. This examination should be avoided due to the risk that bacteria might be translocated with the probe and cause an infection.

After classification of the wound, the next step in wound management is to consider whether a wound should be closed by primary or delayed closure. This consideration is dependent on the vascularization of the involved tissue, the body area and the amount of devitalized tissue, the contamination grade, the skin available, the age of the wound etc. Pavletic (2018) explains this approach with an injury on the caput. The tissue in this area is highly vascularized and the skin is thicker, allowing for a good surgical closure. Lesions involving the head have a much higher rate of healing by primary intention, unlike wounds on the lower extremities where there is poor blood supply and the skin has lack of laxity.

2.2.1 Wound Closure

2.2.1.1 Primary Closure

Primary closure, as mentioned above, means that a wound can be closed directly after an injury, such as a surgical wound created through the use of sterile surgical techniques. These wounds can be sutured directly after the surgery, while other traumatic wounds must be cleaned before closure. During cleaning, the surrounding hair must be clipped, devitalized tissue must be removed, the wound margins must be refreshed, all the contamination must be removed by lavaging with sterile solutions, and the tissue should appear vital. After cleaning, a primary wound closure can be considered when the wound is not older than between 6h to 24h, it has no visible tissue damage or contamination and wound tension must be avoided with special suture or grafting techniques. If those criteria are not fulfilled, there are several possibilities of further wound management. (Williams and Moores 2009)

2.2.1.2. Delayed Primary Closure

If the surgeon doubts that wound healing by primary closure is possible, wound closure can be delayed for an additional 3d to 5d (Dimick et al.1988) while reassessing the wound daily. This option is mostly chosen for lesions that contain tissue with questionable viability, remaining contamination or possible infection. Therefore, Pavletic (2018) recommends a reassessment to assure the best wound care and the optimal time to close the wound by inspecting it, evaluating possible infection and debriding it several times if necessary. Delayed primary closure is performed before the appearance of granulation tissue in the wound (Williams and Moores 2009).

2.2.1.3. Secondary Closure

After this period the wound can be closed surgically when the mentioned criteria are given, otherwise a secondary closure is recommended. This method delays closure for an additional 5d to 10d after the trauma and after granulation. It is used when the wound shows a persistence of infection or necrotizing tissue, or the wound needs further debridement after the fifth day of wound healing when granulation tissue is already present in the wound.

2.2.1.4. Healing by Secondary Intention

An alternative to wound closure is healing by secondary intention: leaving a wound open in order to heal by contraction and reepithelialization. Wounds selected for this procedure are those which are classified as dirty and infected and therefore are not suitable for the previous closure techniques. Additionally, wounds that are located on parts of the body with skin that have a lack of flexibility and cannot be covered or have a possibility to develop dehiscence because of tension on the sutures are good candidates for this procedure. When the surgeon determines during the operation that closing the incision may lead to a loss of circulation, he can also decide to leave a part of the wound open to heal by secondary intention to prevent the tissue from necrotizing. Younger patients such as kittens and puppies have a higher rate of healing because of their age and the resulting higher activity in mitotic processes, so wounds in these patients are mostly left to heal by second intention because of the likely positive outcome (Pavletic 2018).

2.2.2 Wound Dressing Classification

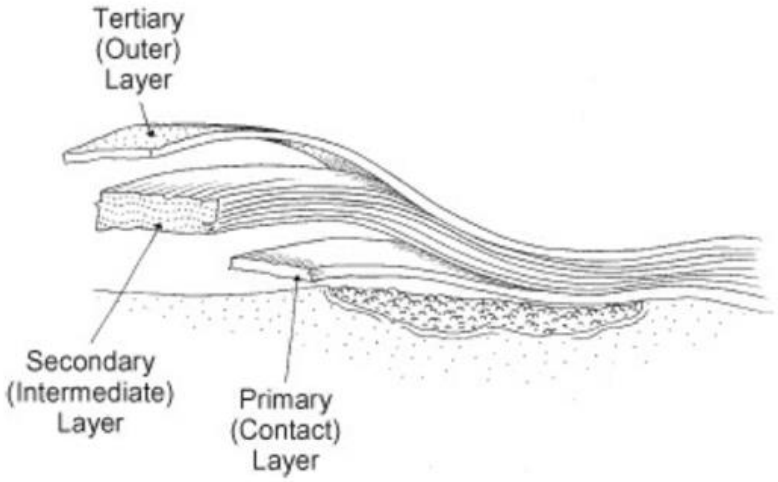

Fig. 4 Layers of a common bandage (Swain et al. 2011)

To protect a wound from environmental influences like humidity or mechanical irritation by the patient, covering the lesion with a bandage is necessary. A common bandage is composed of three layers: the contact layer, the intermediate layer and the outer layer (Fig. 3).

The first layer is always in contact with the wounds surface and therefore it must contain some special properties. Depending on the wounds need, the primary layer can debride tissue when it is changed, absorb exudate, deliver medication (e.g. antibiotics) or it can form a seal over the lesion (Swain et al. 2011). All these mentioned properties shall lead to a better healing process with minimal complications and as such, it is important to select the wound dressing that is appropriate to the current status of wound healing.

2.2.2.1 Wound Healing Enhancing Properties

The best healing outcomes are given in a moist wound environment (Anderson et al. 2009), so most available wound dressings provide it. These wound dressings can be transferred from human medicine, which is possible without a special license. However, dressings that contain some medical substances can only be used by using the veterinary cascade system (Anderson et al. 2009). The discussed dressings are mostly synthetic and can have more

than one property, so the categories may overlap in some cases. The variety of wound dressings is due to the fact that no existing dressing is perfect for all lesions or all stages of wound healing. Pavletic (2018) demonstrates this fact on hydrogel. A topical hydrogel has the same basic properties as a hydrogel dressing, but the topical gel is preferable in deeper wounds whereas the dressing may be more suitable for shallower wounds. The most common wound dressings are topical agents, adherent and non-adherent dressings, absorptive or moisture-retentive dressings, antimicrobial, bioactive or chitosan dressings.

The main difference between these wound dressings is their function: they are either passive dressings like non adherent dressings or they can play an interactive role like hydrogels or bioactive dressings (Pavletic 2018).

2.2.2.2 Topical Agents

In addition to the traditional dressings, topical agents can be applied to the wound to promote healing in several ways. Topical agents primarily exist in a gel or powder form. However, Anderson (2009) recommends not to use these because they may inhibit cell proliferation, irritate the wound or be diluted by the exudate. But if a topical agent is applied, it is important to use the right concentration as recommended by the manufacturer to prevent cytotoxicity (e.g. chlorhexidine in 0,05% dilution (Lozier et al. 1992)). Anderson (2009) also recommends not to use dressings containing antibiotics because they are diluted by the wound`s exudate and therefore promote the development of antibiotic resistance. More recent studies reveal that the positive effects of these dressings are promising (Negut et al. 2018). All of them have their own benefits but they must be held in place by a covering material, so some authors (e.g. Fossum et al 2018) do not classify them as wound dressings in the strict sense of the term. For instance, hydrogels are synthesized gels in which water is the liquid constituent, where particles trap the liquid medium. In contrast, xerogels are dry components that absorb wound exudate by transforming into a gel. Hydrogels provide a moist environment in the wound but have limited absorption abilities (Pavletic 2018). Alternatively, there are natural products like sugar or honey, that are also used in veterinary practice. The use of natural honey has been described in wound management for decades and there are some varieties that have shown beneficial effects in wound healing. The most popular option is Manuka honey from New Zealand which contains methylglyoxal, acting as an antibacterial agent (Binden-Birkenmaier et al. 2018). Unlike these antibacterial properties, sugar has a

high osmolarity and therefore, works as a bacteriostatic agent by reducing moisture in the wound environment. Another topical agent is platelet-rich plasma gel, which was initially mentioned in 1990 and since then has been described in many studies as a promising medical agent. It is autologous plasma, where due to special centrifugation the plasma is enriched with platelets and injected into the wound or applied to it in form of a gel.

2.2.2.3 Adherent Dressings

Adherent wound dressings are used to promote debridement in wounds with necrotic tissue or contamination. Debridement is required in early stages of wound healing, when an infection occurs, or necrotic tissue accumulates on the wound´s surface. Adherent dressings are applied wet or dry and they absorb exudative fluids. When these bandages dry, they lift the fluids on their removal and as such they are not suitable to cover the wound for more than 24h or they will form a crust (Anderson et al. 2009). In a later stage of wound healing, the dressing is changed to another type, like a moisture- retentive dressing (Swain et al. 2011). The simplest and most economic type of an adherent dressing is gauze. It is a multi-layer product with a loose open weave and a common wound dressing for highly exudative wounds and recommended for wounds that need a bandage change multiple times a day. The application should be wet-to-dry or dry-to-dry, which means that in the case of a wet-to-dry bandage the dressing is soaked in sterile saline solution (or similar solution) and placed on the wound, while in the case of a dry-to-dry bandage the gauze is placed directly on the wound without previous preparation. These types of application are indicated for different wounds. For highly viscous exudate, a wet-to-dry application is recommended, whereas for lesions with low-viscosity exudation, dry-to-dry bandages are the better choice. When the gauze dries, it adheres to the lesion´s surface, so the removal may be painful. Because of this, it may be necessary to soak the dressing in warm saline solution or lidocaine 2% without epinephrine (Swain et al. 2011). The disadvantages of adherent dressings must be considered when an adequate wound dressing is chosen because dry gauze may debride not only necrotic tissue but also vital tissue. Fibers of the gauze may remain in the wound environment and cause irritation and essential growth factors may be removed with the dressing when it is changed (Swain et al. 2011).

2.2.2.4 Non adherent or Low adherent Dressings

These dressings are designed not to adhere to the wound´s surface to avoid tissue damage when removed. They are recommended in the granulation and epithelialization stage of wound healing where damage of the new grown tissue is contra-indicated (Anderson et al. 2009). They are applied to the lesion to avoid adherence with the secondary layer, and are synthetic dressings that are mostly fine woven meshes impregnated with paraffin or silicone to improve their non-adherence and allows the exudate to pass through the dressing into the absorptive secondary layer (Abdelrahman et al. 2011). Non-adherent dressings are commonly used in conjunction with topical agents such as ointments, gels or creams to maintain their contact with the wound surface. This combination may lead to a semi-occlusive dressing, that helps provide the moist environment (Pavletic 2018).

2.2.2.5 Absorptive Dressings

In the first seven days after trauma, the wound has a high rate of exudation due to the inflammation processes and the increased permeability of the vessels. This exudate can be retained by an absorptive dressing and the secondary layer (Pavletic 2018). Polyurethane foams are very absorptive and used in wounds with a high volume of exudate in the early stage of wound healing. These dressings have a fine porous membrane and therefore, are non-adherent. But because of this surface, they are not as effective in debridement as alginate or hydrocolloid dressings. It should also be taken into consideration, that a polyurethane dressing does not provide any humidity on its own, so before application on dry wounds the dressing should be moistened (Pavletic 2018). Another example for this wound dressing class are alginate containing dressings. Alginate is derived from various seaweed varieties (Pavletic 2018) and shows promising outcomes in wound healing due to moisture retention and bacterial inhibition (Blessing et al. 2018). In some cases, manufacturers offer dressings where alginate is combined with another medical agent such as zinc or calcium to enhance their advantages in bacterial inhibition (Pavletic 2018). Swaim (et al. 2011) recommends not to use alginate dressings on dry wounds or exposed bones, tendons or muscles. Because of its interaction with the sodium in wound fluids and the formation of a gel-like seal over the surface, the alginate dressing can lead to dehydration of the wound when the exudation level decreases (Swain et al. 2011). When this type of wound dressing is left on the wound for too long, it may dry out and form an eschar, which is hard to remove and should be soaked with saline solution before removal.

2.2.2.6 Moisture-Retentive Dressings

A moist wound environment enhances the wound healing process, so this type of dressing is designed to maintain moisture and hydrate the wound when applied. There are several dressings that can be classified as MRDs (Moisture-Retentive Dressings) such as hydrogel or hydrocolloid dressings. These dressings have the ability to absorb a limited level of exudate and should not be applied to infected wounds (Nickerson et al. 1995). MRDs have many advantages, like hydrating the underlying tissue and facilitating debridement. Intact skin physiologically loses water, which is defined as transdermal water loss. Normal human skin has a transdermal water loss of 4-9 g/m^2/h, whereas in skin defects the rate can increase to 70-90 g/m^2/h. MRDs are classified as dressings, with a moisture vapor transmission less than 35 g/m^2/h (Pavletic 2018).

2.2.2.7 Wet-to-wet Dressings

These are bandages that are frequently remoistened with sterile saline solutions or similar liquids and they are used to hydrate necrotic or mummified tissue. Wet-to-wet dressings are mostly soaked sponges and are fixated with a secure overlying bandage. Pavletic (2018) describes in his book, to use a tube between the bandage layers to facilitate the rehydration of the sponge and to maintain a high moisture level. The bandage should be left in place for 24h.

2.2.2.8 Hydrogel Dressings

Hydrogels are dressings that contain mostly water (up to 90%) which is retained in a fibre network and form a protective gel over the wound much like hydrocolloid dressings (Pavletic 2018). In both cases, excessive overlapping with wound margins is not recommended, because this may lead to maceration of the healthy tissue (Pavletic 2018).

2.2.2.9 Antimicrobial Dressings

There are many dressings currently available that contain antimicrobial agents like nanocrystalline silver or PHMB (Polyhexamethylene Biguanide). The characteristics of silver are historically documented. For example, in ancient cultures silver was contained in vessels to transport water. Nanocrystalline silver (particle size <20nm) is commonly added to many wound dressings, because of its many medical advantages. Silver is known to inhibit bacteria growth by forming reactive oxygen molecules and therefore causing cell damage when it is absorbed by bacteria (Leaper 2012). PHMB is a cationic surface-active agent (comparable to chlorhexidine) which irreversibly damages cytoplasmic membranes (Lee et al. 2004).

2.2.2.10 Bioactive Dressings

Bioactive dressings are wound dressings that originate from living tissue components. Some manufacturers may produce dressings that combine these natural components with hydrocolloid or hydrogel. For example, Manuka Honey dressings are available in small animal medicine and their benefits are as described above (2.2.2.1 Topical Agents). Additionally, collagen derived from purified bovine, porcine, equine or avian sources can be applied as a topical agent or as a wound dressing. The organised collagen fibers are said to promote angiogenesis and chemotaxis and therefore, promote scar maturation (Brett 2008). A new agent currently combined with wound dressings is porcine small intestinal submucosa (PSIS). This tissue contains diverse collagen types such as collagen type I, III or V and different growth factors, that could promote healing and has been used in human medicine in reconstructive medicine (Winkler et al. 2002).

2.2.2.11 Chitosan Dressings

Chitin and its derivates are mostly found in crustacean exoskeletons and are one of the most common polysaccharides in nature. Its structure occurs in macrofibrils and has various characteristics that promote wound healing such as antimicrobial and hydrating properties. Chitin is mostly converted into its derivates like chitosan and combined with other products (Azuma et al. 2015).

2.2.3 Secondary and Tertiary Layer

The secondary layer serves as an absorptive and protective layer, securing the primary layer on the wound and padding the body part or extremity. Common materials used as a secondary layer are gauze pads, cotton rolls or cast padding. The materials used and the thickness of the layer depends on the function of the bandage and the phase of wound healing (Pavletic 2018, Swaim et al. 2011). For example, a fracture must have a much thicker pad layer than a simple protective bandage for an abrasion. The technique that should be used to wrap the secondary layer is simple: the single layers should overlap about 50% and the limb should be wrapped from distal to proximal to prevent circulation problems (Pavletic 2018, Swaim et al. 2011). The tertiary bandage is a protective bandage for the underlying layers, it is mostly a self-adherent and elastic material. The materials are oxygen permeable but may also let moisture through, so it is important to protect exposed parts of bandages on the distal end on extremities with a water-resistant material like duct tape.

2.2.4 Methods used to assess wound healing

The following chapters shall give an overview of the most common methods used to assess wound healing progress.

2.2.4.1 Macroscopical Assessment

A macroscopical assessment means, that the examiner determines criteria before he starts a trial. These criteria are assessed in specific intervals (e.g. every 2d) without the assistance of technology. This method was used earlier in medical history, when there was no access to modern technologies. It is a subjective evaluation and therefore, has a very low level of significance.

2.2.4.2 Observation and Assessment with Photography

A more objective method is to take photos of the area that must be assessed. The examiner takes photos from the determined case (e.g. a wound) at a specific interval (e.g. every day) and at the end of the trial the file with the photos from each patient can be evaluated by a blind external assessor. This method can guarantee a certain objectivity as long as the assessor is not involved in the trial except for the evaluation of the photos. In addition to this, some authors used a software to analyze the pictures to create a more objective method than a person can.

2.2.4.3 Observation and Assessment with Measurement

Assessment with measurement tools is similar to the method mentioned in 2.2.4.2 The examiner uses different measurement instruments (e.g. transparent sheets or a ruler) to evaluate the progress of the case. In the included records, the measurement methods are used to evaluate the wound healing progress with different wound dressings.

2.2.4.4 Histological Assessment

To show progress on the cellular level a common method is to take biopsies at different intervals from the examined tissue (e.g. a wound). In specialised laboratories, those samples are prepared in an internationally standardised way and then examined. This method can give an objective assessment of the progress and has a high level of informative value.

2.2.4.5 Laser Doppler Perfusion Imaging (LDI)

This method is used to show blood-flow in vascularized tissue. It works like an ultrasound by projecting laser beams in between visible and infrared frequency to the surface of the tissue. These laser beams then interact with the erythrocytes in the vascular system and are rejected according to the Doppler Effect. The LDI probe detects those shifted beams and converts them into an electric signal which can be shown on a screen. In wounds, a great number of vessels is an advantage to the wound healing process, because essential growth factors, leucocytes and other stimulating factors can get to the affected body area. This objective method has a high level of scientific value and therefore a high significance (Leutenegger et al. 2011).

3. Material and Methods

3.1 Literature Research

For this systematic review, different electronic search engines were used (Tab. 2). The record research was restricted to veterinary topics that included wound healing with several wound dressings in canine and feline patients with traumatic or experimentally induced wounds. Once several records were found, a search for other publications from the author was performed. Records that satisfy the inclusion criteria were screened by the criteria mentioned below (p. 23) The duration of the research was from 07-21 October 2019 and the following chart (Tab. 2) gives an overview of the selection criteria used.

Tab. 2 Research Criteria

Criteria	
Language	German, English
Research Aid	PubMed Scopus Isis Web of Knowledge Google Scholar Vetmed seeker References of the included records
Keywords	wound healing veterinary wound dressing small animal clinical trial wounds and injuries wound management Wundauflage Veterinär Kleintier

3.2 Data Collection

This systematic review was written according to the principles of the PRISMA guidelines (Preferred Reported Items For Systematic Review and Meta-Analyses) (Moher et al. 2009) and the Cochrane Handbook for Systematic Reviews of Interventions (Santesso et al. 2009, Higgins et al. 2011). The eligibility criteria for the inclusion of each study were determined before the research started. The types of studies that were primarily included were randomized and non-randomized controlled trials, case reports and retrospective studies that used wound dressings in dogs and cats. Studies including all breeds and ages were considered. Studies that included wound dressings used on full and partial thickness wounds on all body parts and lesions that were of traumatic or experimental origin were included as well. Furthermore, only in vivo studies were accommodated to maintain comparability of the outcome and restrictions were placed regarding language, so that only records in German and English were chosen.

On the other hand, all records that did not match those criteria such as wrong language (e.g. Spanish), in vitro trials, and records that do not have their focus on wound healing (e.g. growth of fibroblasts) were excluded.

The following keywords were used in the search engines, separated by commas: wound healing, Veterinary, wound dressing, small animal, clinical trial, wounds and injuries, wound management, Wundauflage, Veterinär, Kleintier.

The screening was performed by one reviewer and 152 records were identified based on the inclusion/ exclusion criteria. The next step included the determination of duplicates from one or more research sources, so in this phase it was possible to exclude 90 publications. After this analysis, the title and abstract of each record was screened to identify content that did not satisfy the inclusion criteria. Afterwards the full text screen of each record was performed, and it was decided if a publication was included to the qualitative synthesis or not. In this phase eleven records were excluded and for each of those records, the reason for exclusion was determined (Please refer Tab. 3). Finally, 39 records about wound dressings in small animal medicine were classified as included in this systematic review (Fig.4). The criteria of each record were extracted and listed in an excel document by the following characteristics:

- Study characteristics (title, author, year of publication)
- Type of trial (in vivo, randomized/non-randomized, blind, case report etc.)
- Study design (Size of groups, use of wound dressings, treated animals)
- Treatment protocol (control group, exclusions during test period, duration of trial, follow-ups

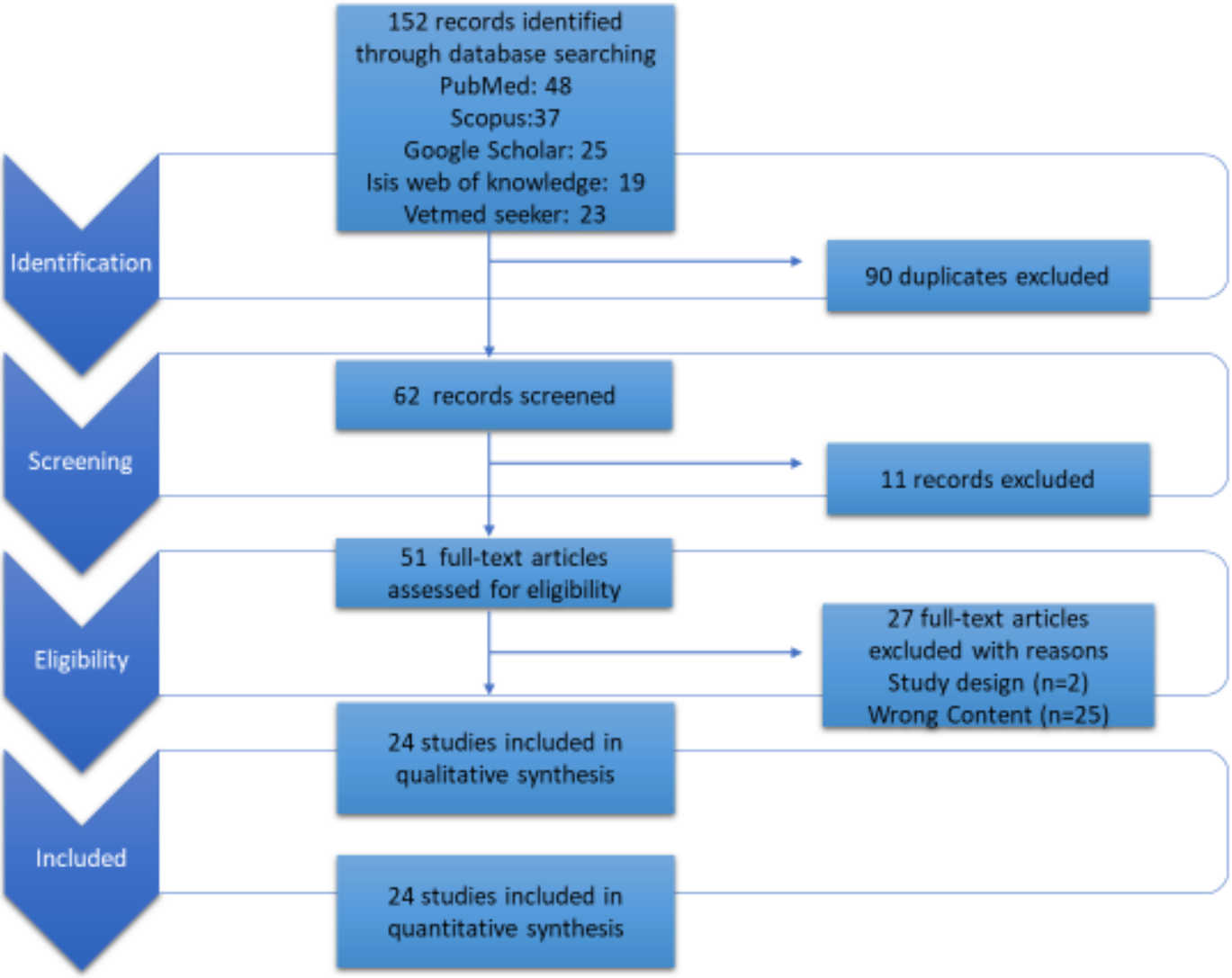

Fig. 5 Selection of primary studies: flow diagram (Moher et al. 2009)

Tab. 3 Characteristics of excluded records (alphabetic order)

Publication	Reason of Exclusion
Abramo et al. (2008)	Closed wounds
Ashrafi et al. (2016)	wrong species of treated animals
Ben-Amotz et al. (2007)	No wound dressing, VAC
Bristow et al. (2013)	No wound dressing, VAC
Cochrane et al. (1999)	In vitro model
Coutin et al. (2014)	Cefazolin concentration in wounds, not about wound healing
Demaria et al. (2011)	No wound dressing, NPWT
Devriende et al. (2018)	No wound dressing, NPWT
Gianetto et al. (2018)	Closed wounds
Guille et al. (2007)	No wound dressing, VAC
Lee et al. (2004)	In vitro trial
Lucroy et al. (1999)	No wound dressing, Laser-light induced wound healing
Meyer-Lindenberg (2015)	No wound dressing, NPWT
Mullally et al. (2010)	No wound dressing, vacuum-assisted closure (VAC)
Nolff et al. (2015)	No wound dressing, NPWT
Nolff et al. (2016)	No wound dressing, NPWT
Nolff et al. (2017)	No wound dressing, NPWT
Nolff et al. (2018)	No wound dressing, NPWT
Nolff et al. 2018	Evaluation of Protein expression, not about wound healing
Nollf et al. (2015)	No wound dressing, NPWT
Or et al. (2017)	No wound dressing, NPWT
Perry et al. (2015)	No wound dressing, NPWT
Petelin et al. 2004	In vitro trial
Pitt et al. (2014)	No wound dressing, NPWT
Stanley et al. (2013)	No wound dressing, NPWT

Summer I 2010	Not about wound healing but wound measurement
Woods et al. (2012)	No wound dressing, NPWT

3.3 Criteria of Evidence – Classes

To ensure objectivity, all included records were classified based on the criteria of the Cochrane Musculoskeletal Group (Santesso et al. 2006).

There are four different levels of evidence: platinum, gold, silver and bronze. To be classified in one of these classes, the record must fulfill certain criteria. The considered criteria are blinding, randomization, size of the groups, existence of control groups, concealment of instructions and patient follow-ups. Because of the variety of species, breeds and other factors, group sizes of more than 50 per group are mostly impossible to achieve and the comparability between breeds is not given because of the great diversity of breed characteristics like skin thickness, hair growth or mobility. Therefore, for this thesis, an adaption of the criteria of the Cochrane Musculoskeletal Group was made, to adjust those criteria to the veterinary field and to consider the variety of factors of the patients in these studies. In this thesis, the group size was reduced to 20 patients. This adjustment was made based on the average group size of the screened records. In human medicine a medical term called “placebo effect” exists. This is an effect where due to the patient´s belief and imagination, medication with no pharmacological ingredients can have a curative effect similar to the original drug. The veterinary patient does not have an influence on the impact of used medications or wound dressings and therefore, the concealment of the treatment allocations can be neglected. The follow-up rate of 80% was not adjusted, because in trials it is important not just to assess the short-time effects of the examined products, but also the long-term effects or side-effects. Another characteristic that was changed is the blinding of accessors and patients. In this thesis, studies were included that used wound dressings on small animal patients, which means a blinding of the patient only plays a role in human medicine. On the other hand, the blindness of the accessor is still important to secure the objectivity of the trial whenever there are no measurement methods that guarantee such objectivity.

The following chart gives an overview to the modified evidence levels of the Cochrane Musculoskeletal Group (Tab. 4).

Tab. 4 Evidence – Levels (modified from Santesso et al. 2006)

Evidence-class	Criteria
Platinum Level	2 individually randomized controlled trials Sample sizes of min. 20 per group Blinding of assessors >80% showed to follow-ups
Gold Level	1 randomized controlled trial Sample size min. 20 per group Blinding of accessors >80% showed for follow-up
Silver Level	A randomized controlled trial fits neither gold nor platinum criteria One non-randomized trial with a control group (or patient is its own control) Evidence from one case-control study
Bronze Level	One case series without control group (or patient is its own control) Expert opinions based on clinical experience

3.4 Analysis of the Included Publications

The included publications were first ordered after their type of trial, such as randomized controlled trials, non- randomized trials, retrospective studies and case reports. This was made to create an overview and, based on this classification, other criteria were determined. There was no classification made based on used wound dressings, because it was not possible due to the variability of the examined products.

4. Results

4.1 Included Publications

After intense analysis, 24 records could be included in the quantitative synthesis. The following chart gives an overview of the aim of each of these publications (Tab.5).

Tab. 5 Included publications and their aim (alphabetical order)

Author	Aim
Adeyemi et al. (2017)	Case Report: the management of a chronic necrotizing wound in a dog using natural honey
Apaydin et al. (2019)	Comparison of Manuka Honey and Rivanol used on infected wounds in cats
Ayman et al. (2014)	Comparison of Aloe Vera and Silver Sulfadiazine in the treatment of second-degree burn in dogs
Chansiripornchai et al. (2008)	Case Report: Treatment of infected wounds on two dogs using a Film Dressing extracted from the Hulls of Durian
Cho-Hee et al. (2015)	Evaluate the effectiveness of locally injected PRP (platelet-rich plasma) on acute cutaneous wounds in dogs
Ferrari et al. (2015)	Evaluate the effectiveness of hyaluronic acid on open skin wounds in dogs
Fukuyama et al. (2016)	Explore the palliative efficacy of modified Mohs paste in dogs and cats
Guanghui et al. (2011)	Evaluate the efficacy of thiolated carboxymethyl- hyaluronic-acid- based biomaterial on wound healing in several species
Hadley et al. (2012)	Comparison of cross-linked hyaluronic-acid- based gel to a standard wound

	management protocol on full thickness wounds in dogs
Hiroshi et al. (1999)	To explore the effects of chitosan on wound healing of experimental wounds in dogs
Karayannopoulou et al. (2011)	To compare the effects of locally injected PRP on secondary intention wound healing of full-thickness wounds in dogs
Karayannopoulou et al. (2013)	Evaluate the effectiveness of an Alkannin/Shikonin based ointment from humans on secondary intention wound healing in dogs in comparison to wound flushing with lactated ringer´s solution
Lee et al. (1987)	Comparison of four nonadherent dressing materials on the healing of open wounds in dogs
Lozier et al. (1992)	Comparison of four preparations of 0,05% Chlorhexidine Diacetate on Wound healing in dogs
Maijer et al. (2018)	Evaluate the effectiveness of bioelectric dressing support on complex wound healing in feline and canine patients
Okamoto et al. (1993)	Comparison of several Chitin products applied to various types of wounds and species
Ramsey et al. (1995)	Comparison of three occlusive wound dressings and a standard nonadherent dressing used on full-thickness wounds in dogs
Schallberger et al. (2008)	Evaluate the effects of porcine small intestinal submucosa on healing of full-thickness wounds in dogs, measured on appearance of granulation tissue, percent

	epithelialization and contraction and other factors
Swaim et al. (2000)	Explore the effects of a hydrolyzed bovine collagen dressing on wound healing of open wounds in dogs
Tambella et al. (2014)	Evaluate the efficacy of autologous platelet gel on canine chronic decubital ulcers
Tanaka et al. (2005)	Examination of effects of a gelatin film sheet with epidermal growth factor for cutaneous wound repair in dogs
Tsioli et al. (2016)	Determine the effects of two occlusive, hydrocolloid dressings on second intention wound healing in cats
Tsioli et al. (2018)	Evaluate the effect of a hydrocolloid dressing on secondary intention wound healing in cats
Winkler et al. (2002)	Determine the effects of a porcine small intestinal submucosa product measured on healing time, epithelialization, angiogenesis, contraction and inflammation of wounds with exposed bone on the distal aspect of the limb of dogs

4.2 Classification of the Publications after SANTESSO et al. (2006)

After an intense quantitative evaluation of the included publications and their criteria (Please refer Tab. 6) none of them could be classified as platinum or gold. 15 of the 24 included records could be classified as Silver (Tab. 6). Furthermore, 9 of the publications could be classified as bronze level (Tab. 6).

Tab. 6 Criteria of the included records

Article	Wound Dressing	Treatened animals	Control group (y/n)	Exclusion (y/n)	Randomization	Blinding	Period of time	Follow-up	Evidence-Class
Adeyemi AB et al. (2017)	Natural Honey	1 dog	n	n	n	n	168d	twice a day - daily / during	Silver
Apaydin N. et al. (2019)	Manuka® Honey and Rivanol®	32 cats	n=16	n	n	n	at least 13 days (some cases longer)	every 3d / during	Bronze
Ayman A. et al. (2014)	Aloe Vera and Silver Sulfadiazine	5 dogs	n (same dogs as control)	n	y	n	27d	every 3d / during	Silver
Chansiripornchai P. et al. (2008)	Durian Hulls extrac	2 dogs	n	n	n	n	14 weeks	every 1-3d / during	Bronze
Cho-Hee J. et al. (2015)	Autologous platelet-rich plasma	3 dogs	n (same dogs as control)	n	n	n	28d	every 2d / during	Silver
Ferrari R. et al. (2015)	Hyaluronic acid	10 dogs	n	n	n	n	range 21-88d	individually	Bronze
Fukuyama Y. et al. (2016)	Modified Mohs Paste	7 (n=4 dogs, n=3 cats)	n	n	n	n	range 14- 32d	individually	Silver
Guanghui Y. et al. (2001)	Carboxymethyl-Hyaluronic- Acid based Biomaterials	9 dogs	n	n	y	n	21d	every 7d / during	Silver
Hadley HS. et al. (2012)	Hyaluronic Acid Based Gel	10 dogs	n (same dogs as control)	n	y	n	32d	every 2-3d / during	Silver
Karayannopoulou M. et al. (2011)	Alkannin/Shikonin ointment	10 dogs	n (same dogs as control)	n	n	n	20d	daily / during	Silver
Karayannopoulou M. et al. (2013)	Autologous platelet-rich plasma	6 dogs	n (same dogs as control)	n	y	n	20d	every 2d / during	Silver
Lee AH. et al. (1987)	Nonadherent dressing materials	12 dogs	n (same dogs as control)	n	n	n	21d	daily / during	Bronze
Lozier S. et al. (1992)	Chlorhexidine	6 dogs	n (same dogs as control)	n	n	n	24d	daily / during	Bronze
Maijer A. et al. (2018)	Bioelectric Dressing	5 (n=1 cat, n=4 dogs)	n	n	n	n	1-4 Weeks	various from 8h to 6d/ during	Bronze
Okamoto Y. et al. (1993)	Chitin	105 (n=72 dogs, n=33 cats)	n (case review)	n	n	n	x (not named)	x (not named)	Bronze
Ramsey DT. et al. (1995)	Occlusive dressing materials	12 dogs	n (same dogs as control)	n	n	n	28d	every 1-3d / during	Bronze
Schallenberger S. et al. (2008)	Procine Small Intestinal Submucosa	10 dogs	n (same dogs as control)	n	n	n	70d	every 2-3d / during	Silver
Swaim SF. et al. (2000)	Hydrolyzed Collagen Dressing	10 dogs	n (same dogs as control)	y	n	n	7d	daily / during	Silver
Tambella AM. Et al. (2014)	Autologous platelet gel	18 dogs	n (same dogs as control)	n	y	y	25d	every 5d / during	Silver
Tanaka A. et al. (2005)	Gelatin film Dressing with EGF	2 dogs	n (same dogs as control)	n	n	n	15d	x (not named)	Silver
Tsioli V. et al. (2016)	Occlusive, hydrocolloid dressing materials	10 cats	n (same cats as control)	n	y	n	21d	daily / during	Silver
Tsioli V. et al. (2018)	Hydrocolloid Dressing	10 cats	n (same cats as control	n	y	n	21d	every 2-7d /during	Silver
Hiroshi U. et al. (1999)	Chitosan	3 dogs	n (same dogs as control)	n	n	n	15d	every 3d / during	Silver
Winkler JT. et al. (2002)	Porcine Small Intestinal Submucosa	10 dogs	n (same dogs as control)	n	n	n	21d	daily / during the first 7 days	Silver

4.3 Results Publication Outcomes

4.3.1 Classification of the included Publications

Based on the used wound dressings, the publications were classified into eight separate groups (Tab 7.). These eight groups are:

- Experimental Dressing Materials (3)
- Hydrocolloid Dressings (2)
- Nonadherent Dressings (5)
- Occlusive/ Adherent Dressings (1)
- Autologous Plasma (3)
- Topical Agents (10)

Outcome Group	Publication
Experimental Dressing Materials	Maijer et al. (2018)
	Schallberger et al. (2008)
	Winkler et al. (2002)
Hydrocolloid Dressings	Tsioli et al. (2016)
	Tsioli et al. (2018)
Non adherent Dressings	Chansiripornchai et al. (2008)
	Hiroshi et al. (1999)
	Lee et al. (1987)
	Okamoto et al. (1993)
	Tanaka et al. (2005)
Occlusive/ Adherent Dressings	Ramsey et al. (1995)
Autologous Plasma	Cho-Hee et al. (2015)
	Karayannopoulou et al. (2011)
	Tambella et al. (2014)
Topical Agents	Adeyemi et al. (2017)
	Apaydin et al. (2019)
	Ayman et al. (2014)
	Ferrari et al. (2015)
	Fukuyama et al. (2016)

	Guanghui et al. (2011)
	Hadley et al. (2012)
	Karayannopoulou et al. (2013)
	Lozier et al. (1992)
	Swaim et al. (2000)

4.3.2 Experimental Dressing Materials

Three publications could be identified that used experimental dressing materials: Maijer et al. (2018), Schallberger et al. (2008), Winkler et al. (2002).

Maijer et al. (2018) discusses the benefit of a microcell battery- impregnated bioelectric dressing (BED) on five different small animal patients (one cat and four dogs). All patients had a wound with complicating factors like infection or exudation and received a BED for 1- 4 weeks. Maijer et al. (2018) discusses the potential of bioelectric dressings in the management of complex wounds.The dressing recreates the physiological electric field and stimulates fibroblasts to synthesize collagen, glycoproteins and other proteins that are essential to restore the extracellular matrix. The documentation of the wound healing process was made subjectively by the treating veterinarian and not based on a standard protocol. The general outcome was a “faster than expected” wound healing, but due to the lack of measurement methods and the retrospective study design this outcome has a very low evidence level (bronze level).

Schallberger et al. (2008) and Winkler et al. (2002) worked with an experimental biological material extracted from swine small intestinal tissue. This porcine small intestinal submucosa was used on exposed bones (Winkler et al. 2008) and acute full thickness wounds (Schallberger et al. 2002). Both studies were prospective controlled experimental trials conducted on purpose-bred dogs. In both publications the wound were experimentally induced, and the treatment based on a protocol individually defined by each examiner. Winkler et al. (2002) tried to examine the advantage of PSIS on exposed-bone extremity wounds. After the wounds were created, one side was to be treated with PSIS, whereas the other side served as the control and was treated only with standard bandage. After 48 days, all wounds healed without the need of surgical interference, and the trial showed no benefit of PSIS on exposed-bone wounds at all. There was no significant difference in wound contraction, epithelialization, tissue perfusion or inflammatory response. To maintain

objectivity, the wounds were evaluated subjectively, with planimetry, histological assessment and DPI.

This study design guarantees a higher level of evidence than case-reports, but the selection of the treated extremity was made non-randomized, which means the outcome of this trial has a medium level of evidence (silver level).

The other trial (Schallberger et al. 2008) investigated the possible advantages of PSIS on acute full thickness wounds. It was designed similar to the publication that was described earlier. The examined wounds were induced experimentally on the trunk, but the deciding factor which determined which wound would be treated with PSIS was a randomized coin toss. Whereas the other side was then treated with a commercial hydrogel dressing. The wounds were studied for 70 days and assessed at a specific interval. All measurement parameters like wound contraction, epithelialization and granulation tissue formation were significantly higher in the control group than in the wounds treated with PSIS. In the histological assessment, an acute inflammation response was found in the PSIS wounds, which is consistent with other reports according to Schallberger et al. (2008). The measurement methods to evaluate the wounds were made with digital photography, histological assessment and microbiological evaluation. Due to this study design and the randomization, the evidence level of this trial is higher than the other PSIS publication.However, because of the small group size (ten dogs), the scientific significance could still be improved (silver level).

In this case, the trials had a low to medium level of evidence and more studies to verify their improvement in medicine are needed. The analysis of these three trials shows that especially new and experimental products need a high-quality study design to show the advantage of their use.

4.3.3 Hydrocolloid Dressings

Two publications investigated the effect of hydrocolloid dressings on wounds in small animals: Tsioli et al. (2016) and Tsioli et al. (2018).

The two publication from Tsioli et al. (2016, 2018) examine the effect of hydrocolloid dressings on second intention wound healing in cats. For the trials purpose-bred laboratory cats were used as test subjects for experimentally created wounds. Whereas in one trial, where Tsioli et al. (2018) used a hydrocolloid dressing to compare it with a non-treated control wound, the other study examined the difference between a hydrocolloid dressing and an oxygen impermeable dressing and compared the outcomes with a control wound (Tsioli et al. 2016). In both trials the wound healing process was evaluated by histological and subjective assessment including planimetry on a daily basis over a period of 21 days. Tsioli et al. (2016) reported that there was no significant difference between the hydrocolloid and the oxygen impermeable dressing, but there was a significant difference when compared to the control group in epithelialization appearance and granulation tissue formation. This outcome is consistent with the other trial (2018), where the adherent characteristic of the hydrocolloid dressing is described to maintain low oxygen tension and therefore, promoted neovascularization and cellular immigration for better wound healing. Because of the randomization the publications have a higher level of evidence (silver level) than non-randomized controlled trials. However, to verify the advantages of hydrocolloid dressings on second intention wound healing in cats, a greater group size would be necessary.

Hydrocolloid dressings are well known to promote several processes in wound healing. Because of animal welfare guidelines, achieving large group sizes (>20 per group) for a trial is nearly impossible, because of the strict specifications for each patient, like kennels and other requirements that are listed in the discussion. Yet, for a high level of evidence and a significanct outcome, two individually randomized controlled trials (modified Santesso et al. 2006) and other criteria are needed. The records about hydrocolloid dressings in this thesis could not achieve this requirement due to strict animal welfare guidelines. Due to the randomization and the presence of a control group, the evidence level is still significant enough to verify the advantages of hydrocolloid dressings in wound management.

4.3.4 Non adherent Dressings

Five publications that examined the use of non-adherent dressing materials on wound healing could be identified: Chansiripornchai et al. (2008), Hiroshi et al. (1999), Lee et al. (1987), Okamoto et al. (1993), Tanaka et al. (2005).

Chansiripornchai et al. (2008) developed a film dressing with peptidoglycan (PG) extracted from the hulls of durian and used it on two infected open wounds in dogs. Both dogs were already treated in an animal clinic with different methods and medications but failed to heal. The wounds were covered with PG and the bandages were changed every 1-3 days. When the bandages where changed, the wounds were evaluated and photographs were taken for documentation. The dogs were sent home wound area was satisfactorily reduced, and further treatment was carried out by the owner. Chansiripornchai et al. (2008) tried to develop a new wound dressing material, because the long-term use of commercial dressings is expensive in Thailand. The outcome of this case report was promising, because the PG film dressing provided a moist wound environment similar to hydrocolloids. However, a better study design is necessary to verify the positive effect of PG on infected wounds or other wound models. Therefore, the level of evidence in this publication is very low (bronze level) and further trials with controlled randomized animal models are needed.

Hiroshi et al. (1999) tested a cotton fiber-type chitosan on experimentally created wounds on dogs. While one side of the bilaterally induced wounds were treated with the chitosan dressing, the other served as a control. Over a period of 15 days the wounds were checked every three days and evaluated using histological assessment. Chitosan is known to activate inflammatory cells and macrophage migration to the wound area. Hiroshi et al. (1999) also noticed, that in the chitosan treated specimen the amount of mitotic cells in the granulation tissue was significantly higher than in the control group. Also, the neovascularization was accelerated by chitosan, which leads to the assumption that it increases the wound healing rate. The publication was conducted on three dogs with no control group other than the dogs themselves. This study design classifies the evidence level of this publication as being medium (silver level), but due to the lack of randomization and the small group size the record has no scientific significance. A trial with a more modern protocol like larger randomized controlled studies with advanced technologies is needed to confirm the outcome of Hiroshi et al. (1999).

Lee et al. (1987) used four different non adherent dressing materials to compare their outcome on surgically created wounds on the dorsum of dogs. In her trial, Lee et al. (1987) compared the advantages of a rayon/polyethylene dressing, a cotton nonadherent dressing, a fine mesh gauze impregnated with petrolatum and a commercial petrolatum emulsion dressing. The evaluation period was 21 days and the bandages were changed daily. To assess the progress of the wounds, the wounds were traced on transparent sheets on day 0 and then on re-assessed on different days with an orthoplex digital coordinate sensor to measure the percentage of wound contraction. Additionally, a bacterial culture was made from each wound to evaluate the microbiological invasion. The outcome of this trial was, that wounds that were treated with either rayon/polyethylene or cotton nonadherent dressings had a significant higher rate of epithelialization in the first week. However, the wounds treated with petrolatum- containing dressing had a higher rate of wound contraction during the first seven days. Later in this trial, there was no significant difference between the used wound dressings. Due to the lack of randomization and the absence of a control group, the level of evidence in this publication is very low (bronze level).

Okamoto et al. (1993) analyzed the impact of chitin (polymeric N-acetyl-D-glucosamine) on different species including 72 dogs and 33 cats. He used different products containing chitin such as sponges, sheets or chitin- cotton. The patients he treated suffered from different problems like abscesses, oncotomy, bite wounds and other traumata. The application of the chitin- containing product was decided on a case by case basis, so it was used as a filling agent after surgical procedures in some cases and as a covering layer after various types of trauma in others. These dressings were changed individually depending on the origin of the wound, and the healing process was assessed macroscopically. In more than 85% of all cases, the wounds healed without serious complications. During this trial, Okamoto et al. (1993) concluded that chitin accelerated the wound healing in various types of trauma and abscesses. The author assumes that chitin enhances the release of collagenase enzymes from different cells but only when the dressing stays in contact with the wound. Due to the lack of further assessment of the effect of chitin on wound healing, the different outcomes from this study are only assumptions from the authors and have a very low evidence (bronze level). To verify these assumptions, further research and high-quality trials focusing on one species and one chitin- containing product are necessary.

Tanaka et al. (2005) used a gelatin film dressing with epidermal growth factor (EGF) on experimentally induced wounds on dogs. A gelatin dressing was manufactured by the

researchers and EGF was added. The main focus of this trial was to evaluate the effect of an EGF- containing dressing on partial thickness wounds in dogs. The dressings were changed every day over a period of 15 days and assessed by taking photos every three days and digital image analysis. At the end of the trial a histological assessment was made, too. Tanaka et al. (2005) observed wound area reduction earlier in wounds treated with EGF than the control wounds. Even histologically, there was a significant difference between the treated and control wounds. In the wounds treated with EGF, there was a higher rate of reepithelialization and an increased degree of matrix density. This leads to the conclusion, that a dressing combined with EGF could be a promising product in wound management. On the other hand, it must be considered that EGF is an unstable polypeptide which needs a stabilizing environment like the gelatin sheet used in this study. Due to the lack of randomization in this publication and the small group size, the scientific significance is low. However, the researchers used the examined dogs as the control group which leads to a medium evidence level (silver level).

The analysis of the publications that examined the effect of non adherent dressing materials in small animals shows the general problem of trials in veterinary medicine. The study design is well-thought- out, but due to the small group sizes and, in most cases, a lack of randomization, the significance and the evidence level are low.

4.3.5 Occlusive/ Adherent Dressings

One publication could be identified that examined the use of occlusive/ adherent dressings: Ramsey et al. (1995).

Ramsay et al. (1995) examined the difference of three occlusive dressing materials on full-thickness skin defects in dogs. Two wounds were created bilaterally on the dorsum of 12 beagles and treated with equine amnion, hydrogel dressing, polyethylene sheeting or a semi occlusive rayon/polyethylene dressing. The trial lasted 28 days and all dogs were examined four times dail. The progress of wound healing was monitored by taking photographs every 2-3 days simultaneously with bandage changes. All wounds were measured with transparent sheets of polyethylene and compared. The wounds treated with equine amnion had significantly better wound contraction and wound healing compared to the other groups. Ramsay et al. (1995) concluded that equine amnion can be used to accelerate healing of full thickness wounds in dogs, but only in controlled wound models. Therefore, they recommend testing this material in naturally acquired wounds. Due to the lack of randomization and the small group size, this trial has a low level of evidence. However, the included dogs were used as a control group. This study design has a medium level of evidence (silver level) but no scientific significance and has to be verified in a well-designed trial like a randomized controlled trial.

4.3.6 Autologous Plasma

Three records investigated the use of autologous plasma: Cho-Hee et al. (2015), Karayannopoulou et al. (2011), Tambella et al. (2014).

Cho-Hee et al. (2015) tried to identify the effectiveness of platelet-rich plasma (PRP) used on acute cutaneous wounds in dogs. PRP was administered via intralesional injection on experimentally created wounds in three beagles. PRP was extracted from whole blood samples of each dog. 0,7ml of PRP was injected into each of the experimental wounds, whereas a saline solution was injected in the control wounds. These injections were repeated on days 2 and 4. Wounds were examined every two days and measured. For histological evaluation, punch biopsies were conducted every 7 days. In the PRP-treated wounds, macroscopically and microscopically faster wound healing was observed, but the difference compared to the control wounds was not significant. Cho-Hee et al. (2015) concluded that PRP is an easily accessible cell therapy, but this method can only be used on healthy

patients, because other conditions could influence the quality of PRP. Additionally, the authors considered, that due to the simplicity of injection techniques, this application method is more practical in veterinary medicine than the traditional gel form. Cho-Hee et al. (2015) mentioned the limitations of his publication, such as the lack of information from patients with health issues. Due to the lack of randomization and the small group size, this publication has very low significance, but the level of evidence is medium (silver level) because of the presence of a control group.

Karayannopoulou et al. (2011) tried to evaluate the effect of locally injected PRP on second intention healing of full thickness wounds in dogs. For this trial, six beagles were anaesthetized, and three skin defects were created bilaterally on the dorsum of each dog. The side that was to be treated with PRP was randomly selected, and the other side was left untreated and served as the control. To evaluate wound healing, each defect was measured by planimetry, laser doppler flowmetry and histological assessment. PRP was extracted from whole blood samples from each dog and analyzed by a hematology analyzer. Bandages were changed every two days until the last day of the experiment (Day 20). Planimetry showed no significant difference in wound size, epithelialization or contraction. Flowmetry revealed significantly higher tissue perfusion in the PRP- treated wounds and histological assessment showed .significantly increased angiogenesis in PRP wounds. The general outcome was, that PRP used for improving second intention wound healing could not be confirmed but PRP induced a significant increase in tissue perfusion and promoted the formation of more and well-organized collagen bundles.

A limitation in this publication was the small group size, but due to randomization and the presence of a control group, the level of evidence is medium (silver level) and the record has valuable scientific significance.

Tambella et al. (2014) examined the efficacy of topically applied autologous platelet gel (APG) in patients with chronic decubital ulcers. 18 client-owned dogs were included that had bilateral chronical wounds. The side which was treated with the platelet gel was randomly selected. APG was applied every five days during bandage changes for 25 days, whereas the control side was treated with a paraffin gauze dressing. To evaluate the healing process, wounds were measured by using planimetry software. In this publication, the promising result was a significantly quicker wound healing than in the control wounds. Additionally, there was no abnormal tissue formation or hypertrophic scarring observed. Tambella et al. (2014)

concluded that APG has great advantages over the use of conventional paraffin gauze dressings in the treatment of chronic non-healing decubital wounds in dogs. This leads to the assumption that APG is an effective, simple and cost-effective treatment for decubital ulcers in dogs. Yet the author recommends further studies to reveal the advantages of APG compared to other conventional wound dressings.

Based on the study design, this publication has high scientific significance, but due to the small group size the level of evidence is medium (silver level).

All three publications showed the advantages of autologous plasma used on different types of wounds. Additionally, all records have well-designed studies but unfortunately group sizes are not large enough to be classified as gold or even platinum level publications.

4.3.7 Topical Agents

Ten publications investigated different topical agents in small animal medicine: Adeyemi et al. (2017), Apaydin et al. (2019), Ayman et al. (2014), Ferrari et al. (2015), Fukuyama et al. (2016), Guanghui et al. (2011), Hadley et al. (2012), Karayannopoulou et al. (2013), Lozier et al. (1992), Swaim et al. (2000).

Adeyemi et al. (2017) presented a case about an indigenous Nigerian dog that was attacked by a baboon and successfully treated with natural honey. The dogs arrived at the small animal clinic with a pre-treatment of two antibiotics, but the wound failed to heal. The dogs had severe tissue loss due to necrotization along the dorsum. After debridement and removal of necrotic tissue, the wound was treated with natural honey twice a day for the first 100 days and then once daily. Additionally, an oral antibiotic therapy was started based on the results of the bacterial culture and sensitivity test. The author reported that natural honey as a wound dressing is very unpopular in Nigeria, but in the case report, it shows promising results in wound closure and antibacterial effects. Due to the study design the level of evidence is very low (bronze level) and so is the scientific significance.

In his publication, Apaydin et al. (2019) compared the use of Manuka honey with ethacridine lactate (Rivanol) on infected wounds in cats. 32 cats with wounds on different parts of the body were included and separated into two groups to examine the effect of Manuka honey. Wounds were measured every 3 days and the healing process was monitored with photographs. In this trial, the decrease of the wound area in both groups were similar. The author concluded that Manuka honey can serve as an alternative to Rivanol. The trial was

non-randomized and therefore the scientific significance is very low but due to the large group size and the presence of a control group the level of evidence is medium (silver level)

In his record, Ayman et al. (2014) evaluates the effect of aloe vera and silver sulfadiazine on second-degree burns in dogs. In five dogs, deep second-degree burn wounds were created and those wounds were divided into three groups: aloe vera, silver sulfadiazine and a control group with no topical treatment. All bandages, as well as the topical treatment if any (either aloe vera or silver sulfadiazine), were changed every 3 days and wounds were photographed during these changes to evaluate the healing progress. The trial was performed for a period of 27 days. Wounds treated with aloe vera had significantly higher wound contraction compared to the other two groups. Additionally, the clinical signs of inflammation such as redness, swelling and exudation were less in the group treated with aloe vera, but the difference was not significant. Ayman et al. (2014) concluded, that the treatment with aloe vera on burn wounds has anti-inflammatory effects and accelerates the wound healing process.

Due to the randomization, the level of evidence is medium (silver level), but the group size is very small, so the scientific significance is low.

In her publication Ferrari et al. (2015) explored the application of a dressing containing hyaluronic acid (HA) on open skin wounds in dogs. For the trial ten client-owned dogs were included. To assess the reepithelialization process, the wounds were independently evaluated by two veterinary surgeons. To monitor the reduction of the wound area, digital photographs were taken and uploaded in a wound tracing software that calculated the wound area. Because of the different assessors, the bandages were changed at different times, but the median was every 4 days. Also, due to the different wounds, the healing process occurred at different durations, but the median time for wound healing was 34 days. The role of HA in wound healing in human medicine has been intensively investigated unlike in the veterinary sector. In this study, HA- containing products from the human medicine sector were used and the authors found them easy to apply without the need of intense training. This leads to the conclusion that HA could be used even in an ambulatory setting. The general outcome showed promising results but unfortunately, due to the lack of a control group, it has no scientific significance. Additionally, the level of evidence is very low (bronze level), because the dogs were not divided into groups to assess the advantages of HA-based products compared to conventional dressings.

Fukuyama et al. (2016) conducted a trial on seven animals (4 dogs and 3 cats) which had malignant skin wounds. These animals were treated with modified Mohs` paste, prepared by mixing zinc chloride, zinc oxide starch powder, glycerin with distilled water, and applied topical. After clinical examination, the Mohs` paste was applied once a day and left in place for one hour. Under this treatment, the size of the malignant wounds significantly decreased. This led to the assumption that Mohs` paste is effective for the reduction of tumor progression and possess other advantages. Fukuyama et al. (2016) still points out that it is a palliative and not a curative treatment for malignant skin wounds. This case series has a low level of evidence (bronze level) due to the lack of a control group and other high-quality signs of controlled trials.

Guanghui et al. (2011) used a crosslinked -hyaluronic -acid- based ointment in his trial on multiple species including dogs. Nine dogs were purchased from a local shelter and anaesthetized for wound creation. The wounds were bilaterally induced, and the side to be treated with the crosslinked HA ointment was decided randomly, while the other side served as control. A bandage check was made daily and the bandages were changed every 7 days. During every bandage change, the wound was documented by taking photographs. The trial lasted for 21 days, before the bandages were removed and the wounds were evaluated. During the study, the dogs were released back to the kennel housing and some dogs managed to remove their bandages. Consequently, the bandages were changed more frequently in some cases than in others. The general outcome was a faster wound healing a greater amount of granulation tissue in the groups treated with crosslinked HA.

The dogs were housed in the local animal shelter, which lead to a deviation from the original treatment protocol. The form of housing resulted in an individual bandage change frequency for each patient. In general, study protocols are strictly determined, and every deviation leads to an exclusion of the patient due to the lack of comparability between the cases and the outcome. Due to this fact, and the small group size, the scientific significance is low, but due to the randomization of the treated side, the level of evidence is medium (silver level).

In her publication Hadley et al. (2012) compared the effect of a crosslinked HA- based gel to a standard wound management protocol on the healing of acute full thickness wounds in dogs.

For the trial, two wounds were created bilaterally on the trunk of ten purpose-bred beagles. It was then randomly decided which side would be treated with the HA- based gel and which

served as control. To assess the wound healing process at each bandage change (every 2-3 days), the wounds were subjectively evaluated and photographs were taken. These photographs were uploaded tp a wound tracing software, and by the end of the trial, evaluated by a blinded assessor. Additionally, a biopsy was taken from the wounds every 7 days to evaluate the effect of the crosslinked HA on wound healing histologically. Wound planimetry showed a greater reduction in the total wound area and a higher percent of contraction in the HA- treated wounds. Yet, the percent of epithelialization was less than in the control wounds. In the histological specimens, the wound treated with HA showed a higher number of fibroblasts than the controls. Hadley et al. (2012) concluded that the topical application of a crosslinked HA does not enhance the healing of acute full thickness wounds in dogs, but further investigations with other treatment protocols are necessary.

In this trial the assessors were blinded with a computer software and the treated side was randomized, which leads to a high scientific significance. This study design results in a high level of evidence, but due to the small group size the evidence level is still improvable (silver level).

Karayannopoulou et al. (2013) investigated the use of an alkannins/ shikonins- based ointment on second intention wound healing in dogs and compared it to wound flushing with lactated Ringer´s solution. For this trial full thickness skin defects were created on the lateral aspect of the antebrachium of ten dogs. The wounds were treated once daily for about 20 days. Assessment was made through laser doppler flowmetry, histological evaluation and planimetry. Every wound was evaluated subjectively first and every finding was documented. After subjective evaluation, laser doppler flowmetry to measure the cutaneous perfusion and planimetry was performed to evaluate the rate of open wound healing. Specimens for histological evaluation were obtained on three different days after surgery under general anesthesia and compared to the specimen that was taken on the day of surgery. Laser doppler flowmetry showed significantly higher tissue perfusion in the alkannins/shikonins treated side than in the control wounds. Additionally, the wound size reduction was greater in the treated sides, but the difference was not significant. In the histological evaluation, the assessors found a higher collagen production score in the alkannins/shikonins- treated wounds compared to the lactated Ringer´s solution- treated wounds. Also, the neovascularization was significantly higher in the treated wounds. The authors concluded that alkannins/shikonins promoted angiogenesis, collagen production and epithelialization in acute non-contaminated wounds in dogs but does not decrease the total wound healing time

compared to control wounds. Due to the study design, the scientific significance is good, but the level of evidence is low. The group size is small, yet due to the presence of a control group this publication can be classified in the silver level.

Lozier et al. (1992) evaluated the effect of four different preparations of 0,05% chlorhexidine diacetate on wound healing in dogs. To investigate the difference, six wounds were surgically induced on each side of the dorsum of six dogs. The solutions tested were 0,05% chlorhexidine diacetate in sterile water, in a sterile 0,9% sodium chloride solution, in a sterile lactated Ringer´s solution titrated to a pH of 7,4 with sodium bicarbonate, and also a sterile lactated Ringer´s solution titrated to a pH of 7,4 with sodium bicarbonate and left to form a heavy white precipitate. For 24 days, each wound was lavaged with one of the prepared solutions or a control solution (sterile water). To evaluate the healing process, each wound was recorded by tracing it on a transparent sheet every 3-5 days. Lozier et al. (1992) did not identify any significant difference in the wound healing parameters among the different solutions. Due to the age of the trial and the limited possibilities in adequate wound documentation, this study has a low scientific significance and a low level of evidence (bronze level). Additionally, in modern wound management, chlorhexidine diacetate has been sidelined due to the appearance of various wound dressings and topical agents with greater advantages.

Swaim et al. (2000) tried to determine the effects of a hydrolyzed bovine collagen dressing on the healing of open wounds in dogs. In his experiment, two full thickness wounds were surgically induced bilaterally on the trunk of nine Beagles. The study was initially designed for ten dogs but Swaim et al. (2000) excluded one patient because it did not tolerate the bandage. One wound was treated with a powder that contained hydrolyzed bovine collagen and the other severed as control. The bandages were changed daily for seven days and fresh bovine collagen was placed on the treated wounds during each bandage change. After day seven, the bandages were changed every two days. Starting from day 14, the authors did not treat either wounds with bovine collagen but still changed the bandages. To assess the healing progress, laser doppler perfusion imaging, planimetry and histological evaluation were used. Laser doppler perfusion imaging detected no significant difference between the two groups. Planimetry showed no difference in wound contraction but the mean percentage of epithelialization was significantly greater in the wounds treated with bovine collagen. Additionally, the histologic evaluation did not detect any difference between the control group and the treated one. Swaim et al. (2000) concluded that hydrolyzed bovine collagen does

enhance a moist wound environment and increase the reepithelialization which is essential to wound healing, but it did not enhance the wound healing itself.

Due to the lack of randomization and the small group size the scientific outcome is not significant, but the presence of a control group shows a medium level of evidence (silver level).

There are several publications about topical agents and a great variety of different products. Each of these products may have their own advantages, but none of these are perfect for all wounds. The analyzed publications show that the same topical agent may be a catalyst for wound healing in one type of wound but does not enhance the healing process in another. Despite the variety of products and publications, the study design for each individual study is worthy of improvement. Only one of the studies used a software to blind their photographs before assessment, additionally most of the publications did not randomize their treatment protocol which lowered the level of evidence for each trial.

5. Discussion

The aim of this thesis was to go through the existing literature about wound dressings and to evaluate their benefits on different types of wounds. For this purpose, various search engines were used to find publications that performed studies about wound dressings in small animal medicine. Furthermore, these publications had to be classified into different evidence levels based on the levels modified from Santesso et al. (2006) (Tab.4), in order to establish an objective analysis of each of the publications.

Because of the diversity of factors that affect the outcomes in veterinary medicine studies, like species or breeds with their different skin characteristics, the evidence level defined from Santesso et al. (2006) for human medicine could not be achieved and an adjustment was needed. Therefore, the group size was reduced to 20 patients per group based on the average group size of the screened records. Also, the blinding of the patient was removed- because of the characteristics of the treated species.

It was assumed that currently less than 30% of all publications detailing the use of wound dressings in dogs and cats are high- quality studies with an evidence level of gold or higher.

Following the analysis of the included publications, this hypothesis could be confirmed.

After an intense analysis, none of the included publications could be classified as gold or platin. Yet 17 of the included 26 publications (65%) were ranked as silver level, whereas only 9 of the 26 publications (35%) are bronze level.

This may follow from the fact that despite the adjustment of the level criteria and the signs of high-quality study design, most of the authors did not randomize their trials or could not achieve the necessary group size.

For each trial that includes working on living animals in veterinary medicine, an approval by an executive organization like an ethics commission is needed. As a result, most researchers would not be able to get this approval for a prospective trial with a large group size. The consent of an ethics committee is bound to several conditions. Most of the included publications used purpose- bred dogs (e.g. beagles) in their prospective trials, which are held in packs. For an authorized trial, these dogs must be separated and kept in a kennel for observation. These kennels must be large enough for the dog to behave in a manner appropriate for their species. It must be ensured that the animal has access to water and

food. Also, to secure animal welfare, it is important to equip these kennels with diverse materials like toys and dog beds for environmental enrichment.

These conditions, alongside many other factors, may limit the researchers´ ability to achieve an authorization for the demanded group size of 20 patients per group or more.

Apart from this, animal welfare is a very important part of scientific research and should not be neglected, because the patients we assess do not have the ability to express themselves. Therefore, supervision of all trials by an executive organization is essential.

The lack of randomization in 63% of the publications is another critical point. This is because most trials relied on decisions to be made in the application of treatment to specific regions. Without randomization, the decisions may become biased simply due to decision fatigue or convenience to the experimenter. Yet 37% of the included publications used software or an equivalent substitute for randomization, which is an easy and cheap way to establish scientific significance. In human medicine, randomization is a very important part of a trial, because it eliminates bias in the assignment of treatment, and facilitates blinding of the assessors and patients. This importance can be transferred to veterinary medicine, because it is essential to secure an objective conclusion for a scientific statement of an examined material or drug.

15% of the included papers were case reports, which represent one of the lowest evidence classes. A case report discusses one or a few cases retrospectively without any scientific methods like histological assessments or even photographs. It reflects the experience of one veterinarian in a case where one material/drug is used and does not match any study criteria.

At least one publication is a randomized blinded trial (Tambella et al. 2014). This study used an autologous platelet gel along with a placebo gel to confirm the benefits of APG to the wound healing process. Alongside randomization, blinding of trials is one of the most important characteristics of a high-quality study. Information that could negatively affect the objectivity of the outcome is withheld. This includes information about the treatment (e.g. being given the active substance or the placebo). This minimizes the risk of bias by the expectations of the assessor or the effects of the observer on the patient.

In the veterinary field, the blinding of the patient can be neglected because the expectations of the participant are not given. Yet the blinding of the assessor or the treating veterinarian is important because the interpretation of the progress might be affected.

In some cases, blinding is not possible (e.g. physical treatment) but it is important to ensure a blinding that is as effective as possible.

In summary, out of from 26 analyzed papers, only 8 (31%) are good-quality studies with a randomized design, but due to the high requirements of the evidence classes none of these trials could be classified in the gold level. Of these eight studies only one (Gianetto et al. 2018) fulfilled the demanded group size of 20 or more. However, they unfortunately did not blind their trial. Regardless, those publications used well- designed study protocols with high scientific significance, which shows that even if a great group size in combination with well-designed trials is the only representative possibility to confirm the effect of a medication/ dressing material, trials that used a smaller group size but have a study-design equal to those used in human medicine may also be a valid method due to limitations in veterinary medicine.

6. Summary

The purpose of this diploma thesis was to show that in veterinary clinical research, only 30% of the currently published records are high-quality trials with well- designed protocols that can be classified as gold or higher.

To give an overview of the topic, the classification of wounds was described and a short summary about current wound management methods was given. To understand the different wound dressings that were detailed in the included publications, it was also necessary to explain the most common wound dressings used in small animal medicine and to compare the possible uses.

In this thesis, all records were included that investigated the effect of different wound dressing materials in small animal medicine, especially in dogs and cats. In vivo publications in English or German were included.

The literature was found through the use of several search engines such as pubmed, scopus, google scholar and vetmedseeker. By searching through this databases, it was possible to identify 126 publications that matched the used keywords. After a rough analysis, nearly 81% of these records could be excluded due to several factors like being written in the wrong language.

Ultimately, 26 publications could be included and were analyzed based on the guidelines definded by GRADE and classified into level based on Santesso et al. (2006).

It became clear, that it is not possible to achieve the evidence level standards that are set in human medicine, so an adjustment to the current evidence classes was made. Yet most of the publications did not fulfill the criteria, despite having well- designed study protocols. These publications, with their great study-design and their objective investigation methods, showed that even in the veterinary field, it is possible to achieve a scienticically significant outcome.

During the course of this systematic review, the hypothesis that was initially set was confirmed, because none of the included papers could achieve gold level or higher.

7. Zusammenfassung

In dieser Diplomarbeit sollte aufgezeigt werden, dass weniger als 30% aller veröffentlichten Publikationen über Wundauflagen in der Tiermedizin Studien von hoher Qualität und Aussagekraft sind. Hierbei wurde festgelegt, dass unter Studien von hoher Qualität solche gemeint sind die in eine Evidenzklasse von Gold oder höher eingeteilt werden können.

Um einen Überblick zu schaffen wurde zunächst erklärt, wie eine Wunde in der Praxis klassifizert wird, um dann entsprechend der aktuellsten Wundmanagement- Methoden behandelt werden zu können. Ferner war es vonnöten, die am meisten verwendeten Wundauflagen in der Kleintiermedizin kurz aufzulisten und deren mögliche Anwendungsgebiete zu erläutern.

In dieser Arbeit wurden Publikationen inkludiert, die die Effizienz von verschiedenen Wundauflagen in der Kleintiermedizin behandeln, hierbei bezogen auf Hund und Katze. Die Studien mussten in deutscher oder englischer Sprache verfasst worden sein.

Um die entsprechende Literatur zu finden, wurden diverse Suchmaschinen eingesetzt wie Pubmed, Scopus, Google scholar und der vetmedseeker. Durch diese Suche konnten insgesamt 126 passende Studien identifizert werden, die mit den festgesetzten Schlüsselworten übereinstimmten, diese wurden in die grobe Auswahl übernommen. Nach einer ersten Analyse konnten 81% dieser Veröffentlichungen wieder exkludiert werden, da sie nicht den engeren Auswahlkriterien entsprachen, wie zum Beispiel der Verfassung in einer anderen Sprache als Deutsch oder Englisch.

Schlussendlich wurden 26 Publikationen inkludiert und mittels der Richtlinien von GRADE für ein Systematic review und den Evidenzklassen nach Santesso et al. (2006) klassifiziert.

Da sich während der Arbeit herausstellte, dass es unmöglich ist für Studien in der Tiermedizin die hohen Anforderungen der Richtlinien, die für die Humanmedizin erhoben wurden, zu erreichen wurde eine Anpassung vorgenommen.Trotz dieser Anpassung war es für die inkludierten Studien nicht möglich diese Kriterien zu erfüllen, jedoch hatten viele von diesen Studien sehr gut ausgearbeitete Studienprotokolle und konnten mit ihren objektiven Untersuchungsmethoden zeigen, dass es möglich ist auch in der Tiermedizin aussagekräftige Ergebnisse zu erzielen.

Die zu Anfang aufgestellte Hypothese konnte damit bestätigt werden, da keine der inkludierten Studien Gold Level oder höher erreichen konnte.

8. Abbreviations

CMG	Cochrane Musculoskeletal Group
GRADE	The Grading of Recommendations Assessment, Development and Evaluation working group
h	hour
e.g.	exempli gratia
NPWT	Negative Pressure Wound Therapy
MRD	Moisture- Retentive Dressing
PHMB	Polyhexamethylene Biguanide
PSIS	Porcine Small Intestinal Submucosa
PRP	Platelet-Rich-Plasma
LDI	Laser Doppler Imaging
BED	Bioelectric Dressing
PG	Peptidoglycan
EGF	Epidermal Growth Factor
2OC	2-octyl cyanoacrylate
SSI	Surgical Side Infection
TPLO	Tibial Plateau Levelling Osteotomy
APG	Autologous Platelet Gel
HA	Hyaluronic Acid

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