# SYSTEMATIC REVIEW OF THE EFFECTIVENESS AND TOLERABILITY OF HYALURONIC ACID FOR ACUTE AND CHRONIC WOUNDS

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**FACULTY OF MEDICINE**
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## ABSTRACT

Hyaluronic Acid (HA) and its derivatives are commonly used for acute and chronic wounds, but evidence of their effectiveness remains unclear. The aim of the study was to evaluate the effectiveness of HA (or its derivatives) for promoting healing in acute and chronic wounds through a systematic review of the available evidence. The Cochrane Central Register of Controlled Trials and relevant databases were searched. Drugs companies and experts in wounds were also contacted. Randomised controlled trials of HA (or its derivatives) compared with control were eligible for inclusion. Ten randomised controlled trials involving 992 participants with acute and chronic wounds were included in the review. The research evidence was weak with poor reporting in many trials. The evidence does not provide strong support for the beneficial effects of HA (or its derivatives) towards improvement of chronic wounds even though there is some evidences that they were effective for reducing pain intensity for mixed arterial and venous ulcers [MD= -6.78 (95% CI: -11.10 to -2.46)]. Evidence to guide decisions regarding the use of HA (or its derivatives) to promote wound healing is still limited. More good quality randomised controlled trials are warranted.

## ABSTRAK

Asid Hialuronik (HA) dan terbitan-terbitannya biasa digunakan untuk penyembuhan luka akut dan luka kronik, namun keberkesanan mengenainya masih tidak meyakinkan. Kajian ini bertujuan untuk menilai keberkesanan HA (atau terbitan-terbitannya) di dalam merangsang penyembuhan luka akut dan luka kronik melalui kaedah tinjauan sistematik bagi bukti-bukti yang sedia ada. Pencarian telah dilakukan melalui Cochrane Central Register of Controlled Trials dan pangkalan data yang berkaitan. Syarikat-syarikat dan pakar-pakar di dalam bidang luka juga telah dihubungi. Kajian-kajian rawak terkawal berkaitan HA (atau terbitan-terbitannya) berbanding dengan unsur kawalan adalah termasuk didalam kriteria. Sepuluh kajian rawak terkawal yang melibatkan 992 peserta luka akut dan luka kronik termasuk di dalam senarai. Bukti-bukti sedia ada adalah lemah kerana terdapat kekurangan laporan di dalam kebanyakan kajian-kajian. Bukti-bukti tersebut tidak menyokong kuat kebaikan efek HA (atau terbitan-terbitannya) terhadap penyembuhan luka kronik walaupun terdapat satu bukti yang menunjukkan efek statistikal signifikan di dalam pengurangan kadar kesakitan bagi ‘mixed arterial and venous ulcers’ [MD= -6.78 (95% CI: -11.10 to -2.46). Bukti sebagai rujukan berkaitan penggunaan HA (atau terbitan-terbitannya) untuk merangsang penyembuhan luka masih terhad. Lebih banyak kajian yang mempunyai kualiti yang tinggi diperlukan.

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| | | |
|---|---|---|
| **CI** | : | Confidence Interval |
| **ep** | : | endpoint |
| **HA** | : | Hyaluronic Acid |
| **MD** | : | Mean difference |
| **RR** | : | Relative Risk |
| **VAS** | : | Visual Analogue Scale (VAS) |
| **vs** | : | versus |

## LIST OF APPENDICES

# CHAPTER 1: INTRODUCTION

Wounds, especially chronic wounds, which failed to heal in an orderly set of healing stages and in a predictable time are usually associated with high costs, poor quality of life and long treatment duration (Beitz & Goldberg, 2005; Ruttermann, Maier-Hasselmann, Nink-Grebe, & Burckhardt, 2013). A study in 2009 showed that $25 billion is spent annually for 6.5 million Americans patients for wounds care (Sen et al., 2009). More recently Driscoll (2013b) reported that the number of cases for acute and chronic wounds in the United States increases every year. It has been shown that, the costs of treatment increased from $3.5 billion in year 2008 to an estimated $6.0 billion by the end of 2013 and the total market for wound care products is expected to rise from $16.8 billion in 2014 to $21 billion in 2015 and will rise further to $4.6 billion by 2016 (Cotthoff & Elder, 2011).

Wound management could be successful when accurate assessment, investigation, diagnosis and proper product have been selected to achieve faster healing process. An ultimate factor known to boost wound healing is to keep a moist environment for the wounds. One recent product increasingly used to keep the wound moist and fasten the healing process is Hyaluronic acid (HA) containing products. HA is a polysaccharide which is the main component of the extracellular matrix found in various connective tissues of different body parts such as skin, heart, eye and synovial fluid. HA is reported to increase during the periods of rapid tissue regeneration, repair or proliferation (Manuskiatti & Maibach, 1996). The capacity of HA to retain water has a positive effect in wound healing as it helps to facilitate the transport of solutes and nutrients (Bansal, Kedige, & Anand, 2010). Specifically, it plays a critical role in maintaining the structure and integrity of the skin as well as in the wound healing process (Schultz et al., 2003).

Due to the reported beneficial effects of HA and its derivatives in managing wounds, HA has been formulated in various dosage forms such as cream and dressing containing HA. The number of researches examining the benefits of HA and its derivatives is also increasing (Necas, Bartosikova, Brauner, & Kolar, 2008). HA have been claimed to enhance both the partitioning of drugs into human skin and its retention and localization in the epidermis, minimise percutaneous absorption of drugs and assists the transport of drugs to the epidermis (Xie, Upton, Richards, Rizzi, & Leavesley, 2011).

Even though several trials reported the beneficial effects of HA-containing products for wound healing (Caravaggi et al., 2003; Dereure, Czubek, & Combemale, 2012a; Humbert, Mikosinki, Benchikhi, & Allaert, 2012; Koller, 2004; Ortonne, 1996; Taddeucci et al., 2004; Uccioli et al., 2011), evidence of its effectiveness is still inconclusive. There are trials which showed that there is no significant difference in the number of wounds healed with the use of HA (or its derivatives) (Dereure, Mikosinki, Zegota, & Allaert, 2012b; Meaume et al., 2008). Most of these trials differed in methodological quality and designs which may have affected their findings.

One systematic review published in 2012 examined HA derivatives and their healing effects on several types of wound such as burns, epithelial surgical wounds and chronic wounds (Voigt & Driver, 2012). However, since the publication of this review several new trials are now available. Thus, our systematic review aimed to update the previous review concerning the effects and tolerability data of all possible HA (or its derivatives). Additionally we incorporated a quality assessment of included trials using risk of bias assessment tool to establish the quality of the evidence.

## 1.1 Aim

The objective of this study is to review the evidence of effectiveness and tolerability of Hyaluronic Acid (or its derivatives) for healing acute and chronic wounds.

## 1.2 Specific Objectives

i. To describe the characteristics of randomised controlled trials of hyaluronic acid (or its derivatives) for patients with acute and chronic wounds
ii. To conduct risk of bias assessment of the included studies
iii. To undertake a meta-analysis of trials of hyaluronic acid (or its derivatives) for patients with acute and chronic wounds if the data are appropriate

## 1.3 Justification of this study

Hyaluronic acid is increasingly used, due to its reported beneficial effects in managing wounds. Several formulations of HA are available such as cream and dressing containing HA. Examples of products containing HA marketed specifically for wound management are Aftamed®, Aloclair®, Atopalm® and Curiosin® gel. Despite the increasing availability products of, there is no clear evidence of HA's effectiveness for patients with acute and chronic wounds.

To date, there is only one review that evaluates the effectiveness of HA for wounds (Voigt & Driver, 2012). However, the review has several limitations. First, the review examined all types of wounds and was not focused for specific types of wounds. Second, the review did not use important outcomes in assessing effectiveness of interventions. Third, the assessment of the quality evidence did not include all seven domains as suggested by the Cochrane (Higgins & Green, 2012) in assessing the

internal quality of the included trials. Finally, since the publication of this review, newer trials have been published. Therefore, the aim of this review is to update the previous review and to do a rigorous assessment of the evidence concerning the effects and safety of HA in managing both acute and chronic wounds. The findings from this review would be useful to guide healthcare professionals in their decision-making regarding the use of hyaluronic acid as an alternative to other standard therapy for managing wounds.

# CHAPTER 2: LITERATURE REVIEW

## 2.1 Types of wounds

Wound has been defined as an injury or damage leading to a break in the continuity of the skin and causes a disturbance or interruption of normal anatomic structure and function (Lazarus et al., 1994). Wounds and wound healing may be classified in terms of types of wounds closure, depth of the wounds and onset of duration (Dealey, 1999; Doughty & Sparks-Defriese, 2007). Generally, depending on the onset and duration of healing, wounds can be classified into two groups: chronic wounds and acute wounds.

### 2.1.1 Acute wounds

An acute wound is an injury to the skin that can be repaired or healed in an orderly and timely process with predictable and expected rate according to the normal wound healing process (Doughty & Sparks-Defriese, 2007; Robson & Barbul, 2006). Acute wounds can happen anywhere on the body and vary from superficial scratches to deep wounds damaging blood vessels, nerves, muscles or other body parts. Examples of acute wounds include penetrations or bites, abrasions, lacerations, surgical wounds and burn wounds (Lazarus et al., 1994).

***Surgical wounds***

Surgical wounds are intentional acute wounds and may be healed either by first intention, where the skin edges are closed together by using sutures, clips and tape until the cut edges merge or by second intention, where the wound is left open to heal, usually to allow drainage of infected material (Dealey, 1999; Vermeulen et al., 2004). However, the primary intention is usually at risk of infection. The sutures or clips may be removed and the secondary intention may take over to heal the wound. The healing process for surgical wounds is classified by their potential for infection. Surgical wound

accounts for the highest prevalence for acute wounds which is about 114, 271 millions worldwide (Driscoll, 2013b).

***Burn wounds***

Burns are part of traumatic wounds that require special care and usually patients are treated in a specialised burn unit (Dealey, 1999). It is an injury caused by excessive heat either by thermal, chemical, electrical or radiation. In reality, a radiation reaction is not a wound but the skin reaction is akin to a superficial burn and has the potential for ulceration. Burns can be classified according to the depth of the injury. They are superficial burns, partial-thickness burns and full-thickness burns (Dealey, 1999).

***Burn depth and its assessment***

Burns can be classified according to the depth of the injury in the epidermis, dermis, subcutaneous fat and underlying structures (Dealey, 1999). First-degree (superficial) burns are injuries confined to the epidermis. Second-degree (partial) burns are injuries affecting epidermal layer as well as dermis. This category includes superficial partial burns and deep thickness burns. Third-degree (full) thickness burns are injuries involving subcutaneous and other structures. Studies have shown that in burnt management, it is important to measure burn wound depth. Several techniques are used to assess burnt depth, from the simplest such as thermography and vital dyes progressing to video angiography, video microscopy and the most accurate predictor which is a laser Doppler technique (Monstrey, Hoeksema, Verbelen, Pirayesh, & Blondeel, 2008).

### 2.1.2 Chronic wounds

Chronic wound has been defined as wound that failed to produce anatomic and functional integrity of the injured site through an orderly and timely reparative process

or in the expected time frame (Sen et al., 2009). Common chronic wounds include leg ulcers, pressure ulcers, and diabetic foot ulcers (Lazarus et al., 1994).

The cause of chronic wounds varies depending upon the genesis of wounds, its depth, involvement of the underlying structures, primary wound care and tissue handling. Wounds are considered to be chronic if time to heal is delayed as a result of impaired tissue repair due to poor oxygenation, malnutrition or infection. The aetiology of the wound is one of the factors that affect healing. Basically, the treatment of these ulcers includes maintenance of a moist wound environment to accelerate wound healing (McNees, 2006; Ruttermann et al., 2013).

***Diabetic foot ulcers***

Diabetic foot ulcers are responsible for most foot and leg amputations in the world. These ulcers are common complications in uncontrolled diabetes mellitus, resulting in impaired immune function, ischemia (due to poor blood circulation) and neuropathy (nerve damage), which eventually lead to breakage of skin and ulceration.

***Pressure ulcers***

Pressure ulcers result from ischemia due to constant pressure and friction resulting from parts of body weight over a localized area for prolonged duration. The pressure can lead to breakage of skin and ulceration (also known as bed sores); especially on the back and on the ankles and feet. They typically occur in paralyzed or unconscious patients who are unable to sense or response to the need for periodic repositioning (Dealey, 1999).

***Venous ulcers***

Venous ulcers result from hypoxia in areas of venous congestion in lower extremities. These ulcers account for more than half of ulcer cases, especially in the lower limbs

(mainly the legs) and are also associated with deep vein thrombosis, varicose veins and venous hypertension.

### 2.1.3 Prevalence and burden of wounds

Chronic skin ulcerations of the lower extremities affect millions of patients in the United States with prevalence range between 0.18% and 1.3% in the adult population (Kurd, Hoffstad, Bilker, & Margolis, 2009). Driscoll (2013b) estimated acute wounds that include surgical wounds, traumatic wounds, lacerations and burn wounds to be about 147 million while chronic wounds that include arterial/venous ulcers, pressure ulcers and diabetic foot ulcers to be about 40 million in the world.

Wounds especially chronic wounds are usually associated with high morbidity, impaired quality of life and account for an increasing huge healthcare costs (Beitz & Goldberg, 2005; Cotthoff & Elder, 2011; Sen et al., 2009). Similarly, with an increasing number of cases for acute and chronic wounds every year, the cost of treating them increased from US $3.0 billion in year 2007 to an estimated of US $3.5 billion by end of year 2008 and reached up to $6.0 billion dollars in 2013 (Cotthoff & Elder, 2011). The amount of money spent on wound care, the loss of productivity for afflicted individuals and the families that care for them and their diminished quality of life come at great cost to the society. Prompt and optimum treatment is necessary to prevent functional, sociopsyhcological and economic burden on the patients and countries as chronic wounds are usually associated with high costs, bad living experiences or quality of life and long treatment times (Beitz & Goldberg, 2005; Ruttermann et al., 2013). Two studies (Chase, Melloni, & Savage, 1997; Cole-King & Harding, 2001) reported that patients with chronic wounds suffered altered sleeping habits, changing eating patterns and experienced stress, anxiety and depression. Studies also showed that patients living

with long-term wounds often have poor psychological wellbeing and a reduced quality of life (Beitz & Goldberg, 2005).

## 2.2 Wound-healing Process

Wound healing process consists of a series of overlapping stages; hemostasis and inflammation, reconstruction or destructive phase, proliferation and maturation or remodelling (Dealey, 1999). It begins with the phase of hemostasis which includes vascular constriction, platelet aggregation, degranulation and fibrin formation. Next is the formation of granulation tissue of inflammatory cells, newly formed blood vessels, and fibroblast embedded in a loose collageneous extracellular matrix. Then, the proliferation and remodelling phases take place. The growth factors that participate in the process are epidermal growth factor (EGF), platelet-derived growth factor (PDGF), transforming growth factor β (TGF-β), insulin-like growth factor (IGF), and granulocyte-macrophage colony-stimulating factor (GM-CSF) (Alster & Tanzi, 2003). Additional group of active compounds important for the healing process are vitamins and mineral supplements including vitamin A, B, C, D, E, K as well as zinc and copper (Reynolds, 2001). A high availability of amino acids is necessary to enhance wound healing due to an increased metabolic activity, thus HA is one of the most important component (Maggio et al., 2012). Figure 2.1 summarises the process of wound healing.

| Phase | Cellular and Bio-physiologic events | Duration of phase |
|---|---|---|

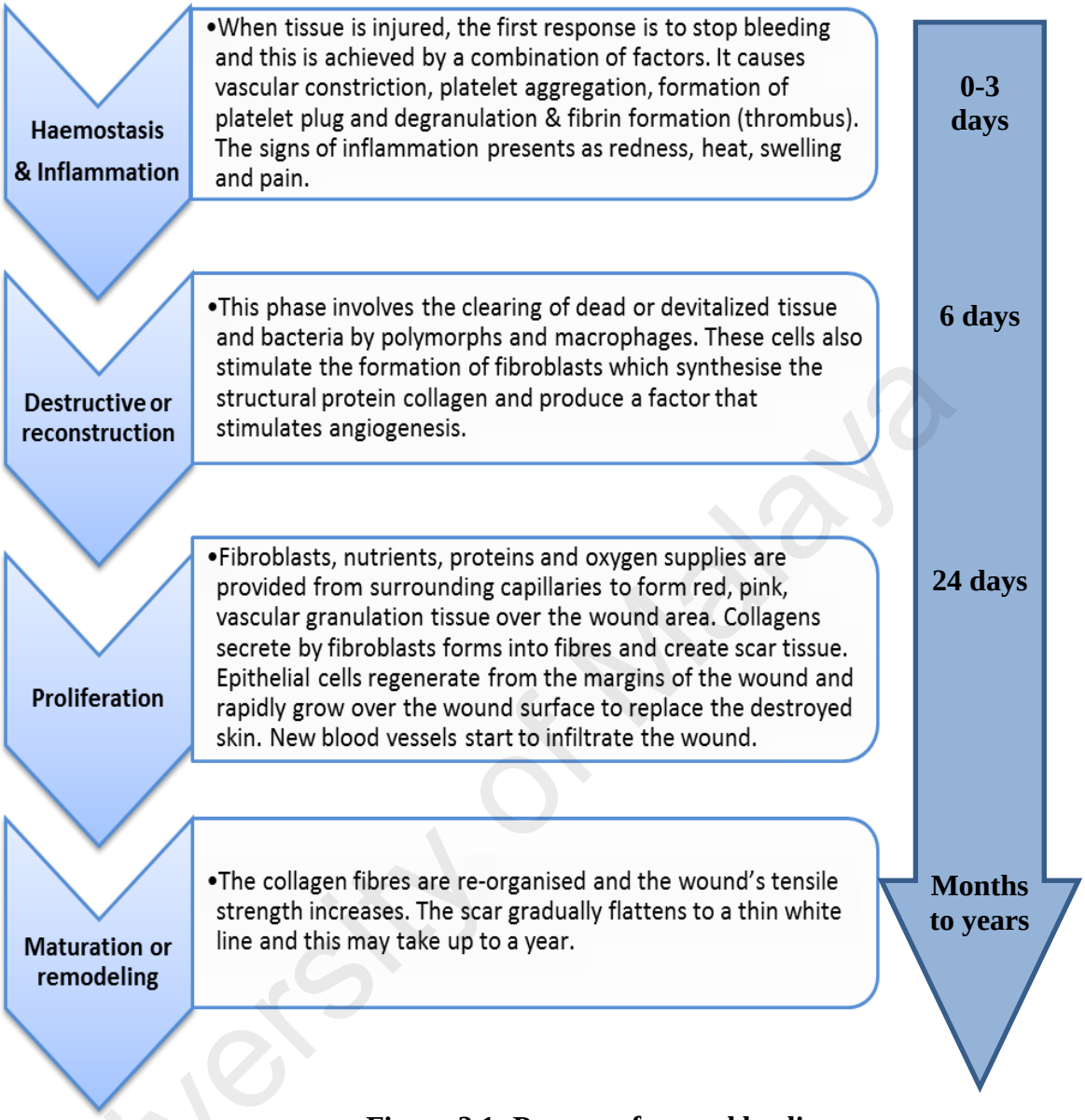


**Figure 2.1: Process of wound healing**

## 2.3 Wound Managements

Accurate assessment, investigation, diagnosis and appropriate product choice are the key to success in the wound management. A major factor known to boost wound healing is to keep a wound moist environment. Rolstad and Ovington (2007) reported that providing moisture to the wound and retaining moisture over time are not the same.

The range of available products for wound care includes hydrocolloids, film overlays, foams, microfiber dressings, alginates and polyacrylates. These are sold in numerous

combinations of materials. Some products such as saline-moistened gauze may not continuously moist the wound, thus the need to occasionally change the dressings while semi occlusive dressings may be able to keep a wound moist by retaining moisture vapour on continual basis.

### 2.3.1 Wound dressings

History of dressings was documented in the Egyptian era since BC 1600 in which grease-soaked gauze and fabrics were frequently used for dressings (Queen, Orsted, Sanada, & Sussman, 2004; Scales, 1963). Presently, dressings like cloth, cotton, gauze have dominated wound dressings and continued to be the main products used. In the 19$^{th}$ century, several efforts were made to improve wound dressings. These include Gamgee tissue. Sampson Gamgee of Birmingham discovered that cotton wool would absorb fluids more rapidly compared to napkin (Scales, 1963). He recommended the combined use of absorbent cotton wool with compressing gauze in aseptic manner. Since then, cotton wool, gauze and lint became the established wound dressings.

The beginning of non-adherent dressing started when Lumiere introduced cotton net impregnated with paraffin wax and balsam which allowed inlet of air to the wound (Scales, 1963). The concept of moist wound healing began in 1970 when film and hydrocolloid dressings were introduced. Since then, more absorbent wound dressings have been developed (Queen et al., 2004).

#### *Traditional wound dressings*

Examples of traditional wound dressing which is also known as passive dressing include dressing pads and tulle dressings. They are either medicated (e.g. containing clorhexidine or povidone-iodine) or non-medicated (e.g. paraffin gauze dressing). Winter (1962) introduced the important concept of moist wound healing for interactive

dressing category. Currently, the most modern dressing products are formulated as interactive dressings by adding some agents in contrast to passive dressings which are dressings alone (Thu, Zulfakar, & Ng, 2012).

### *Interactive dressings*

Another choice of dressings, which is recently used, is interactive dressings. They are either permeable or semi-permeable like film dressing, xerogel dressing, hydrocolloid dressing, hydrogel dressing, alginate dressing, bead dressing and foam dressing (Abdelrahman & Newton, 2011; Scales, 1963; Wardrope & Edhouse, 1999). They are also known as moist interactive wound dressings with high absorbency to low absorbency (foams→ calcium alginates→ hydrocolloids→ hydrogels→ hydrofibre) to prevent bacterial infection due to accumulation of fluid surrounding the wounds.

*Foam dressings*: These are opaque dressings with non-adhesive surface for ulcers with low to medium exudates.

*Alginate dressings*: Composed of alginic acid, they transform a fibre to gel when in contact with wound fluid. They are highly absorbent dressings for wounds with medium to heavy exudates.

*Hydrocolloid dressings*: These are adhesive dressings containing various polymers that will form a gel when in contact with wounds, waterproof and indicated for wounds with low to medium exudates.

*Hydrogel dressings*: These are amorphous, water-based gels or sheets, moisture retentive, non-traumatic removal, indicated for wounds with light to medium exudates.

*Hydrofibre dressings*: These are soft dressings composed of hydrocolloid fibres, indicated for wounds with heavy exudates.

### *Active dressings*

Active dressings have various properties that can change the chemical and cellular make-up of the wounds. Additionally, bioactive products which have endogenous activities are also included in this type of dressings (Agrawal, Soni, Mittal, & Bhatnagar, 2004). Examples of bioactive products include cellular suspensions, growth factors, skin grafts, and biosynthetic skin substitute dressings such as collagen, chitosan, peptides and hyaluronic acid (Queen et al., 2004).

### *Ideal dressings*

Generally, the type of dressing selected depends on the size and types of wounds, the frequency of dressing change, patient comfort and ease of removal and the overall cost of management. Upton, Johnson, Zelazny, and Dailey (2013) suggested that health professionals should minimize pain and stress at dressing change by using the most suitable dressings and techniques which can be easily incorporated into wound care management to expedite faster healing, promote patient health and eventually, reduce the costs of care. Additionally, dressings must have a moisture absorptive capacity in order to manage high drainage levels. The dressing materials should ideally be able to provide water to the tissue to actively rehydrate the dry wound tissues. One online survey reported that the ideal properties of wound dressing for burn wounds should be non-adhesive, absorbent and has anti-microbial properties, easily remove, pain-free dressing, changes required only once or twice a week and are available in different sizes (Selig et al., 2012).

The characteristics of an ideal design for dressing are as outlined in Table 2.1 (Abdelrahman & Newton, 2011; Purser, 2009; Sarabahi, 2012; Scales, 1963; Wardrope & Edhouse, 1999).

**Table 2.1: Ideal Characteristics of an "ideal dressing"**

| Ideal Characteristics of an ideal dressings |
| --- |
| • Promotes a moist environment at wound interface |
| • Allow excess exudates to be removed to the surface of dressings |
| • Provide mechanical protection and thermal insulation |
| • Provide barrier to micro-organisms |
| • Allow for gaseous exchange |
| • Non-adherent and can be removed easily without pain or trauma |
| • Be sterile |
| • Non-allergic, non-sensitising and non-cytotoxic to healthy tissue |
| • Easy to use and cost-effective |

### 2.3.2 Topical preparations

A number of topical agents are available, which aims to change the wound environment such as topical antibiotics (e.g. neomycin, bacitracin, polymyxin B, gentamycin, fucidic acid), topical antiseptics (e.g. chlorhexidine, povidone-iodine), topical steroids, and topical collagen (Vermeulen et al., 2004). These agents were reported to promote the healing process and prevent bacterial colonization which leads to wound infection (Costagliola & Agrosì, 2005). Despite the increasing marketing of topical preparations, conclusive evidence on their efficacy to promote wound healings are unavailable. For example, to date, products containing iodine such as cadexomer-iodine, PVP-iodine ointment, PVP-iodine gel or PVP-iodine gauze have no evidence to support their benefits for wound healing to prevent infection (Rüttermann et al., 2013).

## 2.4 Hyaluronic acid

The molecular formula for HA is $(C_{14}H_{21}NO_{11})n$. HA is a polysaccharide composed of N-acetyl glucosamine and D-glucuronic acid. Karl Meyer and his colleague John Palmer, scientists at Columbia University, New York, discovered HA in 1934. They isolated a chemical substance from the vitreous jelly of cow eyes. They proposed the name hyaluronic acid as it was derived from a Greek word hyalos (glass) and contained two sugar molecules, one of which was uronic acid (Meyer & Palmer, 1934). HA was commercialised in 1942 when Endre Balazs used it to replace egg white in bakery products and patented it. Its discovery was very unique. No other molecule had ever been discovered that has such unique properties to the human body. Sources of commercial HA are microbial fermentation, cock combs or chicken cartilage. Commercial dressings and topical preparations containing HA are shown in Table 2.3.

HA has desirable physicochemical properties which include high viscosity, elasticity, lubrication and high capacity for holding water (Capila & Sasisekharan, 2004). In nature, HA is known to be one of the most hygroscopic molecules. Hydrogen bonding occurs between adjacent carboxyl and an N-acetyl group when it is incorporated into aqueous solutions, which allow it to maintain conformational stiffness and retain water. Furthermore, the high concentration of medium and lower molecular weight hyaluronic acid has the greatest bacteriostatic effect while viscoelastic properties of the material may slow the penetration of viruses and bacteria (Bansal et al., 2010).

**Table 2.2: Hyaluronic acid products in dressings and topical preparations**

| Products | Ingredients | Applications |
|---|---|---|
| **Dressings containing hyaluronic acid** | | |
| Benzyl hyaluronate membrane | Benzyl hyaluronate esters | Wound dressing |
| HA gauze pad | Sodium hyaluronate 0.05% | Cream for wound healing |
| HYAFF® 11 | Esterified HA | Hyaluronic acid ester formed as non-woven, absorbent ,wound dressing |
| Hyalofill-F | Hyaluronic acid | Sheet for wound healing |
| Hyaloskin ® | Hyaluronic acid | Wound dressing |
| Ialuset® | Hyaluronic acid | Gauze pad wound dressing |
| Jossalind® | Hyaluronate sodium | Scaffold used in surgery and wound healing |
| Silver sulfadiazine-hyaluronan collagen membrane | Hyaluronan micropraticles-silver sulfadiazine (AgSD) | Wound healing |
| **Topical preparations containing hyaluronic acid** | | |
| Bionect Start® | 0.2% w/w bacterial fermented sodium hyaluronate | Ointment used in surgery and wound healing |
| Bionect® | Hyaluronic acid (0.98%) | Ointment used in surgery and wound healing |
| Cicactiv® | Hyaluronic acid & zinc | Topical cream for solar keratoses |
| Coladerm H/HM | Collagen/HA temporary biosynthetic dermal skin substitute | Apply for wounds and burns |
| Connettivina® Plus | 0.2% hyaluronic acid, 1% silver-sulfadiazine | Cream use in surgery and wound healing |
| HYAL CT1101 | 3% diclofenac in 2.5% HA | Topical gel for actinic keratosis |
| Hyiodine® | Hyaluronan-iodine complex,$KI_3$ | Gel for wound healing |
| Ialuset® | Hyaluronic acid | Cream for wound healing |
| Ialugen Plus® | Hyaluronic acid | Cream for wound healing |
| Lysial® | Lysine-hyaluronate | Decubitus Ulcers (bedsore/pressure sore) |
| RadiaPlex gel | Hyaluronic acid-based | Preventing radiation dermatitis |
| Solaraze | 3% diclofenac in 2.5% HA | Topical gel for solar keratoses |
| Vulnamin® | Glycine, l-lysine, l-proline, l-leucine, hyaluronic acid | Gel use in chronic ulcers |
| Xclair ™ | Hyaluronic acid | Radiation-induced dermatitis |

### 2.4.1 How hyaluronic acid may acts in wound healing

Specific mechanism of action of HA is still unknown. HA is believed to be an appropriate choice for matrix to support dermal regeneration and augmentation because it is found naturally in most cells in the body and occurs in high concentrations in specific body locations especially skin tissues, eyes as well as in bones, cartilages structures, synovial fluid and connective tissues (Bansal et al., 2010; Price, Berry, & Navsaria, 2007). In each of these locations, HA serves a different function. Skin normally will become dry when the capacity of the skin to hold water is reduced due to the decreasing concentration of hyaluronic acid in the skin (Choulis, 2014).

HA is known to increase cell motility, cell proliferation, cell differentiation, cell interaction and production of cell physiological substances such as cytokines, PGE2 and matrix metalloproteinase (Capila & Sasisekharan, 2004). HA stimulates the development of fibrin, phagocytic activity, neutrophil and macrophage mobility, and the liberation of chemotactic factors for fibroblasts. Additionally, it induces proliferation of fibroblasts and stimulates their metabolism during granulation phase of the cicatrisation process, with a consequent increase in the collagen fibres and deposit of ground substance (Anderson, 2001). Concentration of HA in cell is reported to increase rapidly and reaches its peak three days after a wound occurred thus it provides a transitory matrix for the migration of inflammatory cells and proliferation of fibroblast in the connective tissue (Tammi & Tammi, 2004).

In summary, HA has been reported to be actively involved in all stages of wound healing, from the promotion of early inflammation and granulation tissue formation, through facilitation of cell migration into the wound matrix, to re-epithelialisation, via its free radical scavenging function and role in keratinocyte proliferation and migration.

### 2.4.2 Adverse effects of hyaluronic acid-containing dressings and topical preparations

Generally, most studies reported no serious adverse effects directly related to HA containing dressings and topical preparations (Abbruzzese et al., 2009; Caravaggi et al., 2003; Dereure et al., 2012a; Falanga et al., 1996; Meaume et al., 2008; Primavera et al., 2006).

However, the most common side effects reported are pain and discomfort such as bruising, swelling, redness, itching and tenderness. In one study related to the treatment of solar keratoses, the number of patients with adverse reactions in HA group was reported to be larger than the control group (18 vs 3) (McEwan & Smith, 1997). The local reactions reported for the study were rashes and irritation at the area of gel application.

HA-derived product responses to immune system are believed to be low due to its identical chemical structures across different species (Edwards & Fantasia, 2007). Evidence from available studies seems to indicate that HA is safe and well tolerated.

## 2.5 Assessment of Wound

Wound assessment is important for diagnosis, treatment and management. The correct assessment, diagnosis and appropriate treatment will help in managing wound healing.

The common outcomes used in assessing effectiveness of treatment for chronic and acute wounds are objective measures of healing rate, such as time to complete healing, rate of change in wound area and volume, proportion of wounds healed within the trial period/ percentage of wounds healed, reduction of wound size, visual appearance/quality of the wound surface and patient acceptability (Rüttermann et al., 2013). Other outcomes used are whether wounds are free of infection and pain.

## 2.6 Issues for wound healing assessment

The definition of wound healing is the most problematic followed by healing assessment and evaluation. To enhance communication among all parts of society dealing with this problem, description on definitions and guidelines are the vital steps. Parameter selection and evaluation frequency should be defined appropriately. For example, some researchers might describe a healed wound when more than 95% of the wound has epithelised whilst others described complete wound healing with 100% epithelialization and 0% residual wound area (Bettinger, Mast, & Gore, 1996; Costagliola & Agrosì, 2005; Koller, 2004).

Although recently, researches on wound healing have progressed rapidly, standardised outcome measurements are still lacking, thus making it tough to compare results from different studies. Lazarus et al. (1994) suggested that the complete wound assessment is required to include the extent of the wound (parameter involves are perimeter/area, volume), associated elements of the wound (e.g. duration, blood flow, oxygen, infection, edema, inflammation), host factors that influence wound status or wound effects on the host (e.g. wound burden or wound severity), and environmental status that affects wound management.

The time or duration to measure wound healing is also another issue. Complete healing, is defined as complete epithelialisation of the wound without drainage (Dereure et al., 2012a). The time-point on 45 days, is considered as a valid surrogate endpoint for leg ulcer healing by a board of experts approached for the trial design to assess the percentage of wound size reduction (Dereure et al., 2012a). However, for diabetic foot ulcers, 12-week healing rate was the reported time-point in most studies related to neuropathic ulcers of the foot in diabetes (Ince, Game, & Jeffcoate, 2007).

Fife, Carter, Walker, and Thomson (2012) reported that there are many aspects of costs which are important in wound-healing assessment. Therefore, evaluation of cost effectiveness should also be parts of the ideal wound management (Fonder et al., 2008). Abdelrahman and Newton (2011) suggested that minimizing dressing change will help reduce nursing time demand that lead to the reducing of cost in the overall wound management.

# CHAPTER 3: METHODS

## 3.1 Inclusion criteria for considering studies in this review

### 3.1.1 Types of studies

Studies reviewed include all randomised controlled trials (RCTs) evaluating the effects of HA (or its derivatives) used in the form of a dressing or as a topical agent in the treatment of acute and chronic wounds of any aetiology (i.e. diabetic foot ulcers, partial thickness burns, traumatic wounds and lacerations, pressure ulcers, arterial/venous leg ulcers and surgical wounds).

### 3.1.2 Types of participants

The studies involved people of all ages with acute or chronic wounds of any aetiology in any care settings. Studies examining the healing of corneal, foetal, acute radiation, mouth ulcer, bone and joint injuries will be excluded. Studies that do not involve the outer skin wound will also be excluded.

### 3.1.3 Types of interventions

The studies assessed the effects of dressing and topical agents containing HA (or its derivatives) and the likely comparisons were:

a) dressings containing HA (or its derivatives) compared with:
    i. any dressings without HA or;
    ii. another dressings containing other agents or;
    iii. topical preparations of other agents
b) topical preparations of HA compared with:
    i. dressings containing other agents or;
    ii. topical preparations without HA or:
    iii. topical preparations of other agents

### 3.1.4 Types of outcome measures

Two types of outcome measures considered were primary outcomes and secondary outcomes.

**Primary outcomes**

a) Healing time or time to complete wound healing
b) Number of wounds healed
c) Wound area reduction or ulcer size reduction or change in wound surface area

**Secondary Outcomes**

Trials which reported any of the following secondary outcomes involving the performance and safety of Hyaluronic Acid:

a) Pain intensity
b) Adverse events
c) Patient acceptability or satisfaction

## 3.2 Search strategies

Several search strategies were used to identify potentially relevant trials. The search strategies combined the used of various terms and synonyms for HA and wounds such as “hyaluronan”, “ulcers” and “RCT’. Details of the search strategies and search terms used in different databases to retrieve relevant studies are shown in Appendix A. The multiple strategies used were as follows:

### 3.2.1 Electronic database

For this study, we searched the following electronic databases:

i. CINAHL Plus with Full Text @EBSCOhost (inception to August 2015)
ii. Cochrane Central Register of Controlled Trials (CENTRAL) (inception-August 2015)
iii. MEDLINE with Fulltext @EBSCOhost (inception to August 2015)
iv. Ovid Full Text (inception to August 2015)
v. PUBMED (inception to August 2015)
vi. EMBASE (inception to August 2014)

The search was limited to humans for MEDLINE, EMBASE and a filter was applied to identify randomised controlled trials in all databases.

### 3.2.2 Online publishing site search

The following online sites were also searched:

i. Science Direct (inception to August 2015)
ii. SpringerLink
iii. Wiley Interscience
iv. SAGE Journals
v. Internurse
vi. Karger
vii. DART-Europe E-theses Portal

### 3.2.3 Specified electronic journals or websites

The following electronic journals or websites were searched:

i. Wound Healing Society (www.woundheal.org)

ii. ResearchGate (www.researchgate.net/journal)

iii. Wounds UK (www.wounds-uk.com)

iv. Wounds International (www.woundsinternational.com)

v. Diabetes On the Net.com

vi. European Wound Management Association (www.ewma.org)

vii. Worldwide wounds (www.worldwidewounds.com)

viii. Wounds research (www.woundsresearch.com)

ix. Journal od Wound Care (2000 to August 2015)

x. Journal of European Wound Management Association (2000 to August 2015)

xi. CARE-Science and Practice (2000 to August 2015)

xii. The Australasian Journal of Dermatology

### 3.2.4 Hand searches

Hand searches on wounds related topics in conferences and proceedings were as follows:

i. 36th Annual International Urogynecological Association (IUGA) Meeting, 2011

ii. 16th Congress of the Asian Pacific Society of Respirology, 2011

iii. 42nd Annual Meeting of the International Continence Society (ICS), 2012

iv. 28th ESMRMB (European Society for Magnetic Resonance in Medicine and Biology) Annual Scientific Meeting, 2011

v. American Society of Gene & Cell Therapy Annual Meeting, 2010-2011

vi. XXIX EAACI Congress of the European Academy of Allergy and Clinical Immunology, 2010

vii. Annual Congress of the British Society for Immunology, 2010

viii. 3rd TERMIS (Tissue Engineering & Regenerative Medicine International Society) World Congress, 2012

ix. First Eastern Asia Dermatology Congress. Fukuoka, Japan, 2010

x. 20th European Conference on General Thoracic Surgery, 2012

xi. 39th Congress of the German Society for Rheumatology, 2011

xii. Annual Meeting of the Society for Investigative Dermatology, 2011

xiii. 10th World Congress on Inflammation, 2011

xiv. Annual Meeting of the German Society for Experimental and Clinical Pharmacology and Toxicology, 2011-2012

xv. 38th Annual Meeting of the Arbeitsgemeinschaft Dermatologische Forschung (ADF), 2011

xvi. 47th Annual Meeting of the European Association for the Study of Diabetes, 2011

### 3.2.5 Additional sources of articles

The references of published papers on clinical trials and reviews from ClinicalTrials.gov and DART-Europe E-theses portal were also searched for additional articles.

## 3.3 Selection criteria and Data extraction

Two review authors (Atikah Shaharudin, AS; Zoriah Aziz, ZA) independently screened titles and abstracts of studies identified from the searches. We obtained full text articles if they appeared to satisfy, or to potentially satisfy, the inclusion criteria. The two review authors then independently checked full papers to identify those trials that were eligible for inclusion. Any disagreement between the two review authors was resolved through discussions. One review author (AS) undertook data extraction using a uniform data extraction form. The second review author (ZA) checked for accuracy. If any data was missing, attempts were made to obtain it by contacting the authors.

### 3.4 Data collection and analysis

The data were pooled using Review Manager (Revman) 5.3 if heterogeneity, $I^2$ is less than 80% (Higgins & Green, 2012). We used either a fixed-effect model or random effect model if pooling seemed appropriate in view of clinical and methodological similarities between studies. Relative risk (RR) and risk difference (RD) were calculated for dichotomous data and the results were reported as RR with 95% confidence intervals (CI). For continuous outcomes, the mean difference (MD), the weighted mean difference (WMD), or standardised mean difference (SMD) with 95% CI was reported as appropriate. Statistical significance was set at $p < 0.05$ for all outcomes. Relative risk was chosen in preferences to odd ratio (OR) on the basis that OR can be misinterpreted when event rates are high (>20%) (Deeks, Higgins, & Altman, 2008).

Studies that evaluated similar intervention in a similar population were assessed for the presence of statistical heterogeneity by using chi-squared, $\chi^2$ test. The amount of heterogeneity was estimated using $I^2$ statistic (which indicates the percentage of variation between studies that is due to heterogeneity rather than chance). We requested from authors those relevant outcome results if the data were missing. Alternatively, we calculated required data from available statistics. We imputed the data for standard deviation difference ($SD_{diff}$) when standard error value was available (Borenstein, Hedges, Higgins, & Rothstein, 2009; Follmann, Elliott, Suh, & Cutler, 1992).

### 3.5 Quality assessment of included studies

We assessed the risk of bias in the included RCTs using criteria suggested by the Cochrane Collaboration (Higgins & Green, 2012). The following methodological domains were assessed: sequence generation, allocation sequence concealment, blinding of participants, researchers and outcome assessors, incomplete outcome data, selective outcome reporting, and other potential threats to validity (Appendix D).

We clearly classified risk of bias for each of the domains as either unclear risk of bias, low risk of bias or high risk of bias. Unclear risk of bias indicates either deficiency of information or ambiguity over the potential for bias. The two reviewers discussed to resolve any disagreement at any stages of selecting studies, data extraction, data analysis and risk of bias assessment.

# CHAPTER 4: RESULTS

## 4.1 Results of the search

The search for RCTs from all different sources produced 3466 records out of which 2606 were duplicates (Figure 4.1). We examined their potential relevance by screening through titles and abstracts of these 860 records. Further 823 records were excluded. The full texts of the remaining 37 studies were retrieved to assess whether they could be included in the review. Another 27 studies were excluded for not meeting the inclusion criteria (Appendix B). The reasons for exclusion include: non-RCT (12 studies), comparing hyaluronic acid dressing or hyaluronic acid topical with other hyaluronic products or hyaluronic-added products (7 studies), trials without control group (4 studies), the unit of analysis was wound sites instead of participants (3 studies) and trial reporting secondary outcome only (1 study). Data from 10 included studies were extracted by using the data extraction form (Appendix C).

The ten trials included were conducted in three countries (six in France, three in Italy and one in Slovakia) and were published in English language between 1996 and 2012.

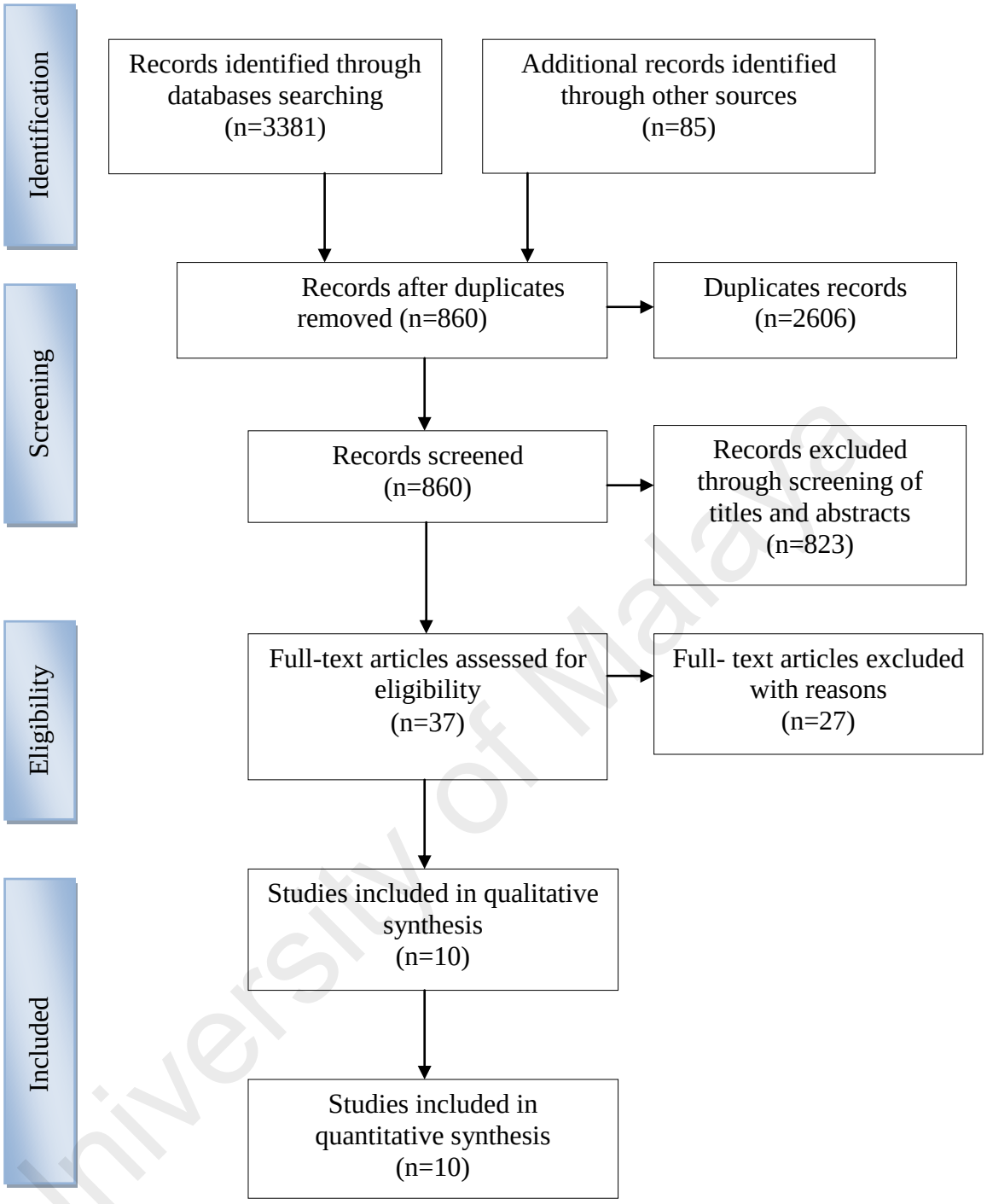




**Figure 4.1: Flow chart of the study selection process**

## 4.2 Description of the studies

The sample sizes of these trials ranged from 33 to 180 involving a total of 992 patients where their ages ranged from 18 to 80 years old. One trial did not provide information on the age of patients (Caravaggi et al., 2003). Out of 992 participants, 503 were

allocated to hyaluronic acid group and 489 for control group. Five trials enrolled more than 100 participants and five trials were multi-centred (Table 4.1).

Eight trials assessed chronic wounds: mixed arterial and venous ulcer (n=5), venous leg ulcer (n=1) and diabetic foot ulcer (n=2). Two trials assessed acute wounds of superficial and deep partial-thickness burns.

In seven trials, the interventions were HA-containing dressings compared with a variety of controls. The comparators were non-HA dressings (non-adherent paraffin gauze, OASIS® dressing, DuoDERME®, hydrocolloid dressings, normal gauze pad) and other topical agents (dextranomer paste). Three trials compared topical HA with other topical agent (neutral cream without HA, silver sulfadiazine (SSD) cream). Durations of study varied between three weeks and 18 months (Table 4.2).

***Types of outcomes assessed***

All papers reported at least one outcome of healing for their primary outcomes such as wound area reduction, number of wounds healed and healing time (Table 4.3). However, healed wounds were defined differently for several trials. Two trials did not provide any definition (Humbert et al., 2012; Ortonne, 1996). Seven trials defined complete healing as 100% epithelialisation without residual exudate (Caravaggi et al., 2003; Costagliola & Agrosì, 2005; Dereure et al., 2012a; Dereure et al., 2012b; Koller, 2004; Romanelli, Dini, Brilli, & Bertone, 2007; Uccioli et al., 2011). One trial considered the presence of epithelialisation as an indicator of healing and Meaume et al. (2008) reported that at least 90% reduction of wound area signified healing. Most of the trials measured wound area reduction either by 'planimetry and photograph' or 'tracing-paper and digital planimetry (Visitrak®)'.

For secondary outcome measures, a few general outcomes were reported in several trials as shown in the summary on types of outcomes assessed (Table 4.3). Pain was reported in nine trials (Costagliola & Agrosì, 2005; Dereure et al., 2012a; Dereure et al., 2012b; Humbert et al., 2012; Koller, 2004; Meaume et al., 2008; Ortonne, 1996; Romanelli et al., 2007). The majority of trials reported pain by using Huskisson's Visual Analogue Scale (VAS) and only two trials measured pain through patients' complaints during the treatment. The incident of adverse events was assessed in ten trials by counting the number of cases or patients with adverse events.

In nine trials acceptability of patients (patients' assessments) was measured through counting the number of applications performed and also the use of four-point scale ("bad", "fair", "good", "excellent") (Costagliola & Agrosì, 2005; Dereure et al., 2012a; Dereure et al., 2012b; Humbert et al., 2012; Koller, 2004; Meaume et al., 2008; Ortonne, 1996; Romanelli et al., 2007).

The measurements of wound appearance varied across trials, therefore this was not included in the assessment of secondary outcomes. Consumption of oral analgesic was reported in two trials (Meaume et al., 2008 and Costagliola and Agrosi, 2005) while local infection was reported in one patient with the application of Hyaluronic cream (Ialugen Plus®) (Koller 2004).

**Table 4.1: Descriptions of included trials: Study designs, study settings, number and age of participants**

| Study | Study Design | Setting: Country (number of centres) | Participants | Age in years (mean (SD)) Intervention (I) & Control (C) |
|---|---|---|---|---|
| **Chronic wounds** | | | | |
| Ortonne (1996) | RCT | Hospital : France (NR) | 50 patients | I: 66.2 (15.8), C:69.7 (17.6) |
| Caravaggi et al. (2003) | Open, RCT | Diabetes foot clinic: Italy (6) | 79 patients | NR |
| Romanelli et al. (2007) | RCT | Leg Ulcer Clinic: Italy (1) | 54 patients | Age: > 18<br>I: 62 (8), C: 64 (13) |
| Meaume et al. (2008) | Open-label, RCT | Hospital: France (15); Italy (2); Switzerland (1) | 125 patients | Age: ≥18<br>I: 73 (11.1), C: 75 (11.0) |
| Uccioli et al. (2011) | Open, RCT | Diabetic foot centers: Italy (7) | 180 patients | I: 61 (10), C: 62 (11) |

Note: NR: Not Reported

**Table 4.1: Continued**

| Study | Study Design | Types of centres: Country (number of centres) | Participants | Age in years (mean (SD)) Intervention (I) & Control (C) |
|---|---|---|---|---|
| **Chronic wounds** | | | | |
| Dereure et al. (2012a) | Double-blinded RCT | Hospital: France (17); Poland (7) | 101 patients | Age: ≥ 18<br>I: 68.6 (12.4), C: 69.7 (14.7) |
| Dereure et al. (2012b) | Single-blinded RCT | Hospital: France (4); Poland (16) | 170 patients | Age: ≥ 18<br>I: 64.2 (14.4), C:68.5 (13.1) |
| Humbert et al. (2012) | Double-blinded RCT | Hospital: France (18); Poland ( 8 ); Morocco (3) | 89 patients | Age: ≥18<br>I: 59.4 (16.8), C:64.1 (17.9) |
| **Acute wounds** | | | | |
| Koller (2004) | Double-blinded RCT | Hospital: Slovakia (1) | 33 patients | Range: 18-80<br>Mean: I: 35 (14.5), C: 40.7 (11.6) |
| Costagliola and Agrosi (2005) | Double-blinded RCT | Clinical centers: France (2); Croatia (1); Slovenia (1); Germany (1) | 111 patients | Range: I:19-62, C:18-75<br>Mean: I: 38.2 (12.4), C: 38.5 (15.1) |

Note: NR: Not Reported

**Table 4.2: Descriptions of included trials: Types of wounds, interventions & controls and study durations**

| Study | Wound types | Intervention (number of participants) | Control (number of participants) | Study duration (week) |
|---|---|---|---|---|
| **Chronic wounds** | | | | |
| Ortonne (1996) | Venous leg ulcers | Gauze pad impregnated with Sodium hyaluronate cream 0.05% (26) | Dextranomer paste (24) | 3 |
| Caravaggi et al. (2003) | Diabetic foot ulcers | Hyalograft 3D (HYAFF-11®) (43) | Non-adherent paraffin gauze (36) | 11 |
| Romanelli et al. (2007) | Mixed arterial & venous ulcers | Dressing consisting of single component ECM: Hyaluronic acid (Hyaloskin®) (27) | dressing containing all ECM components (OASIS®) (27) | 16 |
| Meaume et al. (2008) | Mixed arterial & venous ulcers | Hydrocolloid-Hyaluronic acid 0.2% dressing (63) | Hydrocolloid dressing (62) | 6 |
| Uccioli et al. (2011) | Diabetic foot ulcers | HYAFF-Hyalograft 3D(90) | Non-adherent paraffin gauze (90) | 72 |

**Table 4.2: Continued**

| Study | Participants | Intervention (number of participants) | Control (number of participants) | Durations (week) |
|---|---|---|---|---|
| Dereure et al. (2012a) | Mixed arterial & venous ulcers | Hyaluronic acid 0.2% cream (Ialuset®) (50) | Neutral Cream without Hyaluronic acid (51) | 8.6 |
| Dereure et al. (2012b) | Mixed arterial & venous ulcers | Hyaluronic acid 0.05% gauze pad (Ialuset®) (85) | DuoDERME (85) -Hydrocolloid dressing | 8 |
| Humbert et al. (2012) | Mixed arterial & venous ulcers | Hyaluronic acid 0.05% gauze pad (Ialuset®) (45) | Gauze pad without Hyaluronic acid (44) | 8.6 |
| **Acute wounds** | | | | |
| Koller (2004) | Superficial & deep partial-thickness burns | Hyaluronic acid-silver sulfadiazine 1% (Ialugen Plus®) cream (18) | Silver sulfadiazine cream 1% (15) | 4 |
| Costagliola and Agrosi (2005) | Superficial & deep partial-thickness burns | Hyaluronic acid-silver sulfadiazine 1% (Connettivina® Plus) cream (56) | Silver Sulfadiazine cream 1% (55) | 4 |

**Table 4.3: Summary for types of outcomes assessed**

| Study | Wound area reduction | Number of wounds healed | Healing Time | Pain intensity | Adverse events | Patients' assessment |
|---|---|---|---|---|---|---|
| **Chronic wounds** | | | | | | |
| Ortonne (1996) | ✓ | - | - | ✓ | ✓ | ✓ |
| Caravaggi et al. (2003) | - | ✓ | ✓ | - | ✓ | - |
| Romanelli et al. (2007) | - | ✓ | - | ✓ | ✓ | ✓ |
| Meaume et al. (2008) | ✓ | ✓ | - | ✓ | ✓ | ✓ |
| Uccioli et al. (2011) | ✓ | ✓ | ✓ | - | ✓ | - |
| Dereure et al. (2012a) | ✓ | ✓ | - | ✓ | ✓ | ✓ |
| Dereure et al. (2012b) | ✓ | ✓ | - | ✓ | ✓ | ✓ |
| Humbert et al. (2012) | ✓ | ✓ | - | ✓ | ✓ | ✓ |
| **Acute wounds** | | | | | | |
| Koller (2004) | ✓ | - | ✓ | ✓ | ✓ | ✓ |
| Costagliola and Agrosi (2005) | ✓ | - | ✓ | ✓ | ✓ | ✓ |

Note: ✓ outcome assessed or reported

\- outcome not assessed or not reported

## 4.3 Risk of bias assessment

Figure 4.2 and 4.3 show the summaries of the qualities of the 10 included trials based on the Cochrane collaboration tool for assessing risk of bias (Higgins & Altman, 2012). Appendix F provides the details on the risk of bias assessment for each of the included RCTs. Five out of ten trials were overall at low to moderate risk of bias for the eight domains assessed (Dereure et al., 2012a; Dereure et al., 2012b; Humbert et al., 2012; Meaume et al., 2008; Uccioli et al., 2011). Three trials had more than three domains judged to have unclear risk of bias (Costagliola & Agrosì, 2005; Koller, 2004; Ortonne, 1996) while the remaining two trials had at least one domain judged as having high risk of bias (Caravaggi et al., 2003; Romanelli et al., 2007).

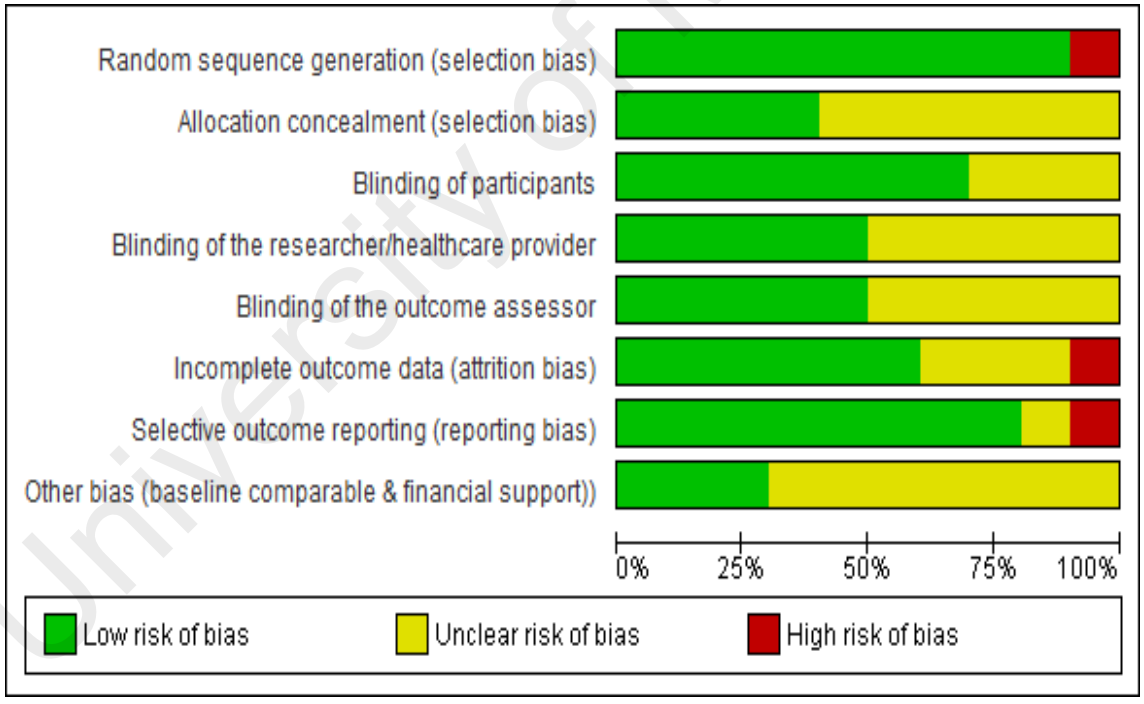


**Figure 4.2: Risk of bias graph**

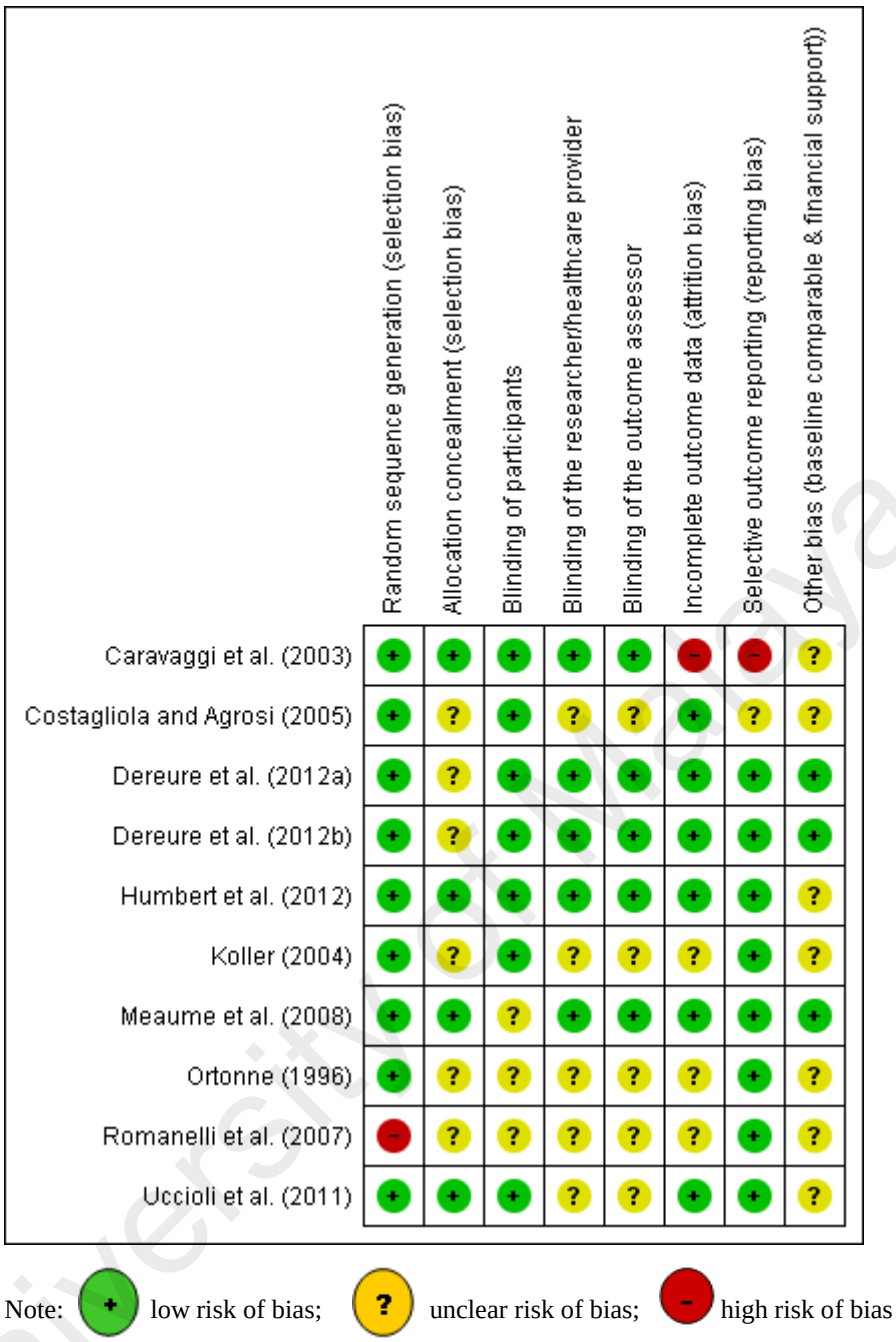


**Figure 4.3: Risk of bias assessment summary**

### 4.3.1 Random sequence generation

Nine out of ten trials (Caravaggi et al., 2003; Costagliola & Agrosì, 2005; Dereure et al., 2012a; Dereure et al., 2012b; Humbert et al., 2012; Koller, 2004; Meaume et al., 2008; Ortonne, 1996; Uccioli et al., 2011) clearly stated the method of generating the randomisation sequence, thus were classified to have low risk of bias whilst one trial

(Romanelli et al., 2007) was judged to have a high risk of bias as the randomisation sequence was generated through every other patient selected by the clinician. Among the studies that gave detail of the randomisation, one study stated using sealed envelope (Meaume et al., 2008), another study stated telephone-randomisation (Caravaggi et al., 2003) while five other studies reported computer-generated randomisation list (Costagliola & Agrosì, 2005; Dereure et al., 2012a; Dereure et al., 2012b; Koller, 2004; Meaume et al., 2008).

### 4.3.1 Allocation concealment

Only four trials (Caravaggi et al., 2003; Humbert et al., 2012; Meaume et al., 2008; Uccioli et al., 2011) were judged to be at low risk of bias as they described the method of concealing allocation for example by the use of sealed envelopes and coding by an independent department. For another six trials (Costagliola & Agrosì, 2005; Dereure et al., 2012a; Dereure et al., 2012b; Koller, 2004; Ortonne, 1996; Romanelli et al., 2007), the risk of bias were considered as unclear because the information provided for this domain was insufficient to make judgement.

### 4.3.2 Blinding

The trials had varying levels of blinding. Four trials (Caravaggi et al., 2003; Dereure et al., 2012a; Dereure et al., 2012b; Humbert et al., 2012) reported blinding of participants, researcher/healthcare provider and outcome assessor whilst another two trials (Ortonne, 1996; Romanelli et al., 2007) did not mention whether blinding was employed in all levels. The remaining four trials had insufficient information at least for one level either on blinding of participants, researcher or assessor (Costagliola & Agrosì, 2005; Koller, 2004; Meaume et al., 2008; Uccioli et al., 2011).

### 4.3.3 Incomplete outcome data (intention-to-treat analysis)

Six trials conducted intention-to-treat (ITT) analysis because the final analysis included all randomised patients. Therefore, these trials were classified as having low risk of bias. One trial (Romanelli et al., 2007) did not report whether ITT analysis was carried out but had a low dropout rate (7.4%), while in another two trials (Koller, 2004; Ortonne, 1996) it was unknown whether the ITT was carried out and these trials were thus classified as having unclear risk of bias. Caravaggi et al. (2003) had a high dropout rate of 22.8% with the number of randomised patients not accounted for in the final analysis, hence were judged to be at high risk of bias.

### 4.3.4 Selective outcome reporting

Eight trials were judged as having low risk of bias to selective outcome reporting as the main outcome measures stated in the method section were included in the result section. Caravaggi et al. (2003) was judged to be at high risk of selective outcome reporting bias as they did not report the pain intensity outcome as mentioned in the method section, while one trial (Costagliola & Agrosì, 2005) had unclear risk of bias for this domain as the outcome results for wound area reduction and pain intensity were not completely reported.

### 4.3.5 Other sources of bias

Two other important sources of risks of bias were assessed. They were baseline comparability and the financial support received to fund the trials.

Three trials (Dereure et al., 2012a; Dereure et al., 2012b; Meaume et al., 2008) were judged as having low risk of bias as the baseline characteristics were comparable between intervention and control group. Additionally, they have no conflict of interest regarding financial support. One trial (Romanelli et al., 2007) was funded by the manufacturer of the Oasis product (control group), Healthpoint, Ltd., but we judged the

risk of bias to be unclear as we could not determine whether this has affected the findings of the trial.

Six trials did not provide sufficient information on financial support thus the risk of potential bias was unclear (Caravaggi et al. 2003; Costagliola and Agrosi 2005; Humbert et al. 2012; Koller 2004; Ortonne, 1996; Uccioli et al. 2011).

## 4.4 Effects of the interventions

A total of 992 patients (with 992 wounds) were enrolled in 10 RCTs; eight trials involved chronic wounds and two on acute wounds. The results were presented separately for trials involving chronic and acute wounds.

Within each wound types (chronic or acute), the results were presented based on the different outcomes as follows; wound area reduction, number of wounds healed, healing time, pain intensity, adverse event, quality of the wound, patients' assessments and consumption of oral analgesic. The types of wound, number of trials, and outcomes reported were summarised in Table 4.4.

Pooling for several trials was possible only for several outcomes, which have complete essential data reported (Appendix E). For studies with incomplete data on variability we imputed the missing data according to the methods previously recommended (Follmann et al., 1992; Higgins, Deeks, & Altman, 2008).

**Table 4.4: Number of trials with outcome data**

| **Types of wounds** | **Chronic wounds** | | | **Acute wounds** |
|---|---|---|---|---|
| | Mixed arterial and venous ulcers (n=5) | Venous leg ulcers (n=1) | Diabetic foot ulcers (n=2) | Burn wounds (n=2) |
| **Types of outcomes** | Number of trials provided data for each outcome | | | |
| Wound area reduction | 4 | 1 | 1 | 2 |
| Number of wounds healed | 5 | NA | 2 | NA |
| Healing time | NA | NA | 2 | 2 |
| Pain intensity | 5 | 1 | NA | 2 |
| Adverse events | 5 | 1 | 2 | 2 |
| Patients' assessments | 5 | 1 | NA | 2 |
| Oral analgesic consumption | 1 | NA | NA | 2 |

Notes: n: number of trials; NA: not assessed

### 4.4.1 Effects of interventions on chronic wounds

#### 4.4.1.1 Wound area reduction

Six trials for chronic wounds reported the outcome wound area reduction. However only four trials provided quantitative data:

*(a)* ***Mixed arterial and venous ulcers***

Four out of five trials reported wound area reduction. However, only two trials provided quantitative data. The results were as follows:

*i HA cream (Ialuset®) versus neutral cream (without HA)*

Dereure et al. (2012a) reported significantly greater median wound area reduction in HA group compared to the control group (39% versus 5%).

*ii HA gauze pad (Ialuset®) versus Hydrocolloid dressings (DuoDERME®)*

Dereure et al. (2012b) reported that there was no significant difference in wound area reduction between HA group and hydrocolloid dressing group (95% CI: -0.128 to 0.164).

*iii HA gauze pad (Ialuset®) versus normal gauze pad (without HA)*

Humbert et al. (2012) reported that there was a statistically significant effect in the wound size reduction favouring HA gauze pad compared to normal gauze pad (Figure 4.4).

*iv HA-Hydrocolloid dressings versus Hydrocolloid dressings*

Meaume et al. (2008) reported that treatment with 0.2% HA-added hydrocolloid dressings was significantly comparable with the hydrocolloid dressings alone (Figure 4.4).

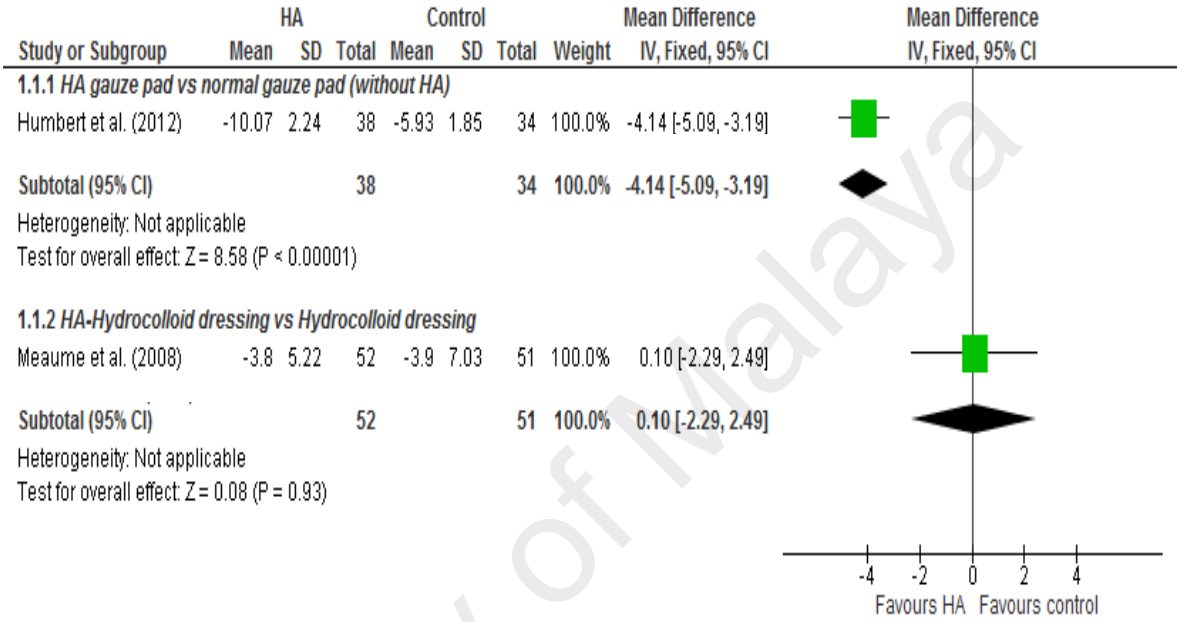


**Figure 4.4: Chronic wounds (Mixed arterial and venous ulcers); Outcome: Wound area reduction**

*(b) **Venous leg ulcers***

Only one trial reported wound area reduction for venous leg ulcers:

*i HA gauze pad versus Dextranomer paste*

Ortonne (1996) reported that there was no significant difference in the reduction of wound area between the two groups (Figure 4.5).

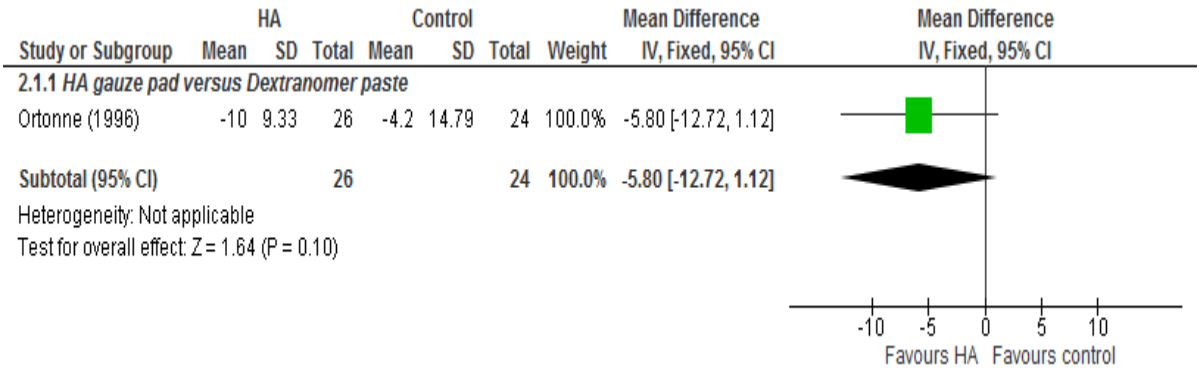


**Figure 4.5: Chronic wounds (Venous leg ulcers); Outcome: Wound area reduction**

*(c)* ***Diabetic foot ulcers***

Two trials compared similar type of dressing, HYAFF-11 with paraffin gauze. However, only one trial provided the outcome data for wound area reduction.

*i Hyalograft 3D (HYAFF-11®) versus non-adherent paraffin gauze*

Uccioli et al. (2011) found that the HA group reduced wound area by 29% compared to 14% in the control group. However this difference was not statistically significant (Figure 4.6).

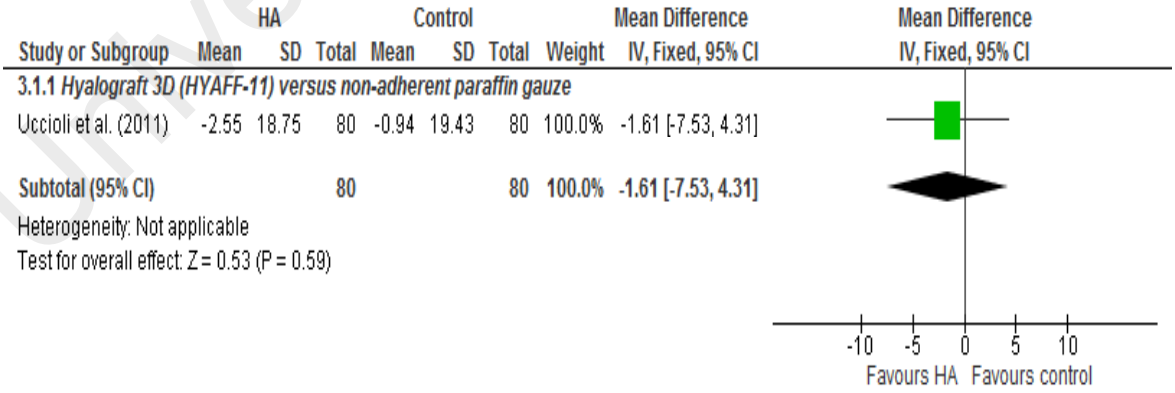


**Figure 4.6: Chronic wounds (Diabetic foot ulcers); Outcome: Wound area reduction**

#### 4.4.1.2 Number of wounds healed

Seven trials for chronic wounds reported number of wounds healed. However, only six trials provided quantitative data:

*(a)* ***Mixed arterial and venous ulcers***

All five trials reported number of wounds healed and provided quantitative data. Pooled data from these trials showed that there was no significant difference in the number of wounds healed between HA (or its derivatives) with control (Figure 4.7). The results were presented as follows:

*i HA cream (Ialuset®) versus neutral cream (without HA)*

Dereure et al. (2012a) reported that there was no significant difference between HA cream and neutral cream in terms of number of wounds healed (Figure 4.7).

*ii HA gauze pad (Ialuset®) versus Hydrocolloid dressing (DuoDERME®)*

Dereure et al. (2012b) defined ulcer healing as patients having at least 40% decrease of initial target ulcer surface after eight weeks. On this basis, for patients with mixed arterial and venous ulcers, the result showed that there was no significant difference between the two groups (Figure 4.7).

*iii HA gauze pad (Ialuset®) versus normal gauze pad (without HA)*

Humbert et al. (2012) enrolled 89 patients with mixed arterial and venous leg ulcer. Eighteen drop-out patients were not included in final analysis. No definition on wound healing was given. They found an increased number of wounds healed in the HA group compared to gauze pad group but the effect was not statistically significant (Figure 4.7).

### *iv HA-Hydrocolloid dressing versus Hydrocolloid dressing*

Meaume et al. (2008) trial which involved patients with mixed arterial and venous leg ulcer showed that there was no significant difference in the number of wounds healed between group with dressing added HA compared to hydrocolloid agent alone (Figure 4.7).

### *v HA dressing (Hyaloskin®) versus OASIS® dressing*

Romanelli et al. (2007) enrolled 54 patients with mixed arterial and venous leg ulcer. Four patients dropped out from the trial and were not included in the final analysis. In this trial, complete wound closure was defined by a fully re-epithelialised area. The result showed that statistically more wounds were healed with the use of OASIS dressings compared to HA dressings (Figure 4.7)

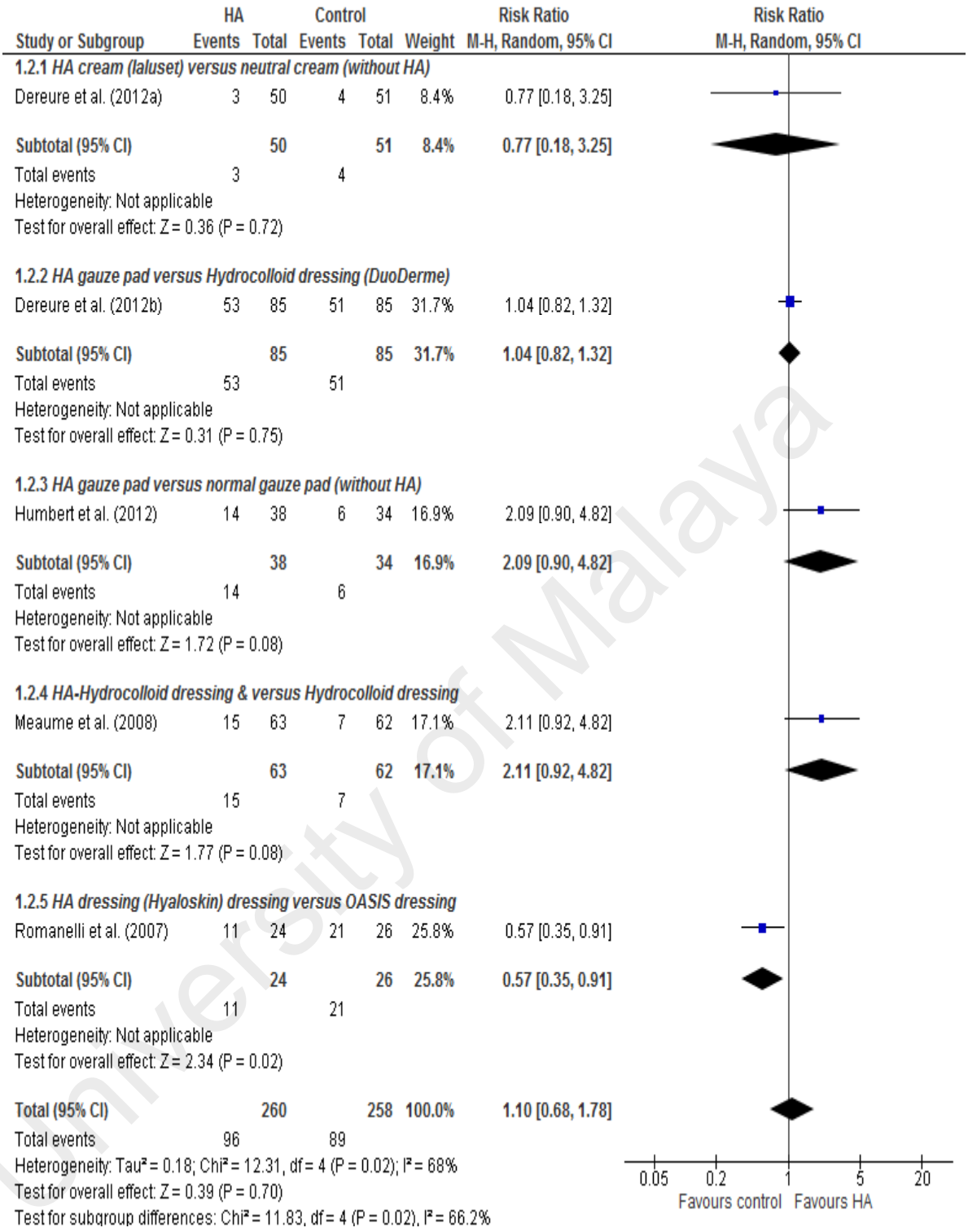


**Figure 4.7: Chronic wounds (Mixed arterial and venous ulcers); Outcome: Number of wounds healed**

*(b)* ***Diabetic foot ulcers***

Two trials reported number of wounds healed and provided quantitative data:

*i Hyalograft 3D (HYAFF-11®) versus non-adherent paraffin gauze*

Two trials (Caravaggi et al. 2003; Uccioli et al. 2011) which involved 239 patients with diabetic foot ulcer. Both trials defined healed wound as complete re-epithelialisation without residual exudate, crusting or eschar. The pooled result showed that there was no significant difference between HA group and non-adherent paraffin gauze in terms of number of wounds healed (Figure 4.8).

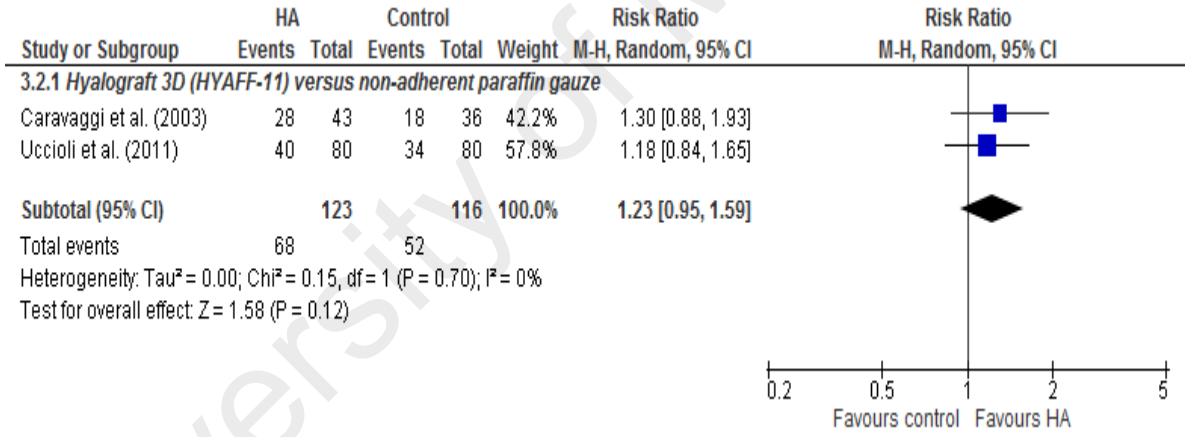


**Figure 4.8: Chronic wounds (Diabetic foot ulcers); Outcome: Number of wounds healed**

#### 4.4.1.3 Healing Time

Only two trials for chronic wounds with diabetic foot ulcers patients reported the outcome healing time. However one trial (Caravaggi et al., 2003) did not report the measure of variability (standard deviation) for both baseline and endpoint values, so the results of the trial could not be pooled. Another one trial (Uccioli et al., 2011) provided quantitative data:

*(a)* ***Diabetic foot ulcers***

The result was presented as follow:

*i* *Hyalograft 3D (HYAFF-11®) versus non-adherent paraffin gauze*

Caravaggi et al. (2003) reported the healing time was significantly better for HA group compared to non-adherent paraffin gauze (median: 57 days versus 77 days). Another trial, Uccioli et al. (2011) found a tendency towards improvement in healing time in the HA group but that the difference between the two groups was not statistically significant (Figure 4.9).

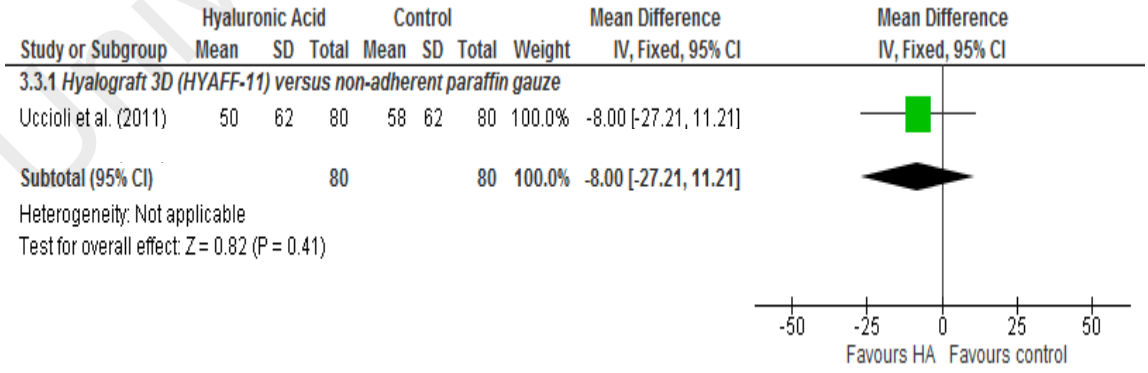


**Figure 4.9: Chronic wounds (Diabetic foot ulcers); Outcome: Healing time**

#### 4.4.1.4 Pain Intensity

Six trials for chronic wounds reported the outcome pain intensity. However, only three trials with mixed arterial and venous ulcers patients provided quantitative data:

*(a)* ***Mixed arterial and venous ulcers***

All five trials reported pain intensity. However, only three trials provided quantitative data. Pain data in these three trials used 100mm Visual Analogue Scale (VAS)..

*i* *HA cream (Ialuset®) versus neutral cream (without HA)*

Dereure et al. (2012a) reported pain intensity using the scale 100mm VAS. There was a significant pain reduction in group treated with Ialuset® cream compared to group given neutral cream (Figure 4.10).

*ii* *HA gauze pad (Ialuset®) versus Hydrocolloid dressing (DuoDERME)*

Dereure et al. (2012b) did not provide quantitative data even though they reported that there was no statistically significant difference in pain reduction between HA group and hydrocolloid dressing group (p=0.6658).

*iii* *HA gauze pad (Ialuset®) versus normal gauze pad (without HA)*

Humbert et al. (2012) found a tendency on the improvement of pain in patients dressed with HA gauze pad than patients dressed with normal gauze pad, however the difference was not statistically significant (Figure 4.10).

*iv* *HA-Hydrocolloid dressing versus Hydrocolloid dressing*

Meaume et al. (2008) reported patients dressed with HA-hydrocolloid dressing experienced significantly less pain than patients dressed with hydrocolloid dressing alone (Figure 4.10).

*v HA dressing (Hyaloskin®) versus OASIS® dressing*

Romanelli et al. (2007) did not report the baseline value for pain intensity. However, they reported that there was a significant difference in pain reduction between HA group (VAS=6.2) and control group (VAS= 3.7).

The pooled data from these trials showed that there was a statistically significant benefit of HA in improving pain intensity (Figure 4.10)

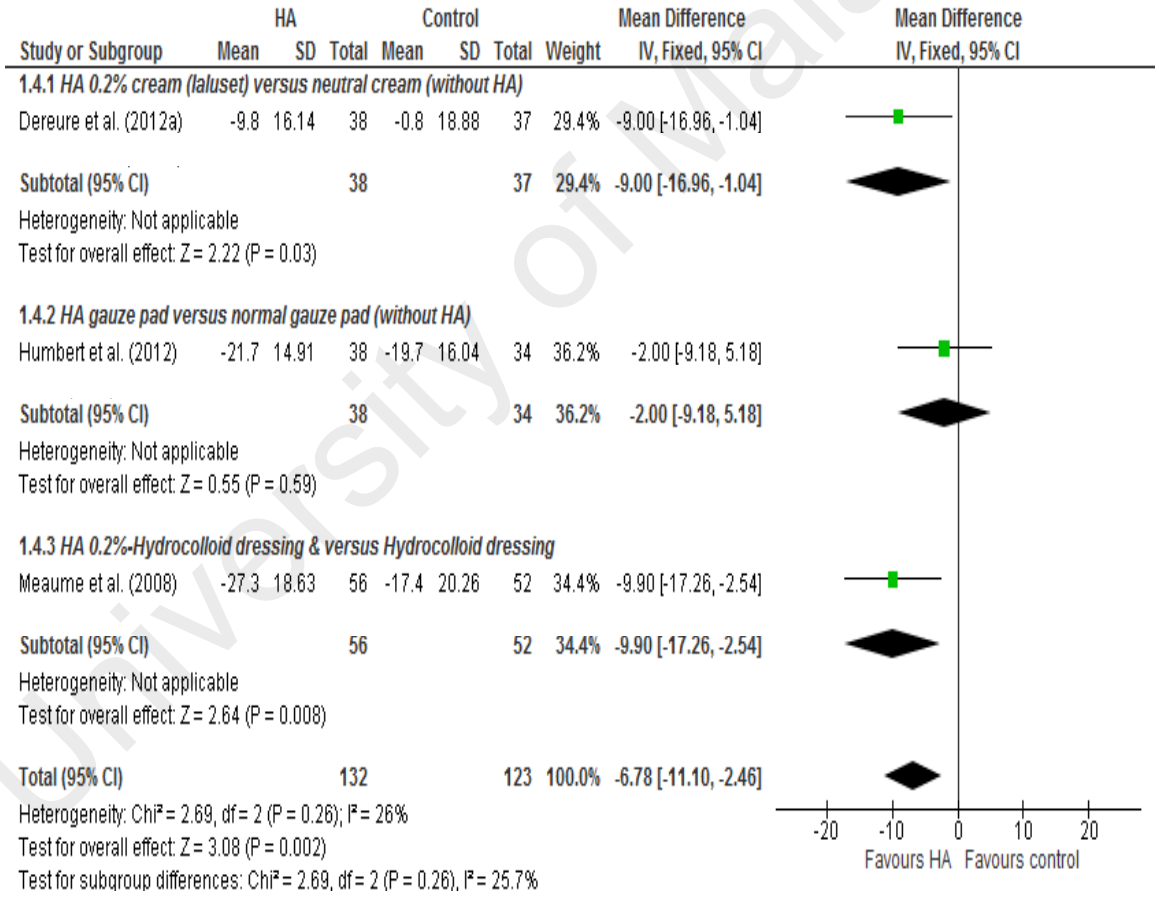


**Figure 4.10: Chronic wounds (Mixed arterial and venous ulcers); Outcome: Pain intensity**

*(a)* ***Venous leg ulcers***

Only one trial reported pain intensity for venous leg ulcers but did not provide the quantitative data:

*i HA gauze pad versus Dextranomer paste*

Ortonne (1996) reported severity of pain scale by using Kruskall-Wallis test. The results showed a significant beneficial effect in reducing severity of pain with HA gauze pad compared to Dextranomer paste (from 1.00 to 0.24 vs 1.10 to 0.33 respectively).

#### 4.4.1.5 Number of patients with adverse events

Eight trials for chronic wounds reported the outcome adverse events. The majority of the trials reported the data either in terms of number of adverse events occurred or number of patients who experienced adverse events. To standardise the results, we used the number of patients experiencing adverse events as most of the trials provided this data. Only six trials provided quantitative data:

*(a)* ***Mixed arterial and venous leg ulcers***

All five trials reported adverse events. However, only four trials provided quantitative data. The results were presented as follows:

*i HA cream (Ialuset®) versus neutral cream (without HA)*

Dereure et al. (2012a) has not clearly defined adverse events. However, inflammation was one of the events reported. The trial found no significant difference in adverse event between the intervention and control groups (Figure 4.11).

### *ii HA gauze pad (Ialuset®) versus Hydrocolloid dressings (DuoDERME®)*

Dereure et al. (2012b) reported number of adverse events instead of number of patients with adverse events. The trial found that less adverse events occurred in HA group (n=36) as compared to control group (n=41). Apart from that, 77% of adverse event was mild to moderate, while 23% was severe.

### *iii HA gauze pad (Ialuset®) versus normal gauze pad (without HA)*

Humbert et al. (2012) reported 75% of the adverse events was mild to moderate, while 25% was severe (total number of patients=27). There was no significant difference in the number of adverse events reported for both intervention and control groups (Figure 4.11).

### *iv HA-Hydrocolloid dressing versus Hydrocolloid dressing*

The main adverse events reported in Meaume et al. (2008) were itching and edema, erosion, eczema, rash, and pain. There was no significant difference in the number of patients experiencing adverse events between the two groups (Figure 4.11).

### *v HA sheet (Hyaloskin®) versus OASIS® dressing*

Romanelli et al. (2007) reported no incidence of ADR during the trial for both groups. They concluded that both intervention and control were equally safe for the treatment of chronic wounds.

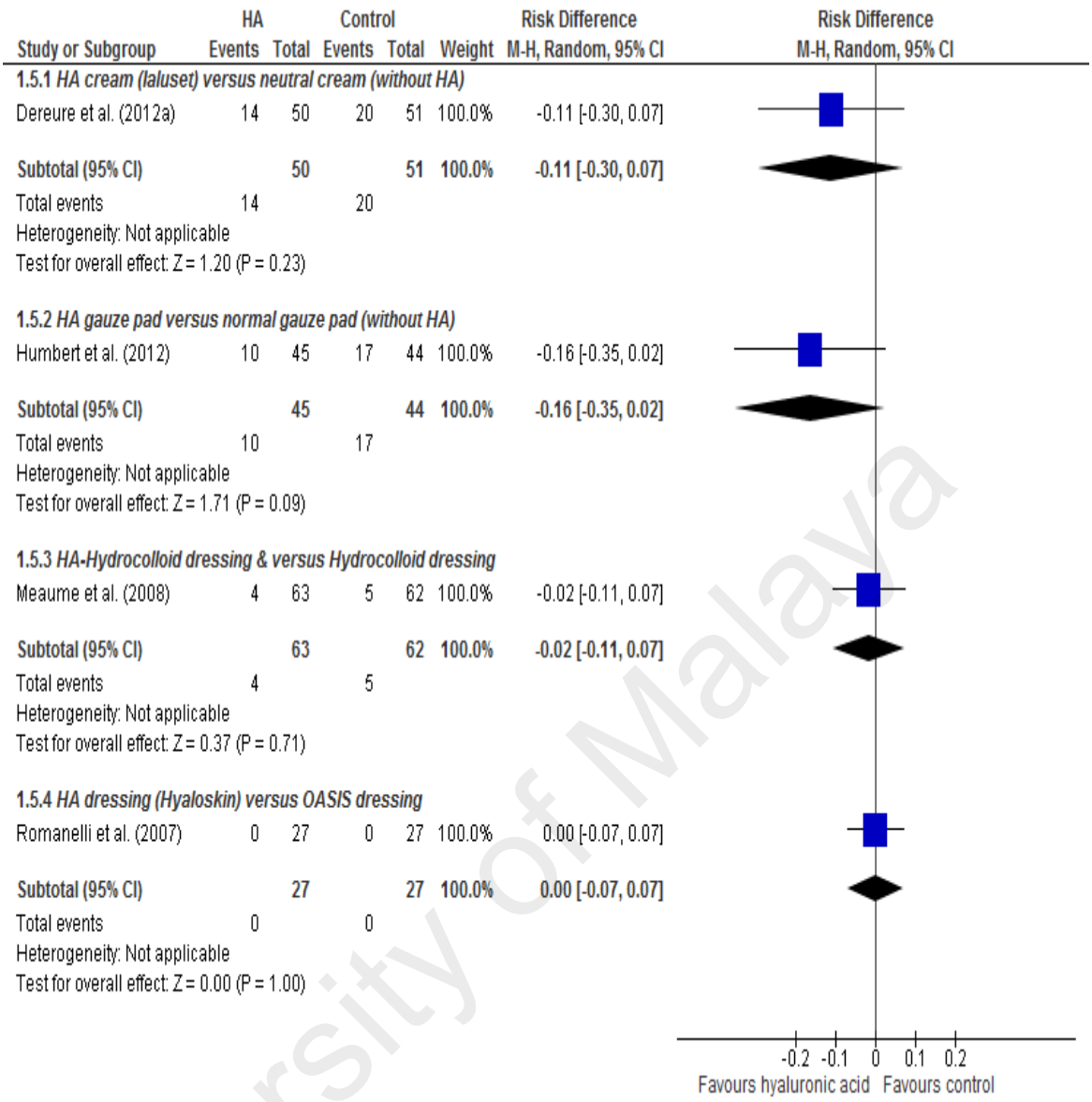


**Figure 4.11: Chronic wounds (Mixed arterial and venous ulcers); Outcome: Number of patients with adverse events**

### *(b) Venous leg ulcers*

Only one trial reported adverse events and provided the quantitative data:

#### *i HA gauze pad versus Dextranomer paste*

Ortonne (1996) reported local pain, local burning sensation, panniculitis, eczema, and prickling sensation as the adverse events. The trial found that there was no significant difference between the two groups (Figure 4.12).

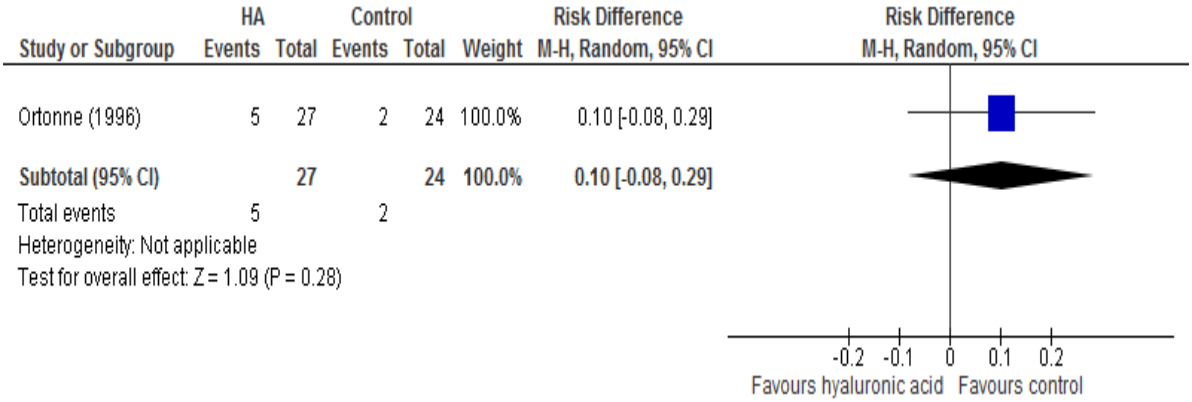


**Figure 4.12: Chronic wounds (venous leg ulcers); Outcome: Number of patients with adverse events**

### *(c) Diabetic foot ulcers*

Both trials reported adverse events and provided quantitative data:

#### *i. Hyalograft 3D (HYAFF-11®) versus non-adherent paraffin gauze*

Caravaggi et al. (2003) reported the main adverse events occurred were wound infection, inflammation, and worsening of ischemia for both groups. Meanwhile Uccioli et al. (2011) reported adverse events were mainly due to infections. The pooled result for both trials showed no significant difference in the number of patients having adverse events between the two groups (Figure 4.13).

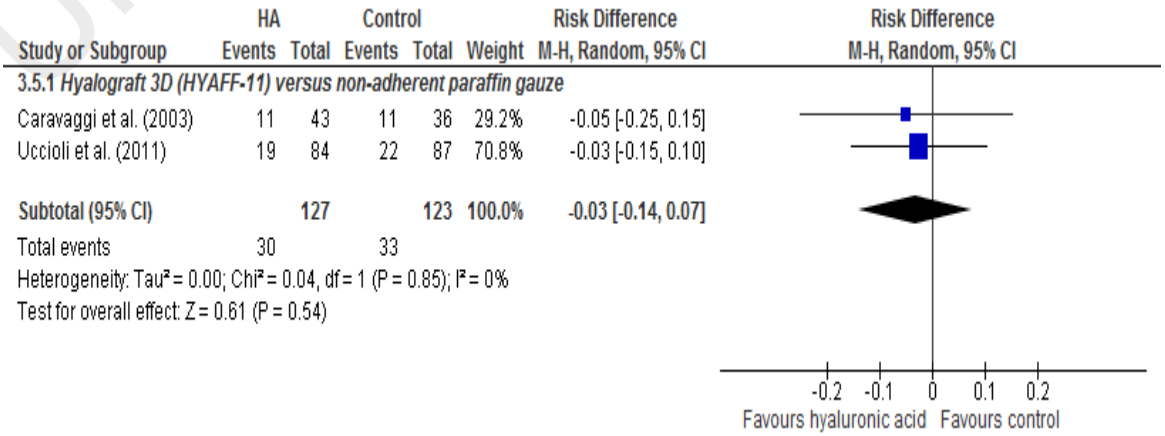


**Figure 4.13: Chronic wounds (Diabetic foot ulcers); Outcome: Number of patients with adverse events**

#### 4.4.1.6 Quality of wound healing

Five trials for chronic wounds reported on quality of wound healing by description of the wound appearance. Quality of healing was reported in many ways such as percentage of fibrous tissue and granulation tissue, skin maceration and presence of exudate. However no quantitative data were provided for all these trials.

*(a)* ***Mixed arterial and venous ulcers***

All five trials came from patients with mixed arterial and venous ulcers but no data could be pooled. The results were presented as follows:

*i HA cream (Ialuset®) versus neutral cream (without HA)*

Dereure et al. (2012a) reported that there was no statistically significant difference in the percentage of fibrous tissue and granulation tissue between the HA and control groups.

*ii HA gauze pad (Ialuset®) versus Hydrocolloid dressing (DuoDERME)*

Dereure et al. (2012b) reported two different aspects of wound quality. There was no statistically significant difference between groups in term of ulcer characteristics (p=0.8544 for fibrinous tissue, p=0.6704 for granulation tissue). However, in the aspect of peri-ulcerous skin, the trial showed a statistically significant between the two groups with more favourable result for patients treated with HA gauze pad (p=0.04 for oedema; p=0.009 for purpura and p=0.003 for maceration).

*iii HA gauze pad (Ialuset®) versus normal gauze pad (without HA)*

Humbert et al. (2012) reported the percentage of granulation tissue in the patients treated with HA decreased by 8.5% while it increased in the patients treated with gauze

pad (9.0%). This showed that healing was faster in HA groups as granulation tended to disappear at the end of the healing process.

*iv HA-Hydrocolloid dressing versus Hydrocolloid dressing*

In Meaume et al. (2008), the quality of wound was not clearly defined. They reported that the difference between the HA and control groups was statistically significant on day 28 favouring the HA group (p=0.04). They also stated that skin maceration was less intense and oozing was less severe in the HA group as compared to the control group (p=0.05 and p=0.03 respectively).

*(b)* ***Diabetic foot ulcers***

Only one trial reported quality of wound. The result was presented as follow:

*i Hyalograft 3D (HYAFF-11®) versus non-adherent paraffin gauze*

Caravaggi et al. (2003) indicated that quality of wound was worst with the presence of exudate. Quality of wound was better in patients treated with HA as 86% patients had no exudate as compared to the patients treated with paraffin gauze (69.4% absent of exudate).

#### 4.4.1.7 Patients' assessments of tolerability

Six trials for chronic wounds reported on patients' assessments towards the treatments received. Results were reported in different ways and no data could be pooled:

*(a)* ***Mixed arterial and venous leg ulcers***

All five trials reported patients' assessments. The results were presented as follows:

*i* *HA cream (Ialuset®) versus neutral cream (without HA)*

Dereure et al. (2012a) reported that there was no significant difference between groups in terms of patients who did not miss any daily application of the allocated treatment (>79% of patients).

*ii* *HA gauze pad (Ialuset®) versus Hydrocolloid dressing (DuoDERME)*

Dereure et al. (2012b) reported that there was no significant difference between the two groups in terms of tolerability of application.

*iii* *HA gauze pad (Ialuset®) versus normal gauze pad (without HA)*

Humbert et al. (2012) considered patients were compliant if they did not miss any of their daily applications. Both groups were reported to be highly satisfied with their treatment as more than 87% patients did not miss their daily applications and the difference between groups was not statistically significant.

*iv* *HA-Hydrocolloid dressing versus Hydrocolloid dressing*

In Meaume et al. (2008), tolerability was assessed using a four-point scale ("very good", "good", "fair" and "poor"). Tolerability of application for the two groups was comparable.

*v HA dressing (Hyaloskin®) versus OASIS® dressing*

Romanelli et al. (2007) measured patient comfort at dressing change using VAS scale from 0=excellent to 10=critical. They reported that patients treated as control group had significantly greater comfort compared to the HA group.

*(b)* ***Venous leg ulcers***

Only one trial reported patients' assessments. The result was presented as follow:

*i HA gauze pad versus Dextranomer paste*

Ortonne (1996) reported patients' judgement towards tolerability of treatment by using a four-point scale (good, average, nil, worsened). The difference between groups was not statistically significant although a higher proportion (58%) in the HA gauze pad rated good treatment tolerability as compared to Dextranomer paste (42%) at the end of 21-day treatment.

#### 4.4.1.8 Oral analgesic consumption

Of the eight trials for chronic wounds, only one trial reported oral analgesic consumption (Meaume et al., 2008). They reported that lower proportion of patients with mixed arterial and venous ulcers took oral analgesic in the HA group compared to the control group. However the difference between both groups was not statistically significant.

### 4.4.2 Effects of interventions on acute wounds

#### 4.4.2.1 Wound area reduction

Two trials for acute wounds reported the outcome wound area reduction. However none of them provided quantitative data:

*(a)* ***Burn wounds***

Koller (2004) did not report baseline value for intervention and control group, thus data could not be pooled. The result was presented as follow:

*i HA-silver sulfadiazine cream versus silver sulfadiazine (SSD) cream*

Both trials (Koller 2004; Costagliola & Agrosi 2005) defined wound healing as 100% epithelialisation and 0% residual wound area. Koller (2004) (Ialugen Plus® cream) reported for HA group mean reduction was 5.83cm$^2$ from baseline while for SSD group reduction was 30.59 cm$^2$. As for Costagliola and Agrosi (2005) (Connettivina® Plus cream), no data was provided.

#### 4.4.2.2 Number of wounds healed

None of the trials reported the outcome number of wounds healed.

#### 4.4.2.3 Healing time

Both trials reported the outcome healing time and provided quantitative data:

*(a)* ***Burn wounds***

*i HA-silver sulfadiazine cream versus silver sulfadiazine cream*

The pooled results of two trials (Koller 2004; Costagliola and Agrosi 2005) showed HA group shows significantly shorter healing time compared to the control group (Figure 4.14).

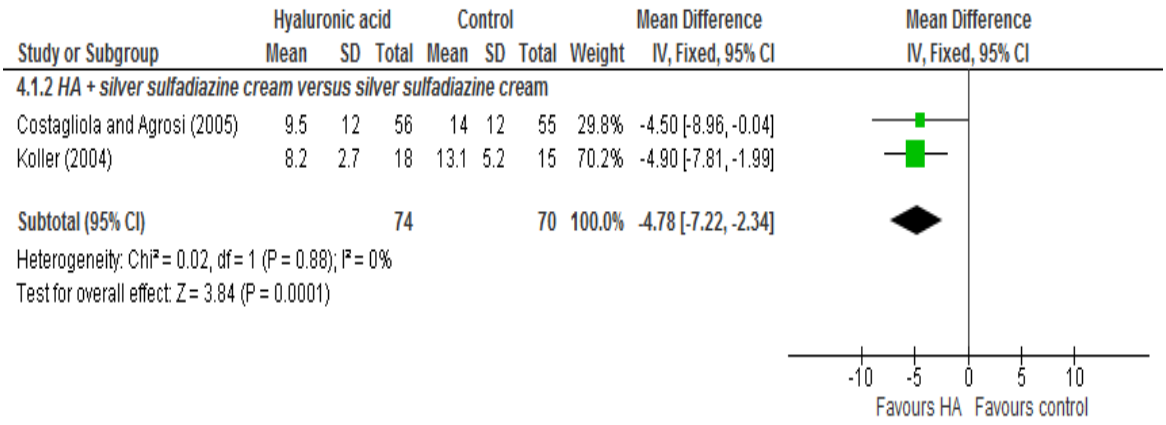


**Figure 4.14: Acute wounds (Burn wounds); Outcome: Healing time**

#### 4.4.2.4 Pain Intensity

Both trials reported pain intensity in their trials. We did not combine the results from these trials as the results were reported in different ways. The effects of each comparison are as follows:

*(a)* ***Burn wounds***

*i* *HA-silver sulfadiazine cream versus silver sulfadiazine cream*

Koller (2004) reported pain intensity using four-point severity scale. The result showed that there was a greater pain reduction from the baseline in HA-silver sulfadiazine cream group compared to the silver sulfadiazine cream alone group (1.3 versus 1.1). Costagliola and Agrosi (2005) measured pain by using the Huskisson scale. They showed that there was no significant difference between the HA group and SSD cream group.

#### 4.4.2.5 Number of patients with adverse events

Costagliola and Agrosi (2005) reported adverse effects like shivering, fever and headache occurred only in one patient using silver sulfadiazine cream. The remaining two trials reported that no adverse effects were observed for HA and control groups.

#### 4.4.2.6 Quality of wound healing

None of the two trials on acute wounds reported the outcome quality of wound healing.

#### 4.4.2.7 Patients' assessments on tolerability

Two trials reported on physician and patients' assessments of tolerability (Koller 2004; Costagliola and Agrosi 2005).

*(a)* ***Burn wounds***

*i* *HA-silver sulfadiazine cream versus silver sulfadiazine cream*

Koller (2004) reported tolerability using a four-point scale (none, fair, good, excellent). The result was not statistically different between the two groups with 80-100% patients rated treatment as good to excellent. Costagliola and Agrosi (2005) assessed tolerability by frequency of visits. The result showed that there was no significant difference between the two groups (76.8% good-excellent in HA-SSD group vs 75.9% good-excellent in SSD group alone).

#### 4.4.2.8 Oral analgesic consumption

Only one trial for acute wounds reported oral analgesic consumption as an outcome.

*(a)* ***Burn wounds***

*i* *HA-silver sulfadiazine cream versus silver sulfadiazine cream*

Costagliola and Agrosi (2005) assessed oral analgesic given other than acetylsalicylic acid. They found the mean number of oral analgesic taken was greater in the silver sulfadiazine group compared to HA- silver sulfadiazine group (0.69 vs 0.57) while the mean number of days patients took analgesic was higher in silver sulfadiazine group compared to HA- silver sulfadiazine group (4 days vs 2.4 days). However, the differences between the two groups were not statistically significant for both measures.

# CHAPTER 5: DISCUSSIONS

Our systematic review included 10 RCTs and we found that HA-containing products produced some favourable outcomes in acute and chronic wound healing. However, the available evidence is not consistent enough to make a firm conclusion that HA-containing dressings and topical preparations are effective in enhancing wound healing for acute and chronic wounds. However, we found evidence to indicate that, HA (or its derivatives) are beneficial in reducing pain. This finding is in agreement with one systematic review published in 2012 (Voigt & Driver, 2012).

## 5.1 Interpretation of the evidence

It has been suggested that wound healing should be measured using the outcome healed wound because this measure is more established, objective and quantifiable (Lazarus et al., 1994; Morison, 1992; Rolstad & Ovington, 2007; Wardrope & Edhouse, 1999). Even though most of the included studies included outcomes such as wound area reduction, number of wounds healed and healing time, the results of several trials could not be pooled because of different definition of healing used or incomplete data given in the paper. Despite attempts to contact the authors to get relevant information, most authors did not response to our request. Non response for request of data is a common problem in most meta-analysis studies (Flather, Farkouh, Pogue, & Yusuf, 1997; Higgins et al., 2008; Stevens & Wu, 2007).

The findings on the outcome wound area reduction are contradictory. For example, one trial (Humbert et al., 2012) reported greater reduction in wound area for HA group compared to the control group. On the other hand, a bigger trial (Meaume et al., 2008) found that patients given hydrocolloid dressing showed a higher reduction in wound area compared to HA group. Generally, our findings show little evidence of the effectiveness of HA-containing dressing in reducing wound area.

It is also worth noting that for similar studies, when the outcome "number of wounds healed" was considered, the findings show little evidence that HA (or its derivatives) has notable beneficial effects for the three types of chronic wounds. For acute wounds, none of the trials reported the outcome "number of wounds healed".

We found that most of the trials involved did not report the healing time as an outcome although many claims made for hyaluronic acid preparations is to shorten healing time for chronic wounds. The claims are made because in certain pathological conditions, it has been shown that there is degradation of local hyaluronic acid, thus leading to insufficient regeneration of the connective tissues, poor angiogenesis, and deficient differentiation of histiocyte and fibroblast populations (Edwards & Fantasia, 2007). Adding exogenous hyaluronic acid will help in speeding up the tissue processing.

The duration of study was short which on average was only 8 weeks and there was even a study that lasted three weeks. Only two trials assessing the effectiveness for acute wounds (Costagliola & Agrosì, 2005; Koller, 2004) and one trial for chronic wounds (Caravaggi et al. 2003) reported significantly better healing time with HA products compared to the comparators. However, quantitative data given was incomplete. Therefore we did not find sufficient evidence to support the use of HA dressings and topical preparations to shorten wound healing time.

Interestingly, pooled data on pain intensity for three similar trials involving patients with mixed arterial and venous leg ulcers (Dereure et al., 2012a; Humbert et al., 2012; Meaume et al., 2008) showed that groups receiving HA experienced less intense pain as compared to the control groups. Additionally, another five trials for acute and chronic wounds with different pain measurements also reported beneficial effect favouring HA group (Costagliola & Agrosì, 2005; Dereure et al., 2012b; Koller, 2004; Ortonne, 1996; Taddeucci et al., 2004). These results support several findings that HA has greater

improvement in pain level in any type of ulcer (Goa & Benfield, 1994; Kirova et al., 2011; Nolan, Badminton, Maguire, & Seymour, 2009; Nolan, Baillie, Badminton, Rudralingham, & Seymour, 2006; Onesti et al., 2013). The evidence seems to indicate that HA-containing dressing is effective in reducing pain.

For all seven trials which reported the number of patients with adverse events, there was no significant difference between HA groups and control groups. However, five trials assessing chronic wounds (Caravaggi et al. 2003; Dereure at al. 2012a; Humbert et al. 2012; Meaume et al. 2008; Uccioli et al. 2011) found less adverse effects in HA groups compared to control groups. Given that the occurrence of adverse events was less frequent in HA groups compared with the control groups it seems that HA is well tolerated without serious unwanted effects.

Quality of wounds healed was interpreted by the appearance of the wounds. Majority of the chronic wounds' patients have better wounds appearance when used HA products rather than patients who used comparators, thus the authors found a beneficial effect favouring the HA group (Caravaggi et al. 2003; Dereure et al. 2012b; Humbert et al. 2012; Meaume et al. 2008). However, no differences on the appearance of the wounds between the HA groups and control groups for acute wounds.

By referring to the two trials reported on consumption of oral analgesic was found to be less in patients of HA groups compared to control groups in two trials (Costagliola and Agrosi 2005; Meaume et al. 2008), HA-containing dressings and topical preparations of HA seem to be better or no worse than the comparators. Thus, overall cost could eventually be the factor to use HA-containing products to enhance wound healing. However, all trials did not assess the cost-effectiveness outcome, thus negating the ability to evaluate the effectiveness of HA on economic scale.

## 5.2 Quality of the evidence

To ensure reliability of the evidence, we have decided to include only randomised controlled trials (RCTs) for this review. Thus, we were able to include only 10 trials. Several trials were of moderate quality. Poor reporting of method design and blinding was common among these trials. For example, six trials (Costagliola & Agrosì, 2005; Dereure et al., 2012a; Dereure et al., 2012b; Koller, 2004; Ortonne, 1996; Romanelli et al., 2007) did not adequately report allocation concealment which might lead to selection bias. Additionally, only four trials completely described how blinding of participants, researchers or healthcare providers and outcome assessors was carried out in the trials. Insufficient allocation concealment and poor blinding conducted in any trial could lead to higher estimation effects of treatment (Egger, Smith, Schneider, & Minder, 1997). Blinding in a trial should be performed on as many parties as possible including participants, clinicians, data collectors, outcomes assessors, and data analysts to minimize differentials interventions and outcome biased assessments (Karanicolas, Farrokhyar, & Bhandari, 2010).

Of 10 included trials, five trials (Costagliola & Agrosì, 2005; Humbert et al., 2012; Ortonne, 1996; Romanelli et al., 2007; Uccioli et al., 2011) were financially funded by product manufacturers. Therefore, the positive outcomes on the company products might have potential of bias. One review in 2003 found that research sponsored by the drug manufacturers was four times more likely to produce outcomes favouring the manufacturer's product than research sponsored by other sources (Lexchin, Bero, Djulbegovic, & Clark, 2003).

We were careful as not to pool the results of several trials as pooling results from trials with clinical and methodological heterogeneity is controversial (Ioannidis, Patsopoulos, & Evangelou, 2007; Stevens & Wu, 2007). The lack of standard guideline for wound

care make, it difficult to assess wound healing. This issue affected wound healing assessment, thus trials produce different parameters or measurements (Purser, 2009; Robson & Barbul, 2006). However, the diversity of the studies such as wound types, and treatments given is useful rather than a problem because the findings could be generalisable to a broader group of patients (Borenstein et al., 2009).

### 5.3 Strengths and Limitations

The main strength of this review is the degree of rigour in the conduct of the review. The methods were in accordance with those proposed by the Cochrane Collaboration for conducting systematic review of interventions (Higgins & Green, 2012). Additionally we assessed the quality of the included trials.

This study has several limitations. First, there is difficulty in combining the outcome effects from various studies due to different parameters used and missing data. Second, a common problem to most meta-analysis studies is the heterogeneity of the included RCTs, particularly regarding the definitions of healing, duration of treatment, outcome measures used and the trials quality might limit the value of evidence for this systematic review (Flather et al., 1997). As suggested by Lazarus et al. (1994), standard guidelines in evaluating the healing of wound is crucial in order to organise a uniform outcome in setting the end points of any study. Third, there are four excluded trials worth to be included however the combination compounds with HA without a control group (such as zinc-HA versus normal saline solution) might have confounding effect in wound healing. With the expanding health care expenditure, future studies should consider the cost-efficiency of HA in managing wounds in order to help reduce the cost of treating acute and chronic wounds (Driscoll, 2013a; Landro, 2012).

# CHAPTER 6: CONCLUSIONS

## 6.1 Implication for practice

At present, the evidence does not support the benefits of HA or its derivatives to improve chronic wound healing even though there is some evidence on their effectiveness especially on reducing pain intensity. The availability of high quality evidence is still limited.

## 6.2 Implication for research

The use of relevant measurements is necessary for assessing efficacy to aid the interpretation of the findings. Different wounds-type might give different therapeutic effects. Therefore, trials should clearly describe the location of wounds.

Trials also require adequate number of patients to ensure sufficient statistical power to detect true treatment effects. An economic evaluation should be conducted to determine if the costs of HA-containing dressings and topical agents justify its potential benefits.

Additionally randomised controlled trials need to use the revised CONSORT statement to improve the quality of reporting randomised controlled trials (Mills, Wu, Gagnier, & Devereaux, 2005; Schulz, Altman, & Moher, 2010).

If the trials incorporate all recommendations as outlined, it is anticipated for future systematic review to be able to provide more conclusive evidence on the effectiveness of HA-containing dressings and topical agents in enhancing wound healing.

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Upton, D. C., Johnson, M., Zelazny, S. K., & Dailey, S. H. (2013). Prospective evaluation of office-based injection laryngoplasty with hyaluronic acid gel. *Annals of Otology, Rhinology & Laryngology, 122*(9), 541-546.

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Voigt, J., & Driver, V. R. (2012). Hyaluronic acid derivatives and their healing effect on burns, epithelial surgical wounds, and chronic wounds: A systematic review and meta-analysis of randomized controlled trials. *Wound Repair Regeneration, 20*(3), 317-331. doi:10.1111/j.1524-475X.2012.00777.x

Voinchet, V., Vasseur, P., & Kern, J. (2006). Efficacy and safety of hyaluronic acid in the management of acute wounds. *American Journal Of Clinical Dermatology, 7*(6), 353-357. doi:1175-0561/06/0006-0353

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# APPENDICES

## Appendix A

**Search strategies used for electronic databases**

### A) CINAHL Plus with Full Text @EBSCOhost

S1 (MH “Wound”)
S2 (MH “Fungating Wounds”)
S3 (MH “Wounds, Penetrating”)
S4 (MH “Wounds, Stab”)
S5 (MH “Wounds, Nonpenetrating”)
S6 (MH “Wounds, Chronic”)
S7 (MH “Wounds, Gunshot”)
S8 (MH “Wounds and Injuries”)
S9 (MH “Surgical Wound”)
S10 (MH “Surgical Wound Infection”)
S11 (MH "Surgical Wound Dehiscence")
S12 (MH "Wound Infection")
S13 acute wound*
S14 surgical wound*
S15 traumatic wound*
S16 incised wound*
S17 contused wound*
S18 lacerated wound*
S19 puncture wound*
S20 avulsion fracture*
S21 burn wound*
S22 chronic wound*
S23 infected wound*
S24 radiation poisoning wound*
S25 ulcer*

S26 arterial ulcer*

S27 venous ulcer*

S28 abscess

S29 diabetic foot ulcer*

S30 pressure ulcer*

S31 leg ulcer*

S32 skin ulcer*

S33 varicose ulcer*

S34 or/S1-S33

S35 (MH "Hyaluronic Acid")

S36 hyaluronan

S37 hyaluronate

S38 sodium hyaluronate

S39 hylan

S40 Ialugen

S41 Ialuset

S42 Vulnamin

S43 or/S35-S42

S44 (MH "Randomized Controlled Trials")

S45 (MH "Clinical Trials")

S46 clinic* trial*

S47 random* control* trial*

S48 random* allocat*

S49 double blind*

S50 single blind*

S51 placebo*

S52 or/S44-S51

S53 effective*

S54 efficacy

S55 wound* heal*

S56 therapeutic

S57 safe*

S58 ((effective* OR safe*) AND adj. hyaluronic acid)

S59 or/S53-S58

S60 S34 and S43 and S52 and S60

**B) Cochrane Central Register of Controlled Trials (CENTRAL)**

#1 MeSH descriptor [Wound and Injuries] explode all trees

#2 acute wound

#3 surgical wound

#4 traumatic wound

#5 incised wound

#6 contused wound

#7 lacerated wound

#8 puncture wound

#9 avulsion fracture

#10 burn wound

#11 chronic wound

#12 infected wound

#13 radiation poisoning wound

#14 ulcer*

#15 arterial ulcer*

#16 venous ulcer*

#17 diabetic foot ulcer*

#18 pressure ulcer*

#19 leg ulcer*

#20 skin ulcer*

#21 varicose ulcer*

#22 abscess

#23 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or#13 or #14 or #15 or #16 or#17 or #18 or #19 or #20 or#21 or #22)

#24 MeSH descriptor: [Hyaluronic Acid] explode all tress

#25 hyaluronan

#26 hylan

#27 Ialugen

#28 Vulnamin

#29 (#24 or #25 or #26 or #27 or #28)

#30 MeSH descriptor: [Randomized Controlled Trial] explode all trees

#31 random allocation

#32 clinical trial

#33 double blind

#34 single blind

#35 (#30 or #31 or #32 or #33 or #34)

#36 (#23 and #29 and #35)

**C) MEDLINE with Fulltext @EBSCOhost**

1. exp Wounds/

2. exp Acute Wounds/
3. surgical wound$/
4. traumatic wound$/
5. incised wound$/
6. contused wound$/
7. lacerated wound$/
8. puncture wound$/
9. avulsion fracture/
10. burn wound$/
11. or/1-10
12. exp Chronic Wounds/
13. infected wound$/
14. radiation poisoning wound$/
15. ulcer$/
16. skin abscess$/
17. ((arterial or venous or diabetic foot or pressure or leg or skin or varicose) adj. ulcer$)
18. or/12-17
19. exp Hyaluronic Acid/
20. hyaluronan/
21. hyaluronate/
22. hylan/
23. “sodium hyaluronate”/
24. Ialuset
25. Vulnamin

26. or/19-25
27. effective$
28. efficacy/
29. efficacious/
30. efficient/
31. efficiency/
32. wound area reduction/
33. wound heal$/
34. wound care$/
35. wound manage$/
36. adverse event$/
37. adverse effect$/
38. safe$/
39. ((effective OR safe) adj. hyaluronic acid)
40. or/27-39
41. dress$/
42. topical$/
43. apply$/
44. ((dressing or topical) adj. hyaluronic acid)
45. or/41-44
46. MH ‘”Randomized Controlled Trial$ as Topic”
47. MH “Controlled Clinical Trial$ as Topic”
48. random$ allocate$
49. double-blind method
50. single-blind method

51. comparative study/
52. (clinic$ adj trial$)
53. placebo$/
54. or/46-53
55. case report/
56. letter/
57. review/
58. review of reported case$/
59. or/55-58
60. 54 not 59
61. 11 and 18 and 26 and 40 and 45 and 60

**D) PubMed**

1. wound$/
2. acute wounds$/
3. surgical wound$/
4. traumatic wound$/
5. incised wound$/
6. contused wound$/
7. lacerated wound$/
8. puncture wound$/
9. avulsion fracture/
10. burn wound$/
11. chronic wound$/

12. infected wound$/

13. ulcer$/

14. arterial ulcer$/

15. venous ulcer$/

16. diabetic foot ulcer$/

17. pressure ulcer$/

18. leg ulcer$/

19. skin ulcer$/

20. skin abscess/

21. or/1-20

22. hyaluronic acid/

23. hyaluronan/

24. hyaluronate/

25. hylan/

26. sodium hyaluronate/

27. Ialuset/

28. Ialugen/

29. Vulnamin

30. or/22-29

31. random$ control$ trial$/

32. control$ clinical trial$/

33. random$ allocate$/

34. double-blind method/

35. single-blind method/

36. comparative study/

37. placebo$/

38. or/31-37

39. 21 and 30 and 38

**E) Journals@Ovid Full Text**

1. wound$.af.
2. acute wound$.af.
3. chronic wound$.af.
4. ((surgical or traumatic or incised or contused or lacerated or puncture or avulsion or burn or infected or radiation poisoning) adj5 wound$).ti.ab.
5. skin abscess$.ti.ab.
6. ulcer$.af.
7. ((arterial or venous or diabetic foot or pressure or leg or skin or varicose) adj5 ulcer$).ti.ab.
8. or/1-7
9. hyaluronic acid.af.
10. hyaluronan.af.
11. hyaluronate.af.
12. hylan.af.
13. sodium hyaluronate.af.
14. Ialuset.af.
15. Ialugen.af.
16. Vulnamin.af.
17. ((effective$ OR safe$) adj hyaluronic acid).af.
18. ((dressing$ or topical$) adj hyaluronic acid).af.

19. or/9-18
20. random$ control$ trial$.ti.ab.
21. control$ clinical trial$.ti.ab
22. random$ allocat$.ti.ab.
23. ((double blind or single blind) adj method).ti.ab.
24. comparative study.ti.ab.
25. placebo$.ti.ab.
26. or/20-25
27. 8 and 19 and 26 (274) removes duplicates (205)

**Appendix B**

**List of excluded studies and reasons for exclusion**

| Studies | Reason for exclusion |
|---|---|
| Abbruzzese et al. 2009 | No control group: amino acids (contain HA) vs inert gel vehicle |
| Bettinger et al. 1996 | Patients are not randomised (unit of analysis was wound sites) |
| Campanati et al. 2013 | Non RCT (controlled clinical trial) |
| Caravaggi et al. 2011 | Non RCT (observational study) |
| Cassino & Ricci 2010 | Non RCT (observational study) |
| Cervelli et al. 2010 | Non RCT (retrospective study) |
| Colletta et al. 2003 | Non RCT (pilot clinical trial) |
| Cuevas et al. 2007 | No control group: zinc hyaluronate (zn+HA) vs normal saline) |
| Dechert et al. 2006 | Non RCT (human skin samples) |
| Falanga et al. 1996 | Compared a different formulation of HA (tissue plasminogen activator with 1% sodium hyaluronate vs HA) |
| Fariba et al. 2005 | Compared a different formulation of HA (3% diclofenac in 2.5% HA vs 2% HA) |
| Gebauer et al. 2003 | Compared a different topical of HA (3% diclofenac in 2.5% HA vs 2.5% HA) |
| Goodman et al. 2011 | Non RCT (observational study) |
| Kim et al. 2008 | Only secondary outcomes reported |
| Lobmann et al. 2003 | Non RCT (pilot study) |
| Maggio et al. 2012 | No control group: amino acids (contain HA) vs Ca-alginate |
| McEwan & Smith 1997 | Compared a different formulation of HA (3% diclofenac in 2.5% HA vs 2.5% HA) |
| Mekkes & Nahuys 2001 | Patients are not randomised (unit of analysis was wound sites) |
| Onesti et al. 2013 | Non RCT (open study) |
| Pirard et al. 2005 | Non RCT (meta-analyses) |
| Rivers et al. 2002 | Compared a different formulation of HA (3% diclofenac in 2.5% HA vs 2.5% HA) |
| Rossi et al. 2007 | Non RCT (histology study) |
| Saxen et al. 1997 | Compared a different formulation of HA (3% diclofenac in 2.5% HA vs 2.5% HA) |
| Taddeucci et. al 2004 | Patients are not randomised (unit of analysis was wound sites) |
| Tankova et al. 2001 | No control group: zinc hyaluronate vs normal saline solution |
| Upton et al. 2013 | Non RCT (prospective study) |
| Voinchet et al. 2006 | Compared a different formulation of HA (dressing vs cream) |

**Appendix C**

**Data extraction form**

| **DATA EXTRACTION FORM**<br>**(The data extraction form used for each individual study included in this review)** | |
|---|---|
| **ARTICLE DETAILS** | |
| **ID** | |
| **Author(s), Year** | |
| **Title** | |
| **Journal, Sources** | |
| **Country of Origin** | |
| **Corresponding author & contact details** | |
| | |
| **Study design** | |
| **Country** | |
| **Setting** | |
| **Treatments:**<br>**-Intervention (I)**<br>**-Control (C)** | |
| **Total study duration** | |
| **Single centre/multicentre trial:** | |
| **Method used to generate random allocation sequence:**<br>**Method used to implement the random allocation sequence:**<br>**Allocation sequence concealment:** | |
| **Was the participant blinded?**<br>**Was the researcher blinded?**<br>**Was the assessor blinded?** | |
| **Inter-assessor reliability measured?** | |
| **PARTICIPANTS** | |
| **Total number** | |
| **Type of participants** | |
| **Age** | |
| **Sex** | |
| **Record of drop-out (with reasons)** | |
| **All relevant outcomes reported** | |

| | |
|---|---|
| **No. of sample size**<br>**Participant population (how sampled)** | |
| **No. of arm in trial** | |
| **No. of each arm** | |
| **Power calculation** | |
| **INTERVENTIONS & CONTROL GROUP** | |
| **Total number of intervention group:**<br>**Total number of control group:**<br>**Dosage of intervention**<br>**Duration of intervention**<br>**Who delivered the intervention?** | |
| **OUTCOMES** | |
| **Outcomes** | |
| **Primary Outcome** | |
| **Outcome measures** | |
| **Results** | |
| **Method of the measurement** | |
| **Time to measure** | |
| **Length of follow-up** | |
| **Secondary Outcomes** | |
| **Outcome measures** | |
| **Results** | |
| **Method of the measurement** | |
| **Secondary Outcomes** | |
| **Outcome measures** | |
| **Results** | |
| **Method of the measurement** | |
| **Secondary Outcomes** | |
| **Outcome measures** | |
| **Results** | |
| **Method of the measurement** | |
| **Secondary Outcomes** | |
| **Outcome measures** | |
| **Results** | |
| **Method of the measurement** | |

| ANALYSIS | |
|---|---|
| **Which analysis performed? :**<br>**Method of analysis:**<br>**Intention-to-treat analysis? :** | |
| **RESULTS** | |
| **Sample size:**<br>**No. of withdrawals and loss to follow-up:**<br>**Reasons for withdrawals:** | |
| **MISCELLANEOUS** | |
| **Funding source:**<br>**Key conclusions of the study authors:** | |
| **AUTHOR'S CONCLUSION** | |
| **Other comment and interests:** | |

| QUALITY ASSESSMENT FORM OF INCLUDED STUDIES | | |
|---|---|---|
| **Risk of Bias (Item)** | **Judgement** | **Description** |
| 1. Allocation sequence? | | |
| 2. Allocation concealment? | | |
| 3. Blinding: participants, researchers, assessors | | |
| 4. Incomplete outcome data addressed (ITT) | | |
| 5. Free selective outcome reporting | | |
| 6. Free from other bias?<br>i) Baseline comparability | | |
| ii) Financial support | | |

**Appendix D**

**Quality Assessment Form**

| **QUALITY ASSESSMENT FORM OF INCLUDED STUDIES** |
|---|
| **METHODOLOGICAL QUALITY** |
| 1. Allocation sequence?<br>Q: was the allocation sequence randomly generated? :<br><br>2. Allocation concealment<br>Q: Was allocation adequately concealed? :<br><br>3. Blinding<br>Q: Was the participants/ researchers/ outcome assessor blinded to the intervention? :<br><br>4. Incomplete outcome data<br>Q: Were all randomised participants analysed in the group to which they were collected i.e.by using ITT analysis? :<br><br>5. Free selective outcome reporting<br>Q: Are reports of the trials free of suggestion of selective outcome reporting? :<br><br>6. Other sources of potential bias<br>Q: i) Were the groups similar at baseline for most important prognostic indicators? :<br><br>ii) Was the trial NOT sponsored by a manufacturer who had the potential interest in the results? |

**Appendix E**

## Availability of the outcomes data reported

| Study | Wound area reduction | Number of wounds healed | Healing Time | Pain intensity | Quality of the wound | Adverse events | Physician & Patient assessment | Oral analgesic consumption |
|---|---|---|---|---|---|---|---|---|
| ***Chronic Wounds*** | | | | | | | | |
| **A) Mixed arterial and venous ulcers** | | | | | | | | |
| Dereure et al. (2012a) | ✓ (median) | ✓ | - | ✓ | ✓ | ✓ | ✓ | - |
| Dereure et al. (2012b) | ✓ (ep in CI) | ✓ | - | ✓ (in PV) | ✓ | ✓ (only cases) | ✓ | - |
| Humbert et al. | ✓ | ✓ | - | ✓ | ✓ | ✓ | ✓ | - |
| Meaume et al. | ✓ | ✓ | - | ✓ | ✓ | ✓ | ✓ | ✓ |
| Romanelli et al. (2007) | - | ✓ | - | ✓ (baseline is NR) | - | ✓ | ✓ | - |
| **B) Venous leg ulcers** | | | | | | | | |
| Ortonne (1996) | ✓ | - | - | ✓ (diff. scale) | - | ✓ | ✓ | - |
| **C) Diabetic foot ulcers** | | | | | | | | |
| Caravaggi et al. (2003) | - | ✓ | ✓ (SD is NR) | - | ✓ | ✓ | - | - |
| Uccioli et al. (2011) | ✓ (SD is NR) | ✓ | ✓ (SD is NR) | - | - | ✓ | - | - |
| ***Acute wounds*** | | | | | | | | |
| **A) Burn wounds** | | | | | | | | |
| Koller (2004) | ✓ (baseline is NR) | - | ✓ | ✓ (diff. scale) | ✓ (local edema) | ✓ | ✓ | ✓ (none) |
| Costagliola and Agrosi (2005) | ✓ (ep is NR) | - | ✓ | ✓ (baseline is NR) | - | ✓ | ✓ | ✓ (in PV) |

Notes: NR: Not Reported; SD: standard deviation; ep: endpoint; CI: confidence interval; PV: p-value;
✓ : outcome reported; - : outcome not reported

**Appendix F**

**Details of the risk of bias assessment for included trials**

| Study | Random sequence generation | Allocation sequence concealment | Blinding | | | Incomplete outcome data (ITT) | Free selective outcome reporting | Free from other bias | |
|---|---|---|---|---|---|---|---|---|---|
| | | | participants | researcher | assessors | | | baseline comparability | Financial supports |
| **Chronic wounds- Mixed arterial and venous ulcers** | | | | | | | | | |
| Dereure et al. (2012a) | Low. Computer-generated randomisation list. | Unclear. Not described method of allocation concealment | Low. Intervention & Control were supply in the same form, external packaging, shape, odour & texture. participants were assigned to a treatment group based on the sequential order of the randomisation | Low. Treatment allocation & evaluation were assessed by a blinded physician | Low. Independent readers | Low. The dropouts rates are quite high but reasons were available Dropouts= 25.7% | Low. Include all expected outcomes | Low. Patients' characteristics are comparable | Low. No conflict of interest. |
| Dereure et al. (2012b) | Low. Computer-generated randomisation list. | Unclear. Insufficient detail. | Low. Intervention & Control were supply in the same form, external packaging, shape, odour & texture, participants were assigned to a treatment group based on the sequential order of the randomisation | Low. Blinded observer. | Low. Treatment allocation & evaluation were assessed by a blinded physician | Low. All participants included Dropouts= 15.9% (<20%) | Low. Include all expected outcomes. | Low. Patients' characteristics are comparable | Low. No conflict of interest. |

| Study | Random sequence generation | Allocation sequence concealment | Blinding | | | Incomplete outcome data (ITT) | Free selective outcome reporting | Free from other bias | |
|---|---|---|---|---|---|---|---|---|---|
| | | | participants | researcher | assessors | | | baseline comparability | Financial supports |
| **Chronic wounds- Mixed arterial and venous ulcers** | | | | | | | | | |
| Humbert et al. (2012) | Low. Parallel-group randomised. Randomisation list balanced per blocks of 4 based on sequential order at each site | Low. Randomisation list was prepared by Data Management &Statistics Unit of IBSA | Low. Participants are blinded | Low. 2 independent readers (blinded) measured the wound size | Low. 2 independent readers (blinded) measured the wound size | Low. Missing outcome data balance across groups. Dropouts= 19% (<20%) | Low. All outcomes reported in a specific ways | Low. Baseline are comparable | Unclear. Project was carried out by the Sponsor Laboratoires Genevrier |
| Meaume et al. (2008) | Low. Computer-generated randomisation list | Low. Sealed envelopes containing treatment code. | Unclear. No information provided | Low. Sealed envelopes containing the treatment code for each patient were given to the investigator | Low. Independent personnel | Low. All participants included Dropouts= 18.4% | Low. All outcome reported in a specific ways | Low. Demographic characteristics are comparable | Low. No conflict of interest. |

| Study | Random sequence generation | Allocation sequence concealment | Blinding | | | Incomplete outcome data (ITT) | Free selective outcome reporting | Free from other bias | |
|---|---|---|---|---|---|---|---|---|---|
| | | | participants | researcher | assessors | | | baseline comparability | Financial supports |
| **Chronic wounds- Mixed arterial and venous ulcers** | | | | | | | | | |
| Romanelli et al. (2007) | No. The sequence of randomisation was generated through every other patient selection by the clinician "According to Cochrane page 198: high risk because of allocation by judgement of the clinician" | Unclear. No information provided | Unclear. No information provided | Unclear. No information provided | Unclear. No information provided | Unclear. No ITT Was carried out | Low. Include all expected outcomes | Low. Patients ulcer characteristics are comparable | Unclear. Supported by Healthpoint Biopharma ceutical. |

| Study | Random sequence generation | Allocation sequence concealment | Blinding | | | Incomplete outcome data (ITT) | Free selective outcome reporting | Free from other bias | |
|---|---|---|---|---|---|---|---|---|---|
| | | | participants | researcher | assessors | | | baseline comparability | Financial supports |
| **Chronic wounds- Venous leg ulcers** | | | | | | | | | |
| Ortonne (1996) | Low. Randomised into two groups of equal size | Unclear. No information provided | Unclear. No information provided | Unclear. No information provided | Unclear. No information provided | Unclear. No ITT, not all randomised patients included in final analysis Dropouts= 0% | Low. Include all expected outcomes | Low. Patients characteristics are comparable | Unclear. Supported by Bioplax UK Ltd. |

| Study | Random sequence generation | Allocation sequence concealment | Blinding | | | Incomplete outcome data (ITT) | Free selective outcome reporting | Free from other bias | |
|---|---|---|---|---|---|---|---|---|---|
| | | | participants | researcher | assessors | | | baseline comparability | Financial supports |
| **Chronic wounds- Diabetic foot ulcers** | | | | | | | | | |
| Caravaggi et al. (2003) | Low. Telephone-randomisation | Low. Central allocation (telephone) | Low. Intervention & control were identical | Low. Blinded physicians | Low. Blinded podiatrist | High. Total participants is 82 were randomised but did not stated patients in each of the arm. Left only 79 participants. Dropouts= 22.8% | High. No outcomes on pain intensity were reported As mentioned in method section | Low. Patients' characteristics are comparable | Unclear. Insufficient data about financial support |
| Uccioli et al. (2011) | Low. Computer-generated randomisation list | Low. Sealed envelopes | Low. Patients were blinded | Unclear. No information provided | Unclear. No information provided | Low. All participants included dropouts= 11.1% | Low. All outcomes reported in a specific way | Low. Baseline are comparable | Unclear. Project was carried out by the Sponsor, Anika Therapeutics |

| Study | Random sequence generation | Allocation sequence concealment | Blinding | | | Incomplete outcome data (ITT) | Free selective outcome reporting | Free from other bias | |
|---|---|---|---|---|---|---|---|---|---|
| | | | participants | researcher | assessors | | | baseline comparability | Financial supports |
| **Acute wounds- Burn wounds** | | | | | | | | | |
| Koller (2004) | Low. Computer-generated randomisation list. Quote: "the recruited patients were randomly allocated". | Unclear. Insufficient details | Low. Same appearance, colour, consistency, unmarked tubes of cream | Unclear. No information provided | Unclear. Insufficient details | Unclear. For wound area reduction, baseline value and endpoint value were not equally reported | Low. Pre-specified outcomes have been reported. | Low. Baseline are comparable | Unclear. No information reported on financial support |
| Costagliola and Agrosi (2005) | Low. Quote: "patients were randomly allocated according to a computer-generated randomisation list" | Unclear. Not reported | Low. Intervention & control were provided in unmarked, white tubes containing 25g | Unclear. Not reported | Unclear. Insufficient details. | Low. All participants included Dropouts= 0.9% | Unclear. Endpoint for wound area reduction & pain intensity were not completely reported | Low. Patients characteristics are comparable | Unclear. Insufficient details |

**Appendix G**

## Detailed information of included trials

1. Caravaggi et al., 2003

| DATA EXTRACTION FORM | |
|---|---|
| **ARTICLE DETAILS** | |
| **ID** | Caravaggi et al. (2003) |
| **Author(s), Year** | Carlo Caravaggi, Roberto De Giglio, Chiara Pritelli, Manuela Sommaria, Sergio Dalla Noce, Ezio Faglia, Manuela Mantero, Giacomo Clerici, Pietro Fratino, Luca Dalla Paola, Giulio Mariani, Roberto Mingardi and Alberto Morabito, 2003 |
| **Title** | HYAFF 11-Based autologous dermal and epidermal grafts in the treatment of non-infected diabetic plantar and dorsal foot ulcers |
| **Journal, Sources** | Diabetes Care, Volume 26, Number 10; 2853-2859 Cochrane Databases |
| **Country of Origin** | Milan, Italy |
| **Corresponding author & contact details** | Dr. Carlo Caravaggi, Centre for Study and Treatment of Diabetic Foot Pathology, Ospedale di Abbiategrasso (MI), Piazza Mussi, !, 20081 Abbiategrasso (MI), Italy. Email: carlo.caravaggi@fastwebnet.it |
| **METHODS** | |
| **Study design** | Open, stratified, randomised and controlled multicentre study |
| **Country** | Italy |
| **Setting** | Six centers: Diabetes foot clinic |
| **Treatments:**<br>**-Intervention (I)**<br><br>**-Control (C)** | <br>I: HYAFF 11(Hyalograft 3D)+ dressing sterile cotton pad and gauze<br>C: Non-adherent paraffin gauze + dressing sterile cotton pad and gauze |
| **Total study duration** | 11 weeks |
| **Single centre/multicentre trial:** | Multicentre (6 centres) |
| **Method used to generate random allocation sequence:**<br>**Method used to implement the random allocation sequence:**<br>**Allocation sequence concealment:** | Telephone-randomisation<br><br>Randomisation list was generated by sponsor<br><br>Yes by telephone (central allocation) |
| **Was the participant blinded?**<br>**Was the researcher/healthcare provider blinded?**<br>**Was the assessor blinded?** | Yes. Intervention & Control were identical<br>Yes. Blinded trained podiatrist & physicians |
| **Inter-assessor reliability measured?** | NA |
| **PARTICIPANTS** | |
| **Total number** | 82 |

| | |
|---|---|
| **Type of participants** | Diabetic foot ulcers |
| **Age** | NA |
| **Sex** | Male & Female |
| **Record of drop-out (with reasons)** | 3, area of ulcer < 1cm$^2$ (n=2), severe acute ischemia of the foot (n=1) |
| **No. of sample size**<br>**Participant population (how sampled)** | 79 (ITT)<br>NA |
| **No. of arm in trial** | Two |
| **No. of each arm** | I: 43 C:36 |
| **Power calculation** | Based on α=0.005, β=95%, an estimated mean healing time of 30 days required 78 subjects to detect any statistically significant. |
| **Inclusion criteria** | Ulcer > 2cm$^2$, duration of ulcer <1 month |
| **INTERVENTION & CONTROL GROUP** | |
| **Total number of intervention group:**<br>**Total number of control group:**<br>**Dosage of intervention & control**<br>**Duration of intervention & control**<br>**Who delivered the intervention & control** | 43<br>36<br>NA<br>NA<br>NA |
| **OUTCOMES** | |
| **All relevant outcomes reported** | No. pain intensity data was not reported |
| **Outcomes** | Primary: Percentage of healed ulcers & time to closure (Complete re-epithelisation)<br>Secondary: Presence of fibrous slough & necrotic tissue, Appearance of granulation tissue, Maceration, Presence & amount of exudate, Presence of odor & infection, Pain Intensity |
| **Primary Outcome** | Percentage of participants healed & time for complete healing (Healing time) |
| **Outcome measures** | Percentage & days |
| **Results** | I: 65.3% (28/43), 57 days(median)→ 47.8 days (mean)<br>C: 49.6% (18/36), 77 days (median)→ 57.8 days (mean) |
| **Method of the analysis** | Kaplan-Meier |
| **Secondary Outcomes** | Number of wounds healed |
| **Outcome measures** | Percentage & Number of ulcer |
| **Results** | I: Plantar=55% (12/22), 57 days, Dorsal=66.7% (14/21), 63days<br>Total: 60% (28/43)<br>C: Plantar=50% (10/20), 58.5 days, Dorsal= 31.25% (5/16), complete closure was not apparent at 77 days<br>Total: 41.7% (18/36) |
| **Method of the analysis** | Kaplan-Meier |
| **Secondary Outcomes** | Complete wound healing (for PP to assess robustness) |
| **Outcome measures** | Percentage of participants & days |

| | |
|---|---|
| **Results** | I: 63.7%, 59 days<br>C: 50%, >77days |
| **Method of the analysis** | Kaplan-Meier |
| **Secondary Outcomes** | Presence of exudate |
| **Outcome measures** | Percentage |
| **Results** | Absent I: 86%, C; 69.4% |
| **Method of the measurement** | NA |
| **Secondary Outcomes** | Adverse events |
| **Outcome measures** | Percentage & number of cases |
| **Results** | serious AE(I=7, C=10)-wound infection, inflammation, worsening of ischemia<br>36.4% (8 cases) severe,<br>36.4% (8cases) moderate,<br>36.4% (8cases) low |
| **Method of the measurement** | NA |
| **ANALYSIS** | |
| **Method of measurement :**<br>**Method of analysis:**<br><br><br><br>**Intention-to-treat analysis? :** | Computerised morphometric measurement<br>Continuous variables: by Student's t-test, Qualitative variables: by Fisher's exact test, Median time to closure: by Kaplan-Meier (log-rank test). Using SAS statistical software (SAS, Cary, NC)<br>Yes. All patients who were randomised included. |
| **RESULTS** | |
| **Sample size:**<br>**No. of withdrawals & loss to follow-up:**<br>**Reasons for withdrawals:** | 79<br>I:8, C:10<br>Serious adverse events (I=3, C=5)<br>Investigator decision (C=1)<br>Protocol violations (I=5, C=4) |
| **MISCELLANEOUS** | |
| **Funding source:**<br><br>**Key conclusions of the study authors:** | Supported by a research grant from Fidia Advanced Biopolymers (Abano Terme, Italy)<br>NA |
| **AUTHOR'S CONCLUSION** | |
| **Other comment and interests:** | NA |

2. Costagliola and Agrosi, 2005

| DATA EXTRACTION FORM | |
|---|---|
| **ARTICLE DETAILS** | |
| **ID** | Costagliola and Agrosi (2005) |
| **Author(s), Year** | M. Costagliola and M. Agrosi, 2005 |
| **Title** | Second-degree burns: a comparative, multicenter, randomized trial of hyaluronic acid plus silver sulfadiazine vs. silver sulfadiazine alone |
| **Journal, Sources** | Current Medical Research and Opinion, Vol 21, No.8: 1235-1240<br>CINAHL Databases |
| **Country of Origin** | France |
| **Corresponding author & contact details** | Dr.ssa Mirella Agrosi, Direzione Ricerca e Marketing Strategico, Fidia Farmaceutici SpA, Via Ponte della Fabbrica 3/A, 35031 Abano Term (PD), Italy.<br>Email: magrosi@fidiapharma.it |

| **METHODS** | |
|---|---|
| **Study design** | Double-blind, Randomised Controlled Trial |
| **Country** | France (2), Croatia(1), Slovenia(1), Germany(1) |
| **Setting** | Clinical centres |
| **Treatments:**<br>**-Intervention (I)**<br>**-Control (C)** | <br>I: Connettivina® Plus cream<br>C: Silver sulfadiazine cream<br>Covered with sterile line gauze fixed with bandages |
| **Total study duration** | 4 weeks |
| **Single centre/multicentre trial:** | Multicentre |
| **Method used to generate random allocation sequence:**<br>**Method used to implement the random allocation sequence:**<br>**Allocation sequence concealment:** | Computer-generated randomisation list<br><br>NA<br>NA |
| **Was the participant blinded?**<br><br>**Was the researcher/healthcare provider blinded?**<br>**Was the assessor blinded?** | Intervention & Control were provided in unmarked white tubes containing 25g<br>Unclear. Clinical evaluations were performed by suitably trained and qualified staff surgeons at the participating centres |
| **Inter-assessor reliability measured?** | NA |

| **PARTICIPANTS** | |
|---|---|
| **Total number** | 111 |
| **Type of participants** | Second-degree burns |
| **Age (range) & Mean ± SD** | (I: 19-62, C:18-75 years) & I: 38.2 $\pm$ 12.4, C: 38.5 $\pm$ 15.1 |
| **Sex** | Male (n=70) & Female (n=41) |

| | |
|---|---|
| **Record of drop-out (with reasons)** | 1 male patient in SSD group (lost at follow-up) |
| **No. of sample size**<br>**Participant population (how sampled)** | 110<br>Randomly allocated |
| **No. of arm in trial** | Two |
| **No. of each arm** | n=56, 54 |
| **Power calculation** | NA |
| **Inclusion criteria** | Burns not exceed 5% of body surface area, burns have occurred within 48hours from the start treatment |
| **INTERVENTION & CONTROL GROUP** | |
| **Total number of intervention group:**<br>**Total number of control group:**<br>**Dosage of intervention & control**<br><br>**Duration of intervention & control**<br><br>**Who delivered the intervention & control** | 56<br>54<br>I: 0.2% hyaluronic acid & 1% silver sulfadiazine (HA-SSD)<br>C: 1% silver sulfadiazine (HA-SSD)<br>Applied once daily until 4 weeks<br>NA |
| **OUTCOMES** | |
| **All relevant outcomes reported** | Yes |
| **Outcomes** | Primary: Evolution of healing (complete/incomplete)<br>Secondary: Consumption of analgesics, Pain, Itching, Impairment to movement, Global comfort, Adverse events. |
| **Primary Outcome** | Time to heal/Evolution of healing (complete/incomplete) |
| **Outcome measures** | Total time in days required for complete healing of the wound (time to healing) |
| **Results** | I: 9.5 days<br>C: 14 days<br>A difference of 4.5 days, p=0.0073 |
| **Method of the measurement** | 95% CI, p=0.0073 |
| **Secondary Outcomes** | Area of wound |
| **Outcome measures** | Wound area size |
| **Results** | I: baseline 97.3 ± 100.7 $cm^2$ to 39.13% (≤ 50$cm^2$), 26.09% (51-100$cm^2$), 21.74% (101-150 $cm^2$), 13.04% (>150$cm^2$)<br>C: baseline 91.4 ± 55.9 cm2 to 26.67% (≤ 50cm2), 26.67% (51-100cm2), 30% (101-150 cm2), 16.67% (>150cm2) |
| **Secondary Outcomes** | Consumption of analgesics |
| **Outcome measures** | No. of tablets & days of use |
| **Results** | I: 0.57 ± 0.89 tablets & 4.0 ± 6.1 days (p=0.5830)<br>C: 0.69 ± 1.08 tablets & 2.4 ± 3.9 days (p=0.1764) |
| **Method of the analysis** | Fisher's exact test |
| **Secondary Outcomes** | Pain |
| **Outcome measures** | Means of a visual analog scale |
| **Results** | No statistically significant difference between groups (95% CI, -0.43, 1.48) |
| **Method of the measurement** | Huskisson scale; 0-10cm |

| | |
|---|---|
| **Time to measure** | One week after treatment |
| **Secondary Outcomes** | Itching |
| **Outcome measures** | Percentage by class |
| **Results** | I: 87.5% of class Absent-Mild, 12.5% of class Moderate-Severe<br>C: 81.5% of class Absent-Mild, 18.5% of class Moderate-Severe<br>No statistically significant difference between groups (p=0.2701, p=0.3551) |
| **Method of the analysis** | Qualitative approach, Fisher's exact test |
| **Secondary Outcomes** | Impairment to movement |
| **Outcome measures** | Percentage by class |
| **Results** | I: 73.2% of class No-Mild, 26.8% of class Moderate-Severe<br>C: 63% of class Absent-Mild, 37% of class Moderate-Severe |
| **Method of the analysis** | Qualitative approach |
| **Secondary Outcomes** | Global comfort/ Tolerability |
| **Outcome measures** | Percentage by class |
| **Results** | I: 76.8% of class Excellent-Good, 23.2% of class Bad-Very bad<br>C: 75.9% of class Absent-Mild, 24.1% in class Moderate-Severe<br>No statistically significant difference between groups (p=0.2054, p=0.3122) |
| **Method of the analysis** | Qualitative approach, Fisher's exact test |
| **Secondary Outcomes** | Adverse events |
| **Outcome measures** | Number of patient |
| **Results** | I: None C: 1 patient (shivering, fever, headache) |
| **ANALYSIS** | |
| **Method of measurements :**<br>**Method of analysis:**<br><br>**Intention-to-treat analysis? :** | Digitalized macrophotography<br>1. Mean of survival analysis with the Wilcoxon test<br>2. Qualitative approach with the Fisher's exact test<br>3. Descriptive way, visit by visit<br>Yes. |
| **RESULTS** | |
| **Sample size:**<br>**No. of withdrawals and loss to follow-up:**<br>**Reasons for withdrawals:** | 110<br>1<br>Shivering, fever. headache<br>Fixed combination HA-SSD caused a significantly more rapid re-epithelialisation of burns |
| **MISCELLANEOUS** | |
| **Funding source:** | Study support was provided by Fidia Farmaceutici SpA, Abano Terme (PD), Italy |
| **AUTHOR'S CONCLUSION** | |
| **Other comment and interests:** | Fixed combination promoted significantly faster healing of the burn than SSD alone |

3. Dereure et al., 2012a

| DATA EXTRACTION FORM | |
|---|---|
| **ARTICLE DETAILS** | |
| **ID** | Dereure et al. (2012a) |
| **Author(s), Year** | O. Dereure, M. Czubek, P. Combemale, 2012 |
| **Title** | Efficacy and safety of hyaluronic acid in treatment of leg ulcers: a double-blind RCT |
| **Journal, Sources** | Journal of Wound Care, Vol 21, No.3, March CINAHL Databases |
| **Country of Origin** | France |
| **Corresponding author & contact details** | O.Dereure, Hospital Saint Eloi, Department of Dermatology, Motpellier, France<br>Email: o-dereure@chu-montpellier.fr |

| **METHODS** | |
|---|---|
| **Study design** | Double-blind, Randomised Controlled Trial |
| **Country** | France (17), Poland (7) |
| **Setting** | Hospital, June 2007-November 2009 |
| **Treatments:**<br>**-Intervention (I)**<br>**-Control (C)** | I: Ialuset® cream<br>C: Neutral vehicle<br>With long-stretch elastic bandage & multilayer bandages |
| **Total study duration** | 60 days |
| **Single centre/multicentre trial:** | Multicentre |
| **Method used to generate random allocation sequence:**<br>**Method used to implement the random allocation sequence:**<br>**Allocation sequence concealment:** | Computer-generated randomisation list<br><br>Used validated software (SAS, Institute Inc.)<br>By Data Management & Statistic Unit IBSA (Institut Biochimique S.A) |
| **Was the participant blinded?**<br><br><br><br>**Was the researcher/investigator blinded?**<br>**Was the assessor blinded?** | Yes. Intervention & Control were supplied in the same form, external packaging, shape, odour & texture, participants were assigned to a treatment group based on the sequential order of the randomisation<br>Yes. 54 investigators<br>Yes. Treatment allocation & evaluation were assessed by a blinded physician |
| **Inter-assessor reliability measured?** | NA |

| **PARTICIPANTS** | |
|---|---|
| **Total number** | 101 |
| **Type of participants** | Leg Ulcers |
| **Age (range) & mean ± SD** | (> 18 Years)<br>I: 68.6 $\pm$ 12.4, C: 69.7 $\pm$ 14.7 |
| **Sex** | Male (n=45) & Female (n=56) |

| | |
|---|---|
| **Record of drop-out (with reasons)** | I= 12, C=14 |
| **No. of sample size**<br>**Participant population (how sampled)** | 75<br>Randomly allocated |
| **No. of arm in trial** | Two |
| **No. of each arm** | I; 50, C:51 |
| **Power calculation** | 140 patients for 90% power (89% for 101 patients) |
| **Inclusion criteria** | >2 months ulcer < 4 years, ulcer surface area 5-40cm$^2$ with no necrotic tissue |
| **INTERVENTION & CONTROL GROUP** | |
| **Total number of intervention group:**<br>**Total number of control group:**<br>**Dosage of intervention & control**<br>**Duration of intervention & control**<br>**Who delivered the intervention & control** | 50<br>51<br>0.2% hyaluronic acid<br>Once daily until 60 days<br>By a nurse and investigator (during evaluation visit) |
| **OUTCOMES** | |
| **All relevant outcomes reported** | Yes |
| **Outcomes** | Primary: Percentage of wound size reduction at day 45<br>Secondary: pain intensity, burden of pain, cumulative no. healed ulcers, percentage of fibrous tissue, percentage of granulation tissue, acceptability, adverse events |
| **Primary Outcome** | Percentage of wound size reduction at day 45 |
| **Outcome measures** | Median percentage reduction in wound area |
| **Results** | I: baseline 11.1cm2 →mean: 16.08<br>Endpoint: (day 45=39±6%)mean ± SEM → SD 9.81 [4.17]<br>C: baseline 11.7cm2 →mean: 17.04<br>Endpoint (day 45=5±9%)mean ± SEM→ 16.55 [10.64] P=0.002 |
| **Method of the measurement** | Traced the wound margins on sterile tracing paper, measured the wound size based on tracings, using digital planimetry (Visitrak; Smith & Nephew) |
| **Time to measure** | Day 15±2, 30±3, 45±3 and 60 |
| **Length of follow-up** | 45 days |
| **Secondary Outcomes** | Percentage of wound size reduction at day 15, 30 and 60 |
| **Outcome measures** | Mean percentage reduction in wound area |
| **Results** | I: day 15=27%, day30=33%,<br>C: day 15=27%, day30=33%, |
| **Method of the measurement** | using digital planimetry (Visitrak; Smith & Nephew) |
| **Secondary Outcomes** | Pain intensity |
| **Results** | I: 23.0 to 13.2 mm (by 9.8 ± 3.5 mm)<br>C: 26.6 to 25.8 mm (by 0.8 ± 3.2 mm) |
| **Method of the measurement** | 0 (no pain) -100 (severe pain) mm VAS |
| **Secondary Outcomes** | Cumulative no. healed ulcers |
| **Outcome measures** | Number of ulcer |

| | |
|---|---|
| **Results** | I: day15=0, day 30=1, day 45=1, day60=3<br>C: day15=0, day 30=3, day45=3, day60=4<br>No statistically significant |
| **Secondary Outcomes** | Percentage of fibrous tissue (Healing wound process) |
| **Outcome measures** | Percentage |
| **Results** | I: day1=40.9% to day 60=28.6%<br>C: day1=44.0% to day 60=37.6% |
| **Secondary Outcomes** | Percentage of granulation tissue (Healing wound process) |
| **Outcome measures** | Percentage |
| **Results** | I: day1=59.1% to day 60=63.5%<br>C: day1=56.0% to day 60=58.5% |
| **Secondary Outcomes** | Acceptability |
| **Outcome measures** | Counting the number of application performed |
| **Results** | >79% did not miss any daily application |
| **Method of the measurement** | Excellent=0, Good=0-3, Fair=3-7, Poor= ≥7 |
| **Secondary Outcomes** | Adverse events |
| **Outcome measures** | Percentage of cases |
| **Results** | I=20 AE, C=19 AE<br>Mild to moderate=88%, Severe=11% (application site burn, inflammation or pain and aggravated condition) |
| **ANALYSIS** | |
| **Which analysis performed? :**<br>**Method of analysis:**<br><br>**Intention-to-treat analysis? (ITT)** | 1. Analysis of variance (ANNOVA)<br>2. Qualitative variables use Chi-square test or Fisher's exact test<br>Yes, 101 patients analysed in the ITT |
| **RESULTS** | |
| **Sample size:**<br><br><br>**No. of withdrawals & loss to follow-up:**<br>**Reasons for withdrawals:**<br>**Summary of results' analyses:** | 20% difference in the % of wound size reduction between groups at day 45 would be significant, theoretical sample size was 140 patients, taking into account 10% of dropouts<br>I=3, C=5<br>I: inefficacy(n=2), healing (n=1)<br>C: inefficacy (n=2), healing (n=3)<br>These results support hypothesis that hyaluronic acid significantly contributes to the restoration of optimal local physiologic conditions which necessary to promote ulcer healing |
| **MISCELLANEOUS** | |
| **Funding source:**<br>**Key conclusions of the study authors:** | Study was sponsored by Laboratoires Genevrier<br>Hyaluronic acid might have a positive impact on quality of life through a significant reduction in pain intensity |
| **AUTHOR'S CONCLUSION** | |
| **Other comment and interests:** | Application of hyaluronic acid on leg ulcers is significantly more effective than a neutral vehicle |

4. Dereure et al., 2012b

| DATA EXTRACTION FORM | |
|---|---|
| **ARTICLE DETAILS** | |
| **ID** | Dereure et al. (2012b) |
| **Author(s), Year** | O. Dereure, J. Mikosinki, Z. Zegota, F.A. Allaert, 2012 |
| **Title** | RCT to evaluate a hyaluronic acid containing gauze pad in leg ulcers of venous or mixed aetiology |
| **Journal, Sources** | Journal of Wound Care, Vol 21, No.11, November CINAHL Databases |
| **Country of Origin** | France |
| **Corresponding author & contact details** | O.Dereure, Hospital Saint Eloi, Department of Dermatology, Motpellier, France<br>Email: o-dereure@chu-montpellier.fr |
| **METHODS** | |
| **Study design** | Single-blind, Randomised Controlled Trial |
| **Country** | France (4), Poland (16) |
| **Setting** | Hospital, Sept 2009-December 2009 |
| **Treatments:**<br>**-Intervention (I)**<br>**-Control (C)** | <br>I: Ialuset® gauze pad<br>C: DuoDERM E (HC dressing)<br>Covered with sterile gauze & compression bandage |
| **Total study duration** | 56 days |
| **Single Centre/Multicentre trial:** | Multicentre |
| **Method used to generate random allocation sequence:**<br>**Method used to implement the random allocation sequence:**<br>**Allocation sequence concealment:** | Computer-generated randomisation list<br><br>Used validated software (SAS, Institute Inc.)<br>By Data Management & Statistic Unit IBSA (Institut Biochimique S.A) |
| **Was the participant blinded?**<br><br><br><br>**Was the researcher/healthcare provider blinded?**<br>**Was the assessor blinded?** | Yes. Intervention & Control were supplied in the same form, external packaging, shape, odour & texture, participants were assigned to a treatment group based on the sequential order of the randomisation<br>Yes. Blind-observer<br><br>Yes. Treatment allocation & evaluation were assessed by a blinded physician |
| **Inter-assessor reliability measured?** | NA |
| **PARTICIPANTS** | |
| **Total number** | 170 |
| **Type of participants** | Arterial/venous Leg Ulcers |
| **Age (range) & Mean ± SD** | ≥ 18 years<br>I: 64.2 ± 14.4, C: 68.5 ± 13.1 |
| **Sex** | Male (n=57) & Female (n=86) |

| | |
|---|---|
| **Record of drop-out (with reasons)** | I= 13, C=14<br>did not meet inclusion criteria (I=6, C=6)<br>major protocol deviation (I=7, C=8) |
| **No. of sample size**<br>**Participant population (how sampled)** | 143<br>Randomly allocated according to a central randomisation list balanced per blocks of four |
| **No. of arm in trial** | Two |
| **No. of each arm** | n=72, 71 |
| **Power calculation** | 136 patients for 90% power (170 patients if 20% dropout) |
| **Inclusion criteria** | Ulcer >2months < 4years, surface target ulcer 5-40cm$^2$ |
| **INTERVENTION & CONTROL GROUP** | |
| **Total number of intervention group:**<br>**Total number of control group:**<br>**Dosage of intervention & control**<br>**Duration of intervention & control**<br>**Who delivered the intervention & control** | 85<br>85<br>0.05% HA-impregnated cotton gauze pad<br>I: once daily, C: every2-3days until 56 days<br>By a nurse and investigator (during evaluation visit) |
| **OUTCOMES** | |
| **All relevant outcomes reported** | Yes |
| **Outcomes** | Primary: Percentages of patients achieving a reduction of at least 40%of the initial wound surface after 56 days of treatment<br>Secondary: percentage of wound size reduction at day 14, 28& 56, pain intensity, burden of pain, aspect of peri-ulcerous skin, percentage of complete healed ulcer, pattern of the wound, patient acceptability and adverse events |
| **Primary Outcome** | Percentages of patients achievement a reduction of at least 40%of the initial wound surface after 56 days of treatment |
| **Outcome measures** | 95% CI of the difference between the two groups |
| **Results** | I: baseline 14.4 (9.0) to 74% (53 patients)<br>C: baseline 15.8 (9.5) to 72% (51 patients)<br>CI [-0.128, 0.164] |
| **Method of the measurement** | Traced the wound margins on sterile tracing paper, measured the wound size based on tracings, using digital planimetry (Visitrak; Smith & Nephew) |
| **Time to measure** | Day 14, 28 and 56 |
| **Length of follow-up** | 56 days |
| **Secondary Outcomes** | Percentage of wound size reduction at day 14, 28 & 56 |
| **Outcome measures** | 95% CI |
| **Results** | P=0.3931 |
| **Secondary Outcomes** | Pain intensity |
| **Outcome measures** | 95% CI |
| **Results** | I: 29.3 ± 25.0 to 11.6 mm<br>C: 29.7 ± 24.9 to 21.6 mm |

| | |
|---|---|
| | P=0.6658 |
| **Method of the measurement** | 0 (no pain) -100 (severe pain) mm VAS |
| **Secondary Outcomes** | Burden of pain |
| **Outcome measures** | Means of a visual analog scale |
| **Results** | I: 121.9 ± 20.7 mm<br>C: 207.4 ± 32.9 mm<br>P=0.028 |
| **Primary Outcomes** | Percentage of complete healed ulcer (full epithelialisation) |
| **Outcome measures** | 95% CI |
| **Results** | P=0.6007 |
| **Secondary Outcomes** | Aspect of peri-ulcerous skin |
| **Outcome measures** | Qualitative measure |
| **Results** | P=0.8544 for fibrinous tissue<br>P=0.6704 for granulation tissue |
| **Secondary Outcomes** | Acceptability |
| **Outcome measures** | Counting the number of application performed |
| **Results** | >97% had >80% of applications |
| **Method of the measurement** | Good=>80%, Fair=50%-80%, Poor= <50% |
| **Secondary Outcomes** | Adverse events |
| **Outcome measures** | Qualitative measure |
| **Results** | I=36 AE, C=41 AE<br>Mild to moderate=77%, Severe=23% (I=4, C=14) |
| **ANALYSIS** | |
| **Which analysis performed? :**<br>**Method of analysis:**<br><br>**Intention-to-treat analysis? (ITT):** | 1. Analysis of variance (ANNOVA)<br>2. Qualitative variables use Chi-square test or Fisher's exact test<br>Yes, 170 patients analysed in the ITT |
| **RESULTS** | |
| **Sample size:**<br><br><br>**No. of withdrawals and loss to follow-up:**<br>**Reasons for withdrawals:** | 170.20% difference in the % of wound size reduction between groups at day 45 would be significant, theoretical sample size was 170 patients, taking into account 20% of dropouts<br>I=13, C=13<br>Ulcer healing (n=12)<br>Treatment related AE (n=7)<br>NA |
| **MISCELLANEOUS** | |
| **Funding source:**<br>**Key conclusions of the study authors:** | Study was sponsored by Laboratoires Genevrier<br>NA |
| **AUTHOR'S CONCLUSION** | |
| **Other comment and interests:** | Local application of HA using an impregnated gauze pad is more favourable as compared with HC dressing. The study confirmed the good safety profile of the HA gauze pad. |

5. Humbert et al., 2012

| DATA EXTRACTION FORM | |
|---|---|
| **ARTICLE DETAILS** | |
| **ID** | Humbert et al. (2012) |
| **Author(s), Year** | Philippe Humbert, Jacek Mikosinski, Hakima benchikhi and Francois-Andre Allaert, 2012 |
| **Title** | Efficacy and safety of a gauze pad containing hyaluronic acid in treatment of leg ulcers of venous or mixed origin: a double-blind, randomised, controlled trial |
| **Journal, Sources** | International Wound Journal, CINAHL database |
| **Country of Origin** | France |
| **Corresponding author & contact details** | P Humbert, Service de Dermatologie, CHU de Besancon, 2 place Saint-Jacques, 25030 Besancon, France<br>Email: philippe.humbert@univ-fcomte.fr |

| METHODS | |
|---|---|
| **Study design** | Double-blind, randomised controlled trial |
| **Country** | France, Morocco, Poland |
| **Setting** | 31 investigators from 29 centres<br>France (18 centres), Morocco (3 centres), Poland (8 centres) from Nov 2007-November 2009 |
| **Treatments:**<br>**-Intervention (I)**<br>**-Control (C)** | <br>Ialuset® gauze pad<br>Neutral vehicle gauze pad<br>Covered with sterile gauze & an appropriate bandage |
| **Total study duration** | 60 days |
| **Single centre/multicentre trial:** | Multicentre |
| **Method used to generate random allocation sequence:**<br>**Method used to implement the random allocation sequence:**<br><br>**Allocation sequence concealment:** | Parallel-group randomised<br><br>Validated software from SAS Institute Inc, Cary, NC<br>Randomisation list was prepared by Data Management &Statistics Unit of IBSA Institut Biochimique SA, Switzerland |
| **Was the participant blinded?**<br><br>**Was the researcher/healthcare provider blinded?**<br>**Was the assessor blinded?** | Yes, randomization list balanced per blocks of 4 based on sequential order at each site<br>Yes<br><br>Yes, 2 independent readers (blinded) measured the wound size |
| **Inter-rater reliability measured?** | NA |

| PARTICIPANTS | |
|---|---|
| **Total number** | 89 |

| | |
|---|---|
| **Type of participants** | Arterial/venous Leg ulcer |
| **Age (range) & Mean ± SD** | ≥18 years<br>I=59.4 (2.5), C=64.1 (2.7) |
| **Sex** | Female=44, Male=45 |
| **Record of drop-out (with reasons)** | I=7, C=10<br>Did not meet inclusion criteria (1=5, C=5)<br>Protocol deviation (I=1, C=3)<br>Visit outside the specific range for primary evaluation (I=1, C=1)<br>Poor compliance (C=1) |
| **No. of sample size**<br>**Participant population (how sampled)** | 89<br>In-patients & Out-patients |
| **No. of arm in trial** | Two |
| **No. of each arm** | I: 45, C:44 |
| **Power calculation** | Hypothesis: 20% difference between the percentages of wound size reduction with HA compared with neutral at D45<br>Theoretical sample size: 140 patients (with 10% dropouts) |
| **Inclusion criteria** | One/several leg ulcers (arterial/venous), present for >2mths, < 4 years, surface ulcer 5-40cm$^2$ with no necrotic tissue. |
| **INTERVENTION & CONTROL GROUP** | |
| **Total number of intervention group:**<br>**Total number of control group:**<br>**Dosage of intervention & control**<br>**Duration of intervention & control**<br>**Who delivered the intervention & control** | 45<br><br>44<br>0.05% Hyaluronic acid<br>Maximum 60 days<br><br>Nurse |
| **OUTCOMES** | |
| **All relevant outcomes reported** | Yes |
| **Outcomes** | Primary: Percentage of wound size reduction after 45 days, Secondary: Percentage of wound size reduction at D15, D30, D60, Percentage of patients with healed ulcer at day 45 & day 60, Pain intensity, Burden of pain, Tolerance, Systemic anaelgesic & antibiotics used, Aspect of wound, Aspect of peri-ulcerous skin, Adverse events |
| **Primary Outcome** | Percentage of wound size reduction after 45 days |
| **Outcome measures** | Percentage of wound size reduction |
| **Results** | I=from 13.8 ± 1.3cm$^2$ decreased by 73±4.6%, →<br>SD (±8.72) to (±8.32)<br>C= from 12.9 ± 1.3 cm2 decreased by 46±9.6%<br>SD (±8.62) to (±7.8)<br>P=0.011 (statistically significant different) |

| | |
|---|---|
| **Method of the measurement** | Shape of the wound was drawn by the investigator using a sterile tracing paper at each evaluation visit for measure of wound size by a Digital Planimetrics System, Visitrak® |
| **Time to measure** | Evaluation visit: day 0, day 45±3 |
| **Length of follow-up** | 60 days |
| **Secondary Outcomes** | Percentage of wound size reduction at D15, D30, D60 |
| **Outcome measures** | Percentage |
| **Results** | day15 (I=40%, C=29%), day30 (I=64%, C=36%), day60 (I=77%, C=52%) |
| **Method of the measurement** | Shape of the wound was drawn by the investigator using a sterile tracing paper at each evaluation visit for measure of wound size by a Digital Planimetrics System, Visitrak® |
| **Time to measure** | Evaluation visit: day 0, day 15±2, day 30±3, day 45±3 and day 60±3 |
| **Secondary Outcomes** | Percentage of patients with healed ulcer at day 45 & day 60 |
| **Outcome measures** | Percentage |
| **Results** | D45 (I=31.1%, C=9.3%) P=0.011 =(14/38, 6/34)<br>D60 (I=37.8%, C=16.3%) P=0.024 (17/45, 7/44) |
| **Secondary Outcomes** | Pain intensity |
| **Outcome measures** | Mean ± SEM |
| **Results** | Day 60<br>I= 33.2± 3.7mm to 11.5 ± 2.8mm (SEM)<br>C=33.4± 4.0mm to 13.7 ±2.9mm (SEM)<br>Day 30<br>I= to 12.4 ± 2.6mm<br>C=to 22.8 ± 3.8mm |
| **Method of the measurement** | 0-100mm Visual Analogue Scale (VAS) |
| **Secondary Outcomes** | Aspect of wound |
| **Outcome measures** | Percentage of necrotic, fibronous or granulation tissue |
| **Results** | I= 8.5% ±7.6, C=9.0%±8.0 |
| **Method of the measurement** | Semi-quantitative four-point scale (nil=0, slight=1, moderate=2, important=3) |
| **Secondary Outcomes** | Aspect of peri-ulcerous skin |
| **Outcome measures** | Oedema, purpura, erythema, maceration, oozing and horny edges |
| **Results** | NA |
| **Method of the measurement** | Semi-quantitative four-point scale (nil=0, slight=1, moderate=2, important=3) |
| **Secondary Outcomes** | Tolerance/Compliance |
| **Outcome measures** | Counting the number of applications performed |
| **Results** | 87% =Excellent |

| | |
|---|---|
| **Method of the measurement** | Excellent=no day of missed application, Good<3 days, Fair=3-7 days missed application, Poor>7 days of missed application |
| **Secondary Outcomes** | Adverse events |
| **Outcome measures** | Nature, Severity, Time of onset, Duration, Degree of relationship to the study treatment & description of any action/pharmacological treatment undertaken |
| **Results** | 48 AE in 27 patients<br>I=22.2%, C=38.6%<br>I=6.7%, C=18.2% treatment-related AE<br>75%=mild to moderate, 25%=severe |
| **ANALYSIS** | |
| **Which analysis performed? :**<br>**Method of analysis:**<br>**Intention-to-treat analysis? (ITT):** | To look at individual outcomes<br><br>Yes, on all randomised patients |
| **RESULTS** | |
| **Sample size:**<br><br>**No. of withdrawals and loss to follow-up:**<br><br>**Reasons for withdrawals:**<br><br>**Summary of results' analyses:** | 89 (ITT), 72(PP)<br><br>28 patients did not complete the study (18 HA; 10 control)<br>17 patients from ITT were reported with major protocol violations<br>NA<br>The results showed significantly greater reduction of wound size after 45days with HA compared to neutral vehicle. The proportion of healed ulcer was significantly higher in the HA group than in the neutral vehicle group. Pain management also favoured in the HA arm. |
| **MISCELLANEOUS** | |
| **Funding source:**<br>**Key conclusions of the study authors:** | Sponsor, Laboratoires Genevrier.<br>Study clearly shows that the local application of HA using an impregnated gauze pad on venous leg ulcers is significantly more effective than neutral vehicle gauze pad and effective wound closure with a good safety profile. |
| **AUTHOR'S CONCLUSION** | |
| **Other comment and interests:** | NA |

6. Koller, 2004

| DATA EXTRACTION FORM | |
|---|---|
| **ARTICLE DETAILS** | |
| **ID** | Koller (2004) |
| **Author(s), Year** | Koller J, 2004 |
| **Title** | Topical treatment of partial thickness burns by silver sulfadiazine plus hyaluronic acid compared to silver sulfadiazine alone: a double-blind, clinical study |
| **Journal, Sources** | Drugs Experimental and Clinical Research, Vol:30, Issue:5/6; 183-190 |
| **Country of Origin** | Republic Slovakia |
| **Corresponding author & contact details** | Jan Koller, Head of Teaching Department for Burns and Reconstructive Surgery, Central Tissue Bank, University Hospital Bratislava Ruzinov, Ruzinoska 6-821 02 Bratislava, Slovak Republic<br>Email: koller@nspr.sk, jankoller@hotmail.com |
| **METHODS** | |
| **Study design** | Prospective, Double-blind controlled Experimental |
| **Country** | Republic Slovakia |
| **Setting** | General Hospital, Bratislava |
| **Treatments:**<br>**-Intervention (I)**<br><br>**-Control (C)** | <br>Ialugen Plus® cream (IBSA Institut Biochimique SA)<br>Silver Sulfadiazine cream<br>Covered with sterile line gauze & bandages |
| **Total study duration** | 4 weeks |
| **Single centre/multicentre trial:** | Single centre |
| **Method used to generate random allocation sequence:**<br>**Method used to implement the random allocation sequence:**<br>**Allocation sequence concealment:** | Computer-generated randomisation list<br><br>NA<br><br>NA |
| **Was the participant blinded?**<br><br>**Was the researcher/healthcare provider blinded?**<br>**Was the assessor blinded?** | Yes, Same appearance, colour, consistency, unmarked tubes of cream<br>Unclear. Performed by suitably trained & qualified staff surgeons |
| **Inter-rater reliability measured?** | NA |
| **PARTICIPANTS** | |
| **Total number** | 33 |
| **Type of participants** | Second-degree burns |
| **Age (range) & mean±SD** | (18-80 years) & I: 35 ± 14.5, C: 40.7 ± 11.6 |
| **Sex** | Male:24, Female:9 |
| **Record of drop-out (with reasons)** | None |
| **No. of sample size**<br>**Participant population (how sampled)** | 33<br>Selected according to the inclusion and exclusion criteria |

| | |
|---|---|
| **No. of arm in trial** | Two |
| **No. of each arm** | I: 18, C:15 |
| **Power calculation** | NA |
| **Inclusion criteria** | Superficial & partial thickness burn exceeding 5% of the body surface area, 900cm$^2$ in an average adult patient. |
| **INTERVENTION & CONTROL GROUP** | |
| **Total number of intervention group:**<br>**Total number of control group:**<br>**Dosage of intervention & control**<br>**Duration of intervention & control**<br>**Who delivered the intervention & control** | 18<br><br>15<br>I: 0.2% HA, 1% silver sulfadiazine C: 1% silver sulfadiazine<br>Once daily until 4weeks<br>NA |
| **OUTCOMES** | |
| **All relevant outcomes reported** | Yes |
| **Outcomes** | Primary: Wound area<br>Secondary: Time to heal, Local edema, Local infection, Global response to the treatment, Local tolerability, Adverse event, Concomitant medications |
| **Primary Outcome** | Wound area |
| **Outcome measures** | Percentage of pre-treatment value |
| **Results** | I: day7= 5.83±14.17, day14=0, day 21=0<br>C; day7=30.59±28.17, day 14=6.25±12.58, day 21=0<br>P-value day7=0.002, day14=0.043 |
| **Time to measure** | Day 7, 14, 21 |
| **Secondary Outcomes** | The severity and the extent of the burn |
| **Outcome measures** | Percentage of the burned skin area |
| **Results** | I: 9.88 ± 6.89%, C: 11.3 ± 3.53%<br>P=0.61 |
| **Secondary Outcomes** | Time to heal |
| **Outcome measures** | Total time in days required for complete healing ,<br>Record the percentage of the residual wound area |
| **Results** | I: 8.17± 2.7 days<br>C: 13.07 ± 5.20 days, P=0.0015 |
| **Method of the analysis** | Student's t-test for unpaired data |
| **Time to measure** | Day 1, 7, 14, 21,28 |
| **Secondary Outcomes** | Local edema |
| **Outcome measures** | Mean local edema, Four-point severity scale (0=absent, 3=severe pain) |
| **Results** | I: 0.11 ± 0.32<br>C: 0.50 ± 0.51<br>P=0.024 |
| **Method of the measurement** | Kruskal-Wallis test |
| **Time to measure** | Day 7 |
| **Secondary Outcomes** | Pain |
| **Outcome measures** | Score |
| **Results** | I: baseline=1.5, day7=0.2 |

| | |
|---|---|
| | C: baseline=1.8, day7=0.7<br>No stat. significant |
| **Method of the measurement** | Kruskal-Wallis test |
| **Secondary Outcomes** | Local infection |
| **Outcome measures** | Number of patient |
| **Results** | I: present at day 7 in one patient<br>C: absent |
| **Method of the measurement** | Present or Absent |
| **Secondary Outcomes** | Global response to the treatment |
| **Outcome measures** | Percentage of participants |
| **Results** | 80-90%: good/excellent |
| **Method of the measurement** | Four-point scale (none, fair, good, excellent) |
| **Secondary Outcomes** | Local tolerability to treatment |
| **Outcome measures** | Scale |
| **Results** | Good/Excellent |
| **Method of the measurement** | Four-point scale (bad, fair, good, excellent) |
| **Secondary Outcomes** | Adverse event |
| **Outcome measures** | NA |
| **Results** | Absence |
| **ANALYSIS** | |
| **Which analysis performed? :**<br>**Method of analysis:**<br><br><br><br><br><br>**Intention-to-treat analysis? (ITT):** | Continous variables were analysed by analysis of variance (ANOVA) with repeated measures.<br>Multiple comparisons were performed using Student's t-test for unpaired data.<br>Discrete variables were analyzed using Wilcoxon Signed Rank Test, Kruskal-Willis test, Fisher's exact test, Chi-squared test and linear trend test<br>Analyzed by independent organisation (IBIS Informatica & Idee S.r.I, Milan, Italy)<br>Yes. |
| **RESULTS** | |
| **Sample size:**<br>**No. of withdrawals and loss to follow-up:**<br>**Reasons for withdrawals:**<br>**Summary of results' analyses:** | 33<br>None<br><br>None<br>The findings of this study confirmed that the association of the two compounds in a new topical treatment significantly reduced the healing time and significantly accelerated the reduction of local edema occurring shortly after injury. |
| **MISCELLANEOUS** | |
| **Funding source:**<br>**Key conclusions of the study authors:** | NA<br>The combination of SS-HA succeeded the wound healing process. The most favourable effect in SS-HA is the statistically significant of time to complete healing |
| **AUTHOR'S CONCLUSION** | |
| **Other comment and interests:** | NA |

7. Meaume et al., 2008

| DATA EXTRACTION FORM | |
|---|---|
| **ARTICLE DETAILS** | |
| **ID** | Meaume et al. (2008) |
| **Author(s), Year** | Sylvie Meaume, Zohra Ourabah, Marco Romanelli, Roberto Manopulo, Florent De Vathaire, Denis Salomon and Jean-Hilaire Saurat, 2008 |
| **Title** | Efficacy and tolerance of a hydrocolloid dressing containing hyaluronic acid for the treatment of leg ulcers of venous or mixed origin |
| **Journal, Sources** | Current Medical Research and Opinions, Vol: 24, No:10; 2729-2739 |
| **Country of Origin** | France |
| **Corresponding author & contact details** | S. Meaume, APHP Groupe Hospitalier Charles Foix, Service de Gerontologie 'L'ORBE' 7, Avenue de la Republique, F-94205 Ivy-sur-Seine Cedex, France.<br>Email: Sylvie.meaume@cfx.ap-hop-paris.fr |
| **METHODS** | |
| **Study design** | Open-label, prospective, randomised controlled trial |
| **Country** | France, Italy, Switzerland |
| **Setting** | France: 15 centres, Italy: 2 centres, Switzerland: 1 Centre, November 2001- March 2003 |
| **Treatments:**<br>**-Intervention (I)**<br><br>**-Control (C)** | <br>Hydrocolloid dressing containing Hyaluronic acid (HC + HA)<br>Hydrocolloid dressing<br>Covered with elastic stocking |
| **Total study duration** | 42 days |
| **Single centre/multicentre trial:** | Multicentre |
| **Method used to generate random allocation sequence:**<br>**Method used to implement the random allocation sequence:**<br>**Allocation sequence concealment:** | Computer-generated randomisation list<br><br>Yes. Sealed envelopes<br><br>Yes |
| **Was the participant blinded?**<br>**Was the researcher/healthcare provider blinded?**<br>**Was the assessor blinded?** | Unclear<br>Yes. Sealed envelopes containing the treatment code for each patient were given to the investigator<br>Yes, independent personnel |
| **Inter-rater reliability measured?** | Yes. |
| **PARTICIPANTS** | |
| **Total number** | 125 |

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|---|---|
| **Type of participants** | Arterial/venous Leg ulcers |
| **Age (range) & Mean ± SD** | ≥18 years<br>I: 73± 1.4 (mean ± SEM) 73± 11.11, C: 75 ± 1.4 |
| **Sex** | Male: 54, Female: 71 |
| **Record of drop-out (with reasons)** | I: 11, C:11 |
| **No. of sample size**<br>**Participant population (how sampled)** | 125<br>NA |
| **No. of arm in trial** | Two |
| **No. of each arm** | I: 63, C:62 |
| **Power calculation** | 120 patients (80% power with 20% drop-outs) |
| **Inclusion criteria** | Ulcers >2months < 1year and size 5-40cm$^2$ with no necrotic tissue |
| **INTERVENTION & CONTROL GROUP** | |
| **Total number of intervention group:** | 63 |
| **Total number of control group:** | 62 |
| **Dosage of intervention & control** | NA |
| **Duration of intervention & control** | At least once a week until 6 weeks |
| **Who delivered the intervention & control** | Investigator |
| **OUTCOMES** | |
| **All relevant outcomes reported** | Yes. |
| **Outcomes** | Primary: Reduction of wound area<br>Secondary: Wound bed condition and Surrounding skin conditions, Complete ulcer healing, Presence & severity of symptoms pain and itching, Oral anaelgesic consumption, Overall efficacy and tolerance, Adverse event |
| **Primary Outcome** | Reduction of wound area |
| **Outcome measures** | Cumulative percentage with at least 90% of ulcer reduction |
| **Results** | I= SEM 11.7 ± 1.2 to 7.9 ± 1.4 cm$^2$ → SD(±9.53) to (±10.1)<br>C=SEM 12.2 ± 1.7 to 8.3 ± 1.4 cm$^2$ →SD (±13.39) to (±9.9) |
| **Method of the measurement** | Photographs with graduated scale, Digital planimeter, PLACOM KP-80 (Koizumi Sokki MFG. Co.Ltd. Niigata, Japan), t-test |
| **Time to measure** | Day 1, 7, 14, 28 and 42 |
| **Secondary Outcomes** | Number of patients success |
| **Outcome measures** | Reduction at least 90% of ulcer area |
| **Results** | I: 15/63, C: 7/62 |
| **Secondary Outcomes** | Wound bed condition |
| **Outcome measures** | Percentage of necrotic, fibrinous and granulation tissues |

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| **Results** | Necrotic: I=0.19 ± 0.2 to 0.2 ± 0.2 , C=0.27 ± 3.0 to 0±0<br>SD: (±1.59) to (±1.59), (±23.6)<br>Fibrinous: I=29 ± 3.3 to 9.3± 2.3 , C=27 ± 3.0 to 13.5 ± 2.5<br>SD: (±26.19) to (±18.26), (±23.62) to (±19.69)<br>Granulation: I=70.8 ± 3.3 to 89.0 ± 2.7, C= 73 ± 3.1 to 86.5 ± 2.5<br>SD: (±26.19) to (±21.43), (±24.41) to (±19.69) |
| **Time to measure** | Day 1, 7, 14, 28 and 42 |
| **Secondary Outcomes** | Surrounding skin conditions |
| **Outcome measures** | Intensity of oedema, purpura, erythema, oozing, maceration, horny edges and smell |
| **Results** | I: skin maceration p=0.05, oozing p=0.05 |
| **Method of the analysis** | Mantel- Haenszel test |
| **Secondary Outcomes** | Complete ulcer healing |
| **Outcome measures** | Day of complete healing |
| **Results** | I & C= 4 complete healing each group before 42 days |
| **Method of the analysis** | Wilcoxon non parametric test |
| **Secondary Outcomes** | Presence & severity of symptoms pain and itching |
| **Outcome measures** | Mean ± SD |
| **Results** | Itching: I=26.8±3.9 to 6.5±2.5 mm, C=14.3±2.9 to 8.4±2.5 mm→<br>SD (±30.95) to (± 19.8), (±23.01) to (±19.69)<br>Pain: I=39.4±3.9 to 12.1±3.0 mm, C=27.4 ± 3.9 to 10.0±2.7 mm →<br>SD (±30.96) to (±23.81), (±30.71) to (±21.26) |
| **Method of the measurement** | 100mm Huskisson's Visual Analogue Scale (VAS) |
| **Secondary Outcomes** | Oral anaelgesic consumption |
| **Outcome measures** | Percentage |
| **Results** | I=52% (33) to 30% (19)<br>C=42% (26) to 29% (18) |
| **Method of the analysis** | Wilcoxon's non-parametric test and Fisher's exact test |
| **Secondary Outcomes** | Overall efficacy and tolerance |
| **Outcome measures** | Number of patients |
| **Results** | Efficacy: I day 7 =0/7/44/12 to day 42= 1/13/21/28<br>Efficacy: C day 7 =1/18/35/8 to day 42= |

| | |
|---|---|
| | 1/12/33/16<br><br>Tolerance: I day7= 0/4/44/15 to day 42=2/10/22/29<br>Tolerance: C day7= 1/8/43/10 to day 42=1/7/38/16 |
| **Method of the measurement** | Four-point scale (nil/poor//good/very good) |
| **Secondary Outcomes** | Adverse event |
| **Outcome measures** | Percentage |
| **Results** | I= 4 patients (6.4%) at least one AE<br>Itching and oedema (1), Erosion of the peri-ulcer skin (1)<br>Rash (1), Pain (1)<br><br>C=5 patients (8.1%) at least one AE<br>Heavy exudates & erosion (1), pruritus & eczema (1), eczema & purpura (1), site of application (3) |
| **Method of the analysis** | Fisher exact test |
| **ANALYSIS** | |
| **Which analysis performed? :**<br>**Method of analysis:**<br><br><br>**Intention-to-treat analysis? (ITT) :** | Statistical analysis was performed by an Independent institute (ECOSTAT, France) using Wilcoxon's non-parametric test, ANOVA for repeated measures. Mantel-Haenszel test for ordinal variables<br>Yes, all included patients. |
| **RESULTS** | |
| **Sample size:**<br>**No. of withdrawals and loss to follow-up:**<br>**Reasons for withdrawals:**<br>**Summary of results' analyses:** | 125<br><br>22 patients<br>8= complete healing, 7= due to AE, 7=other reasons<br>Reduction area and changes in wound bed condition were not statistically significant between two groups, A reduction of > 90% of initial ulcer was seen in 15 patients in the HC+HA group & 7 in HC group. Marked reduction of fibrinous tissue in the HC+HA |
| **MISCELLANEOUS** | |
| **Funding source:**<br><br>**Key conclusions of the study authors:** | Supported by IBSA Institut Biochimique SA (Switzerland) & Laboratoires Genevrier (France)<br>The HA+HC was equally well tolerated and with trend to be more effective than HC group in the treatment of leg ulcers of venous or mixed origin. |
| **AUTHOR'S CONCLUSION** | |
| **Other comment and interests:** | HC+ HA dressing could become an alternative choice for the treatment of leg ulcers. |

8. Ortonne, 1996

| DATA EXTRACTION FORM | |
|---|---|
| **ARTICLE DETAILS** | |
| **ID** | Ortonne (1996) |
| **Author(s), Year** | JP Ortonne, 1996 |
| **Title** | A controlled study of the activity of hyaluronic acid in the treatment of venous leg ulcers. |
| **Journal, Sources** | Journal of Dermatological Treatment, Volume: 7; |
| **Country of Origin** | France |
| **Corresponding author & contact details** | Professor JP Ortonne, Dermatology Department, Pasteur Hospital, 30 Voie Romaine, BP 69-06002 Nice, France |
| **METHODS** | |
| **Study design** | Randomized Controlled Trial |
| **Country** | France |
| **Setting** | Hospital, Multicentre |
| **Treatments:**<br>**-Intervention (I)**<br>**-Control (C)** | <br>HA gauze pad<br>Dextranomer paste |
| **Total study duration** | 21 days |
| **Single centre/multicentre trial:** | Multicentre, Hospital |
| **Method used to generate random allocation sequence:**<br>**Method used to implement the random allocation sequence:**<br>**Allocation sequence concealment:** | Randomised into two groups of equal size.<br><br>NA<br><br>NA |
| **Was the participant blinded?**<br>**Was the researcher/healthcare provider blinded?**<br>**Was the assessor blinded?** | NA<br><br>NA<br>NA |
| **Inter-rater reliability measured?** | NA |
| **PARTICIPANTS** | |
| **Total number** | 51 |
| **Type of participants** | Venous leg ulcers |
| **Age (range) & mean ± SD** | I: 66.2 ± 3.1 (mean±SEM)→SD 16.11<br>C: 69.7 ± 3.6 (mean±SEM)→ SD 17.64 |
| **Sex** | Male=17, Female=33 |
| **Record of drop-out (with reasons)** | I=1 (onset of pain and burning sensation) |
| **No. of sample size**<br>**Participant population (how sampled)** | 50<br>NA |
| **No. of arm in trial** | Two |
| **No. of each arm** | I=26, C=24 |
| **Power calculation** | NA |
| **Inclusion criteria** | Ulcer is not debrided, ulcer between 3-12 cm, >3months |

| INTERVENTIONS & CONTROL GROUP | |
|---|---|
| **Total number of intervention group:**<br>**Total number of control group:**<br>**Dosage of intervention & control**<br>**Duration of intervention & control**<br><br>**Who delivered the intervention & control** | 26<br>24<br>I: 4g of cream containing 0.05% sodium hyaluronate<br>C: 6.4g Dextranomer/sachet, once daily until 21days<br>Investigator/researcher |
| **OUTCOMES** | |
| **All relevant outcomes reported** | Yes |
| **Outcomes** | Primary: Evolution of the ulcer appearance & dimensions (Reduction of ulcer surface area)<br>Secondary: Sclerous edges, Re-epitheliased edges |
| **Primary Outcome** | Evolution of the ulcer appearance & dimensions (Wound area reduction) |
| **Outcome measures** | Mean ± SEM |
| **Results** | I: 20.8 ± 4.4 to 10.8 ± 4.0$cm^2$ (day 21) (48%)→ SD (±22.86) to (±21.56)<br>C: 23.1 ± 4.4 to 18.9 ± 3.2$cm^2$ (day 21) (18%)→ SD (±20.40) to (±15.68)<br>Stat. Siginificant: I: day 7 (P<0.001) (23%) C: day 14 (P<0.05) |
| **Method of the analysis** | Wilcoxon test |
| **Time to measure** | Day0, 7, 14 and 21 |
| **Secondary Outcomes** | Sclerous edges, Re-epitheliased edges |
| **Outcome measures** | Area Size |
| **Results** | Sclerous edges (day21)<br>I: 18.5 to 9.4 cm C: 25.9 to 13.1cm<br>Re-epitheliazed edges (day21)<br>I: 21 to 18.4cm C: 16.3 to 22.2cm |
| **Secondary Outcomes** | Area of granulation tissue (budding zone) |
| **Outcome measures** | Area size |
| **Results** | I: 5.8 to 7.1 $cm^2$ C: 11.1 to 14$cm^2$ |
| **Secondary Outcomes** | Oedema |
| **Outcome measures** | Severity of oedema |
| **Results** | I: baseline 15 patients to 8 patients (day7), 1 patient (day21)<br>C: 15 patients to 12 patients (day7), 6 patients (day21) |
| **Method of the analysis** | Kruskall-Wallis test |
| **Secondary Outcomes** | Oozing |
| **Outcome measures** | Severity of oozing |
| **Results** | I: day 14 (P<0.001) C: day 21 (P<0.001) |

| | |
|---|---|
| **Method of the analysis** | Kruskall-Wallis test, Wilcoxon test |
| **Secondary Outcomes** | Pain |
| **Outcome measures** | Number of patients showing symptom of pain, severity |
| **Results** | I: no. of patients= P<0.05 (from day 7), severity= P<0.01<br>I: Day 0=15/27 severity=1.00 to 5/26 severity=0.24<br>C: Day 0=15/24 severity=1.10 to 7/24 severity=0.33 |
| **Method of the analysis** | Kruskall-Wallis test |
| **Secondary Outcomes** | Efficacy judgement |
| **Outcome measures** | Number of patient/physician |
| **Results** | Patient I: 15/8/0/0 C: 14/8/1/0<br>Physician I: 15/9/0/0 C: 10/11/2/1 |
| **Method of the measurement** | (good/average/nil/worsened) |
| **Secondary Outcomes** | Tolerability |
| **Outcome measures** | Number of cases |
| **Results** | I: 5 side effects (local pain, local burning sensation, panniculitis & prickling sensation)<br>C: 2 side effects (surrounding eczema & local pain) |
| **ANALYSIS** | |
| **Which analysis performed? :**<br>**Method of analysis:**<br><br>**Intention-to-treat analysis?(ITT):** | Student's t-test for parametric data, Kruskall-Wallis, Wilcoxon and mann-Whitney tests for comparison of the score data.<br>Yes |
| **RESULTS** | |
| **Sample size:**<br>**No. of withdrawals and loss to follow-up:**<br>**Reasons for withdrawals:**<br>**Summary of results' analyses:** | 50<br>1<br>onset of pain and burning sensation<br>Greater & faster reduction in the ulcer dimensions in the hyaluronic acid group. Both treatments improve surrounding erythema, pain, oozing, and necrosis. Hyaluronic acid cause significant decrease in oedema. |
| **MISCELLANEOUS** | |
| **Funding source:**<br>**Key conclusions of the study authors:** | IBSA (institute Biochimique SA), Lugano, Switzerland.<br>Due to its pharmacological properties, HA caused an earlier and larger decrease in ulcer dimensions. The demonstrated efficacy of HA together with its excellent safety profile makes it an ideal first choice drug for the treatment of venous leg ulcers. |
| **AUTHOR'S CONCLUSION** | |
| **Other comment and interests:** | NA |

9. Romanelli et al., 2007.

| DATA EXTRACTION FORM | |
|---|---|
| **ARTICLE DETAILS** | |
| **ID** | Romanelli et al. (2007) |
| **Author(s), Year** | Marco Romanelli, Valentina Dini, Mariastefania Bertone, Sabrina Barbanera, Cinzia Brilli, 2007 |
| **Title** | OASIS® wound matrix versus Hyaloskin® in the treatment of difficult-to-heal wounds of mixed |
| **Journal, Sources** | International Wound Journal, Vol: 4, No:1; 3-7 Cochrane database. |
| **Country of Origin** | Italy |
| **Corresponding author & contact details** | Prof M. Romanelli, Department of Dermatology, University of Pisa, Via Roma, 67, 56126 Pisa, Italy Email: m.romanelli@med.unipi.it |

| **METHODS** | |
|---|---|
| **Study design** | RCT |
| **Country** | Italy |
| **Setting** | Leg ulcer clinic |
| **Treatments:**<br>**-Intervention (I)**<br>**-Control (C)** | <br>Hyaloskin® dressing-Hyaluronic acid based dressing consisting of single component ECM<br>OASIS® dressing-ECM components<br>Covered with secondary non adherent dressing |
| **Total study duration** | 16 weeks |
| **Single centre/multicentre trial:** | Single centre |
| **Method used to generate random allocation sequence:**<br>**Method used to implement the random allocation sequence:**<br>**Allocation sequence concealment:** | The sequence of randomisation was generated through every other patient selection by the clinician |
| **Was the participant blinded?**<br>**Was the researcher/healthcare provider blinded?**<br>**Was the assessor blinded?** | NA<br>NA<br>NA |
| **Inter-rater reliability measured?** | NA |

| **PARTICIPANTS** | |
|---|---|
| **Total number** | 54 |
| **Type of participants** | Arterial/Venus ulcer |
| **Age (range) & mean±SD** | (> 18 years) Mean: I: 62±8, C; 64±13 |
| **Sex** | Male (26) & Female (28) |
| **Record of drop-out (with reasons)** | 4 |
| **No. of sample size**<br>**Participant population (how sampled)** | 54<br>NA |
| **No. of arm in trial** | 2 |
| **No. of each arm** | 27 |
| **Power calculation** | NA |

| | |
|---|---|
| **Inclusion criteria** | A/V leg ulcer, ulcer duration >6 weeks, size 2.5-10cm$^2$ |
| **INTERVENTIONS & CONTROL GROUP** | |
| **Total number of intervention group:**<br>**Total number of control group:**<br>**Dosage of intervention**<br>**Duration of intervention**<br>**Who delivered the intervention?** | 26<br>24<br>Once or more/week<br>16 weeks<br>Clinical inspection |
| **OUTCOMES** | |
| **All relevant outcomes reported** | Yes |
| **Outcomes** | Primary: Complete wound closure; time to dressing change;<br>pain; comfort; adverse events |
| **Primary Outcome** | Complete wound closure→(Number of wounds healed) |
| **Outcome measures** | Number of patients |
| **Results** | I: 11 patients (46.2%) C: 21 patients(82.6%) |
| **Secondary Outcomes** | Comfort |
| **Outcome measures** | Scale Visual Analogue Scale (VAS) |
| **Results** | I: 6.7, C: 2.5 |
| **Types of measurement** | (0=excellent, 10=critical) |
| **Secondary Outcomes** | Pain |
| **Outcome measures** | Scale Visual Analogue Scale (VAS) |
| **Results** | I: 6.2, C: 3.7 ($p< 0.05$) |
| **Types of measurement** | (0=none, 10=severe) |
| **Secondary Outcomes** | Adverse effect |
| **Outcome measures** | NA |
| **Results** | NA |
| **ANALYSIS** | |
| **Which analysis performed? :**<br>**Method of analysis:**<br>**Intention-to-treat analysis? (ITT) :** | NA<br>Variance for multiple comparisons<br>NA |
| **RESULTS** | |
| **Sample size:**<br>**No. of withdrawals and loss to follow-up:**<br>**Reasons for withdrawals:**<br>**Summary of results' analyses:** | 50<br>4<br>Loss to follow-up (n=3) and family problem (n=1)<br>This study found that OASIS was superior to Hyaloskin for the treatment of patients with mixed A/V ulcers |
| **MISCELLANEOUS** | |
| **Funding source:**<br>**Key conclusions of the study authors:** | Supported by Healthpoint Biopharmaceutical<br>NA |
| **AUTHOR'S CONCLUSION** | |
| **Other comment and interests:** | OASIS is a useful and well-tolerated treatment for mixed A/V ulcers that has the potential to improve quality of life and reduce costs associated with standard of care. |

10. Uccioli et al., 2011

| DATA EXTRACTION FORM<br>(The data extraction form used for each individual study included in this review) | |
|---|---|
| **ARTICLE DETAILS** | |
| **ID** | Uccioli et al. (2011) |
| **Author(s), Year** | Luigi Uccioli, Laura Giurato, Valeria Ruotolo, Adolfo Ciavarella, Michele S. Grimaldi, Alberto Piaggesi, Ilaria Teobaldi, Lucia Ricci, Luciano Scionti, Cristiana Vermigli, Roberto Seguro, Lorena mancini and Giovanni |
| **Title** | Two-steps autologous grafting using HYAFF scaffolds in treating difficult diabetic foot ulcers: results of a multicenter, randomised controlled clinical trial with long- |
| **Journal, Sources** | The International Journal of Lower Extremity Wounds, Vol:10, Issue: 80; 80-85 |
| **Country of Origin** | Italy |
| **Corresponding author & contact details** | Luigi Uccioli, Policlinico of Tor Vergata, Department of Internal Medicine, Viale Oxford 81, 00133 Rome Italy<br>Email: luigi.uccioli@ptvonline.it |

| **METHODS** | |
|---|---|
| **Study design** | Open, Randomised Controlled Clinical Trial |
| **Country** | Italy |
| **Setting** | Diabetic Foot Centers (7) |
| **Treatments:**<br>**-Intervention (I)**<br>**-Control (C)** | <br>HYAFF-Hyalograft -3D<br>Non-adherent paraffin gauze Covered with non-adherent paraffin gauze + bandage of sterile cotton pads and gauze |
| **Total study duration** | 18 months |
| **Single centre/multicentre trial:** | Multicenter |
| **Method used to generate random allocation sequence:**<br>**Method used to implement the random allocation sequence:**<br>**Allocation sequence concealment:** | Computer-generated randomization list<br>In a block of 4 & stratified by center<br>Sealed envelope in numerical order |
| **Was the participant blinded?**<br>**Was the researcher/healthcare provider blinded?**<br>**Was the assessor blinded?** | Yes<br>NA<br>NA |
| **Inter-rater reliability measured?** | NA |

| **PARTICIPANTS** | |
|---|---|
| **Total number** | 180 |
| **Type of participants** | Diabetic foot ulcer |
| **Age Mean ± SD** | I: 61 ± 10, C: 62 ± 11 |

| | |
|---|---|
| **Sex** | NA |
| **Record of drop-out (with reasons)** | 20 n=1 ulcer area <1cm$^2$, n=13 did not return to investigational site after baseline visit |
| **No. of sample size**<br>**Participant population (how sampled)** | 160<br>Selected according to the inclusion and exclusion criteria |
| **No. of arm in trial** | Two |
| **No. of each arm** | I: 80, C:80 |
| **Power calculation** | NA |
| **Inclusion criteria** | Dorsal/plantar diabetic foot ulcer, type 1/2 diabetes mellitus, ulcer>1 month, >2cm$^2$ |
| **INTERVENTIONS & CONTROL GROUP** | |
| **Total number of intervention group:**<br>**Total number of control group:**<br>**Dosage of intervention & control**<br>**Duration of intervention & control**<br>**Who delivered the intervention & control** | 80<br>80<br>I: Hyalograft-3D after 2 weeks Laserskin autograft<br>Daily until 12 weeks<br>NA |
| **OUTCOMES** | |
| **All relevant outcomes reported** | Yes |
| **Outcomes** | Primary: Complete ulcer healing at 12 weeks<br>Secondary: Ulcer healing time, time to achieve 50% ulcer area reduction, percentage of ulcer reduction, tolerability/adverse events |
| **Primary Outcome** | Complete ulcer healing at 12 weeks (number of wounds healed & healing time) |
| **Outcome measures** | Number/Percentage of patients & Mean days |
| **Results** | I: 19 patients (24%), C: 17 patients (21%) P=0.85<br>I: 50 days, C: 58 days P=0.25<br>AT 20 week: I: 50% (40 patients), C: 43% ( 34 patients) |
| **Secondary Outcomes** | Time to achieved 50% ulcer area reduction |
| **Outcome measures** | Mean days |
| **Results** | I: 50 days, C: 58 days, P=0.18 |
| **Secondary Outcomes** | Percentage of ulcer reduction |
| **Outcome measures** | Area of ulcer |
| **Results** | Baseline: I: 8.8 ± 9.4 cm$^2$, C: 6.7 ± 7.7 cm$^2$<br>Endpoint: I; 29% (6.25), C: 14% (5.76) |
| **Secondary Outcomes** | Adverse Event |
| **Outcome measures** | Percentage of patients |
| **Results** | I: 18 (21%) patients C: 14 (16%) patients<br>Majority mild to moderate (41/46)<br>Infection I: 13 (15.4%), C: 10 (11.4%) |

| ANALYSIS | |
|---|---|
| **Which analysis performed? :**<br>**Method of analysis:**<br><br><br><br><br>**Intention-to-treat analysis? (ITT) :** | Frequency distribution for discrete data<br>Mean & SD to describe continuous data<br>Comparisons between group using the chi square-discrete data<br>Or Mann-whitney & Student's T-test –continuous data<br>Analysis of covariance model SAS Software.<br>Yes. |
| **RESULTS** | |
| **Sample size:**<br>**No. of withdrawals and loss to follow-up:**<br>**Reasons for withdrawals:**<br>**Summary of results' analyses:** | 160<br>20<br>NA<br>NA |
| **MISCELLANEOUS** | |
| **Funding source:**<br>**Key conclusions of the study authors:** | NA<br>The results demonstrate the safety and effectiveness of autologous skin substitutes in the hard-to-heal diabetic dorsal foot ulcer population |
| **AUTHOR'S CONCLUSION** | |
| **Other comment and interests:** | There is a need for larger studies to clearly demonstrate treatment benefits and how suitable patients may be Identified |

## SUPPLEMENTARY

### List of Publications and Papers Presented

1. A Shaharudin, Z Aziz, NJ Chong. Effectiveness and tolerability of hyaluronic acid for chronic wounds healing: A systematic Review. Malaysian Journal of Pharmacy (2014), 1(11), pp 112. (*Non-ISI/Non-SCOPUS Cited Publication*). Proceeding (FAPA conference October 2014)

2. A Shaharudin and Z Aziz (2015). Effectiveness of Hyaluronic Acid and its derivatives for chronic wounds: A Systematic Review. *Journal of Wound Care.* (*ISI/SCOPUS Cited Publication*). Submitted (4 August 2015).