Management of Paediatric Burns:

Current Strategies and Future Perspectives

DOCTORAL (PHD) DISSERTATION

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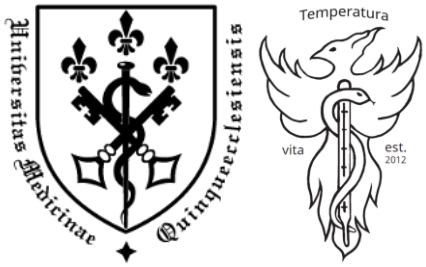

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1. List of abbreviations

II: Second-degree or partial-thickness (PT) burns**,**

II/A: Superficial partial-thickness thermal injuries**,**

II/B: Deep second-degree burns**,**

III: Full-thickness or third-degree burn,

ABA: American Burn Association,

AI: Artificial Intelligence,

AM: Amnion Membrane**,**

bFGF: basic Fibroblast Growth Factor**,**

CIs: Confidence Intervals**,**

CRT: Capillary Refill Time,

CPR: CardioPulmonary Resuscitation,

day 10 RE: the fraction of ReEpithelisation on the tenth day**,**

DIP: Distal InterPhalangeal joint,

IQR: InterQuartile Range**,**

IRT: InfraRed Thermography,

HABS: Hand Burn Severity Score,

HIS: HyperSpectral Imaging,

LDI: Laser Doppler Imaging,

LOS: Length Of hospital Stay**,**

MD: Mid-Dermal or Mixed-Depth burn injury**,**

ML: Machine Learning,

MODS: Multi-Organ Dysfunction Syndrome,

NPWT: Negative Pressure Wound Therapy,

NA: Not Applicable,

NIR: Near-InfraRed,

NR: Not Reported,

NSAIDs: Non-Steroid Anti-Inflammatory Drugs,

PMB: PolyMyxin B,

PHMB: PolyHexaMethylen Biguanide or Polyhexanide,

PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analysis protocols,

PT: Partial-Thickness (burn injury),

RCT: Randomised Controlled Trial,

rhEGF: recombinant human Epidermal Growth Factor,

rhGM-CSF: recombinant human Granulocyte-Macrophage Colony-Stimulating Factor,

SD: Standard Deviation,

SEM: Standard Error of Mean,

SIRS: Systemic Inflammatory Response Syndrome,

SSD: Silver SulphaDiazine,

StO2: Saturation of tissue Oxygen

SUM: The summarised average of the same interventions from different studies,

T%/T: TBSA%/TTRE or how much TBSA% regenerates each day,

TBSA: Total Body Surface Area**,**

TBSA%: Total Burned Surface Area percentage of the TBSA**,**

tHb: total Hemoglobin,

TT: Traditional Treatment,

TEWL: TransEpidermal Water Loss,

TTRE: Time To ReEpithelisation**,**

TTRE red%: The healing time reduction of the intervention, compared to its control,

VIS: Visible Spectrum Light**,**

VR: Virtual Reality,

wIRA: water-filtered InfraRed-A

2. Introduction

It is well-known that due to improperly prevented, treated, or rehabilitated burns, a high degree of scarring, contractures, and other deterioration of function can occur, which children have to face throughout their life. In addition, after orthopaedic, psychological and aesthetic complications resulting from combustion, they are often excluded from certain jobs. Thus, they become socially disadvantaged, leading to a severe decline in their quality of life[1]. These are especially true for burns during infancy because of the growth deformations and secondary contractures, which are critical due to their constant high incidence worldwide[2].

A core intention of this thesis is to evaluate the existing interventions employed in paediatric partial-thickness (PT) burn care via a meta-analysis. We also present our findings in detail from clinical studies about observations of different treatments post-transplantation and during follow-up. In addition, two special gels were investigated, one in the facial region and the other on different limbs. Furthermore, the management and complications of electrical finger burns were studied.

This thesis' secondary goal is to provide a comprehensive picture of the range of contemporary traditional and modern diagnostic and therapeutic possibilities. Meanwhile, it aims at offering the rudimentary information necessary for their optimal application.

2.1. Definition and aetiologies of burn injuries

Combustion is coagulative necrosis of the skin, or deeper tissues, which can be caused by heat – due to scalding, electricity, friction, contact and flame burn – as well as

ionising radiation and various chemicals. Thermally disrupted cutaneous systems will cease to have a barrier, thermoregulation and sensory functions; therefore, they will not be able to provide the body with internal homeostasis. In the first hours, combustion has a dynamic pathology. In case of inadequate care, burns are accompanied by the permanent death of the reversibly damaged stasis zone between the central coagulated and peripheral hyperaemic tissues **(Figure 1)**. The process of burn deepening is called a conversion[3,4].

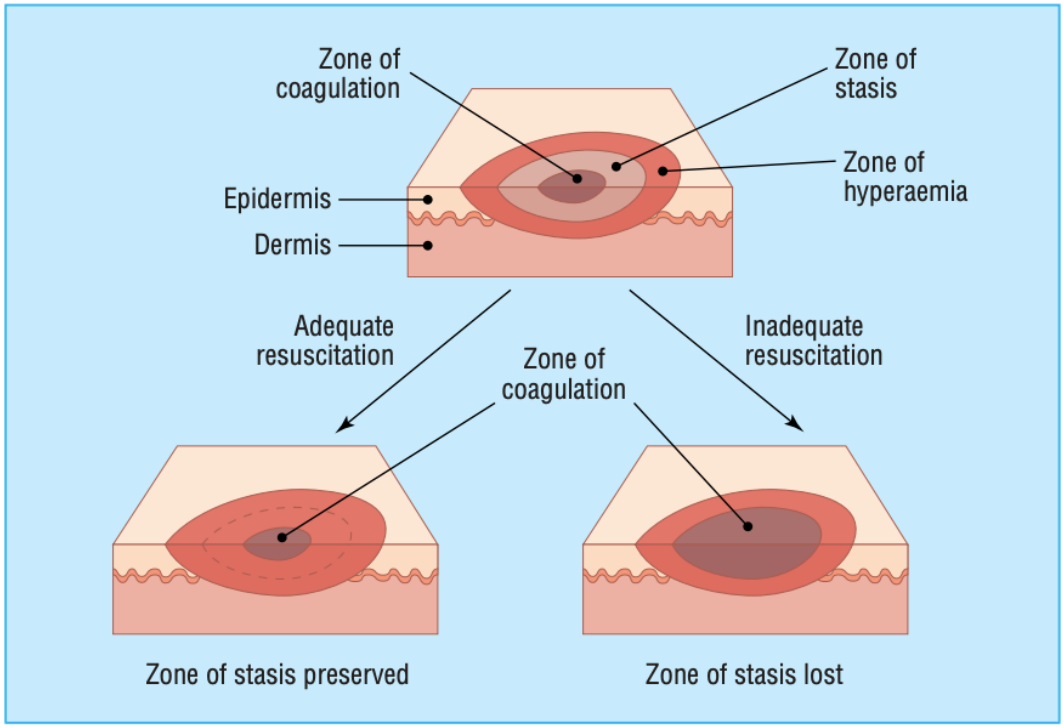

Figure 1. *Jackson's burn wound model*[4].

2.2. Epidemiology of paediatric combustions

Nearly one hundred thousand children are fatally injured from preventable, predominantly (~93%) flame-related burn traumas each year. However, the probability of a non-fatal injury is presumed to be at least ten times higher (i.e., 1-7,000,000/year).

Furthermore, due to the absence of a successfully coordinated management strategy, almost half of them (49%) suffer from various permanent complications after the combustion[2,5].

In developing countries, burns are seven times more frequent: 90% of deaths occur in these regions. Meantime, within the developed world, families of low socioeconomic status and education level are at the highest risk – and it mainly strikes minorities. These are of crucial importance because 85% of burns occur at home[2,6,7]. On average, around half a million hospitalisations are required annually in the United States due to thermal injuries[8]. In Hungary, approximately 40,000-50,000 burn incidents occur per annum. A tenth of these combustions (4-5,000) necessitates hospitalisation, of which only 1/5 are children, about 800-1,000 patients[9].

All forms of burns are more common in boys due to their risk-taking behaviour; the sex ratio is 3:2. Yet in girls, the mortality rate is 24% higher after severe combustions involving cooking-related activities. During thermal injuries, the most regularly damaged body parts are the upper limbs, facial area, and lower limbs in 51, 39, and 26% of all cases, respectively. Sixty-five per cent of burns affect children under the age of 5, while 35% of all paediatric combustions happen to 5-16-year-olds[10].

Thermal injury mechanisms with the highest prevalence are scalding (41.0% of all types of burns), contact (40.6%) and electrical burns (1.2%), all at the age of one - when injuries are ten times more common than in school-aged groups. The peak prevalence of chemical (9.2% of all cases) and friction burns (1.1%) is at two years of age. Flame burns (3.7%) occur dominantly at the age of 12 and radiation (4.0%) at the age 15[6].

2.3. Unique aspects of childhood burns

Skin, immune and neural development are a series of continuous changes[11,12]. Although these systems may seem anatomically mature at birth, they evolve structurally and functionally until the end of life. Children younger than five are at the maximum risk for a thermal injury because their balance and reflexes are still improving. Furthermore, they have a tremendous inherent curiosity about their surroundings and have limited experience with hot objects and surfaces. These distinctions make it easy to see why their injuries could be more frequent and severe than those in the adult population.

In newborns, the acid mantle begins to develop under the influence of bacterial colonisation; thus, their resistance to pathogens is lower[13,14]. Moreover, children have a greater total body surface area (TBSA) to body volume ratio; additionally, the skin's water content is higher than in adults. Due to their increased blood supply and underdeveloped barrier functions, their transepidermal water loss (TEWL) is also higher. Consequently, these differences make them prone to dehydration. In addition, juveniles have fewer functional sweat glands, so temperature changes are more challenging to tolerate[15].

In children, the epidermis is thinner, less keratinised, and consists of several rapidly-dividing basal cell lines, so ionising radiations more easily damage it than in adults. However, in the cases of non-mutagenic noxae, it has a better regenerative predisposition [16].

Their papillary layer is more pleated and broader, thus better equipped with blood vessels and nutrients. Because of the abovementioned features, the most critical difference is that the skin is smoother and more hydrated in children than adults. At the same time, it is

easier for various compounds to dissolve in their epidermis and for pathogens to pass through it.

With the onset of puberty, under the influence of sex steroids, a thicker subcutis layer forms in girls, filled with fatty tissue in places covered with thin skin. In addition, sebaceous glands' overactivity begins, predisposing them to local infections, such as acne[17,18].

2.4. Pathophysiology and complications of combustions

Direct heat causes microvascular damage, and the chemical mediators involved in the inflammatory response reaction trigger vasodilatation. Consequently, combustions are accompanied by the formation of severe oedema. Additionally, an increase in venous permeability produced by histamine release in the initial phase exacerbates interstitial fluid formation. Above 44 degrees Celsius, proteins lose their three-dimensional structure and cease functioning. The body cannot compensate for the significant protein and volume loss with increased albumin production in extensive area injuries. Thus, this condition predisposes the patient to hypovolaemic shock[19].

Locally, free radicals that exit from leukocytes are harmful to cell membranes. They also increase the activity of enzymes that hydrolyse precursor arachidonic acid. Hence, free radicals increase prostaglandin levels and inhibit norepinephrine release with the adrenergic neuroendocrine response.

On the other hand, the rest of the body experiences increased catecholamine secretion[20]. As a result, it has an amplified heart rate and vasoconstriction caused by Cannon’s emergency response. These are accompanied by intensified metabolic activity and

demand, which anaerobic metabolism compensates. Therefore, metabolic lactic acidosis often develops. This hypermetabolic state may persist for years after a significant burn and can lead to osteo- and sarcopenia[21,22]. Trauma-induced anxiety results in hyperventilation and the loss of carbon dioxide, in addition to the further activation of the sympathetic nervous system, complicating metabolic acidosis with a respiratory alkalosis component.

The constant loss of fluid attributable to skin deficiency and oedema creates a situation associated with cellular hypoperfusion, rapidly decreasing plasma volume plus cardiac output, and increasing haematocrit values. Due to intensified viscosity, the risk of thrombosis and other perfusion disorders is significantly higher[23]. Coagulopathy, along with lactic acidosis from hypoperfusion and hypothermia due to increased evaporation, are parts of the "trauma triad of death", which significantly increases mortality rates in patients with severe burns. Thermal effects directly trigger the lysis of the cells, which can cause hyperkalaemia and the release of myoglobin from the muscles. Electrical and circumferential injuries often result in compartment syndrome, significantly raising the possibility of rhabdomyolysis and, thereby, acute renal insufficiency[24].

Combustions are also a gateway of intrusion for pathogens. General immunosuppression occurs, which is connected to a reduction in the number of immunoglobulins (this process is called consumption) and immune-competent cells[11]. Therefore, severely burned children on an extensive surface have a high risk for infections and septic shock. Pneumonia and respiratory failure occur particularly common in those with inhalation injuries; however, cellulitis and urinary tract infections are also frequent. Burn sites are specifically susceptible to tetanus, although children are usually vaccinated against

it[25]. The generalised and exaggerated inflammatory reaction to noxious stressors is SIRS (systemic inflammatory response syndrome), commonly referred to as “burn disease” in the case of thermal injuries. This condition is characterised by parenchymatic organ malfunction that potentiates each other, leading to multi-organ dysfunction syndrome (MODS)[3].

Burn anaemia usually occurs on the 3rd-4th day after combustion and is primarily of microangiopathic origin, aggravated by blood loss during surgery[26]. Anaemic hypoxia of the digestive tract and a decrease in mesenteric perfusion result in bacterial translocation. Consequently, microorganisms settle in the intestinal wall and scatter their endotoxins into the bloodstream. Diarrhoea based on dysbacteriosis and hypoalbuminaemia further worsen the toxic condition and hypovolaemia of the patient[27].

2.5. Classification of thermal injuries

Grouping combustions are usually done via physical examination. However, there are more precise and sophisticated methods to choose from, although their price is a major obstacle to their widespread and successful utilisation.

2.5.1. Categorisation based on burn depth

Combustion characteristics are mainly influenced by their depth, which can be separated into four main groups **(Figure 2)**. Second-degree (II) burns are divided into subcategories: the diagnostic line suggesting conservative or surgical approaches. Most of the time, these individual types are located irregularly mixed in an alternating mosaic- or map-like pattern, making diagnosis and treatment difficult even for experienced burn specialists. This blend of injuries is often referred to as intermediate-depth burns, where the goal is to save the most viable tissues and treat them conservatively[28].

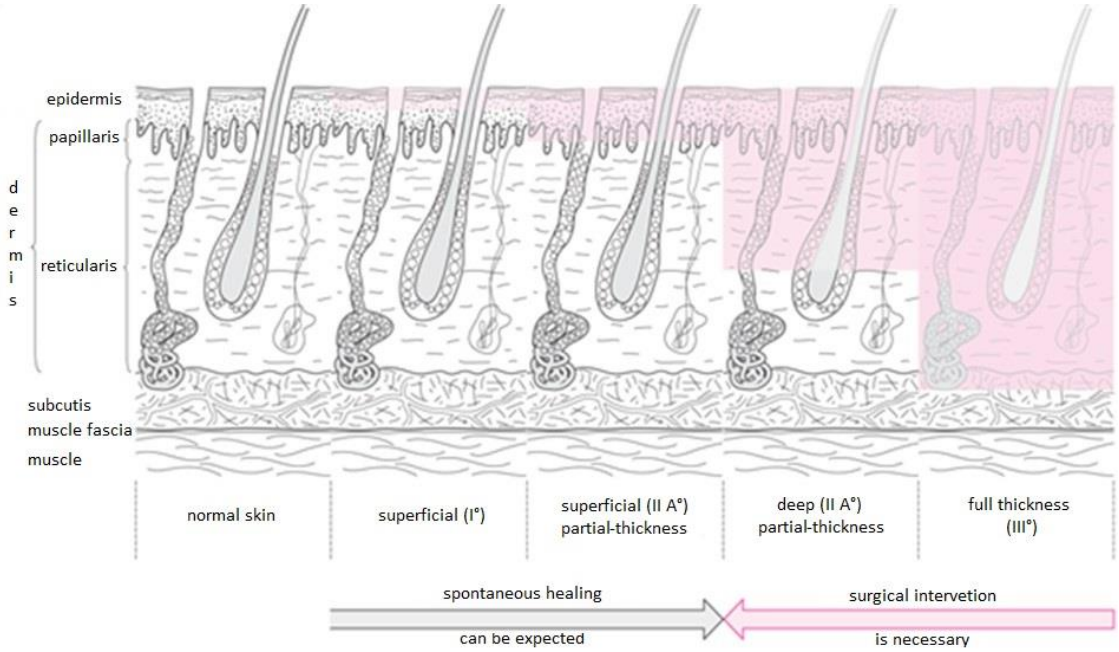

Figure 2. *Categories of burn injuries by the affected skin depth*[29].

2.5.1.1. Superficial or first-degree (I) burns

A red, blister-free epidermis-affecting lesion, most often caused by radiation from the sun. Dry to the touch and painful for 2-3 days, accompanied by peeling of the skin for the next few days. Itching occurs in almost all children during recovery **(Figure 3)**.

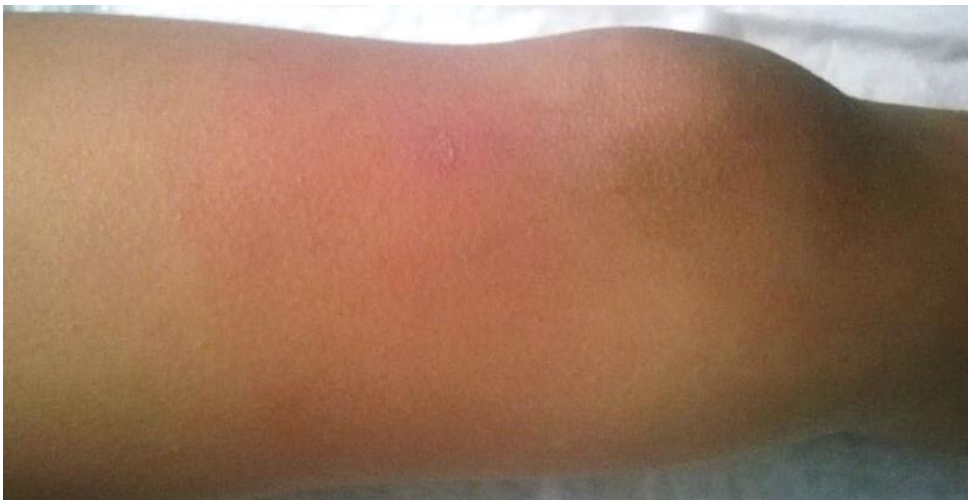

Figure 3. *Combustio erythematosa or 1*st*-degree burn affecting a child's thigh. Image captured by Gergő Józsa, MD.*

Complete regeneration takes 5-10 days, does not require unique medical therapy and heals without complications. However, recurrent suntans increase the risk of developing skin cancer years later[30].

2.5.1.2. Superficial partial-thickness (PT) or second-degree (II/A) burns

The papillary layer of the dermis is injured in these burns. It results in the formation of vesicles and bullae with translucent content **(Figure 4/A)**. The base of the blisters is a pink surface sensitive to pain **(Figure 4/B)**, yet the remaining epithelial cells on the wound base allow the skin to reepithelialise. It is much more painful than I-degree burns due to exposed nerve endings, and complete healing takes 7-14 days without scarring. Usual complications can be pigmentation disorders and local infections. Under pressure, the injured, red areas become white, but they quickly refill when the compression is released (capillary refill time (CRT) is under 2 seconds). Additionally, they are moist to the touch, and the hairs cannot be pulled out easily[31].

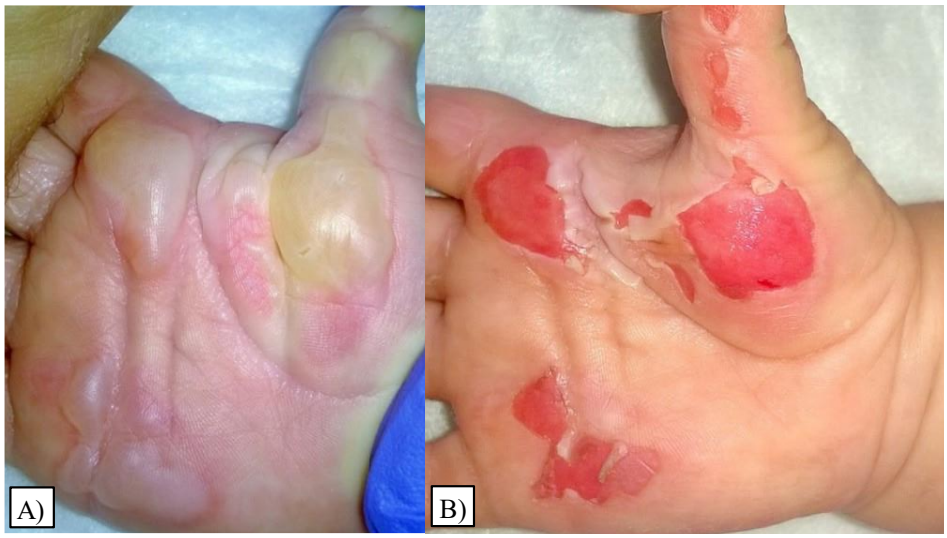

Figure 4. *2nd-degree burns are formerly known as combustio bullosa due to the vesicle formation on the injured surface (A). After necrectomy, the wound beds are seen (B)[32].*

2.5.1.3. Deep PT or second-degree burns (II/B)

White or yellow lesions infiltrating the deep reticular dermis characterise this condition, though blisters may also be present **(Figure 5)**.

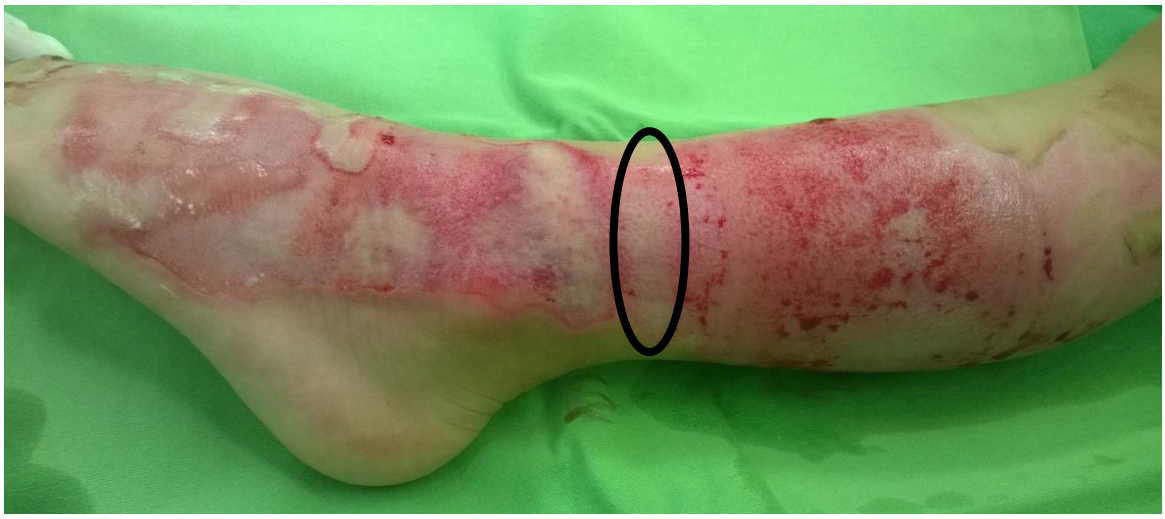

Figure 5. *Deep 2nd-degree burns result in yellowish lesions on the child's lower limb. Gergő Józsa, MD, provided the picture.*

Instead of pain, the injured patients complain of a feeling of pressure and discomfort since their nociceptors were destroyed, but their deeper mechanoreceptors are still intact. Healing can take up to 3-8 weeks without surgery, after which hypertrophic scarring or contracture is often left behind. Under pressure, the capillaries become less white and refill more slowly (CRT>2 seconds). When touched, it is pretty dry, and hairs are easy to pull out[21].

2.5.1.4. Full-thickness or third-degree burns (III)

Serious injury of pearly, pale white or brown colour, affecting the dermis' whole thickness **(Figure 6)**, previously referred to as combustio gangrenosa.

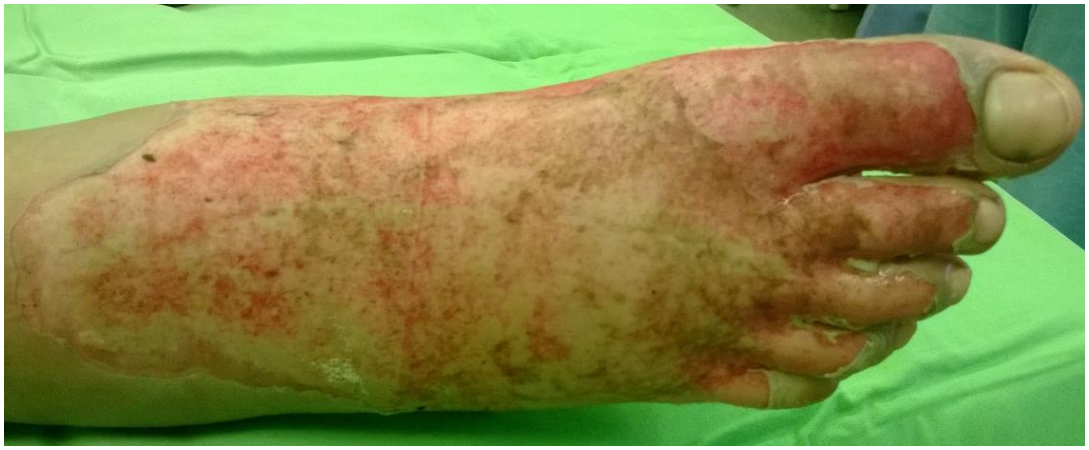

Figure 6. *This 3rd-degree burn injures the subcutis, as seen by the wounds' colour. Image was taken by Gergő Józsa, M.D.*

It has a painless, dry, stiff, tanned skin-like tact and does not whiten under pressure. This injury heals for months and often in partial terms, which definitely requires surgery. Latest groupings combine this category with fourth-degree burns (carbonisation). In that case, subcutaneous tissues, for example, fat, muscle, tendon or even bone, are damaged. Roasted greyish-black or completely charred areas with a burn slough (eschar) containing black necrotised tissues can be seen[33].

2.5.2. Classification based on the burn area

Until the age of fifteen, it is recommended to use the Lund - Browder chart, which takes the open palm size to 1.50 TBSA%[34] **(Figure 7)**. In adolescents over sixteen, Wallace's rule of nines estimates the extent of combustion, in which one side of the hand represents 1 TBSA%[35].

These methods allow a quick approximation of the size of the injury with the child's palm; however, they are erroneous. Non-specialised healthcare professionals tend to over- or underestimate burn areas using traditional charts. A new, more precise technique is

spreading, using the distal phalanx of the thumb as 1 T (thumbprint), equivalent to 1/30 TBSA%[36].

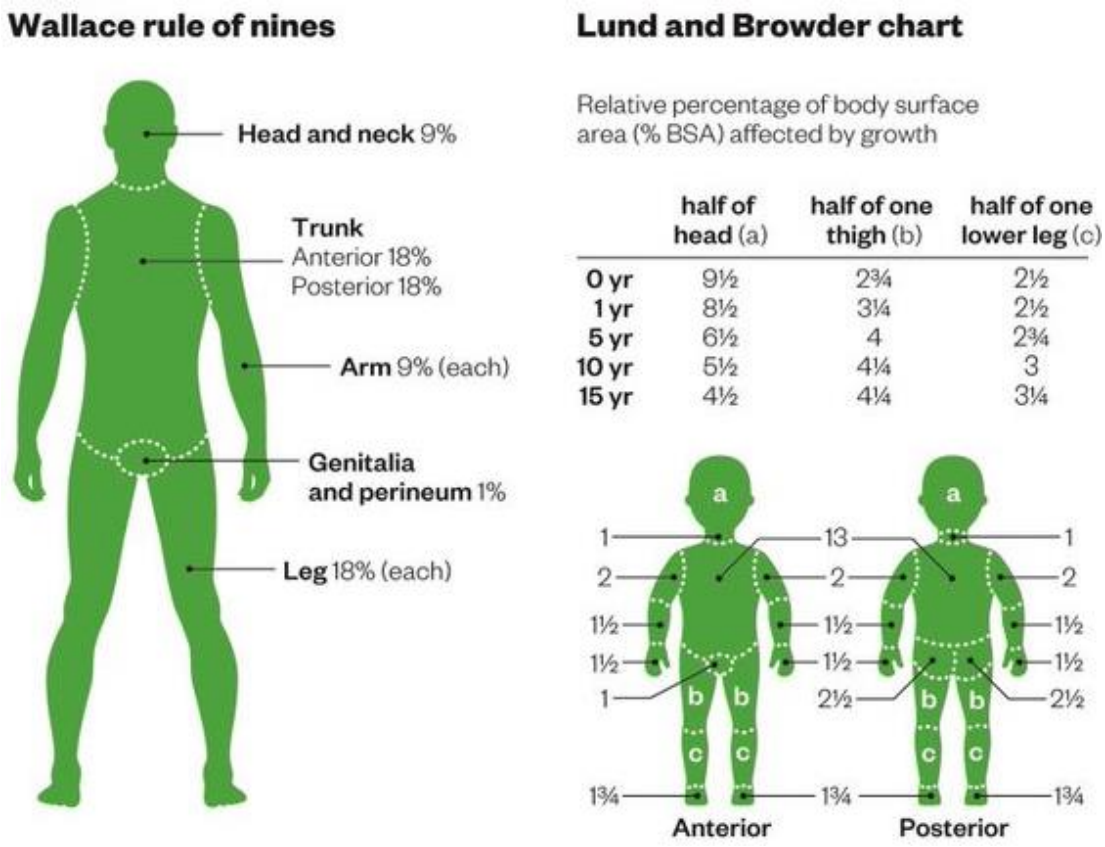

Figure 7. *Burn area estimation protocols*[37].

2.5.3. Categorisation based on burn severity

The severity and prognosis of a thermal injury are determined by the depth, area, location and aetiology of the damage, along with the patient's general health and age, as well as the duration and temperature of the exposure. Classifications created by the American (ABA) or European Burn Associations (EBA) are based on all the above criteria; though over-admission to burn centres have been reported while using them, thus they still need some alterations[38].

There are also particular protocols for specific body parts, which can be used to determine the prognosis more specifically and sensitively, thus predicting when an operation is obligatory. Such a guideline is the Hand Burn Severity (HABS) score system[39].

2.5.4. Semi-/Automatic clustering

Physical examination techniques are routinely excellent, but in more complex cases, they are insufficient due to their subjectivity. Due to the combustion's dynamic nature and mosaic-like depth differences, experienced specialists can only accurately classify mixed combustions in 50-70% of the cases, so they need additional information for correct sorting. Automatic surface, depth, and severity calculators are objective, quicker and more precise than manual methods; still, they need human supervision[40].

The present-day gold standard is the noninvasive LDI (Laser Doppler Imaging) for precise classification. It gives a reproducible result on the perfusion of the burnt body part by analysing tissue micro-vibrations. These oscillations are generated by moving red blood cells, and the different velocities are displayed colour-coded. With LDI, one can track the depth of the combustion with precision above 80%, thereby the need for the operation. It shows the regions with the best circulation in red, which heals within 14 days. Pink, yellow and green colours mean gradually decreasing blood flow, with an increase in the time required for restitution to 14-21 days. For blue and black areas, the number of days required for regeneration is over 21[41].

Another option is infrared thermography (IRT), which detects secondary temperature changes after a perfusion decrease and has a diagnostic accuracy above 85%. Its essence is that if the body's temperature changes less than 3°C, spontaneous reepithelialisation is

expected. If the difference is between 3 and 5°C, it shall be grafted; if the alteration exceeds 5°C, amputation is required[42,43].

More information is provided by HSI (hyperspectral imaging). This method compares the spectra of the reflection of light from oxygenated haemoglobin (saturation of tissue oxygen or StO2) at different concentrations with the characteristic spectrum of burns of different depths. The tHb (total haemoglobin) value can also be used to deduce perfusion (described with the near-infrared (NIR) perfusion index), thereby inferring depth; it increases by an average of 67% in II/A burns and by 16% in II/B burns due to the inflammatory response. In contrast, in III-degree combustions, tHb is reduced by 36% due to the injured blood vessels[44,45].

Interestingly, by analysing the proteome and collagen in the fluid of the blisters, we also get information on the expected burn depth and the healing duration. However, this technique is mainly experimental[46].

2.6. Management of paediatric burns

The care of childhood combustions is a complex task in which prevention should be just as important as the procedures after the injury. Therapy begins with first aid - including pain relief and rehydration - followed by stabilisation by paramedics and transport to the hospital, where definitive treatment commences. The purpose of the interventions is to inhibit conversion and preserve the body’s homeostasis, which can be achieved by removing necrotic tissues and restoring skin continuity while striving for the finest functional and aesthetic results. Comprehensive burn management is performed by an interdisciplinary

team offering intervention in the acute setting and preparing the child and relatives for long-term care and rehabilitation[47].

2.6.1. Prevention strategies

According to estimations, half of the burn injuries would be preventable, and their severity could be significantly reduced. The government and individuals share the responsibility of implementing these policies equally. Measures in this regard include construction according to the appropriate structural regulations and installing automatic fire extinguishing systems with smoke alarms in residential buildings. Their inspection should be done every six months, along with examining electrical networks every ten years.

Smoking and related devices cause the most severe home fires, so smoking cessation and stricter regulations can also reduce the incidence of burn injuries. Fire safety training for children must also start as soon as possible because it is vital to recognise the escape routes and to participate actively in prevention[48].

Routine sunscreen application, even on cloudy days, significantly reduces superficial injuries. Scalding is the most common type of deeper combustion, which can be avoided by checking bathing water with a thermometer, controlling the maximum temperature of water heaters below 48.8 °C and installing stoves with splash guards. When cooking, it is forbidden to leave the young child alone or pick them up since they can quickly pour hot liquids onto themselves. Around toddlers, the use of a tablecloth should also be avoided.

Devices containing hot metals (e.g., clothing irons and hair straighteners) must be unplugged from the power supply and placed at an inaccessible height, together with dangerous chemicals. It would also be helpful to install the electrical sources at such heights,

but blocking plastic pins or safety lids should be installed on the electrical outlets if this cannot be solved[49].

2.6.2. Prehospital care

The long-term prognosis is primarily decided by the first aid and the treatment provided by the paramedics arriving on the scene[47]. Priority should be given to extinguishing the combustion itself, interrupting the power source with the main power switch, and removing the child from the dangerous environment and the clothes caught on fire as soon as possible. If the child is unconscious, an ambulance must be called immediately. While closely monitoring breathing and circulation, cardiopulmonary resuscitation (CPR) must begin if these systems show signs of failure[50].

No accessories must remain in and around the burnt area because oedema forms very quickly - which can be decelerated by constantly elevating the affected area above the heart. If the clothing is stuck in the wound, it must be cut around it and not torn off. Then, it is most optimal to put the injury under running water at 15°C for at least 20 minutes. However, a cold water compress or a cooling gel with high thermal capacity is also beneficial[51]. At lower temperatures, icy liquids can cause frostbite (congelation), and in the case of more extensive combustions, they exacerbate hypothermia. Warmer water's effect on deactivating proteolytic enzymes and heat extraction is insufficient[52].

It is worth leaving the blisters intact until hospitalisation; after cooling, it is possible to cover the wound with a sterile, nonadhesive gause cloth. The use of alcoholic external therapies, ointments, oils and talcum powders is contraindicated because they mask the actual depth of the injury. Any other dressings from folk medicine (such as eggs or sour

cream) will only worsen the situation. Therefore, they are strictly forbidden – except for medical-grade honey, which keeps the wound moist, forms a barrier and has robust anti-inflammatory properties[53].

Cooling should simultaneously begin with analgesia - unfortunately omitted in the vast majority of cases (80-87%) - and shock management via hydration (tea or non-carbonated soft drink), which paramedics continue intravenously in burns above 10 TBSA%. Fluid resuscitation should begin by estimating the liquid need using the Parkland formula. The total volume of fluid to be infused is 3 ml of crystalloid (Ringer-Lactate) × patient's weight (kg) × TBSA burnt (%) every 24 hours. Half of the calculated amount should be administered during the first eight hours following the injury[54].

Over-the-counter NSAIDs (non-steroid anti-inflammatory drugs) are recommended for pain control, administered in the amount described in the package leaflet, depending on the patient's age and weight and the injury's severity. For example, ibuprofen or paracetamol can be given orally. With the arrival of the ambulance, if the pain persists, more potent analgesics are also injected, such as intravenous or intramuscular metamizole or nalbuphine (an opioid). In the most severe cases, parenteral morphine or intranasal fentanyl may be necessary[55].

2.6.3. Hospitalisation

Wound cleansing is the first step. It consists of washing with water or disinfectants (Betadine®, Octenisept®, Repithel®), removing the walls of contaminated blisters (bullectomy), and draining the giant bullae while leaving the smaller ones. Unlike those developed for immunological or dermatological reasons, the fluid in the burn vesicles is

unique because it contains inflammatory and vasoconstrictor compounds. Consequently, inhibiting reepithelialisation; therefore, it is critical to release them[56].

Cooling, moisturising, anti-inflammatory and skin-nourishing agents are suitable for treating grade I burns, such as external formulations with menthol[57], rose oil (Irix®)[58], aloe vera (Aloe First®)[59] and chamomile[60]. Instead of pore-blocking ointments, it is recommended to choose moisturising creams or emulsions. In most of our investigations, we applied skin-friendly, anti-evaporative and analgesic gels with antimicrobial effects (Curiosa®) as an intervention. Moreover, antihistamines can help reduce shedding and itching.

A temporary dressing is applied in the case of II/A-degree combustions, restoring the skin's barrier function, preventing further loss of proteins and fluids, avoiding superinfections of the wound, and promoting reepithelialisation. An ideal dressing should have many excellent qualities to facilitate healing. Such as being absorbent, transparent – to be able to evaluate the injury constantly –and firmly sticking to the surrounding healthy skin until the desired removal while not adhering to the wound bed. Consequently, it must be quickly and painlessly replaced[21].

Traditionally, vaseline-, paraffine-, silicone- (Adaptic®, Klinitulle®, Safe-Tac®), or antimicrobial ointment-soaked gauses are most often used[61]. In the past, paediatric PT burns' gold standard of topical treatments was the soft, white, and water-soluble silver sulphadiazine (SSD) 1% cream[62-73]. Grassolind® is a frequently utilised paraffine-coated woven-cotton dressing, which does not cause hypersensitivity reactions. However, its

changing is painful and may require anaesthesia. Although other factors, like age, burn severity or location, may necessitate narcosis, regardless of the dressing.

The debris layer in II/B burns consists of denatured proteins, tissue fragments and blister residues. These materials inhibit wound closure and are breeding grounds for microorganisms, therefore must be removed during debridement. In addition, delayed primary excision should be carried out if conservative treatment does not cure mixed PT burns within fourteen days[47].

Early tangential necrectomy with electric or manual dermatome (Humby or Weck knife) is commonly performed in conventional combustion surgery, but it is far from ideal in many areas. During debridement, the necrotic area is removed in thin sheet-like planes until we see viable tissue bleeding point-like, shortening TTRE[74]. A gentler mechanical wound cleaning method that saves more viable tissues is Versajet® using high-pressure water. Alternatively, it is possible to debride with ultrasound (SonicOne®, MIST® Therapy System), but the high cost of these devices can hinder their application[75]. Theoretically, it is the best and most accurate technique when the surgeon is not even required. During enzymatic debridement with bromelain (NexoBrid®, Debrase®), the extract from pineapple seeds breaks necrotic tissues precisely and leaves the viable tissue intact[76].

The next task is restoring skin integrity once the wound has been successfully cleaned. Again, temporary coverage of severe burns - until the wound base becomes suitable for final transplantation or enough autograft can be collected – is necessary. For example, in many countries, xenografts such as Nile tilapia or porcine skin are used for this purpose. Biosynthetic and hydrofiber bandages are among the most advanced burn dressings, many

developed explicitly for hydroregulating combustions. The final overlay is usually an autograft; in more severe cases, it is solved by microsurgically relocating local or distant free flaps[77]. A vascularised wound base is a prerequisite for a skin graft, and if one needs to replace a bone or tendon, it is compulsory to have an intact periosteum or paratenon.

When an operation is required, choosing a full-thickness skin graft (FTSG) is recommended due to its cosmetic and functional superiority, despite the more cumbersome adhesion conditions. In addition, these grafts can be expanded before harvesting to cover a larger surface[78]. When transplanting FTSG, all skin appendices, including hair follicles, are relocated - except for sweat glands in the subcutis and Pacinian corpuscles. The graft collection area is chosen primarily according to the slightest aesthetic damage - so it can be covered with a cloth. Most often, FTSG is obtained from the wrist bend, the inguinal or cubital region or from behind the ear by an elliptical-shaped excision. After degreasing the grafts, they are fixed with stitches. Following the transplant, the operated areas are protected with a previously described bandage[79]. Nowadays, these dressings are often utilised in combination, and adjuvant therapies such as negative pressure wound therapy (NPWT) are also widespread.

Split-thickness skin grafts (STSG) usually attach more quickly but tend to have complications such as contractures and scarring. Its disadvantage is that less sensory function returns, and the results are aesthetically inferior, especially for the post-mesh state. STSG mesh graft should only be made if the child has burned extensively and the rest of the body does not have enough donor area. In this case, the priority in restoration must be the face, neck and hands. With dermatome, from the proximal medial or lateral surface of the thigh,

perhaps from the gluteal region or from under the line of underwear, we take the skin tag-free STSG to be transplanted in one or two seats. The two-seater method (Day 1 - excision and temporary overlay; Day 2 - grafting) is preferable in large-surface burns due to minor blood and heat loss[80].

2.6.4. Long-term monitoring and rehabilitation

Due to the length of recovery, it is vital to have a fully educated, designated caregiver for the children who will help them recuperate. If this is solved, most additional treatments can be carried out at home. In children, 20% of burns healed within 21 days, and 92% of mended after 30 days are accompanied by hypertrophic scars. Contractures caused by hand burn scars are the primary source of late morbidity **(Figure 8)**[81].

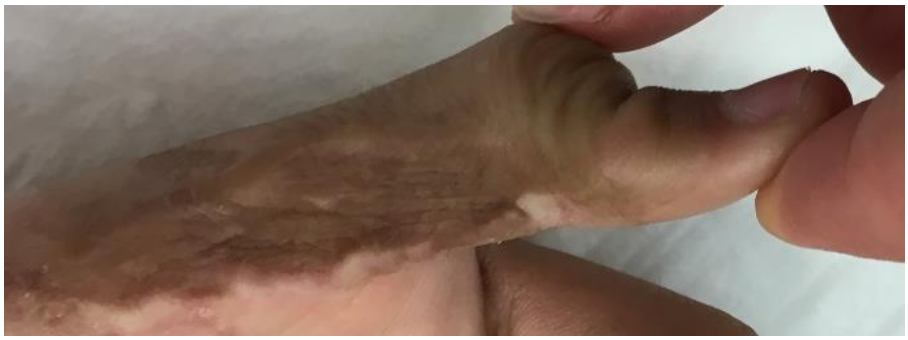

Figure 8. *Contractures can be observed on a child's little finger after a burn. Gergő Józsa, MD, captured the picture.*

These are especially true for paediatric patients, as they are still growing. If the growth exceeds the stretching of the scar, secondary contractures may develop, so follow-up examinations must be carried out until adulthood. If any cosmetic or range of motion constraining complications do occur, they must be corrected with subsequent reconstructive surgeries[82].

Introducing splinting and physiotherapy as soon as possible is paramount to preserving the range of motion and function, thus eluding most complications. In addition, supplementary compression masks, gloves and socks prevent scars from turning into keloids, achieving more beautiful cosmetic result[83]. Correct splinting helps to immobilise the graft and prevents it from shrinking by stretching it until it integrates. After removing the restraining devices, it is advocated to have the child perform individually tailored physiotherapy exercises for motion range improvement training, which are passive, active and against resistance[81].

Concurrently with the final removal of the dressing, it is endorsed to start using anti-scarring ointments. We advocated Contractubex® gel, a mixture of several active ingredients. It contains skin-softening heparin and allantoin that binds water, which acts against contractures, accelerates regeneration and hinders itching[84].

2.7. Aims

Many pieces are still missing from the grand portrait of paediatric partial-thickness burn therapies. This thesis' and meta-analysis' ultimate goal was to summarise our current knowledge on the subject, while the observational studies were meant to explore uncharted regions. Major topics discussed in this thesis are as follows:

1. We conducted a literature search to review the available treatment options for paediatric PT burns systematically. Then, we performed a meta-analysis to get insights into the dressings' healing potential and complications.
2. No data was available on the impact of combining zinc-hyaluronan gel or silver foam dressings in paediatric PT burns after skin transplantation. Therefore, we performed a cohort study on skin-grafted children with severe burn injuries treated simultaneously with Aquacel Ag foam® (ConvaTec Ltd., Deeside, UK) and Curiosa gel® (Richter Gedeon Plc., Budapest, Hungary).
3. We aimed to measure the success of the zinc-hyaluronan gel alone in paediatric facial II/A thermal injuries with a retrospective cohort study - since our literature search concluded that its efficacy had not been investigated.
4. Case reports were written on managing paediatric electrical finger injuries and a unique late-onset complication. We have also evaluated the use of Lavanid gel (Polyhexamethylen biguanide (PHMB) or Polyhexanide; SERAG-WIESSNER GmbH & Co. KG, Naila, Germany) in paediatric burn therapy, which has not been detailed before.

3. Materials and Methods

3.1. Meta-analysis and systematic review

3.1.1. *Search strategy and data extraction*

On the 29th of October 2020, a systematic search was conducted under the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA) in the MEDLINE (via PubMed), Embase, Web of Science, and CENTRAL databases, without filters[85]. We aimed to compile randomised controlled trials (RCTs) about PT burn treatments in children younger than 18 years at the time of the injury.

The outcomes assessed were the time to reepithelialisation (TTRE), grafting and infection rate, number of dressing changes, and length of hospital stay (LOS) - along with demographic data. The risk of bias was judged as “low”, “some concerns”, or “high” with the Cochrane Collaboration’s RoB2.v7 tool[86].

3.1.2. Data synthesis

An expert biostatistician performed analyses using the methods recommended by the working group of the Cochrane Collaboration[87]. In the meta-analysis, the effect sizes were visualised in forest plots using Comprehensive MetaAnalysis.v3 statistical software (Biostat Inc., USA). Heterogeneity was verified with Cochrane’s Q ($\chi 2$) test and I2 statistic, which was considered significant when p-values were < 0.1. Based on the proposition of the Cochrane Handbook, I2 values from 30% to 60% represent moderate and 50% to 90% significant heterogeneity.

DerSimonian and Laird random-effects models were employed in all analyses due to the groups’ generally high heterogeneity[88]. For continuous outcomes means, for

dichotomous outcomes, event rates with 95% confidence intervals were combined in each subgroup to contrast the differences between the interventions.

When the effects' means and standard deviations (SD) were not reported, we derived these data from the graphical representation of the outcomes. Alternatively, we aquired these results by conversion based on the work of Wan et. al. 2014 with the use of medians, minimum, maximum, or quartiles[89].

3.1.3. Reviews of the analysed interventions

Silver sulphadiazine (SSD)[62-73] contains a unique sulphonamide component that does not inhibit folic acid synthesis. This suggests that mainly the silver ion content causes its antibacterial qualities. Ionic silver released from SSD only has limited eschar penetration; thus, they act superficially. SSD's precise bactericidal mechanism of action is still unknown. However, it may damage DNA replication and increase cell wall permeability by directly altering the membrane and producing free radicals. Wounds can be treated openly (SSD only) or closed, depending on the addition of gauze dressings[90].

DuoDERM® (ConvaTec Inc., Bristol-Myers Squibb Co., New York City, NY, USA) [91,92] is an opaque, biodegradable and breathable occlusive hydrocolloid dressing. It can be worn for up to seven days due to an outer film providing an impermeable barrier and a foam layer designed for thermal and mechanical protection. Also, it contains an inner honeycomb matrix of hydrocolloid compounds absorbing exudate to form a soft, moist gel[93].

SilvaSorb® (Medline Industries, Mundelein, IL, USA)[71] is a biocompatible transparent, amorphous hydrogel with a distinctive Micro-Lattice arrangement where the

scaffolding stabilises the silver ions. The dressing exerts its action for three days; therefore, daily dressing changes are unnecessary. The hydrogel is non-irritating or sensitising and exceptional with fluid management without being toxic to host cells, wound staining or pseudo-eschar development[94].

Modern silver-foam dressings (Acticoat, Aquacel Ag, Mepilex Ag) combine the antibacterial trait of SSD with improved mechanical barrier and absorption functions. However, these treatments vary significantly in their total silver concentration, ion release patterns and therapeutic mechanism of action[94,95].

Acticoat™ (Smith and Nephew, St. Petersburg, FL, USA)[72,96-101] is a dual-layered dressing with a nanocrystalline silver coat and a polyethene layer bonded to a polyester core, slowly releasing small amounts of silver in ionised form, caused by the humid environment. Nanocrystalline ionic silver interrupts bacterial and fungal DNA and protein synthesis. It may also disrupt the biofilm and cell wall structures, although in vitro studies suggest it might be cytotoxic to keratinocytes. Adherence to wound beds was also noted, potentially causing skin-stripping and pain upon removal[102].

Mepilex® Ag (Mölnlycke Health Care, Gothenburg, Sweden)[96-98,103,104] consists of two layers: a soft silicone wound contact sheet (Safetac®) and an absorbent polyurethane foam. The foam sheet contains silver and activated carbon. Dressings made from silicone adhere to intact skin and remain in situ on the wound surface without sticking to it, consequently sustaining a moist milieu and providing a less traumatic separation[105].

Radiation-sterilised **amnion membrane (AM)**[66,106,107] allografts are biological skin substitutes and burn dressings. The human placenta's inner amnion layer is shiny and thin, made up of cuboidal, compact epithelial cells and mesenchymal connective tissue. The thick outer chorion of the fetal membrane is composed of transitional epithelium. The placenta can be used in toto (amnion and chorion) on deep burns or amnion alone on superficial wounds. It has low immunogenicity and contains many bioactive factors, such as collagen or cell adhesion compounds (for example laminins, fibronectin, proteo- and glycosaminoglycans). Moreover, it produces growth factors and cytokines with anti-inflammatory -bacterial, -immunogenic and -fibrotic features[108,109].

Xenografts are temporary skin substitutes derived from animal or plant cells and tissues. A widely used example in tropical and subtropical regions is the **Nile tilapia** (Oreochromis niloticus)[62], originating from the East African Nile River basin. Tilapia has a non-infectious microbiome and morphological composition comparable to the human skin but with more beneficial type I collagen[110].

Biosynthetic dressings (Biobrane, EzDerm, Transcyte) contain cells or particles from living organisms combined or modified with modern synthetic compounds[61].

Biobrane™ (Dow Hickman/ Bertek Pharmaceuticals, Sugarland, TX, USA) [64,67,68,72,91,92,100] is a biosynthetic, bi-laminate dressing. It comprises a flexible, woven, non-biodegradable tri-filament nylon mesh with peptides derived from porcine type I collagen embedded into an ultra-thin, semipermeable silicone outer film. The dressing is firmly adherent to the wound and spontaneously detaches when re-epithelialisation has occurred

but has deficits in conformability and handling; thus, it is not ideal for burns of the face and neck region. Furthermore, it does not have any specific antimicrobial qualities[111].

EZderm® (Mölnlycke Health Care, Gothenburg, Sweden)[104,105,112] is a perforated, biosynthetic porcine xenograft, pre-meshed 1:1, where the collagen has been crosslinked with aldehydes to provide strength and durability. They can be used as a diagnostic tool for deep or infected burns as they tend not to adhere to them, unlike superficial ones. Nevertheless, some studies have reported increased hypertrophic scarring, probably due to an immune response against the biological components of the dressing. Furthermore, there are cultural and ethical aspects of using pig donors and a possibility for virus transmission[113].

TransCyte® (Advanced Tissue Sciences, La Jolla, CA, USA)[67] is a translucent, temporary biosynthetic skin substitute consisting of a polymer silicone membrane bonded to a nylon mesh coated with porcine dermal collagen and neonatal human fibroblast cells cultured in vitro on that mesh. These fibroblasts secrete human dermal collagen matrix proteins and growth factors. Following freezing, the tissue matrix and growth factors are left intact while there is no metabolic activity, and after application, these particles facilitate healing until wound closure occurs[114].

ReCell® (Avita Medical Ltd, Cambridge, UK)[92] is a device that processes autologous skin samples collected in the operating theatre into a suspension using a trypsin solution. Later, that can be applied to the wound with its Spray-On Skin system with comparable results to split-thickness skin grafting. ReCell can be combined with traditional

dressings that may improve patient outcomes, but the available information is controversial[115].

Adjunctive therapies (**collagenase, vitamin E+C+Zinc, wIRA, NPWT, heparin, rhGM-CSF, bFGF** and **rhEGF**) are physical or chemical enhancers of tissue regeneration that can be added to traditional occlusive dressings to improve the patients' outcomes.

Collagenase[65] (Santyl® - Healthpoint Biotherapeutics, Fort Worth, TX, USA) ointment is an enzymatic debridement agent (like bromelain or papain[116]) that cleaves denatured collagen at seven specific sites and creates bioactive peptides as byproducts. These particles can stimulate keratinocytes and fibroblasts, induce endothelial cell migration and are related to the proliferative reepithelialisation phase. It can be combined with antimicrobial agents (e.g. nystatin and polymyxin b (PMB)) to form a therapy. However, adding this protein to other occlusive dressings may improve outcomes, which has not been investigated yet in children[117].

Recombinant human epidermal growth factor (rh**EGF**)[118] is a protein that stimulates cellular proliferation, differentiation and survival by binding to its receptor (EGFR)[119].

Basic fibroblast growth factors (**bFGF -** Trafermin, Fiblast Spray®, Kaken Pharmaceutical, Tokyo, Japan**)**[120] are cell signalling proteins pre-synthesised by macrophages, released at the injury site. They are often called pluripotent growth factors due to their multiple actions on many cell types, such as improving angiogenesis and keratinocyte organization[121].

Recombinant human granulocyte-macrophage colony-stimulating factor (rh**GM-CSF**)[122] is a monomeric glycoprotein secreted by many cells in the immune system and functions as a pro-inflammatory cytokine against infections. However, it also increases oedema and reactive oxygen production[123].

Heparin[124] is a naturally occurring glycosaminoglycan and anticoagulant medication released directly into the vasculature from mast cells. Its exact mechanism of action is unknown, but it has been proposed that its primary function is the defence against foreign materials. However, several side effects have been noted, including bleeding, heparin-induced thrombocytopenia, hyperkalaemia and elevated liver enzymes. Fortunately, its impact can be counterbalanced by protamine-sulphate[125].

Vitamin E and C supplementation with Zinc[126] have been administered due to their antioxidant trait, which may reduce the consequences of the pro-inflammatory cytokines after trauma. Moreover, vitamin C plays a vital role in collagen synthesis, and Zinc is an essential part of more than 1000 transcription factors and 300 enzymes from every class[127-129].

Negative pressure wound therapy (NPWT)[73,99,130] is a non-invasive treatment that involves the controlled application of subatmospheric pressure to the wound by using a dressing sealed with a transparent film connected to a vacuum pump to remove excess exudate and promote circulation. Therefore it creates a moist environment with reduced oedema, though it may only be used where there are no exposed blood vessels or nerves because direct foam contact may damage them[131].

Water-filtered infrared-A (wIRA)[132] produces a therapeutic field of heat in the tissue created from full-spectrum light purified by a hermetically sealed water filter that blocks out all the harmful ultraviolet light waves. Therefore, wIRA increases tissue temperature, oxygen partial pressure and perfusion improving energy and oxygen supply. Furthermore, it can reduce inflammation, hypersecretion and the need for analgesics[133].

3.2. Cohort studies

Two comparative clinical trials and a retrospective cohort study were performed at the Surgical Division, Department of Paediatrics, Medical School, University of Pécs, Pécs, Hungary.

First, each patient's burn status was documented and photographed before applying the first dressing and at every control appointment until complete wound closure. Then, we analysed the patient's demographic data, such as sex and age distribution, the mechanisms and depth of the burns, the injured Total Body Surface Area (TBSA), the associated burn regions, and the severity.

Primary outcomes were the mean days until the occurrence of a complete, shiny, new layer of epithelium (TTRE), LOS and complication rates. Results are presented as mean and standard deviation (SD).

3.2.1. Overviews of the applied interventions in the cohort studies

Mepitel® (Mölnlycke Health Care, Gothenburg, Sweden)[69,70,96-99] is a semi-transparent, low-adherent, porous wound contact layer consisting of an elastic polyamide net covered with silicone, and it contains no biological compounds.

The silicone coating is slightly adhesive, which helps the peri-wound area's dressing application, retention and removal. Furthermore, by inhibiting the lateral movement of exudate, it prevents maceration of the surrounding skin. Mepitel is non-absorptive but contains 1mm diameter pores that allow wound fluids to permeate into a secondary absorbent dressing[134].

Grassolind® gauzes (Hartmann, Germany) are widely used as inexpensive, paraffin-impregnated dressings made of open-weave cotton cloth. These dressings are non-medicated and can be safely applied without any sensitising effects after prolonged use. Their primary function is to create a temporary barrier between the host and the environment, thereby also preventing fluid loss.

Betadine® (Egis Gyógyszergyár Zrt., Hungary) is an antiseptic solution. Its active ingredient is povidone-iodine, which has a broad-spectrum antimicrobial effect. These traditionally used dressings are suitable for covering skin defects while treating burn injuries and managing the skin grafts in the post-transplantation phase.

However, none of them has any antibacterial properties, which is why they were combined with Betadine® in our institution.

Curiosa® gel's (Richter Gedeon Nyrt., Budapest, Hungary) main component is zinc-hyaluronan, which promotes cell regeneration and has antioxidant effects. Therefore, it contributes to faster wound closure. Moreover, zinc has antimicrobial properties and is vital to more than a thousand transcription factors and 300 enzymes from every class. Hyaluronan

is an essential component in the extracellular matrix and can modify cellular functions through its hyaluronan receptors and viscoelastic attributes.

The gel formulation helps in the application of the treatment while it creates a moist environment, thereby stimulating wound healing. Zinc-hyaluronan gel also relieves adverse effects from injuries, such as wound pain and tissue inflammation[135].

Aquacel® Ag[63,101] is a comfortable triple-layered Hydrofiber® dressing (ConvaTec, a Bristol-Myers Squibb Company, Skillman, NJ, USA). It holds a layer of sodium carboxymethylcellulose, which forms a gel in contact with wound fluid, and it also has antimicrobial 1.2% w/w ionic silver. The middle foam layer absorbs the wound exudate that contains the infective agents. Then the silver exerts its bactericidal action in the fabric of the dressing without releasing the ions. Therefore, it eliminates the potential for argyria. The top sheet is water-repellent, with controlled vapour permeability and additional protection against microorganisms[136,137].

A study found that optimally, dressings should only be changed every ten days, but this approach may rarely conceal an infection due to its non-transparent design[138].

3.2.2. *Paediatric deep burn management after split-thickness skin graft (STSG)*

The intervention groups' data (zinc-hyaluronan gel and silver foam dressing) were collected prospectively from the 1st of January 2015 to the 31st of December 2020. In addition, the children's characteristics were compared retrospectively with a control group (Grassolind® or Mepitel® net and Betadine® solution) from patients with the same type of injuries treated at our clinic from 2012 to 2020.

In addition to the demographic endpoints listed in the general cohort methodology, the number of anaesthesia and dressing changes after STSG were also assessed.

3.2.3. *Management of paediatric facial burns with zinc-hyaluronan gel graft*

This single-arm, retrospective cohort study weighed the characteristics of 23 children (≤ 17-year-olds) with facial II/A burns and the wound closure capacities of the applied zinc-hyaluronan gel. Patients were admitted consecutively to our clinic between the 1st of January 2016 and the 15th of October 2021. Alongside the general demographic outcomes, the injured regions associated with facial burns were also examined as a unique aspect.

3.3. Case reports

3.3.1. *Paediatric electrical finger burn injuries' management and late-onset complications*

Necrectomy and cross-finger flap surgery was performed on a III-degree burn of a 15-year-old boy. Three weeks after the primary reconstruction, the cross flap was separated.

A two-year-old suffered III-degree burns on her thumb around the interphalangeal joint and hypothenar region. After necrectomy, the thumb's skin defect was reconstructed with a rotated flap, while the donor site received full-thickness skin graft transplantation.

3.3.2. *Management of paediatric PT burns with PHMB gel*

A 6-year-old boy chemically burned his thighs; consequently, necrectomy and autologous STSG transplantation were performed.The donor and grafted areas were covered with Grassolind net and Polyhexanide gel, used as the dressings of a 2-year-old girl's II/A left forearm scald as well.

4. Results

4.1. Paediatric PT burn therapy: a meta-analysis and systematic review of RCTs

Twenty-nine RCTs were evaluated in the qualitative and 25 in the quantitative synthesis, but only three articles compared SSD directly to the same treatment (Biobrane).

SSD was reported in comparison with AM[66,106,107], biosynthetic dressings (a.k.a. Biobrane, EzDerm, Transcyte)[64,67,68,91,92,112], and Biobrane only[64,67,68,91,92]. Additionally, the efficacy of silver foam dressings (a.k.a. Acticoat, Aquacel Ag, Mepilex Ag)[96-98,100,101,104], Acticoat only[97,100,101], and NPWT[73,99,130] were all demonstrated in our meta-analysis.

The attributes of each intervention mentioned above, as well as autografts[106,139], Tilapia[62], and Silvasorb[71], were qualitatively analysed in our systematic review. Adjuvant remedies (viz., bFGF [120], rhEGF[118], rhGM-CSF[122], collagenase[65], heparin[124] and vitamins E + C + Zinc[126], and wIRA[132]) together with combined treatments (Biobrane + Recell[92], Acticoat + Biobrane[72,100], Acticoat + Mepitel[97,99] and Acticoat + Mepitel + NPWT[99]) were also discussed there. Our statistical analysis showed a tendency for quicker recovery times and reduced complication rate linked to silver foam, biosynthetic and amnion membrane (AM) dressings. Fewer mean dressing changes correlated with minor discomfort, anaesthesia and handling duration associated with modern alternatives.

Of 756 children, 14.3% were younger than one, 78.6% were under five, 21.4% were older than five, and the average age of the patients was 4.3 years. Most children were boys: 655 out of 1089 patients (59.1%). 832 patients had a mean 7.5 TBSA%, distributed among them as follows: 23.2% below 5 TBSA%, 46% amid 5–10 TBSA% and 30.8% over 10 TBSA%. Five trials included scalds exclusively. In the remaining studies, the aetiological

allotment of 628 patients' was 65.5% scalds, 18.7% flame, 15.4% contact and 0.5% electric burns. Generally, the risk of bias was deemed high, and the articles habitually lacked essential information.

A total of 623 children from 17 RCTs were included in the meta-analysis of TTRE. The study size ranged from 4 to 145, with an average of 30 participants per trial. Overall, 265 children received SSD with a mean TTRE of 17.89 days, which was the slowest among the examined interventions, although the difference was not statistically significant (p = 0.70). Lower TTRE was seen in 224 patients treated with NPWT (13.92 days) and in 134 receiving biosynthetic dressings (13.84 days), out of which 100 children were remedied with Biobrane only (14.5 days). Further analysis was performed to determine the reason behind the groups' substantial heterogeneity (which was signified by a high I^2 between 75.35–99.85). Expectedly, when the TTRE was ranked by depth, a significant difference (p = 0.0004) was observed amongst II/B (20.53 days), II/A (13.77 days) and combined PT (12.43 days) burns.

If conservative treatment cannot heal the injury, permanent skin transplantation is needed to facilitate wound closure. Because every intervention without grafted patients (zero outcomes) had to be omitted from a previous meta-analysis, we employed the reverse approach: assessing the percentage of the non-grafted patients among the treatments. With this technique, we uncovered that by subtracting the non-grafted population percentages from 100%, the grafting frequency was 13.2%, 13.4%, 13.1% and 9.8% in children treated with SSD, silver foam, biosynthetic and Biobrane, respectively. These outcomes indicate

that among Biobrane-treated children, grafting was required 25.8% less often compared to SSD; however, the difference was not significant ($p = 0.98$).

The patients' percentage that presented signs of infection was calculated similarly to grafting needs. Biosynthetic coverings had the highest microbial contamination proportion of 19.4%, whereas the rate for Biobrane was 11.7% selectively. SSD revealed a lower degree of 7.4% infections, while the infected patients' percentage was 7.0% in silver foams and 3.5% in Acticoat groups ($p = 0.24$)

SSD seemed to be the least proficient option regarding mean bandage reapplications, with an extremely high 65.5 if the wounds were treated openly and 9.6 dressing changes with a closed regimen. Interventions with three or fewer bandage reapplications were silver foams and biografts, such as Acticoat + Mepitel and Tilapia (3.0 dressing changes for both), Acticoat (2.7), NPWT + Acticoat + Mepitel (2.4), Transcyte (1.5), AM alone (1.3). Aquacel Ag (1.0) and AM with nystatin and polymyxin B (PMB) (0.5) proved the most beneficial.

LOS is associated with the total cost of care and immensely influences the children's discomfort. Unfortunately, sufficient data for a meta-analysis was only obtainable for SSD- and AM-based interventions, where the average LOS were 12.5 plus 8.3 days, respectively**.**

4.2. Paediatric deep burn management after STSG transplantation

We have found seven eligible children in our patient database for the control group, all of whom suffered scalding. Their mean age was three years at the time of the accident. Three patients sustained 5-10 TBSA%, and four cases were 10-15 TBSA% burns. The average number of anaesthesias induced was 6.29 times, and 5.29 dressing changes were

done after transplantation. After the graft's appropriate take, the dressing's final removal has been on the 13th day, and the LOS has been 21.89 days.

Nine children were treated in the intervention group, with four scald injuries and five contact burns. The patients' mean age was 4.22 years. Four patients had a <5 TBSA%, two cases were 5-10%, and three children had 10-15% burned surface area injuries. There were 3.56 anaesthesias induced and 1.66 dressing changes on average. Children remedied this way achieved complete wound healing on the 10th day, with a mean LOS of 12.38 days.

4.3. Management of paediatric facial burns with zinc-hyaluronan gel

In this study, the average age of the children was 6.2 years; 30.4% were younger than one year. A mean of 3% total body surface was injured in the facial region, while 47.8% of the patients had other areas damaged, most frequently the left upper limb (30.4%). The mean TTRE was 7.9 days, and the children spent two days in the hospital.

In each circumstance, wound cultures revealed average bacterial growth, and follow-ups found no hypertrophic scarring or other complications.

4.4. Paediatric electrical finger burn injuries' management and complications

A 15-year-old boy touched a wire while changing a lightbulb, which caused a burn injury on his right index finger. During the physical examination, a 25x14 mm, III-degree burn was identified volarly above the distal interphalangeal joint (DIP) as an entry wound. In addition, an 8x7 mm exit site appeared dorsally at the nailbed's lateral edge.

A two-year-old girl inserted a nail into the power outlet, causing III-degree burns on her thumb around the interphalangeal (IP) joint and hypothenar region.

Deviations of the finger joints were observed throughout the follow-up examinations of the two children without functional deterioration. X-rays confirmed the left thumb's IP and the index finger's DIP joints' bone atrophy.

4.5. Management of paediatric PT burns with PHMB gel

Throughout therapy, the transplanted skins adhered completely, in addition to the reepithelialisation of the burn wounds. Infection or other complications were not detected.

The follow-up of the children is still ongoing; short-term results suggest that applying Grassolind net with Polyhexanide gel is an effective burn dressing.

5. Discussion

Partial-thickness burns during childhood are a diverse group of frequent injuries, resulting in various severe complications. Moreover, their optimal treatment is still debated due to the extensive and ever-growing library of alternatives and incomplete guidelines.

We performed a systematic review of 29 and a meta-analysis of 25 RCTs to facilitate this discussion. First, the demographic data of the whole cohort was analysed. It revealed that the mean age of the children was 4.3 years. Of 756 PT injured patients, 14.3% were younger than one year, 78.6% were below five, and 21.4% were older than five. The majority of the children (59.1%) were boys: 655 out of 1089. An average of 7.5 TBSA% was wounded in 832 patients, distributed among the children as follows: 23.2% smaller than 5 TBSA%, 46% between 5–10 TBSA% and 30.8% larger than 10 TBSA%. Five trials reported results exclusively from scalds, which were excluded from the burn mechanism evaluation. In the remaining studies, the aetiological allotment of 628 patients' injuries was 65.5% scalds, 18.7% flame, 15.4% contact and 0.5% electrical burns.

Silver sulphadiazine is among the most commonly administered treatment worldwide, allowing wounds to heal without requiring grafting. Since most of the articles reported their findings correlated to SSD due to its historical significance, we chose this therapy as a comparator in our meta-analysis. It is sold under many product labels like Dermazin®, Flamazine®, Silvadene® or Silvazin®. However, numerous papers revealed several limitations when using SSD, which led to the advance of a wide range of alternative remedies. Alas, these new options' efficacy in managing paediatric PT burns remains essentially unclarified.

Even though SSD usage is widespread as a treatment for burns, our meta-analysis concluded that its shortcomings seem to outweigh its beneficial effects. SSD's advantages are its easy applicability, low cost and established antibacterial efficacy (i.e., an infection rate of 9.22%). Nevertheless, SSD was connected with sluggish lesion resolution (TTRE II/A: 11.0 days; II/B: 25.7 days; II: 18.3 days with 0.39 T%/T) and extended hospital stay (LOS II: 13.8 days). In addition, studies reported a considerable grafting rate (i.e., in 21.5% of the children) and regular, time-consuming dressing changes (II: 9.6 times on average; every 1-3 days), triggering pain and discomfort. Its known side effects include argyria, allergic reactions, and neutropenia[140]. Moreover, the wound bed is discoloured, hindering wound severity evaluation and depth determination[141].

SSD was described compared to AM[66,106,107], biosynthetic dressings (a.k.a. Biobrane, EzDerm, Transcyte)[64,67,68,91,92,112], and Biobrane only[64,67,68,91,92]. Additionally, the efficacy of silver foam dressings (a.k.a. Acticoat, Aquacel Ag, Mepilex Ag)[96-98,100,101,104], Acticoat only[97,100,101], and NPWT[73,99,130] were all determined in our meta-analysis.

In our systematic review, the attributes of each intervention mentioned above, as well as autografts[106,139], Tilapia[62], and Silvasorb[71], were qualitatively analysed. Adjuvant remedies (viz., bFGF [120], rhEGF[118], rhGM-CSF[122], collagenase[65], heparin[124] and vitamins E + C + Zinc[126], and wIRA[132]) jointly with combined treatments (Biobrane + Recell[92], Acticoat + Biobrane[72,100], Acticoat + Mepitel[97,99] and Acticoat + Mepitel + NPWT[99]) were also reviewed there. Our statistical analysis revealed a tendency for hastier recovery periods and diminished complication rate linked to silver foam, biosynthetic and amnion membrane (AM) dressings.

Traditionally, biological xenografts are of paramount importance in the temporary coverage of severe burns - until the wound base becomes suitable for final transplantation or enough autograft can be collected. For this practice, the tilapia skin[110] and the halved skin of the pig's dermis are the most common, while potato and banana peels dominate in some places. In developed countries, lyophilised human amniotic or cadaver allograft is preserved with glycerol, dehydrated or frozen, but these tissues are only available to a limited extent [108].

RCTs were only available for radiation-sterilised AM allografts[66,106,107] and tilapia xenografts[62] combined with antimicrobial agents. They seem surprisingly valuable, low-cost solutions, but their acquisition and storage may be challenging. Nevertheless, their application seems comfortable and less painful during and in-between dressing changes. They were also linked with the least number of mean bandage changes: Tilapia (n=3.0), AM (n=1.3), AM+Nystatin+PMB (n=0.5). Moreover, the time needed for wound closure was among the lowest recounted values, as shown by the TTRE and T%/T in paediatric PT combustions for Tilapia (10.1 days and 1.11%). Surprisingly, AM (13.3 days and 0.56%) was only more effective than Tilapia when it was combined with Nystatin+PMB (6.0 days and 2.00 %). Furthermore, an outstandingly low infection rate was documented in the case of AM+Nystatin+PMB (1.9%).

With the development of biotechnology, tissue-grown skin replacement has also become an option. Between the contemporary biosynthetic dressings, Biobrane and Transcyte had excellent TTRE in PT burns – which was 10.63 days and a T%/T of 0.63% for Biobrane[64,67,68,72,91,100]. Meanwhile, using Transcyte, the TTRE was 7.50 days with a

T%/T of 0.66%[67]. In contrast, EZDerm was less proficient (TTRE in PT injuries: 18.75 days; 0.23 T%/T) than SSD[104,112]. Furthermore, the rates of grafting and infection were exceptionally high using EZDerm (37.0 and 23.9%, in that order) and Biobrane (12.9% for both). However, Transcyte had a low frequency of 5.0% for both. Nevertheless, the need for reapplication was considerably minor in the case of all three biosynthetic coverings (EZDerm (n=5), Biobrane (n=3.4), Transcyte (n=1.5)). According to these results, biosynthetic treatments in children with PT burns are promising interventions. However, to reduce the susceptibility to infection and potentially the need for grafting, it is suggested that they should be applied in combination with antimicrobial agents.

Silver foams entail the Hydrofiber dressing family. Their members contain nanocrystalline silver-coated triple-layer polyethene meshes (Actisorb Plus™, Acticoat 7™, Acticoat Absorbent™). Another group consists of 1.2m/m% silver-soaked carboxymethylcellulose bandages (Aquacel Ag® or Aquacel Ag Burn®). Both sets of dressings can be used with good results, although Aquacel costs less, is lighter and painless to put on, stays in place for up to twenty-one days - so it does not need to be replaced - and there is no need for painkillers or anaesthesia when taken off. Nevertheless, their real drawback is that they are opaque. Therefore, they do not allow to closely monitor the processes underneath it - without taking them off.

Among them stands out the Aquacel Ag® foam, which we used in our investigations. It contains an absorbent foam sheet, a hydrofiber layer that jellifies during water absorption and an outer waterproof polyurethane coating as a barrier. The gel keeps the wound moist, thus promoting autolytic debridement. Silver ions released from the dressing inhibit the

development of infections. With its use in temporary burns, more reversibly damaged tissue survives by strengthening the microcirculation. Therefore, it improves the functional and aesthetic results, while they are reported to be comfortable to wear[94,137].

Our meta-analysis primarily studied silver foam dressings on minor burns (<5 TBSA%)[96-98,100,101,104]. However, the wound's TBSA%[63] and TTRE[101] were not reported in the RCTs of Aquacel products. By the 10th day of the treatment, wound closure was astonishingly high in the case of Acticoat (93%) and Aquacel Ag (94%). Consequently, the TTRE and T%/T in PT burns were acceptable in the case of Acticoat (14.2 days and 0.23%, respectively), likewise with Mepilex (10.3 days and 0.28%) dressings. The sum of bandage changes, grafting needs and infection rates was comparatively small in the case of Acticoat (n=2.7, 20.9%, and 3.5%, respectively) and Mepilex Ag (n=4.0, 3.3%, 16.4%). Aquacel Ag was connected to a small need for dressing changes (n=1.0) and low vulnerability against infections (2.3%).

These outcomes propose that the silver foam dressings are efficient interventions in PT burns of children. However, before they can be firmly advocated for general practice, further studies are warranted to test their effect on more extensive burns.

Several adjuvant interventions were collected in our systematic review that could reduce the time for wound closure (as indicated by TTRE red%) when they were supplemented with the treatment. The list of these therapies (with the corresponding burn depth and TTRE red%) comprised mechanical NPWT (12.6% in II/A and 14.3% in II/B burns)[73,99,130] and optical wIRA (II/A: 30.8%)[132]. In addition, biological modifiers like

rhEGF (II/A: 20.2%; II/B: 20.7%)[118], bFGF (II: 21.1%)[120], vitamin C + E + Zinc (II: 23.7%)[126], rhGM-CSF (II/B: 27.9%)[122], plus heparin (II: 40.0%)[124] were also administered.

Whereas, in several cases, the cost of these treatments represents a considerable obstruction to their use, supplementation with heparin, vitamins, and minerals are promising and economical adjuvants in burn therapies. However, it must be noted that we could identify only a single report for each treatment, which warrants further research to establish the efficacy of these additional interventions.

Similarly to silver foam coverings, combination therapies were mainly investigated on more minor burns, which could have influenced their satisfactory TTRE in PT injuries. Fifteen days were needed for wound closure in the case of Biobrane + Recell[92]. Meanwhile, 10.6 days for Acticoat + Mepitel[97,99] and 8.7 days were required for NPWT + Acticoat + Mepitel[99]. Consequently, the small TBSA% can explain the low T%/T values. These were 0.35% for Biobrane + Recell, 0.14% for Acticoat + Mepitel and 0.17% for NPWT + Acticoat + Mepitel. As an exception, management with the mixture of Biobrane and Acticoat[72,100] resulted in a lengthier TTRE of 21 days and a superior T%/T of 0.87%.

By the 10th day of care, the wound closure percentage was moderate in the cases of Acticoat + Mepitel (42.5%) plus NPWT + Acticoat + Mepitel (68.6%). However, on day 10, the TTRE ratio was astonishingly high (95%) in patients healed with Biobrane + Recell. Every intervention achieved better results than SSD in terms of the lower need for dressing changes, which were a mean of 6.9 times for Biobrane + Acticoat, 4.8 for Biobrane + Recell, 3.0 in the case of Acticoat + Mepitel and 2.4 for NPWT + Acticoat + Mepitel.

Related to SSD, the grafting rates decreased for Biobrane + Acticoat (13.9%) and Acticoat + Mepitel (6.8%). Furthermore, the best outcomes were seen after NPWT + Acticoat + Mepitel (2.1%) and Biobrane + Recell (0%) treatments in this regard. Nevertheless, it should be mentioned that low grafting rates were also discovered with the individual usage of Biobrane (6.2%), Transcyte (5%) as well as Mepilex Ag (3.3%).

Infection percentages were extremely high in the case of Biobrane + Acticoat (60%) and Biobrane + Recell (40%), suggesting that their combination suppresses their germicidal efficacy. Meanwhile, no contagions were reported in children treated with Acticoat + Mepitel, indicating an intense antimicrobial effect. It must be mentioned that the cost of these dressings was greater than the price of SSD, but the operating theatre and nursing time required, along with the anaesthetic use and total fee, were higher in the SSD group. This higher initial cost of the combination treatments is the main difficulty that thwarts them from extensive use as burn remedies.

In our ensuing investigation, entitled “Paediatric deep burn management after split-thickness autologous skin transplantation”, we compared the simultaneous utilisation of Aquacel Ag foam and Curiosa gel with the traditional dressings used at our clinic.

Seven eligible children were found in our patient database for a control group, treated with Grasolind or Mepitel nets, in addition to Betadine ointment. All of them suffered scalding-related injuries, with a mean age of three years at the time of the accident. The average number of anaesthesias induced was 6.29 times, and 5.29 dressing changes were

performed after transplantation. Following the graft's appropriate take, the dressing's final removal has been on the 13th day, with a LOS of 21.89 days.

In the intervention group, nine children were administered combination therapy. The patients' mean age was 4.22 years, with four scald injuries and five contact burns. Remarkably, there were only 3.56 anaesthesias induced and 1.66 dressing changes on average in this group. Children treated this way achieved complete wound healing and had their dressing's last removal on the 10th day, with a mean LOS of 12.38 days.

Summing up, in the intervention group, the need for anaesthesia decreased significantly ($p=0.004$) by 43%. Also, the children required 84% fewer dressing changes after transplantation ($p=0.001$). Finally, the dressing could be removed three days earlier, and the average LOS was reduced by 45%.

Our next approach, with the title "Management of paediatric facial burns with zinc-hyaluronan gel", studied the characteristics of II/A thermal injuries after using only Curiosa. The mean age of the patients was 6.2 years in our cohort; 30.4% were younger than one year. An average of 3% total body surface was injured in the facial region, and 47.8% of the patients had other areas damaged, most frequently the left upper limb (30.4%). The mean TTRE was 7.9 days, and the children spent two days in the hospital.

In each case, wound cultures revealed typical bacterial growth, and follow-up examinations found no complications, such as hypertrophic scarring.

In brief, paediatric facial II/A burns treated with zinc-hyaluronan resulted in rapid wound closure and low complication rates, which were accountable for the moderate

hospitalisation. These benefits, along with the gel's ease of applicability and spontaneous separation, are linked to child-friendly burn care.

We have also discussed our experiences with Lavanid gel in the "Management of paediatric partial-thickness burns with PHMB gel" case report. During therapy, the transplanted skins adhered completely, in addition to the reepithelialisation of the burn wounds. Infection or other complications were not observed.

The follow-up of the children is still ongoing; short-term results suggest that applying Grassolind net with Polyhexanide gel is an effective burn dressing, which creates a suitable environment for wound healing.

Based on our initial experiences, the analysed intervention could be applied gently in a child-friendly manner. In addition, the dressing was associated with favourable burn wound healing capabilities and aesthetic outcomes.

In the last part of our work entitled "Paediatric electrical finger burn injuries' management and late-onset complications", we examined the management of electric traumas at their most common localisation. Deep necrosis (III-degree burn) develops during electrical burns in most instances. These injuries can destroy the skin, soft and bone tissues, and in children, the growth plate, which may cause secondary deformities.

In one child, the ulnar deviation of the distal digit was observed throughout the follow-up examinations. Another showed a radial deviancy on the phalanx. Additionally, X-rays confirmed the distal phalanx base's bone atrophy and the interphalangeal joint's deterioration. It was concluded that planning for a long-term follow-up of these patients is necessary to identify and treat their late-onset complications.

To summarise our results, our primary recommendation for investigators is that children's II/A and II/B burns should be analysed separately due to their significantly different characteristics. Reporting predetermined endpoints of universal interest (e.g., TBSA%, TTRE, grafting and infection rates, number of dressing reapplications, and LOS) along with unique observations is crucial.

Founding a single, internationally acknowledged standard for scar and pain assessment in paediatric burns would significantly enhance this process. Another fascinating imminent aspect could be the analysis of optimum dressing change rates. Additionally, investigators should abide by the CONSORT, STROBE or PRISMA principles to reduce the risk of bias in the field of paediatric burn medicine[142].

While every intervention could facilitate the recovery of II-degree paediatric combustion wounds, individual data analysis showed remarkable variances in secondary outcomes. Regrettably, these differences could not have been statistically verified due to the considerable between-study heterogeneity caused by the injuries' unequal depth subcategory ratios and areas. Therefore, when selecting the ideal intervention for PT burns in children, physicians should deliberate treatments with little need for dressing reapplication. These

choices necessitate the least narcosis and cause minor pain and discomfort for the children. Such an alternative could be zinc-hyaluronan gel alone or combined with silver-foam dressings, which showed favourable results in our studies.

Regarding the future of burn care, automatic algorithms could prove enormously helpful. Artificial intelligence (AI) is increasingly implemented in many medical fields due to its exceptional speed and accuracy in pattern recognition. For instance, fluid administration estimations and crisis management forewarning can be automated since 1990[143]. Nowadays, many researchers are analysing wildfire spreading patterns with machine learning (ML)[144]. At the same time, these programs already predict the weather forecast, which proved beneficial in designing evacuation strategies, resulting in more efficient prevention.

Besides, burn severity classifications were extensively researched. For example, a program was developed to assort burn depths into different groups from digital photographs[145]. It already outperforms clinicians (77%)[146], but its accuracy (83%)[147] is lower than AI-backed IRT's (96%)[44]. However, an ML photogrammetric porcine model has already reached extraordinary precision of 92.5%[148]. A novel method was reported in 2020 that could approximate burn depth via ultrasound images, which could be a widely available and relatively cheap alternative to physical examination[149]. ML can help by pinpointing sepsis[150], acute kidney injury[151] or other rare complications of severe burns. By identifying and monitoring at-risk patients' specific parameters (e.g. lactate or GFR), further complications or even death can be avoided.

Virtual Reality (VR) helps children reduce pain and anxiety during interventions like dressing changes or rehabilitation exercises[152]. As these technologies become progressively affordable, they can capitalise on the inherent interest of adolescent patients in them. However, other distraction interventions (such as hypnosis or imagery-based therapy) also look promising approaches[153].

Utilising ML in burn care holds potential for prevention and may improve diagnostic accuracy in evaluating burn wounds. Furthermore, predicting mortality, complications, and wound closure time facilitates critical care and monitoring. However, existing models remain in the early stages, and additional studies are needed to assess their clinical feasibility. Future research can be enhanced using larger datasets or data augmentation, employing novel deep learning models, and applying these to other subspecialties of child care.

6. Conclusions

Due to their frequency and potentially severe complications, it is essential to care for childhood combustions optimally, so it would be important that the principles of burn management are well-known to all practitioners. However, selecting interventions is challenging due to the abundance of options. Therefore, we present the results of alternatives which worked splendidly in our department and amidst the international competition.

When applying Curiosa® gel, an average of 7.9 days passed until full reepithelialisation in facial II/A burns. However, if the gel was combined with Aquacel Ag Foam® dressing, the mean TTRE was ten days post-transplantation in deep (>II/A) burns. The significant advantage of combination therapy was that its application, removal and replacement were painless compared to traditional bandages. Furthermore, the zinc-hyaluronan gel prevented the wound from dressing adhesion and helped clear necrotic areas.

These interventions did not require repeated analgesia or anaesthesia during their reapplication, thereby avoiding their side effects. Moreover, wearing it proved to be a convenient, effective and child-friendly option because it required less intervention, control examinations and dressing changes during its use, resulting in lower stress levels in children. Another great benefit was that in II/A burns, most patients could be treated ambulatory.

No complications were detected during the studies, which confirmed the antimicrobial effectivity of silver and zinc ions. Compared to the traditional dressings used at our clinic, as the number of interventions, complications, and LOS decreased, the cost of therapy was roughly halved. Favourable wound healing conditions are substantiated by the excellent functionality and cosmetic results experienced after utilising these dressings.

7. Future perspectives

Although the results presented in this thesis will need to be further validated in the future, we aimed to highlight currently unclear parts in our understanding of burn therapy and facilitate further clinical studies in the field. For example, a future network meta-analysis would provide sufficient information to distinguish between individual interventions' efficacy. However, plenty more RCTs are needed before we can conduct an accurate comparison.

More research on the pathophysiology of thermal injuries is essential. A particular emphasis should be on the pharmacological treatment possibilities for different burn depths, areas and demographic groups for the optimal future use of combustion dressings. In addition, the synergistic effects of combination treatments and their optimal reapplication rate ought also to be more widely investigated.

Implementing state-of-the-art diagnostic tools and AI in burn medicine could facilitate this process by objectively describing wounds or predicting and alerting for rare complications.

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10. Appendix

10.1. Publications and scientific activities

Publications related to the subject of the thesis

- Number of publications related to the subject of the thesis: 5
- Number of publications not associated with the subject of the thesis: 3
- Number of book chapters: 1
- Sum of all impact factors: 14.548
- Sum of impact factors from publications related to the topic of PhD thesis: 8.610
- All citations: 1
- Independent citations: 0

Publications in English related to the topic of the PhD thesis

Lőrincz, A., Váradi, A., Hegyi, P., Rumbus, Z., Tuba, M., Lamberti, A. G., Varjú-Solymár, M., Párniczky, A., Erőss, B., Garami, A. and Józsa, G. Paediatric Partial-Thickness Burn Therapy: A Meta-Analysis and Systematic Review of Randomised Controlled Trials. *Life*. 2022; **12**(5):619. doi: 10.3390/life12050619 **(Q2, IF: 3.251)**

Lőrincz, A., Lamberti, A.G., Juhász, Zs., Garami, A. and Józsa, G. Management of Pediatric Facial Burns with Zinc-Hyaluronan Gel. *Children*. 2022; **9**(7):976. doi: 10.3390/children9070976 **(Q2, IF: 2.835)**

Lőrincz, A., Lamberti, A.G., Juhász, Zs., Garami, A. and Józsa G. Pediatric deep burn management after split-thickness autologous skin transplantation: A comparative study. *Medicine* (Baltimore) 2021;**100**(44):e27633. doi: 10.1097/md.0000000000027633 **(Q2, IF: 1.817)**

Józsa, G., Dávidovics, K., **Lőrincz, A.**, Lamberti, A. G., Garami, A. and Juhász, Zs. Management of Pediatric Partial-Thickness Burns with Lavanid Gel (Polyhexamethylen Biguanide, Polyhexanide) "Case Reports". *Journal of Orthopedic Research and Therapy.* 2022;**7**. doi: 10.29011/2575-8241.001213

Publications in Hungarian, related to the topic of the PhD thesis

Lőrincz, A., Csákvári, Zs., Máthé, T., Oberritter, Zs., Garami, A. and Józsa, G. Gyermekkori, áramégés okozta kézujjsérülések ellátásáról és késői szövődményeiről. *Orvosi Hetilap.* 2022;**163**(14):564-68. doi: 10.1556/650.2022.32390 **(Q3, IF: 0.707)**

Other publications, not related to the topic of the PhD thesis

Válik, A., Harangozó, K., Garami, A., Juhász Zs., Józsa G., **Lőrincz, A.**, *Mid-Term Follow-Up Study of Children Undergoing Autologous Skin Transplantation for Burns.* Life. 2023; 13(3):762. doi:10.3390/life13030762 **(Q2, IF: 3.251)**

Csenkey, A., Hargitai, E., Pákai, E., Kajtár, B., Vida, L., **Lőrincz, A.**, Gergics, M., Vajda, P., Józsa, G. and Garami, A.: Experimental study of the effectiveness of different treatment methods in a rat model of partial-thickness burn injury. *Injury.* 2022; doi: 10.1016/j.injury.2022.09.062 **(Q1, IF: 2.687)**

Rumbus, Z., Oláh, E., Lamberti, A. G., **Lőrincz, A.**, Fekete, K., Kelava, L., Pakai, E. and Garami, A. TR(i)Ps in the realm of thermophysiology In: Rakonczay, Z., Kiss, L. (ed.) Proceedings of the EFOP-3.6.2-16-2017-00006 (LIVE LONGER) project Szeged, Hungary: University of Szeged 2020; 99: 51-51.

Manuscripts under preparation

Lőrincz, A., Kedves, A., Garami, A., Kisander, Zs. and Józsa, G. *Convolutional neural networks in the classification and complication prediction of paediatric supracondylaer humerus fractures.*

Kedves, A., Kisiván, K., Glavák, Cs., **Lőrincz, A.**, Kovács, Á. and Lakosi, F. *Assessment of Pretreatment Diffusion Parameters in Low-and Intermediate-Risk Prostate Cancer Patients Treated with Stereotactic Ablative Radiotherapy.*

Nudelman, H., **Lőrincz, A.**, Józsa, G.: Treatment of different articular surface injuries with absorbable implants

Nudelman, H., **Lőrincz, A.**, Józsa, G.: Treatment of pediatric ankle fractures with elastic metal nailing and PLGA absorbable implants.

Vajda, M., Szakó, L., Görbe, A., Szabó, L., Földi, M., **Lőrincz, A.**, Bucsi, L., Hegyi, P., and Józsa, G. *Analysis by fracture type of 214 pediatric cases from the prospective, multicentre, nationwide Hungarian supracondylar humerus fracture registry.*

International oral and poster presentations

Lőrincz, A., Váradi, A., Hegyi, P., Rumbus, Z., Tuba, M., Lamberti, A.G., Varjú-Solymár, M., Párniczky, A., Erőss, B., Garami, A. and Józsa, G. *Pediatric partial-thickness burn therapy: a meta-analysis and systematic review of randomised controlled trials.* 17th Congress of Hungarian Association of Pediatric Surgeons (HAPS) with International Participation, Pécs, Hungary, September 9-11, 2021

Lőrincz, A., Lamberti, A.G., Juhász, Zs., Garami, A. and Józsa, G. *Pediatric deep burn management after split-thickness autologous skin transplantation - a comparative study.* 17th Congress of Hungarian Association of Pediatric Surgeons (HAPS) with International Participation, Pécs, Hungary, September 9-11, 2021

Lőrincz, A., Csákvári, Zs., Máthé, T., Oberritter, Zs., Garami, A. and Józsa G. *Case reports of pediatric electrical finger burn injuries - management and late-onset*

complications. 17th Congress of Hungarian Association of Pediatric Surgeons (HAPS) with International Participation, Pécs, Hungary, September 9-11, 2021

Csenkey, A., Hargitai, E., Pákai, E., Kajtár, B., Vida, L., **Lőrincz, A.**, Gergics, M., Vajda, P., Józsa, G. and Garami, A. *Examination of the effectiveness of different treatment methods on animal combustion models.* 17th Congress of Hungarian Association of Pediatric Surgeons (HAPS) with International Participation, Pécs, Hungary, September 9-11, 2021

Kedves, A., Kisiván, K., Glavák, Cs., **Lőrincz, A.**, Kovács, Á., Lakosi, F. *Assessment of Pretreatment Diffusion Parameters in Low-and Intermediate-Risk Prostate Cancer Patients Treated with Stereotactic Ablative Radiotherapy.* Annual Congress of the European Association of Nuclear Medicine (EANM'22), Barcelona, Spain, October 15-19, 2022

National oral and poster presentations

Lőrincz, A., Lamberti, A.G., Juhász, Zs., Garami, A., Józsa, G. *Égés miatt transzplantált gyermekek posztoperatív kötéseinek összehasonlító vizsgálata*. Magyar Gyermekorvosok Társasága 2021. évi Nagygyűlése, Pécs, June 24-26, 2021

Lőrincz, A., Csákvári, Zs., Máthé, T., Oberritter, Zs., Garami, A. and Józsa G. *Gyermekkori áramégés okozta kézujj sérülések ellátása és késői szövődményei.* Magyar Gyermeksebész Társaság 2021. évi tudományos ülése, Szeged, June 4-5, 2021

Lőrincz, A., Lamberti, A. G., Juhász, Zs., Garami, A. and Józsa, G. *Égés miatt transzplantált gyermekek posztoperatív kötéseinek összehasonlító vizsgálata.* Magyar Gyermeksebész Társaság 2021. évi tudományos ülése, Szeged, June 4-5, 2021

10.2. Supplementary files for the meta-analysis

10.2.1. Search keys.

Search key for the Embase database

('child'/exp OR child OR 'child' OR 'children' OR 'infant'/exp OR infant OR 'infant' OR 'newborn'/exp OR newborn OR 'neonate' OR 'baby'/exp OR baby OR 'toddler'/exp OR toddler OR 'adolescent'/exp OR adolescent OR 'adolescent' OR 'teenager' OR 'pediatric'/exp OR pediatric OR 'paediatric'/exp OR paediatric) AND ('burn'/exp OR burn OR 'scald'/exp OR scald OR 'thermal injury'/exp OR 'thermal injury' OR 'flame'/exp OR flame) AND ('partial thickness' OR 'second degree' OR 'deep partial' OR 'superficial partial' OR 'mid dermal' OR 'intermediate thickness')

Search key for the CENTRAL, MEDLINE (via PubMed) and Web of Science databases

((child* OR pediatric OR paediatric OR infant* OR newborn* OR baby* OR adolescent* OR teenager*) AND (burn* OR scald* OR flame* OR thermal injur*) AND (second degree* OR partial thickness* OR deep partial* OR superficial partial* OR mid dermal* OR intermediate thickness*))

10.2.2. Supplementary Figures

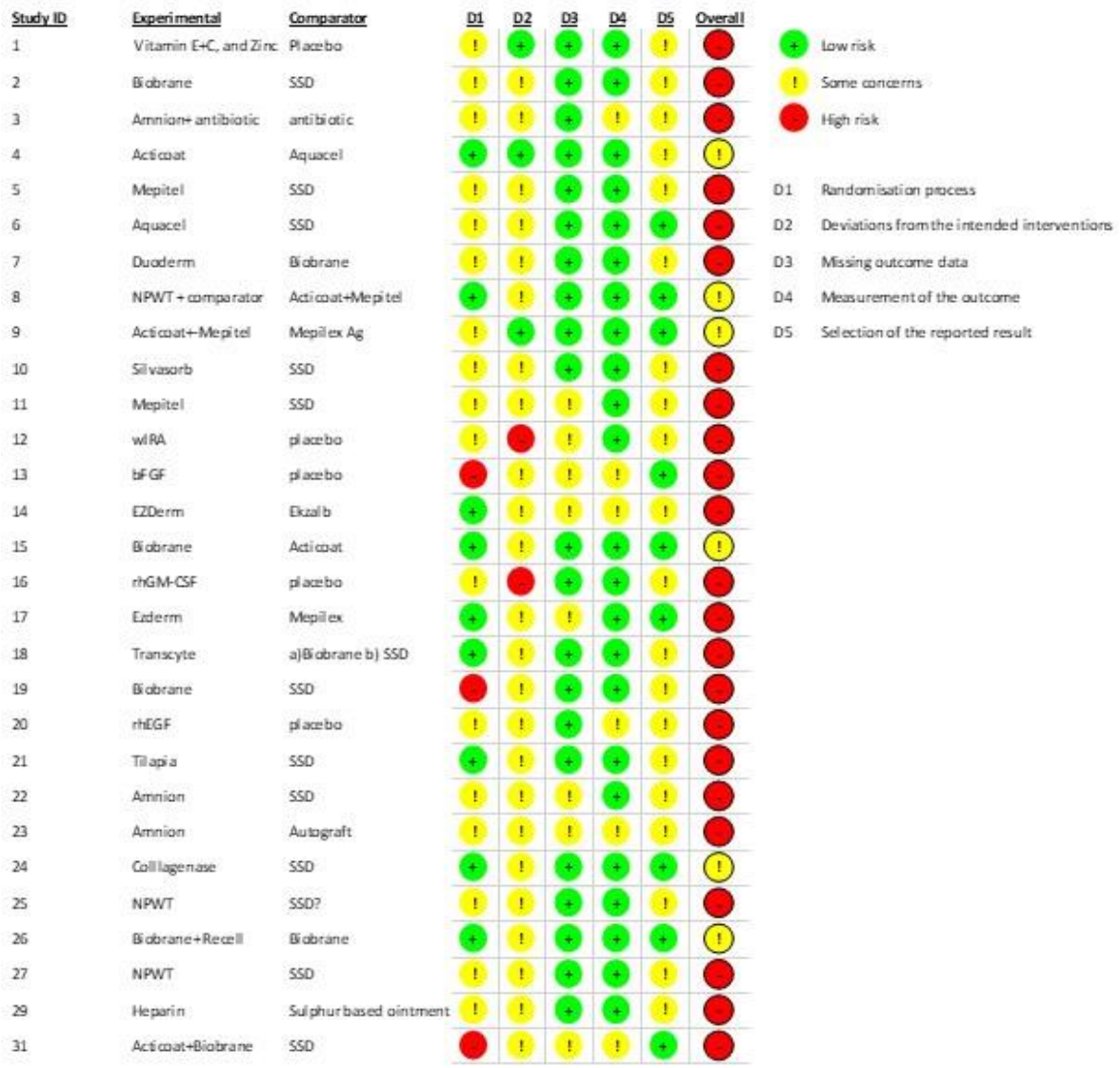

Figure S1: Risk of bias assessment. The RCTs compared paediatric patients with PT burns.

Figure S2: Pooled TTRE of the interventions, adjusted by burn depth. The groups were II/A, II and II/B injuries in children, and the TTRE was measured in days.

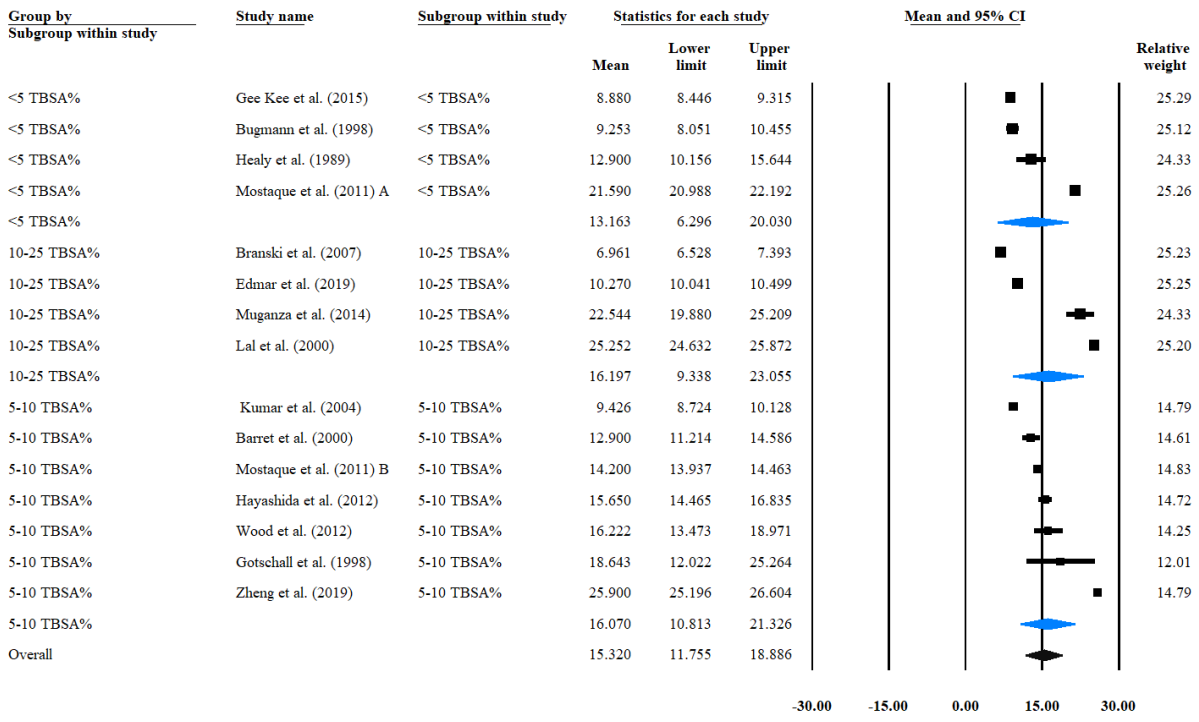

Figure S3: Mean TTRE of the interventions, modified by burn area. The categories were <5, 5-10, 10-25 TBSA% paediatric PT injuries, and the TTRE was calculated in days.

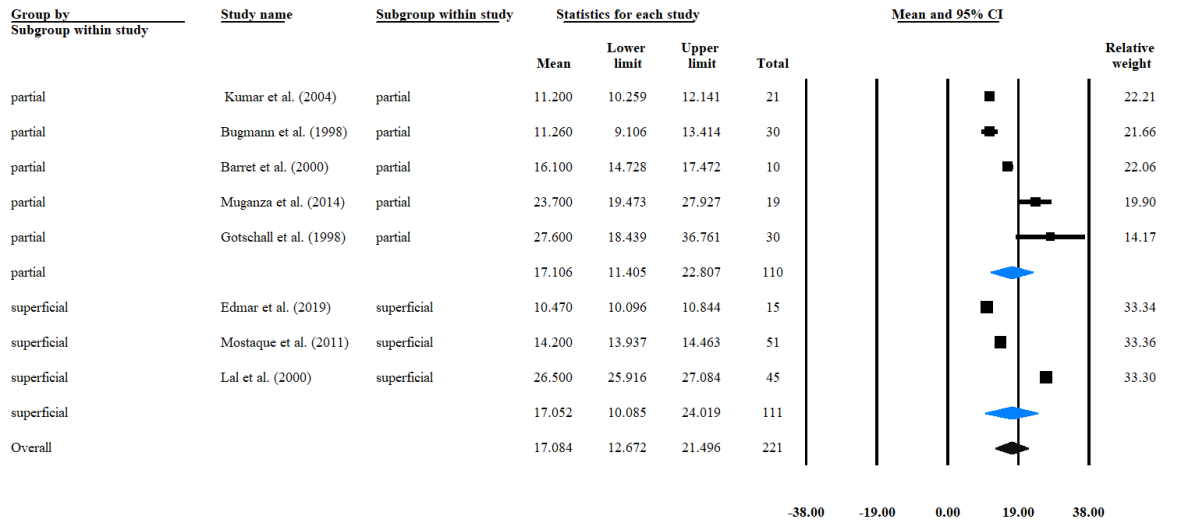

Figure S4: SSD's mean TTRE stratified by depth. The classifications were paediatric II/A and II burns, and the TTRE was determined in days.

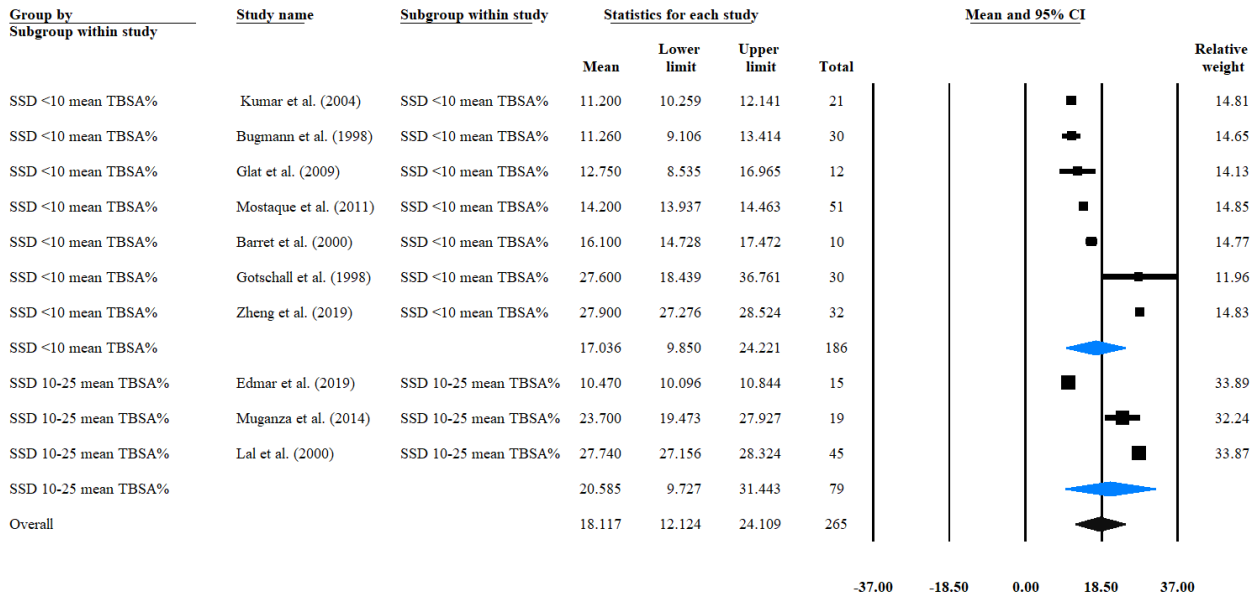

Figure S5: Average TTRE of SSD, modified by burn area. The area cohorts were <10 and 10-25 TBSA% PT injuries, and the TTRE was defined in days.

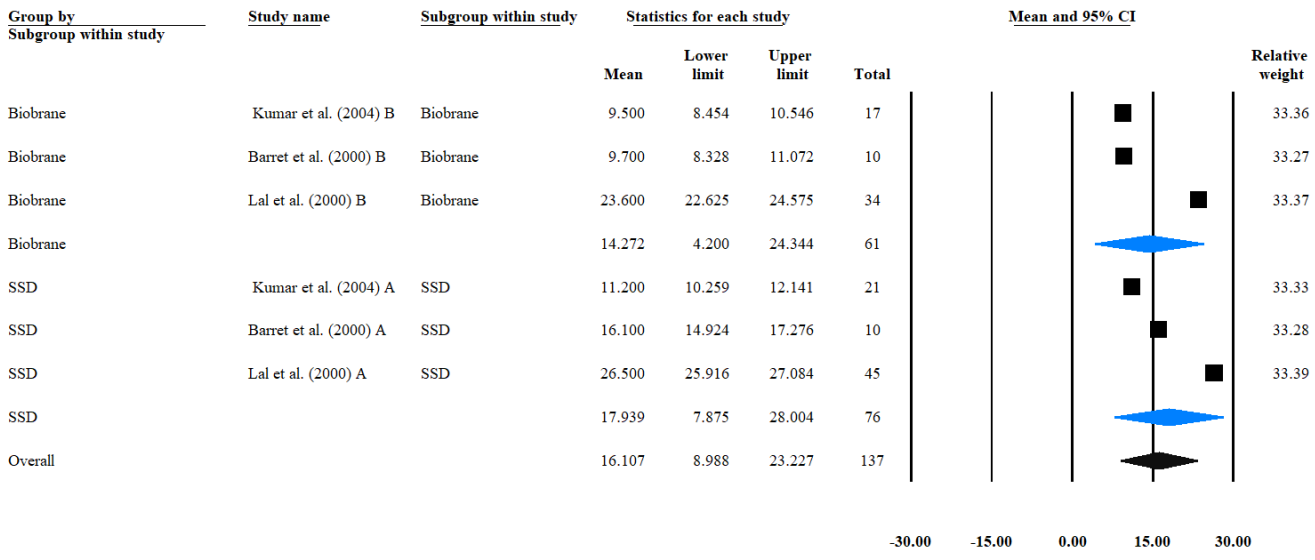

Figure S6: The mean TTRE of SSD and Biobrane. The meta-analysis of TTRE in children with PT was measured in days.

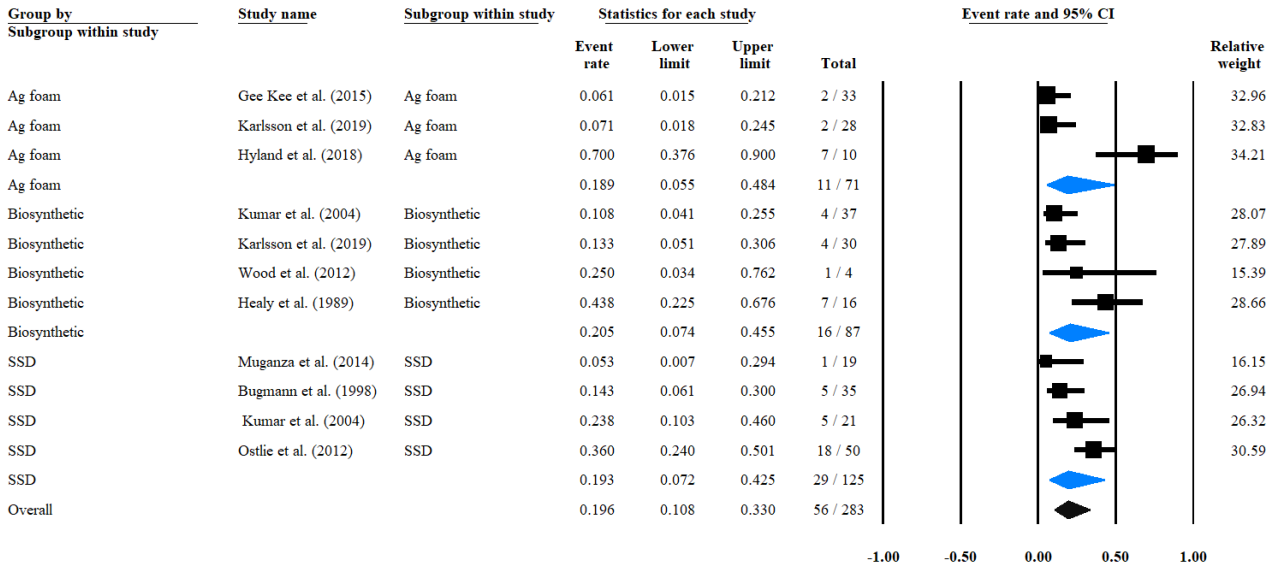

Figure S7: Average grafted percentages. Treatment groups were paediatric PT patients with SSD, silver foam and biosynthetic dressings.

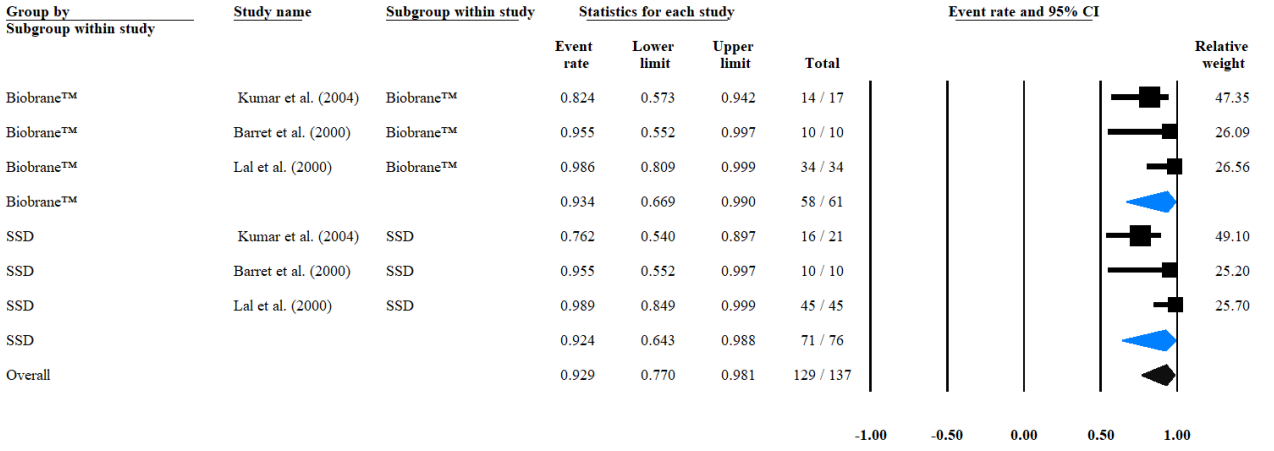

Figure S8: Mean non-grafted patient ratio with SSD and Biobrane. It shows the percentage comparison of successful conservative treatment in PT injuries of children.

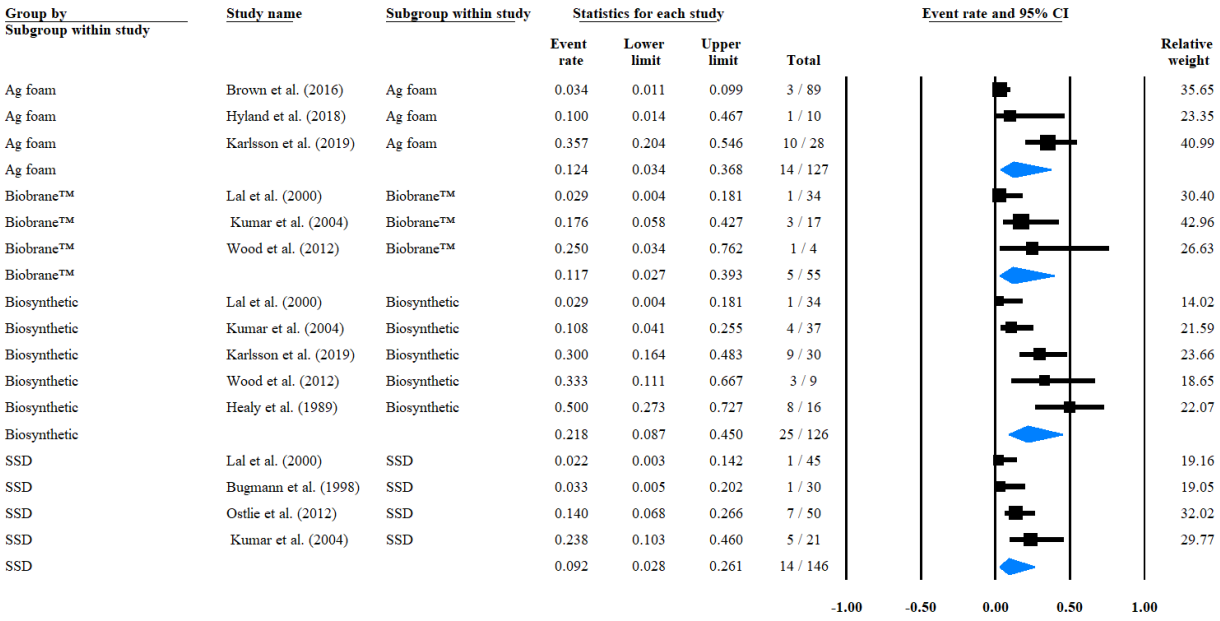

Figure S9: Average infected population percentages. Treatment comparison of SSD, biosynthetic and silver-foam dressings, and Biobrane only in paediatric PT injuries.

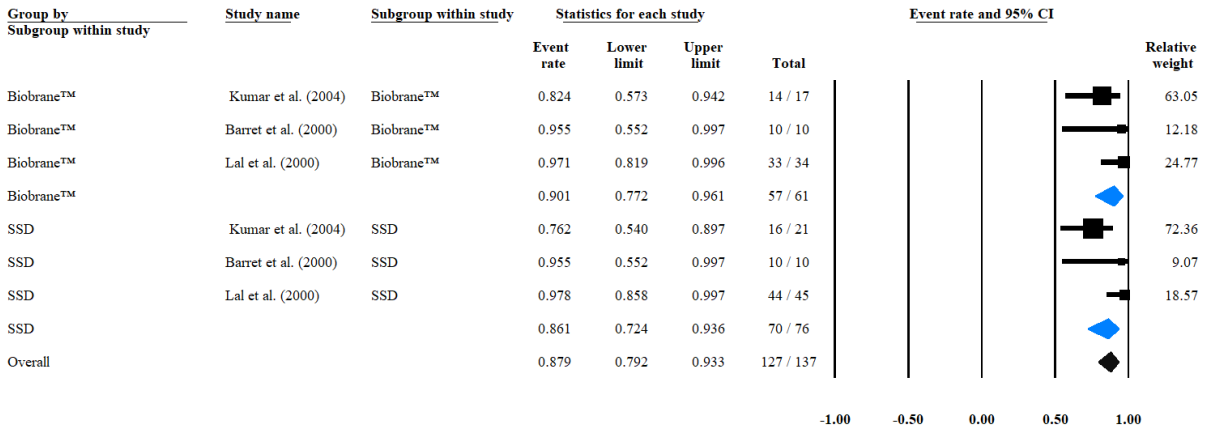

Figure S10: Mean non-infected patients' ratio of SSD compared to Biobrane. The meta-analysis compares the frequencies of complication-free paediatric PT burn treatments in percentages.

10.2.3. Supplementary Tables

Table S1: PRISMA checklist. These page numbers are valid for the meta-analysis only.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1-3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3, S1 Text
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	22
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3-4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3, S2 Text
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3-4, Figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3-4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3-4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5-8, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8, Figure S1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-18
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-18
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8, Figure S1
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9-18
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	19-20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20-21
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	22

Table S2: Mean TTRE of pediatric II/A treatments. Values were calculated in days.

Depth: II/A	**Publication data**	**No. of patients**	**TBSA%**		**TTRE (days)**			
Intervention	**Author (year of publication)**		**mean**	**SD**	**mean**	**SD**	**TBSA/ TTRE**	**TTRE red%**
Biobrane	**Lal et al. (2000)**	**34**	**11.5**	NR	**23.6**	2.9	**0.49**	
SSD SUM		**75**	**10.98**		**20.83**		**0.53**	
SSD	**Lal et al. (2000)**	**45**	11.8	NR	26.5	2	0.45	
SSD	**Mostaque et al. (2011)**	**15**	9.39	4.62	14.2	0.96	0.66	
SSD	**Edmar et al. (2019)**	**15**	10.13	4.16	10.47	0.74	0.97	
Amnion	**Mostaque et al. (2011)**	**29**	**7.39**	3.63	**13.33**	0.95	**0.56**	
Tilapia	**Edmar et al. (2019)**	**15**	**11.13**	4.94	**10.07**	0.46	**1.11**	
NPWT	**Shen et al. (2013)**	**145**	NR	NR	**9.2**	0.6	NA	**12.57**
rhEGF	**Liang et al. (2007)**	**30**	NR	NR	**8.83**	2.48	NA	**20.16**
wIRA(75%)+VIS	**Illing et al. (2008)**	**10**	NR	NR	**9**	NR	NA	**30.77**
placebo (VIS)	**Illing et al. (2008)**	**10**	NR	NR	**13**	NR	NA	NA
placebo (saline gauze)	**Liang et al. (2007)**	**30**	NR	NR	**11.06**	3.05	NA	NA
TT	**Shen et al. (2013)**	**162**	NR	NR	**10.1**	1.6	NA	NA

(II/A= Superficial partial-thickness injury; NA= not applicable; NPWT= negative pressure wound therapy, NR= not reported; SD= standard deviation; SSD= silver sulphadiazine; SUM= the summarized values of the same interventions; TBSA%= burned area of the total body surface; TT= traditional treatment; TTRE= time to reepithelialisation; TBSA%/TTRE= the area of regeneration per day; TTRE red%= the percentage of time reduction, with the addition of the intervention; VIS= visible spectrum light; wIRA= water-filtered infrared A)

Table S3: The average TTRE in paediatric II/A and MD burns. The TTRE was measured in days. Unfortunately, no description was provided about the TBSA% in these instances; thus, the T%/T ratios could not be calculated.

Depth: II/A + MD	**Publication data**	**No. of pati-ents**	**TTRE (days)**	
Intervention	**Author (year of publication)**		**mean**	**SD**
SSD SUM		**31**	**14.74**	
SSD	**Caruso et al. (2006)**	19	16	NR
SSD	**Glat et al. (2009)**	12	12.75	7.45
Aquacel Ag	**Caruso et al. (2006)**	**13**	**14**	NR
Silvasorb	**Glat et al. (2009)**	**12**	**12.42**	3.58
Biobrane	**Cassidy et al. (2005)**	**35**	**12.24**	5.1
Duoderm	**Cassidy et al. (2005)**	**37**	**11.21**	6.5

(II/A= Superficial partial-thickness injury; MD= mid-dermal burn; NR= not reported; SD= standard deviation; SSD= silver sulphadiazine; SUM= the summarized values of the same interventions; TBSA%= burned area of the total body surface; TTRE= time to reepithelialisation)

Table S4: Mean TTRE summary of II/B injuries in children. The TTRE was calculated in days.

Depth: II/B	**Publication data**	**No. of patients**	**TBSA(%)**		**TTRE(days)**		**TBSA%/ TTRE**	**TTRE red%**
Intervention	**Author (year of publication)**		**mean**	**SD**	**mean**	**SD**		
AM	**Mostaque et al. (2011)**	**22**	**2.25**	3.14	**21.59**	1.44	**0.1**	
SSD SUM		**68**	**5.48**		**25.69**		**0.21**	
SSD	**Zheng et al. (2019)**	**32**	5.8	1.6	27.9	1.8	0.21	
SSD	**Mostaque et al. (2011)**	**36**	5.2	5.45	23.72	1.5	0.22	
NPWT	**Zheng et al. (2019)**	**32**	**5.5**	2.2	**23.9**	2.3	**0.23**	**14.3**
rhEGF	**Liang et al. (2007)**	**30**	NR	NR	**15.12**	3.19	NA	**20.7**
rhGM-CSF	**Jiaao et al. (2010)**	**15**	NR	NR	**13.47**	1.08	NA	**27.9**
placebo (saline gauze)	**Liang et al. (2007)**	**30**	NR	NR	**19.06**	3.07		
placebo (hydrogel matrix)	**Jiaao et al. (2010)**	**15**	NR	NR	**18.69**	2.35		

(II/B= Deep partial-thickness burn injury; AM= amnion membrane; NA= not applicable; NPWT= negative pressure wound therapy; NR= not reported; SD= standard deviation; SSD= silver sulphadiazine; SUM= the summarised values of the same interventions; TBSA%= burned area of the total body surface; TTRE= time to reepithelialisation; TBSA%/TTRE= the area of regeneration per day);

Table S5: Average percentage of reepithelialisation on the tenth day (day 10 RE%) in paediatric PT injuries.

Intervention	Burn depth	Publication data	No. of patients	TBSA (%)	TTRE (days)	day 10 RE (%)	TBSA%/ TTRE
		Author (year of publication)		mean	mean		
SSD	II/A	Edmar et al. (2019)	15	10.13	10.47	53.33	0.97
Tilapia		Edmar et al. (2019)	15	11.13	10.07	86.67	1.11
Acticoat+Mepitel	II	Frear et al. (2020)	54	1.35	10.7	42.45	0.13
SSD		Bugmann et al. (1998)	30	1.92	11.26	53.33	0.17
NPWT+Acticoat+Mepitel		Frear et al. (2020)	44	1.5	8.71	68.57	0.17
Mepitel		Bugmann et al. (1998)	36	3.29	7.58	77.77	0.44
Biobrane		Wood et al. (2012)	4	8.00	17.75	83.20	0.63
Acticoat		Brown et al. (2016)	41	2.40	NR	93	NA
Aquacel Ag		Brown et al. (2016)	40	2.50	NR	94	NA
Biobrane + ReCell		Wood et al. (2012)	5	5.20	15	95	0.35

(II= Partial-thickness burn injury (PT); II/A= superficial PT; AM= amnion membrane; day 10 RE= the fraction of reepithelialisation on the tenth day; NA= not applicable; NPWT= negative pressure wound therapy; NR= not reported; SSD= silver sulphadiazine; TBSA%= burned area of the total body surface; TTRE= time to reepithelialisation; TBSA%/TTRE= the area of regeneration per day);

Table S6: Mean length of stay. The time children spent (days) inside the hospital while being treated with different regimens for PT burns.

Intervention	Publication data	No. of patients	LOS (days)	
	Author (year of publication)		mean	SD
Biobrane+Acticoat	**Muganza et al. (2014)**	**26**	**27.77**	25.93
Autograft	**Omranifard et al. (2011)**	**32**	**20.2**	10.3
SSD II		**130**	**13.77**	
AM II		**85**	**11.37**	
AM	**Omranifard et al. (2011)**	34	12.4	7.6
AM	**Mostaque et al. (2011)**	**51**	10.69	3.87
Collagenase+PMB	**Ostlie et al. (2012)**	**50**	**11.3**	5.8
SSD II+II/A		**175**	**10.46**	
SSD	**Muganza et al. (2014)**	19	26.83	21.2
SSD	**Mostaque et al. (2011)**	51	13.43	5.13
SSD	**Ostlie et al. (2012)**	50	11.2	5.2
SSD	**Barret et al. (2000)**	10	3.6	NR
SSD II/A	**Lal et al. (2000)**	45	**5.79**	NR
EZDerm	**Karlsson et al. (2019)**	**30**	**3.36**	3.94
Mepilex	**Karlsson et al. (2019)**	**28**	**3.12**	2.2
Biobrane II+II/A		**44**	**2.36**	
Biobrane	**Barret et al. (2000)**	10	**1.5**	NR
Biobrane II/A	**Lal et al. (2000)**	34	**2.62**	NR
AM+Nystatin+PMB	**Branski et al. (2007)**	**53**	**2**	3
Nystatin+PMB	**Branski et al. (2007)**	**49**	**2**	3

(II= Partial-thickness burn injury (PT); II/A= superficial PT; AM= amnion membrane; LOS= length of hospital stay; NPWT= negative pressure wound therapy; NR= not reported; PMB= polymyxin b; SD= standard deviation; SSD= silver sulphadiazine);

life

Systematic Review

Paediatric Partial-Thickness Burn Therapy: A Meta-Analysis and Systematic Review of Randomised Controlled Trials

Aba Lőrincz [1], Alex Váradi [2], Péter Hegyi [3,4,5], Zoltán Rumbus [1], Máté Tuba [1], Anna Gabriella Lamberti [1,6], Margit Varjú-Solymár [3], Andrea Párniczky [3], Bálint Erőss [3,4,5], András Garami [1] and Gergő Józsa [1,6,*]

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Abstract: Background: Paediatric second-degree burn injuries are a significant source of medical challenges to the population that may cause severe, lifelong complications. Currently, there are dozens of therapeutic modalities and we aimed to summarise their reported outcomes and determine their effectiveness, compared to the widely used silver sulphadiazine (SSD). Methods: We conducted the meta-analysis and systematic review of randomised controlled trials (RCTs), which investigated the performance of dressings in acute paediatric partial-thickness burns. The evaluated endpoints were time until wound closure, grafting and infection rate, number of dressing changes and length of hospitalisation. Results: Twenty-nine RCTs were included in the qualitative and 25 in the quantitative synthesis, but only three trials compared SSD directly to the same intervention (Biobrane). Data analysis showed a tendency for faster healing times and a reduced complication rate linked to biosynthetic, silver foam and amnion membrane dressings. A substantial difference was found between the number of dressing changes associated with less pain, narcosis and treatment duration. Conclusions: Considerable between-study heterogeneity was caused by the unequal depth subcategory ratio and surface area of the injuries; therefore, no significant difference was found in the main outcomes. Further research is necessary to establish the most effective treatment for these burns.

Keywords: paediatric second-degree burn; silver sulphadiazine; silver foam; biosynthetic dressing; skin substitutes

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1. Introduction

Nearly one hundred thousand (viz., ~96,000) children suffer a fatal injury from preventable, mostly flame-related (~93%) burn traumas, each year, that is 263 cases per day, according to the WHO's latest global report. The likelihood of a non-fatal injury is assumed to be at least ten times higher (i.e., 1–7,000,000/year), and due to the absence of a successfully coordinated prevention, treatment or rehabilitation strategy, almost half of them (49%) suffer from some form of irreversible disability after the burn [1,2]. Complications such as extensive contractures and amputations constitute physical impairments, but even a relatively minor scar or the memory of the trauma can provoke lifelong psychological disorders [3–5]. Compared to adults, children, especially infants, have thinner skin and

immature defensive reflexes, with limited environmental experience in addition to their natural curiosity towards their surroundings [6–8]. Therefore, by touching hot surfaces and pulling hot liquids onto themselves, children can severely injure often multiple and critical parts of their body: upper limbs, head and neck, and legs in 51, 39 and 26% of all cases, respectively [9].

The severity and prognosis of a burn are determined by the depth, area and location of the injury, along with the patient's general health and age. Burns are often mixed depth, in a map-like pattern; thus, evaluating their exact severity still constitutes a challenge [10]. In second-degree or partial-thickness burns (PT or II), the skin's dermis layer is affected, and it can be further classified into two subcategories. Superficial partial-thickness thermal injuries (II/A) involve the papillary layer of the dermis. In II/A burns, spontaneous healing takes on average 7 to 10 days and long-term pigmentation changes may occur. Straw-yellow bullae and—after their removal—painful, moist, bright pink wound beds with intact epidermal appendages characterise this condition.

In comparison, deep PT burns (II/B) damage the stratum reticulare as well, and the wound bed turns numb and dry with a blotched pale, white or purple colour and the loss of all epidermal appendages. Spontaneous recovery often results in extensive hypertrophic scar development and contractures. In full-thickness (third-degree or III) thermal injuries, the entire skin is necrotised and becomes leathery dry, painless, as well as pale, and pearly [11]. Complete regeneration does not occur by primary intention, and an operative approach is necessary to help these patients [12].

While advances in medicine have led to the introduction of an abundant number of therapeutic options to treat children with PT burns, many questions remained unanswered regarding their optimal use and effectiveness. The different interventions were primarily developed for the chronic wounds of adult patients, while paediatric burn injuries possess different healing potential qualities, inflammatory status and exudation [10]. Some dressing materials may be better suited for treating burns in younger patients because of their different burn aetiology, physiology and still evolving nature [13]. In the case of delayed or inadequate medical interventions, the frequency, severity and duration of the complications are increased, resulting in extended hospital stays and the higher use of anaesthetic and analgesic drugs, as well as the total cost of care. Therefore, a rapid and effective therapeutic response is critical in these severe forms of burns (i.e., II/B, III) [12]. At the same time, the lack of current evidence-based treatment guidelines makes it hard to determine which materials should be preferred for a specific type of injury.

The management of paediatric PT burns consists of primary care (e.g., cooling, painkillers, fluid resuscitation and transportation), cleaning and disinfecting the wound, then removing the necrotic tissue. After that, the surgeon must restore the damaged skin barrier to protect the patient from fluid loss and infections. The burn wound is either covered in a conservative approach with dressings and topical ointments or surgery is performed by sewing a skin graft onto the injury site followed by the application of a conservative dressing [12–14]. Recent studies confirmed that a moist environment is beneficial for burned tissue regeneration [15]. The ideal temporary skin replacement possesses absorbent and antimicrobial qualities, can be quickly and painlessly changed—so it must not stick to the wound bed—, while it also stays in place during the healing of the wound. It should be transparent as well—to be able to monitor the injury—, and affordable, without causing any irritation or toxicity. Such an ideal dressing, which fulfils all these criteria, unfortunately, does not yet exist, but certain interventions' attributes are closer to the idyllic model than others.

In the past, the gold standard for the topical treatment of paediatric PT burns was the soft, white and water-soluble silver sulphadiazine (SSD) 1% cream, under many product names such as Dermazin®, Flamazine®, Silvadene® or Silvazin® [16–27]. It is still the most commonly administered treatment in many countries as it allows wounds to heal without the need for surgical intervention. Thus, we chose this therapy as a comparator because most of the articles reported their findings correlated to SSD due to its historical relevance.

However, numerous studies revealed several disadvantages to the use of SSD, which led to the development of a wide range of alternative topical treatments. Nevertheless, their efficacy in the management of paediatric PT burns remains largely unclarified. A summary of each intervention that was analysed and compared to SSD in the present study can be found in Text S1.

We performed a literature search to systematically review the available treatment options for paediatric PT burns, then conducted a meta-analysis to obtain insights into the dressings' healing potential and complication rate. We aimed at collecting randomised controlled trials (RCTs) about PT burn treatments that reported the time to reepithelialisation (TTRE), grafting and infection rate, number of dressing changes and length of hospital stay (LOS) in patients younger than 18 years old at the time of the injury.

2. Materials and Methods

2.1. Search Methods for Identification of Records

On 29 October 2020, a systematic search was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA) (Table S1) [28]. We searched for RCTs that compared at least two different interventions in patients under the age of eighteen with PT burns in the MEDLINE (via PubMed), Embase, Web of Science and CENTRAL databases (Figure 1).

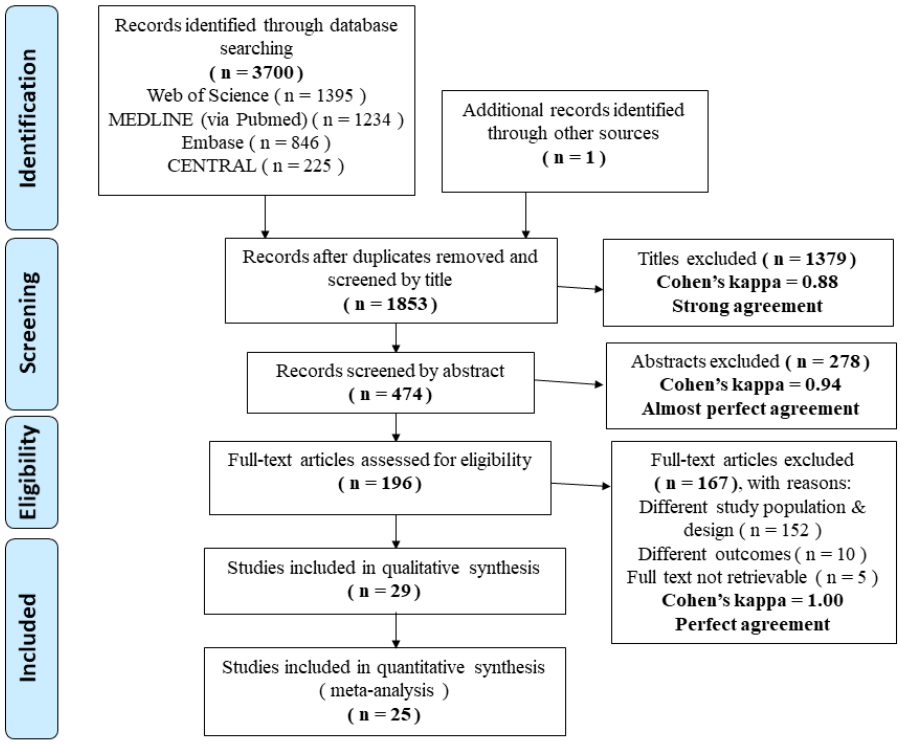

Figure 1. PRISMA flow chart. It represents the process of the study search and selection.

Our search keys can be found in Text S2, and the records identified by them were exported without the use of filters.

2.2. Study Selection, Data Extraction and Management

The studies identified by the search were screened by two independent review authors (AL and MT) to assess their eligibility. The eligible articles were collected in EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA), then the outcomes recorded in Microsoft Excel (Microsoft Corporation, Albuquerque, NM, USA) by two authors independently (AL and MT). Discrepancies were resolved by consensus after re-checking the original article.

The extracted data consisted of the children's characteristics, including the number of participants, age, depth of injury, percentage of burned area compared to total body surface area (TBSA%), and the type of interventions, as well as the reported outcomes, such as TTRE, grafting rate, infection rate, number of dressing changes and LOS. Further parameters, such as treatment cost, pain and scarring could not be analysed among the outcomes because of data ineligibility.

2.3. Assessment of Methodological Quality of Included Records

The risk of bias of the individual RCTs was assessed as "low", "some concerns" or "high", independently by the two investigators (AL and MT) with the use of the Cochrane Collaboration's RoB2.v7 tool. Discrepancies were resolved by consensus. Randomisation process, deviations from the intended interventions, missing outcome data, measurement of the outcome and the selection of the reported results were evaluated to conclude the overall bias of each article.

Additionally, the evaluation of funding sources, conflict of interest statements and adherence to the Consolidated Standards Of Reporting Trials (CONSORT) statement were also conducted, using which, criteria were developed in order to ascertain the standardization and reproducibility of the RCTs [29].

2.4. Data Synthesis

Statistical analysis was performed by an expert biostatistician (AV) using the methods recommended by the working group of the Cochrane Collaboration [30]. In the meta-analysis, the calculated effect sizes were visualised in forest plots using Comprehensive Meta Analysis (Version 3) statistical software (Biostat Inc., Englewood, NJ, USA). Heterogeneity was tested with Cochrane's Q (χ^2) test and the I^2 statistic. Q test was considered significant when *p*-values were less than 0.1. Based on the suggestion of the Cochrane Handbook, I^2 values from 30% to 60% represent moderate and between 50% and 90% substantial heterogeneity. Due to the groups' generally high heterogeneity, DerSimonian and Laird random-effects models were used in all analyses [31].

For continuous outcomes: means, and for dichotomous outcomes: event rates with 95% confidence intervals, were pooled in each subgroup to compare the differences between the intervention groups. In the case of some subgroups, there were studies with more than one intervention group; therefore, we combined these groups based on the suggestion of the 6.5.2.10 section of the Cochrane Handbook [30]. When the means and standard deviations (SD) of the effects were not reported, we derived these data from the graphical representation of the outcomes or by estimation based on the work of Wan et al. 2014 with the use of medians, minimum, maximum or quartiles [32]. In three trials, indicators of SD were not reported [21–23], thus, we obtained them from a previous meta-analysis [33], which included the required data.

3. Results

3.1. Search Results

The search identified 1853 potentially relevant records after duplicate removal that were screened by title (Figure 1). After exclusion, 474 abstracts were assessed. The full texts of a total of 196 articles were retrieved; then, 152 trials were excluded because they had an unmatching or unknown study population or design. Ten studies did not contain the specified outcomes and five full texts could not be obtained; thus, these were also excluded from the analysis. Finally, 24 RCTs containing 21 full-text articles and 3 conference abstracts [27,34,35] were included in this meta-analysis. Another full-text article [26] was identified when the reference lists of the eligible papers were checked; it was included in the qualitative synthesis. In the systematic review, an additional three full-text RCTs [36–38] and one conference abstract [39] were included.

3.2. Description of Included Studies

SSD [16–27] treatment was reported in comparison with amnion membrane (AM) [20,40,41], biosynthetic dressings (Biobrane, EzDerm, Transcyte) [18,21,22,40–44], Biobrane only [18,21,22,42,43], negative pressure wound therapy (NPWT) [27,35,45], silver foam dressings (Acticoat, Aquacel Ag, Mepilex Ag) [43–51] and Acticoat only [46,47,49], which can be seen in the following figures. The attributes of each aforementioned intervention, as well as autografts [41,52], Silvasorb [25], Tilapia [16], additional treatments (viz., collagenase [19], vitamin E + C + Zinc [53], wIRA [36], heparin [38], rhGM-CSF [34], bFGF [37] and rhEGF [39]) and combination therapies (Acticoat + Mepitel [45,46,50,51], NPWT + Acticoat + Mepitel [45], Biobrane + Acticoat [26,49], Biobrane + Recell [43]) are summarised in the following tables and Tables S2–S6. Only one multi-centre study [17] was identified. Six studies reported outcomes from II/A [16,20,22,35,36,39], five from II/B [20,27,34,39,41], three from II/A and MD [17,25,42] and one from MD injuries only [46], while in the remaining studies, the exact depth of the injury was not specified in children with PT burns [18,19,21,23,24,26,37.40,43–45,47,48,53]. The trial and patient characteristics of the 29 RCTs analysed in this study are summarised in Table 1.

Table 1. Characteristics of included studies.

Publication Data			Intervention	Demography		Aetiology			Burn Depth	Age (Years)			
Author	Year of Publication	Country		No. of Patients	Female (%)	Scald (%)	Contact (%)	Flame (%)		Mean	SD	Min (Months)	Max
Barbosa et al. [53]	2009	Brazil	**Vitamin C&E + Zn**	17	35.3	NR	NR	NR	II	4.51	4.32	NR	NR
			placebo	15	33.3	NR	NR	NR		4.53	3.74	NR	NR
Barret et al. [18]	2000	USA, Texas	**Biobrane**	10	30	80	0	20	II	3.1	0.5′	NR	17
			SSD (Silvadene)	10	20	70	0	30		3.7	0.6′	NR	17
Branski et al. [40]	2007	USA, Texas	**Nystatin + PMB**	49	28.57	45	0	55	II	7	4	NR	NR
			AM + Nystatin + PMB	53	30.19	43	0	57		7	4	NR	NR
Brown et al. [47]	2016	New Zealand	**Acticoat**	41	46.67	91	9	0	II	4.3	4	NR	15
			Aquacel Ag foam	40	43.18	95	5	0		3	3.5	NR	15
Bugmann et al. [24]	1998	Switzerland	**Mepitel**	36	46.34	68.3	26.8	4.87	II	3.29	3.09	3	15
			SSD (Flamazin)	30	42.86	60	25.7	11.43		3.43	3.7	3	15
Caruso et al. [17]	2006	USA, Arizona	**Aquacel Ag foam**	13	NR	NR	NR	NR	II/A + MD	NR	NR	2	16
			SSD	19	NR	NR	NR	NR		NR	NR	2	16
Cassidy et al. [42]	2005	USA, Kansas	**Duoderm**	37	NR	NR	NR	NR	II/A + MD	NR	NR	36	18
			Biobrane	35	NR	NR	NR	NR		NR	NR	36	18
Frear et al. [45]	2020	Australia	**Acticoat + Mepitel**	54	42.59	65	33	2	II	4 *	NR	12 **	9^
			NPWT+ Acticoat + Mepitel	47	59.57	60	36	4		4 *	NR	12 **	8^
Gee Kee et al. [46]	2015	Australia	**Acticoat**	31	41.94	58.1	35.5	3.2	II	1	NR	1	5
			Acticoat + Mepitel	32	34.38	62.5	34.4	3.1		1	NR	1	4
			Mepilex	33	51.52	54.5	42.4	0		1	NR	1	4
Glat et al. [25]	2009	USA, Pennsylvania	**Silvasorb**	12	NR	NR	NR	NR	II/A + MD	3.58	2.43	13	5
			SSD (Silvadene)	12	NR	NR	NR	NR		1.9	1.13	9	9
Gotschall et al. [23]	1998	USA, Washington	**Mepitel**	33	NR	100	0	0	II	NR	NR	NR	12
			SSD	30	NR	100	0	0		NR	NR	NR	12
Hartel et al. [36]	2007	Germany	**wIRA(75%) + VIS**	10	NR	NR	NR	NR	II/A	NR	NR	NR	NR
			VIS (placebo)	10	NR	NR	NR	NR		NR	NR	NR	NR

Table 1. *Cont.*

Publication Data			Intervention	Demography		Aetiology			Burn Depth	Age (Years)			
Author	Year of Publication	Country		No. of Patients	Female (%)	Scald (%)	Contact (%)	Flame (%)		Mean	SD	Min (Months)	Max
Hayashida et al. [37]	2012	Japan	**bFGF**	15	NR	66.7	13.3	20	II	NR	NR	8	2.67
			placebo (Ekzalb)	15	NR	73.3	6.7	20		NR	NR	8	2.67
Healy et al. [44]	1989	UK	**EZDerm**	9	NR	NR	NR	NR		2.6	0.6′	NR	NR
Hyland et al. [49]	2018	Australia	**Biobrane + Acticoat**	10	30	NR	NR	NR	MD	NR	NR	0	16
			Acticoat	10	20	NR	NR	NR		NR	NR	0	16
Jiaao et al. [34]	2010	China	**rhGM-CSF**	15	NR	NR	NR	NR	II/B	5.3	NR	NR	NR
			placebo (hydrogel matrix)	15	NR	NR	NR	NR		5.3	NR	NR	NR
Karlsson et al. [48]	2019	Sweden	**Ezderm**	30	36.67	100	0	0	II	1.75 *	NR	11 **	4.92 ^
			Mepilex	28	42.86	100	0	0		1.42 *	NR	8 **	2.92 ^
Kumar et al. [21]	2004	Australia	**Biobrane**	17	NR	NR	NR	NR	II	3.6	NR	NR	NR
			Transcyte	20	NR	NR	NR	NR		3.6	NR	NR	NR
			SSD (Silvazin)	21	NR	NR	NR	NR		3.6	NR	NR	NR
Lal et al. [22]	2000	USA, Texas	**Biobrane**	34	44.12	100	0	0	II/A	2.8	0.5′	0	17
			SSD	45	33.33	100	0	0		3.4	0.6′	0	17
Liang et al. [39]	2007	China	**rhEGF**	30	NR	NR	NR	NR	II/A	NR	NR	NR	14
				30	NR	NR	NR	NR	II/B	NR	NR	NR	14
			placebo (saline gauze)	30	NR	NR	NR	NR	II/A	NR	NR	NR	14
				30	NR	NR	NR	NR	II/B	NR	NR	NR	14
Lima Júnior et al. [16]	2019	Brazil	**Tilapia**	15	33.3	93.3	0	6.67	II/A	5.67	3.66	24	12
			SSD	15	46.67	80	0	20		5.2	2.7	24	12
Mostaque et al. [20]	2011	Bangladesh	**AM**	51	52.9	82.4	0	17.6	II/A	3.61	2.31	0.03	12
				22	NR	NR	NR	NR	II/B	NR	NR	0.03	12
			SSD	51	51	49	0	51	II/A	4.03	2.4	0.03	12
				36	NR	NR	NR	NR	II/B	NR	NR	0.03	12
Muganza et al. [26]	2014	South Africa	**Biobrane + Acticoat**	26	46.15	NR	NR	NR	II	2.3 *	NR	20.4 **	4.1 ^
			SSD	19	57.89	NR	NR	NR		2.7 *	NR	19.2 **	4.1 ^
Omranifard et al. [41]	2011	Iran	**AM**	34	29.41	NR	NR	NR	II/B	5.4	7.5	NR	18
			autograft	32	34.38	NR	NR	NR		4.4	6.9	NR	18
Ostlie et al. [19]	2012	USA, Kansas	**Collagenase + PMB**	50	42	NR	NR	NR	II	4.8	4.5	2	18
			SSD	50	30	NR	NR	NR		5.1	4.5	2	18
Venkatacha lapathy et al. [38]	2012	India	**Heparin**	50	NR	NR	NR	NR	II	NR	NR	NR	NR
			Sulphur-based cream	50	NR	NR	NR	NR		NR	NR	NR	NR
Shen et al. [35]	2013	China	**NPWT**	145	NR	100	0	0	II/A	NR	NR	NR	NR
Wood et al. [43]	2012	Australia	**Biobrane**	4	50	100	0	0	II	4.95	3.91	8	9
			Biobrane + ReCell	5	40	100	0	0		1.32	0.55	8	9
Zheng et al. [27]	2019	China	**NPWT**	32	43.75	NR	NR	NR	II/B	3.9	1.6	NR	NR
			SSD	32	37.5	NR	NR	NR		3.8	1.7	NR	NR

Different markings were used when the analysed endpoints were given in * = median, ** = IQR25, ^ = IQR75 and ′ = SEM. (II = Partial-thickness burn injury (PT); II/A = superficial PT; II/B = deep PT; AM= amnion membrane; MD = mid-dermal or mixed-depth burn injury; NPWT = negative pressure wound therapy; NR = not reported; PMB = polymyxin b; SD = standard deviation; SSD = silver sulphadiazine; TBSA% = burned area of the total body surface; VIS = visible spectrum light; wIRA = water-filtered infrared.)

The mean age of the patients was 4.3 years. Of 756 patients, 14.3% were younger than one year, 78.6% were below the age of five and 21.4% were older than five years. The majority of the patients were boys: 655 out of 1089 children (59.1%). The 832 patients had an average of 7.5 TBSA%, which was distributed among the children as follows: 23.2% under 5 TBSA%, 46% between 5–10 TBSA% and 30.8% above 10 TBSA%. It is important to highlight that six articles did not report TBSA% [17,25,34–36,39]. Moreover, two studies reported median TBSA% without appropriate indicators of SD, thus, proper conversion from median to mean was not possible. Five trials included exclusively scalds [22,23,35,43,48]. In the remaining studies, the aetiological distribution of 628 patients' burns were 65.5% scalds, 18.7% flame, 15.4% contact and 0.5% electrical injuries. In most articles, the TTRE, grafting and infection rates, the number of dressing changes and LOS were assessed as outcome parameters. The TTRE was not discussed in only three trials [19,41,47], while the other parameters were reported in various fashions.

3.3. Methodological Quality of the Included Studies

A summary of the risk of bias assessment is shown in Figure S1. Generally, the risk of bias was considered high, and the articles often lacked essential information. Randomisation protocols were generally not discussed, but studies reported the use of lottery [16,21], tables of random numbers combined with lottery [20] and a randomization schedule [34]. Computer-generated individual unit block randomization [19] and randomization tables [27,35,47,49]—including one that was further stratified by age and area [17]—along with a statistician generated age-stratified permutated block method [45] were also used. One article divided the treatment groups by even and odd admission days [37], and one study contained seven patients with resident preference-based randomisation in addition to a computer-generated randomisation table [22].

Only seven articles mentioned allocation concealment with opaque, sealed envelopes [43,47], sealed envelopes [44], externally created coded envelopes [43,48], burn area stratified sealed envelopes [26], computer-generated results [47], REDCap concealment [45] or by not making them available to the caregivers [19]. Most of the studies could not be blinded due to the interventions' distinctive qualities, but there was one patient-blinded [16], three assessor-blinded [45–47] and five double-blind studies [26,36,39,41,53]. Selective reporting was challenging to estimate because only six articles referred to their original trial protocol [19,26,37,43,46,48].

While evaluating the funding sources, we found that eight articles received either financial or material donations from the manufacturer [17,20,21,25,45,46,53] and two were supported by solely independent grants [37,47], although most of these researchers stated that they had no conflict of interest, with two exceptions. One of the funders supervised the design of the study, the data analyses and the development of the manuscript [17], and another intervention was developed by the first author, who is also the director of the company that sells it [43].

Overall, two studies reported using the CONSORT criteria while conducting the research [45,46], which may be the reason behind the missing data, such as randomisation or concealment protocols.

3.4. Effects of Interventions

3.4.1. Time to Reepithelialisation (TTRE)

Our primary outcome to determine the interventions' effectiveness was the mean TTRE or complete wound closure time. A total of 623 participants (ranging from 4 to 145 in the different studies with an average of 30) from 17 trials were included in this meta-analysis. Interventions with similar characteristics were pooled together to rank this outcome because direct comparisons were only published for SSD and Biobrane in a sufficient quantity. In total, 265 children received SSD with a mean TTRE of 17.89 days, which was the slowest among the analysed interventions, although the difference was not statistically significant ($p = 0.70$). Lower TTRE was seen in 224 children treated with NPWT

(13.92 days) and in 134 patients receiving biosynthetic dressing (13.84 days), out of which 100 children were treated with Biobrane only (14.5 days) (Figure 2).

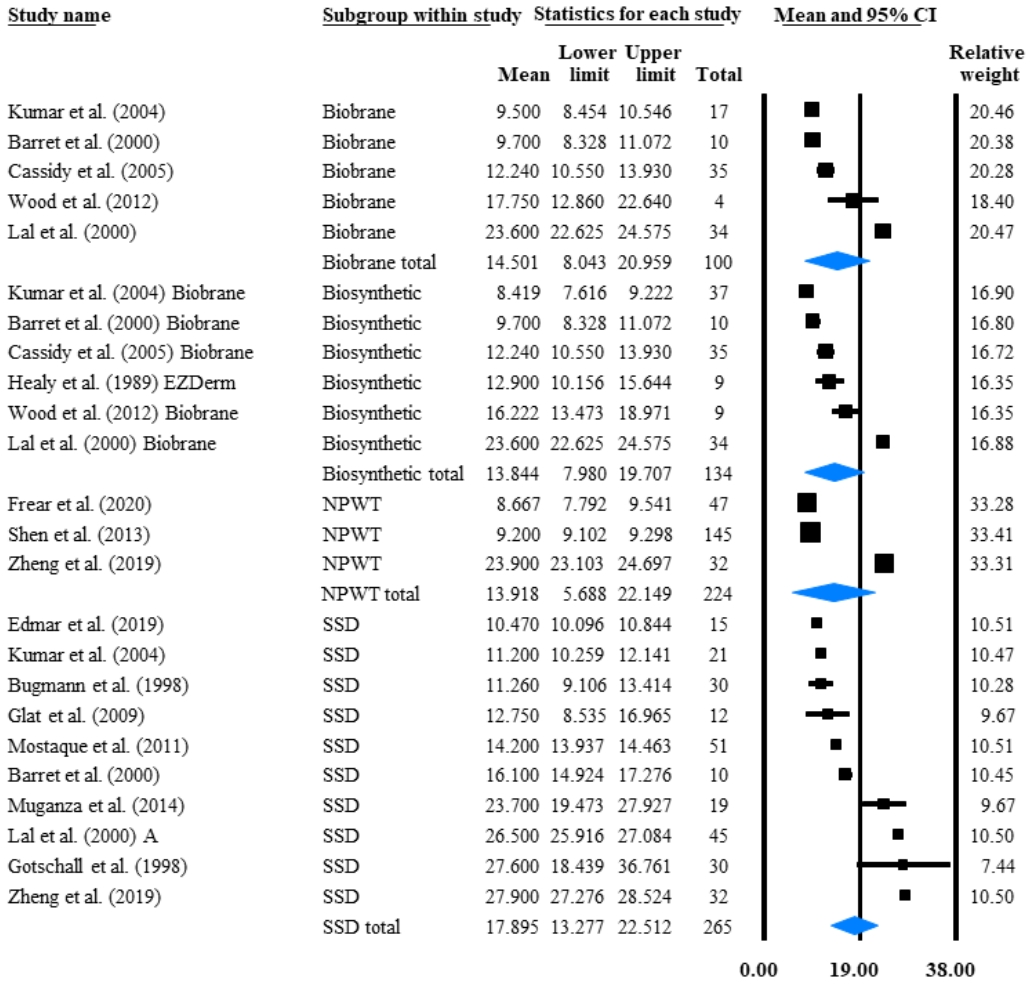

Figure 2. Average wound closure time. This forest plot of studies pools mean TTRE intervals in days, lasting from the time of the paediatric PT burn injury until wound closure. Black squares indicate the TTRE in each study. The size of the black squares represents the individual study weight, and the horizontal lines show their corresponding 95% confidence intervals (CIs). A blue diamond indicates the overall effect, and its outer edges characterise the Cis [16,18,20–27,35,42–45].

Further analysis was conducted to find out the reason behind the groups' considerable heterogeneity (which was indicated by a high I^2 of 75.35–99.85). Not surprisingly, when mean TTRE was stratified by depth, a significant difference ($p = 0.0004$) was found between II/B (20.53 days), II/A (13.77 days) and combined PT (12.43 days) burns (Figure S2). This difference also clearly indicates that PT burn subcategories should be analysed separately, even though most of the articles [18,19,21,23,24,26,37,40,43–45,47,48,53] and a previous review [33] pooled them together. Due to the low number of eligible studies in each subgroup, we were not able to conduct a meta-analysis on the individual intervention's TTRE stratified by the depth of the burn. Nevertheless, we pooled and ranked the treatment options according to their depth; in II (Table 2), II/A (Table S2), II/A + MD (Table S3) and II/B (Table S4) PT burns.

Table 2. Average wound closure time in paediatric PT burns. The synopsis of the available interventions' reported healing potential with an unknown sub-depth ratio.

Depth: II	Publication Data	No. of Patients (*n*)	TBSA(%)		TTRE (Days)		TBSA%/ TTRE	TTRE Red%
Intervention	Author (Year of Publication)		Mean	SD	Mean	SD		
Acticoat + Mepitel SUM		**86**	**1.42**		**10.61**		**0.14**	
Acticoat + Mepitel	Frear et al. (2020) [45]	54	* 1.35	0.76	* 10.7	4.57	0.13	
Acticoat + Mepitel	Gee Kee et al. (2015) [46]	32	* 1.53	1.94	* 10.35	3.91	0.15	
NPWT + Acticoat + Mepitel	Frear et al. (2020) [45]	47	*** 1.5**	0.76	*** 8.71**	3.06	**0.17**	
EZDerm SUM		**39**	**4.26**		**18.75**		**0.23**	
EZDerm	Healy et al. (1989) [44]	9	1.8	3.75	12.9	4.2	0.14	
EZDerm	Karlsson et al. (2019) [48]	30	** 5	NR	20.5	NR	0.24	
Acticoat SUM		**41**	**3.23**		**14.18**		**0.23**	
Acticoat	Hyland et al. (2018) [49]	10	** 8.5	NR	26.5	NR	0.32	
Acticoat	Gee Kee et al. (2015) [46]	31	1.53	1.94	10.21	5.47	0.15	
Mepilex SUM		**61**	**2.85**		**10.29**		**0.28**	
Mepilex	Karlsson et al. (2019) [48]	28	** 5	NR	** 15	NR	0.33	
Mepilex	Gee Kee et al. (2015) [46]	33	* 1.03	1.16	6.29	3.1	0.16	
Biobrane + ReCell	Wood et al. (2012) [43]	**5**	**5.2**	3.19	**15**	3.54	**0.35**	
SSD SUM		**110**	**7.21**		**18.29**		**0.39**	
SSD	Gotschall et al. (1998) [23]	30	5.1	2.2	27.6	NR	0.19	
SSD	Muganza et al. (2014) [26]	19	21	7.1	23.7	9.4	0.89	
SSD	Barret et al. (2000) [18]	10	7.8	2.85	16.1	2.21	0.48	
SSD	Bugmann et al. (1998) [24]	30	1.92	2.05	11.26	6.02	0.17	
SSD	Kumar et al. (2004) [21]	21	5	NR	11.2	NR	0.45	
placebo (Ekzalb)	Hayashida et al. (2012) [37]	**15**	**8.3**	2.9	**17.5**	3.1	**0.47**	
bFGF	Hayashida et al. (2012) [37]	**15**	**7**	2.6	**13.8**	2.4	**0.51**	**21.14**
Mepitel SUM		**69**	**4.97**		**8.98**		**0.55**	
Mepitel	Gotschall et al. (1998) [23]	33	6.8	3.4	10.5	NR	0.65	
Mepitel	Bugmann et al. (1998) [24]	36	3.29	3.09	7.58	3.12	0.43	
Biobrane SUM		**31**	**6.65**		10.63		**0.63**	
Biobrane	Wood et al. (2012) [43]	4	8	5.23	17.75	4.99	0.45	
Biobrane	Barret et al. (2000) [18]	10	8.9	15.5	9.7	2.21	0.92	
Biobrane	Kumar et al. (2004) [21]	17	5	NR	9.5	NR	0.53	
Transcyte	Kumar et al. (2004) [21]	**20**	5	NR	7.5	NR	**0.66**	
Biobrane + Acticoat SUM		**36**	**18.11**		**20.95**		**0.87**	
Biobrane + Acticoat	Muganza et al. (2014) [26]	26	22	7.5	21.7	9	1.01	
Biobrane + Acticoat	Hyland et al. (2018) [49]	10	** 8	NR	19	NR	0.42	

Table 2. *Cont.*

Depth: II	Publication Data	No. of Patients (*n*)	TBSA(%)		TTRE (Days)		TBSA%/ TTRE	TTRE Red%
Intervention	Author (Year of Publication)		Mean	SD	Mean	SD		
Nystatin + PMB	Branski et al. (2007) [40]	**49**	11	6	**8**	2	**1.38**	
AM + Nystatin +PMB	Branski et al. (2007) [40]	**53**	12	7	**6**	2	**2**	
Vitamin C&E + Zinc + TT	Barbosa et al. (2009) [53]	**15**	16.2	5.3	**7.5**	NR	**2.16**	**23.67**

Numbers marked with a single star (*) were converted from median to mean. Two stars (**) signify that the number could not be converted from median due to missing IQR75 or reporting the range in 10 and 90 percentiles (II = partial-thickness burn injury (PT); AM = amnion membrane; NPWT = negative pressure wound therapy; NR = not reported; PMB = polymyxin b; SSD = silver sulphadiazine; SUM = the summarised values of the same interventions; TBSA% = burned area of the total body surface; TT = traditional treatment; TTRE = time to reepithelialisation; TTRE red% = the percentage of time reduction, with the addition of the intervention; TBSA%/TTRE = the area of regeneration per day).

We classified the TTRE by the affected surface area as well (<5 TBSA%: 13.16; 5–10 TBSA%: 16.07; 10–25 TBSA%: 16.20 days) (Figure S3). However, as a result of uneven depth subcategories, no significant difference was found ($p = 0.77$).

Another strong correlation between the burn area and TTRE was observed when we developed a novel ratio of TBSA% to TTRE (T%/T), which indicates what percentage of the TBSA regenerates each day and can also be used to standardise the burn sizes (Table 2 and Tables S2, S4 and S5). A critical limitation of using T%/T is that in smaller (under 5 TBSA%) burns, the ratio will be low, even though reepithelialisation was rapid. The reason behind this, in our hypothesis, is that there seems to be a minimum physiological time for wound regeneration, which is unrelated to the burn size and takes approximately 5–7 days. In studies that did not report TBSA% [17,25,34–36,39] or TTRE [19,41,47], the T%/T ratio could not be calculated (Table S3). Since TTRE alone seems insufficient to determine the additional interventions' effectiveness on wound closure (e.g., vitamins or heparin), we also calculated these therapies' TTRE reduction percentage (TTRE red%). The additional interventions were compared to their control treatment, where they received a placebo (or nothing) instead, on top of the traditional treatments (Table 2, Tables S2 and S4).

For SSD only, TTRE was also compared in subgroups divided by depth (SSD II: 17.11; SSD II/A: 17.05 days; $p = 0.99$) and by area (<10 TBSA%: 17.03; 10–25 TBSA%: 20.59 days) (Figures S4 and S5), but the differences were not significant between the subgroups ($p = 0.59$). This may indicate that the burns categorised as PT were mostly II/A injuries. Some articles reported the fraction of wound closure on the tenth day (day 10 RE%), which is summarised in Table S5.

Only three trials [18,21,22] reported the TTRE of the same comparator (SSD: 17.94 days) and intervention (Biobrane: 14.27 days), which were analysed separately. Despite the lack of a significant difference between the two treatments ($p = 0.61$), every article reported improved results with Biobrane compared to SSD (Figure S6).

3.4.2. Grafting Rate and Non-Grafted Rate

If conservative treatment is unable to heal the injury, a permanent skin transplantation is needed to facilitate wound closure. First, the interventions' mean percentages of how many conservatively treated patients required grafting related to the whole study population were calculated. The ratio of grafted patients was 19.3% in SSD-, 20.5% in biosynthetic-, and 18.9% in silver foam-treated patients ($p = 0.99$) (Figure S7). Because every treatment without any grafted patient (zero outcomes) had to be excluded from the previous meta-analysis, here we used the reverse approach; that is, the comparison of the percentage of the non-grafted patients among the treatments (Figure 3).

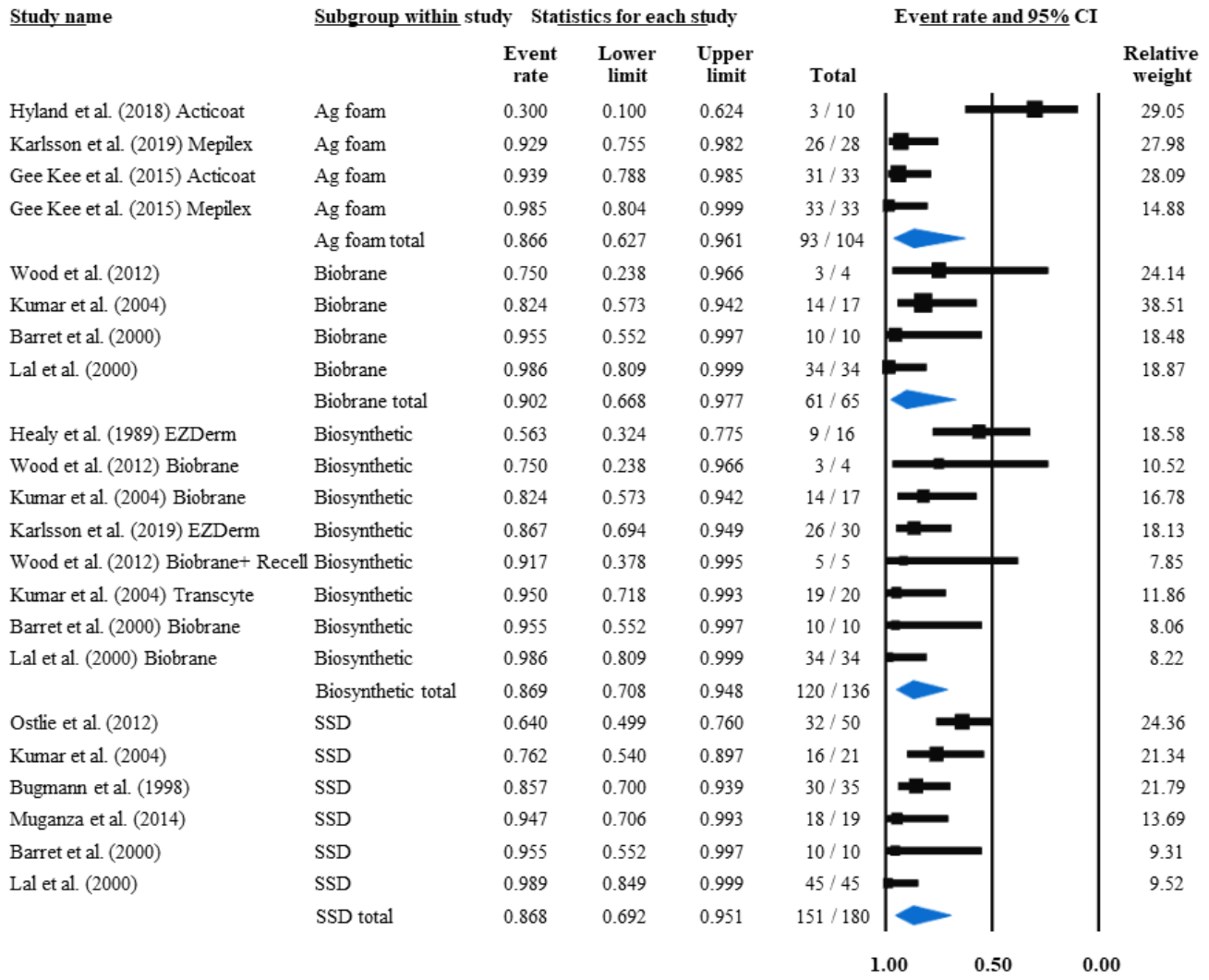

Figure 3. Mean non-grafted population ratios. They should be interpreted as grafting rates of paediatric PT burns when subtracted from 1 (100%). Black squares indicate the TTRE in each study. The size of the black squares represents the individual study weight, and the horizontal lines show their corresponding 95% confidence intervals (CIs). A blue diamond indicates the overall effect, and its outer edges characterise the CIs [18,19,21,22,24,26,43,44,46,48,49].

With this method, we found that by subtracting the non-grafted population percentages from 100%, the grafting rate was 13.2%, 13.4%, 13.1% and 9.8% in patients treated with SSD, silver foam, biosynthetic and Biobrane, respectively. These results indicate that among Biobrane-treated children, grafting was required 25.8% less often compared to SSD; however, the difference between the treatments did not reach the level of significance ($p = 0.98$).

Similarly to TTRE, the grafting rate for SSD (7.6%) and Biobrane (6.6%) was analysed separately in the three articles that compared both of them (Figure S8) [18,21,22], which showed a 13.2% reduction in grafting need ($p = 0.92$) in Biobrane-treated children compared to SSD. The specific intervention analysis revealed therapeutic options that may result in reduced grafting rates, which were Transcyte (5%), Mepilex Ag (3.3%), NPWT + Acticoat + Mepitel (2.1%), and Biobrane + Recell (0%), but due to the scarcity of data, the statistical analysis to detect a significant difference could not be performed (Table 3).

Table 3. Average grafting ratios. Comparison of the need for surgical intervention from the RCTs about PT burns in children, measured in percentages.

Intervention and Burn Depth	Publication Data	No. of Patients (*n*)	Grafted	
	Author (Year of Publication)		No. (*n*)	%
placebo (VIS) II/A	Hartel et al. (2007) [36]	**24**	14	**58.33**
wIRA(75%) + VIS II/A	Hartel et al. (2007) [36]	**21**	11	**52.38**
placebo (Ekzalb) II	Hayashida et al. (2012) [37]	**15**	5	**33.33**
bFGF II	Hayashida et al. (2012) [37]	**15**	5	**33.33**
Collagenase + PMB II	Ostlie et al. (2012) [19]	**50**	16	**32**
EZDerm II		**46**	11	**23.91**
EZDerm	Healy et al. (1989) [44]	16	7	43.75
EZDerm	Karlsson et al. (2019) [48]	30	4	13.33
SSD II		**180**	29	**21.48**
Acticoat II		**43**	9	**20.93**
Acticoat	Hyland et al. (2018) [49]	10	7	70
Acticoat	Gee Kee et al. (2015) [46]	33	2	6.06
Nystatin + PMB II	Branski et al. (2007) [40]	**59**	10	**16.95**
SSD II + II/A		**135**	29	**16.1**
SSD	Ostlie et al. (2012) [19]	50	18	36
SSD	Kumar et al. (2004) [21]	21	5	23.81
SSD	Barret et al. (2000) [18]	10	0	0
SSD	Bugmann et al. (1998) [24]	35	5	14.28
SSD	Muganza et al. (2014) [26]	19	1	5.26
SSD II/A	Lal et al. (2000) [22]	45	0	**0**
Biobrane + Acticoat II		**36**	5	**13.89**
Biobrane + Acticoat	Hyland et al. (2018) [49]	10	4	40
Biobrane + Acticoat	Muganza et al. (2014) [26]	26	1	3.85
AM + Nystatin + PMB II	Branski et al. (2007) [40]	**61**	8	**13.11**
Biobrane II		**31**	4	**12.9**
Mepitel II	Bugmann et al. (1998) [24]	**41**	5	**12.19**
Acticoat + Mepitel II		**88**	6	**6.82**
Acticoat + Mepitel	Frear et al. (2020) [45]	54	4	7.41
Acticoat + Mepitel	Gee Kee et al. (2015) [46]	34	2	5.89
Biobrane II + II/A		**65**	4	**6.15**
Biobrane	Wood et al. (2012) [43]	4	1	25
Biobrane	Kumar et al. (2004) [21]	17	3	17.65
Biobrane	Barret et al. (2000) [18]	10	0	0
Biobrane II/A	Lal et al. (2000) [22]	34	0	**0**
Transcyte II	Kumar et al. (2004) [21]	**20**	1	**5**
Mepilex II		**61**	2	**3.28**
Mepilex	Karlsson et al. (2019) [48]	28	2	7.14
Mepilex	Gee Kee et al. (2015) [46]	33	0	0
NPWT + Acticoat + Mepitel II	Frear et al. (2020) [45]	**47**	1	**2.13**
Biobrane + ReCell II	Wood et al. (2012) [43]	**5**	0	**0**

(II = Partial-thickness burn injury (PT); II/A = superficial PT; AM = amnion membrane; NPWT = negative pressure wound therapy; PMB = polymyxin b; RCTs = randomised controlled trials; SSD = silver sulphadiazine; VIS = visible spectrum light; wIRA = water-filtered infrared A.)

3.4.3. Dressing Changes

There was not enough data to conduct a meta-analysis of the required dressing changes between the two interventions. Nevertheless, the mean frequency of dressing reapplications showed a great variance among interventions, and they positively correlated with pain and discomfort levels. Furthermore, dressing changes were proportional to the rate of anaesthesia induction as well as to the time required for the healthcare professionals and the operating theatre for the administration of the treatments. SSD seemed to be the least efficient option with an extremely high 65.5 mean dressing changes if the wounds were treated openly and 9.6 dressing changes with closed wound treatment. Interventions with three or fewer dressing reapplications were Acticoat + Mepitel and Tilapia (number of changes 3.0 for both), Acticoat (2.7), NPWT + Acticoat + Mepitel (2.4), Transcyte (1.5), AM alone (1.3) or with nystatin and polymyxin B (PMB) (0.5), and Aquacel Ag (1.0) (Table 4).

Table 4. Mean frequency of dressing changes. A brief about the RCTs' average reported need for dressing reapplication in the PT management of children.

Intervention and Burn Depth	Publication Data	No. of Patients	Dressing Changes	
	Author (Year of Publication)		Mean	SD
SSD II + II/A		**198**	**25.16**	
Silvasorb II/A+ MD	Glat et al. (2009) [25]	**12**	**13.5**	4.7
Collagenase + PMB II	Ostlie et al. (2012) [19]	**50**	**11**	4.1
SSD II ex. Mostaque		**132**	**9.56**	
SSD	Mostaque et al. (2011) [20]	51	65.53	18.23
SSD	Glat et al. (2009) [25]	12	13.42	8.26
SSD	Ostlie et al. (2012) [19]	50	11	3.8
SSD	Muganza et al. (2014) [26]	19	10.7	3.8
SSD	Kumar et al. (2004) [21]	21	9.2	NR
SSD	Bugmann et al. (1998) [24]	30	5.13	2.9
SSD II/A	Lima Júnior et al. (2019) [16]	**15**	**9.27**	1.39
Biobrane + Acticoat II		**36**	**6.87**	
Biobrane + Acticoat	Muganza et al. (2014) [26]	26	7.6	4.8
Biobrane + Acticoat	Hyland et al. (2018) [49]	10	* 5	NR
Nystatin + PMB II	Branski et al. (2007) [40]	**49**	**6**	3
EZDerm II	Karlsson et al. (2019) [48]	**30**	*** 5**	NR
Biobrane + ReCell II	Wood et al. (2012) [43]	**5**	**4.8**	1.3
Mepilex II	Karlsson et al. (2019) [48]	**28**	*** 4**	NR
Mepitel II	Bugmann et al. (1998) [24]	**36**	**3.64**	1.5
Biobrane II		**21**	**3.37**	
Biobrane	Wood et al. (2012) [43]	4	7.5	2.64
Biobrane	Kumar et al. (2004) [21]	17	2.4	NR
Acticoat + Mepitel II	Frear et al. (2020) [45]	**54**	**3**	1.48
Tilapia II/A	Lima Júnior et al. (2019) [16]	**15**	**3**	0.76
Acticoat II		**51**	**2.69**	
Acticoat	Hyland et al. (2018) [49]	10	* 5.5	NR
Acticoat	Brown et al. (2016) [47]	41	2	0.2
NPWT + Acticoat + Mepitel II	Frear et al. (2020) [45]	**47**	**2.43**	0.86

Table 4. *Cont.*

Intervention and Burn Depth	Publication Data	No. of Patients	Dressing Changes	
	Author (Year of Publication)		Mean	SD
NPWT II/A	Shen et al. (2013) [35]	**145**	**2.05**	0.22
Transcyte II	Kumar et al. (2004) [21]	**20**	**1.5**	NR
AM II	Mostaque et al. (2011) [20]	**51**	**1.33**	0.55
Aquacel Ag II	Brown et al. (2016) [47]	**40**	**1**	0.1
AM + Nystatin + PMB II	Branski et al. (2007) [40]	**53**	**0.5**	2

Numbers marked with a single star (*) were converted from median to mean. (II = Partial-thickness burn injury (PT); II/A = superficial PT; AM = amnion membrane; ex. Mostaque = this study was excluded from a part of the analysis due to its open treatment regime; MD = mid-dermal or mixed-depth burn injury; NPWT = negative pressure wound therapy; NR = not reported; PMB= polymyxin b; RCTs = randomised controlled trials; SD = standard deviation; SSD = silver sulphadiazine.)

3.4.4. Infection Rate and Non-Infected Rate

The patients' percentage that showed signs of infection during their treatment was calculated similarly to grafting needs. The infection rates in the cases of different interventions were as follows: biosynthetic dressings: 21.8%; silver foam dressings: 12.4%; Biobrane: 11.7%; SSD: 9.2% ($p = 0.65$) (Figure S9). By subtracting the non-infected children's percentages from the whole population, the calculation revealed slightly different results. In this case, biosynthetic dressings still had the highest microbial contamination rate of 19.4%, among which the rate for Biobrane was 11.7%. SSD showed an even lower rate of 7.4% infections, while the percentage of infected patients was 7.0% in silver foam dressings and 3.5% in Acticoat treatment groups ($p = 0.24$) (Figure 4).

Individual intervention effect analysis indicated potential alternatives with more advantageous effects on infection rates, such as Aquacel Ag foam (2.4%) and PMB combination therapies such as collagenase or AM with Nystatin (2.0% and 1.9%, respectively) or Acticoat with Mepitel (0%) (Table 5).

Additionally, the infected population rate in the case of SSD (13.9%) was similar to the rate of Biobrane (9.9%), without a significant difference ($p = 0.91$) between the treatments (Figure S10).

3.4.5. Length of Stay (LOS)

The length of hospital stay—the time spent inside the hospital from admission until discharge—is associated with the total cost of care, and it enormously impacts the children's discomfort levels. Sufficient data for a meta-analysis was only available for SSD- and AM-based treatments, for which treatments the mean LOS were 12.5 and 8.3 days, respectively (Figure 5).

While this indicates a 33.6% shorter LOS in the case of AM-based compared to SSD-based treatments, the difference was non-significant ($p = 0.43$). The analysis of specific interventions showed that without antibiotic coverage, LOS is similar in the case of amniotic membrane and SSD treatments (11.37 vs. 13.77 days), while the addition of nystatin and PMB can reduce LOS to 2 days (Table S6). It is important to note that in the cases of several treatments, such as EZDerm (LOS: 3.4 days), Mepilex (LOS: 3.1 days), Biobrane (LOS: 2.4 days) and AM + Nystatin + PMB (LOS: 2 days), the children could be discharged even before the complete reepithelialisation of their injuries, whereas patients treated with SSD and collagenase stayed in the hospital for the entire duration of dressing changes.

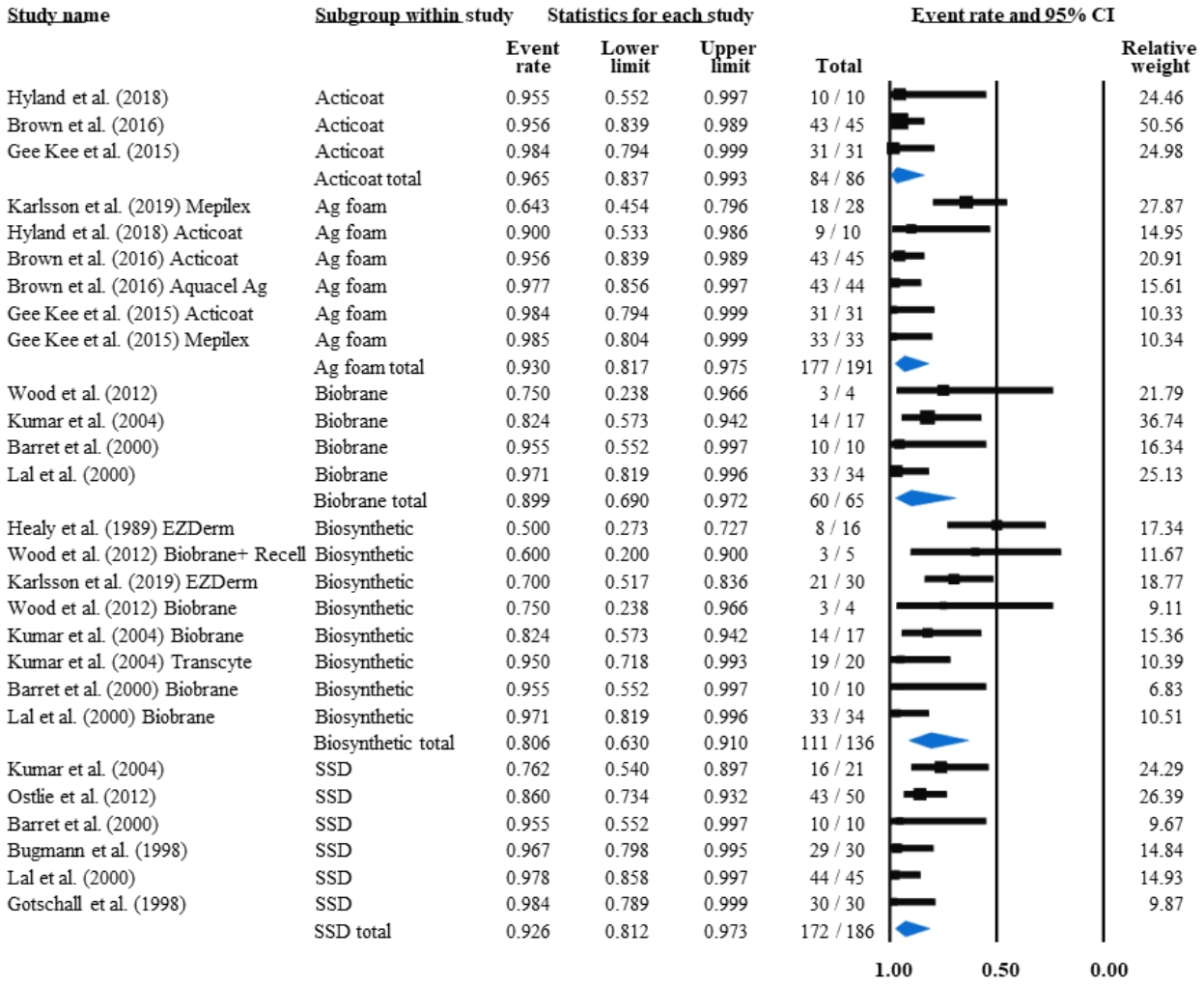

Figure 4. The average non-infected population rates. Five paediatric PT intervention groups' antimicrobial effectiveness was compared. The results should be interpreted as infection rates when subtracted from 1 (100%). Black squares indicate the TTRE in each study. The size of the black squares represents the individual study weight, and the horizontal lines show their corresponding 95% confidence intervals (CIs). A blue diamond indicates the overall effect, and its outer edges characterise the CIs [18,19,21–24,43,44,46–49].

Table 5. Mean infection chance. Summary of percentages when infection occurred during the treatment of PT in children.

Intervention and Burn Depth	Publication Data	No. of Patients (*n*)	Infected	
	Author (Year of Publication)		No. (*n*)	%
Biobrane + Acticoat II	Hyland et al. (2018) [49]	**10**	6	**60**
Biobrane + ReCell II	Wood et al. (2012) [43]	**5**	2	**40**
EZDerm II		**46**	17	**36.96**
EZDerm	Healy et al. (1989) [44]	16	8	50
EZDerm	Karlsson et al. (2019) [48]	30	9	30

Table 5. *Cont.*

Intervention and Burn Depth	Publication Data	No. of Patients (*n*)	Infected	
	Author (Year of Publication)		No. (*n*)	%
NPWT II/A	Shen et al. (2013) [35]	**145**	39	**26.9**
Mepilex II		**61**	10	**16.39**
Mepilex	Karlsson et al. (2019) [48]	28	10	35.72
Mepilex	Gee Kee et al. (2015) [46]	33	0	0
Biobrane II		**31**	4	**12.9**
SSD II		**141**	13	**9.22**
Biobrane II + II/A		**65**	5	**7.69**
Biobrane	Wood et al. (2012) [43]	4	1	25
Biobrane	Kumar et al. (2004) [21]	17	3	17
Biobrane	Barret et al. (2000) [18]	10	0	0
Biobrane II/A	Lal et al. (2000) [22]	34	1	**2.9**
SSD II + II/A		**186**	14	**7.53**
SSD	Kumar et al. (2004) [21]	21	5	24
SSD	Ostlie et al. (2012) [19]	50	7	14
SSD	Bugmann et al. (1998) [24]	30	1	3.33
SSD	Gotschall et al. (1998) [23]	30	0	0
SSD	Barret et al. (2000) [18]	10	0	0
SSD II/A	Lal et al. (2000) [22]	**45**	1	**2.2**
Transcyte II	Kumar et al. (2004) [21]	**20**	1	**5**
Mepitel II		**72**	3	**4.17**
Mepitel	Gotschall et al. (1998) [23]	36	3	8.3
Mepitel	Bugmann et al. (1998) [24]	36	0	0
Nystatin + PMB II	Branski et al. (2007) [40]	**49**	2	**4.08**
Acticoat II		**86**	3	**3.49**
Acticoat	Brown et al. (2016) [47]	45	2	4.44
Acticoat	Hyland et al. (2018) [49]	10	1	10
Acticoat	Gee Kee et al. (2015) [46]	31	0	0
Aquacel Ag II	Brown et al. (2016) [47]	**44**	1	**2.27**
Collagenase + PMB II	Ostlie et al. (2012) [19]	**50**	1	**2**
AM + Nystatin + PMB II	Branski et al. (2007) [40]	**53**	1	**1.89**
Acticoat + Mepitel II	Gee Kee et al. (2015) [46]	**32**	0	**0**

(II = Partial-thickness burn injury (PT); II/A = superficial PT; AM = amnion membrane; NPWT = negative pressure wound therapy; PMB = polymyxin b; SD = standard deviation; SSD = silver sulphadiazine.)

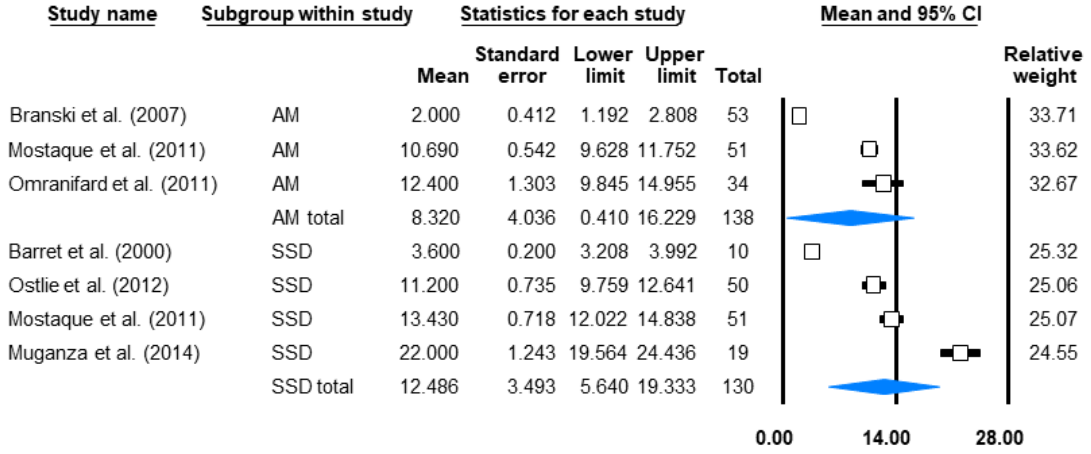

Figure 5. Average length of stay. The days spent inside the hospital by children treated with SSD or AM for PT burns. Black squares indicate the TTRE in each study. The size of the black squares represents the individual study weight, and the horizontal lines show their corresponding 95% confidence intervals (CIs). A blue diamond indicates the overall effect, and its outer edges characterise the CIs [18–20,26,40,41].

4. Discussion

Even though SSD is widely used as a treatment for burns, our study concluded that it has some disadvantages that can outweigh its beneficial effects, which are mainly its applicability, low cost and notable antibacterial efficacy (i.e., an infection rate of 9.22%) [16–27]. However, SSD was associated with slow wound closure (TTRE II/A: 11.0 days; II/B: 25.7 days; II: 18.3 days and 0.39 T%/T) and prolonged hospital stay (LOS II: 13.8 days) as well as with frequent, time-consuming dressing changes (on average 9.6 times; every 1–3 days in PT burns)—also causing pain and anxiety—and a substantial need for grafting (i.e., in 21.5% of the patients). Furthermore, its known side effects include allergic reactions, argyria and neutropenia [54], and it also causes the wound bed's discolouration, which can render wound evaluation and depth determination difficult [55].

Compared to SSD, collagenase combined with PMB showed no difference in TTRE in PT burns, whereas Silvasorb led to improved healing times in II/A and MD burns with 12.4 days (though TBSA% was not reported in Silvasorb-treated patients) [25]. Collagenase + PMB treatment markedly reduced the infection rates (to 2%) in the burned children, but it was associated with a high grafting rate (32%) and prolonged LOS (11.3 days). In the case of both Silvasorb and collagenase + PMB treatments, the dressing change rate was exceptionally high (13.5 and 11 times, respectively), which raises concerns about the recommendation of these treatments in paediatric PT burns.

Among the modern biosynthetic dressings, Biobrane and Transcyte had excellent efficacy with TTRE in PT burns of 10.63 days and T%/T of 0.63% for Biobrane, and TTRE 7.50 days and T%/T of 0.66% for Transcyte. In contrast, EzDerm was less efficient (TTRE in PT burns: 18.75 days; 0.23 T%/T) than SSD. The rates of infection and grafting were high in the case of EZDerm (37.0 and 23.9%, respectively) and Biobrane (12.9% for both), whereas Transcyte had a low rate of 5.0% for both. The need for reapplication was considerably low in the case of all three biosynthetic dressings, as shown by the small number of dressing changes in the case of EZDerm (n = 5), Biobrane (n = 3.4) and Transcyte (n = 1.5). Based on these results, biosynthetic treatments in children with PT burns are promising interventions, but in order to reduce the susceptibility to infection, and potentially the need for grafting, it is suggested that they should be applied in a combination with antimicrobial agents.

Silver foam dressings were mostly studied in small burns (<5 TBSA%) [43–51], though the wound's area [17] and closure time [47] were not reported in the RCTs in the case of Aquacel products. By the 10th day of the treatment, the reepithelialisation was remarkably high in the case of Acticoat (93%) and Aquacel Ag (94%). Accordingly, the TTRE and T%/T

in PT burns were reasonable in the case of Acticoat (14.2 days and 0.23%, respectively) and Mepilex (10.3 days and 0.28%, respectively). The number of dressing changes, infection rates and grafting needs were relatively low in the case of Acticoat (n = 2.7, 3.5% and 20.9%, respectively) and Mepilex Ag (n = 4.0, 16.4% and 3.3%, respectively). The LOS in the hospital was notably short (only 3.1 days) in children treated with Mepilex Ag. Aquacel Ag was also associated with a small need for dressing changes (n = 1.0) and low susceptibility to infections (2.3%). These results suggest that the silver foam dressings are efficient interventions in PT burns of children. However, before they can be firmly recommended for general practice, further studies are warranted to test their effect on more extensive burns as well.

Similarly to silver foam dressings, the combination therapies were mainly analysed on smaller burns, which could contribute to their favourable TTRE in PT burns, viz., 15.0 days for Biobrane + Recell, 10.6 days for Acticoat + Mepitel and 8.7 days for NPWT + Acticoat + Mepitel, as well as to the low T%/T values, which were 0.35% for Biobrane + Recell, 0.14% for Acticoat + Mepitel and 0.17% for NPWT + Acticoat + Mepitel. As an exception, the treatment with the combination of Biobrane and Acticoat resulted in a longer TTRE of 21 days and a higher T%/T of 0.87%. By the 10th day of the treatment, the reepithelialisation percentage was modest in the case of Acticoat + Mepitel (42.5%), and NPWT + Acticoat + Mepitel (68.6%), whereas it was remarkably high (95%) in children treated with Biobrane + Recell. Every intervention performed better than SSD in terms of the lower need for dressing changes, which were on average 6.9 for Biobrane + Acticoat, 4.8 for Biobrane + Recell, 3 for Acticoat + Mepitel and 2.4 for NPWT + Acticoat + Mepitel. It should be noted that the price of these treatments was higher than the cost of SSD, but the nursing and operating theatre time, along with the anaesthetic use and total cost, were high in the SSD group as well. The higher initial cost of the combination treatments is one of the main obstacles that prevent them from widespread use as burn therapies. Compared to SSD, the grafting rates were also reduced for Biobrane + Acticoat (13.9%), Acticoat + Mepitel (6.8%), NPWT + Acticoat + Mepitel (2.1%) and Biobrane + Recell (0%), but it should be mentioned that low grafting rates were also found with the sole treatment of Biobrane (6.2%), Transcyte (5%) and Mepilex Ag (3.3%). The infection rates were exceptionally high in the case of Biobrane + Acticoat (60%) and Biobrane + Recell (40%), which suggests that these combinations suppress the antimicrobial efficacy, while no infections were reported in children treated with Acticoat + Mepitel, which may indicate a powerful antimicrobial effect.

Radiation-sterilised AM allografts combined with antimicrobial agents [20,40,41] and tilapia xenografts [16] seem to be a surprisingly effective, low-cost solution, but their procurement and storage may be challenging. Their application seems comfortable and less painful during and in-between dressing changes, and they were also associated with the least number of average dressing changes: Tilapia (n = 3.0), AM (n = 1.3) and AM + Nystatin + PMB (n = 0.5). Moreover, the times needed for wound closure were among the lowest reported values as indicated by TTRE and T%/T in paediatric PT burns for Tilapia (10.1 days and 1.11%), AM (13.3 days and 0.56%) and AM + Nystatin + PMB (6.0 days and 2.00%). The infection rate in the case of AM + Nystatin + PMB was also very low (1.9%).

We collected several additional interventions that could reduce the time for reepithelialisation (as indicated by TTRE red%, see Methods for details) when they were supplemented to the treatment. The list of these interventions (with the corresponding burn severity and TTRE red%) included NPWT (II/A:12.6%; II/B: 14.3%), rhEGF (II/A: 20.2%; II/B: 20.7%), bFGF (II: 21.1%), vitamin E + C + Zinc (II: 23.7%), rhGM-CSF (II/B: 27.9%), wIRA (II/A: 30.8%) and heparin (II: 40.0%). While in several cases the cost of these interventions presents a considerable obstacle to their use, supplementation with vitamins, minerals and heparin can be promising and inexpensive adjuvants in burn therapies. It must be noted, however, that we could identify only a single report for each treatment, which warrants further research to establish the true efficacy of these additional interventions.

For additional information on the reported advantages and drawbacks of each analysed treatment option see Text S1.

While a similar meta-analysis was previously conducted about the management of partial-thickness burn wounds in children in 2014 by Rashaan ZM et al., they could only compare the effects of non-silver treatment related to silver sulfadiazine due to the scarcity of articles [33]. In recent years, several new research studies were published on this topic; thus, we were able to analyse subgroups such as biosynthetic or silver foam dressings as well. Another systematic review was published by Vloemans et al. in 2014 called the Optimal treatment of partial-thickness burns in children [56]. They separated their findings based on evidence level (RCTs, cohort studies, case reports), but they were not able to conduct statistical analysis for similar reasons as Rashaan et al. Since then, more than twice as many RCTs have been published on this subject, new interventions have been tested—such as the combination or additional therapies—and more articles have been issued for the already existing therapies, which have now been added to this updated summary.

Limitations of our study must also be discussed. We aimed at collecting and evaluating articles strictly with the highest evidence level, namely RCTs; therefore, we had to exclude a lot of potentially relevant observational and case studies. It was surprising that despite the thorough review of the databases, we could identify a relatively low number of articles that fulfilled our inclusion criteria, especially if we consider the vast number of available treatment options. These RCTs were often describing a small and significantly heterogeneous population—due to the burns' mixed sub-depth ratios and various average areas. The low number of studies limited our options for a more extensive meta-analysis on individual interventions and resulted predominantly in a qualitative synthesis of the available data. As another limitation of our study, it can also be mentioned that secondary outcomes were scarcely reported, and even then, they were assessed in diverse ways, mainly in the cases of cost, pain sensation and scar formation; hence, we were not able to compare these three endpoints. Moreover, some of the research was conducted over two decades ago when many of the more accurate diagnostic devices for burn depth classification and area determination (such as Laser Doppler Imaging) were not as widely available as now [57]. Thus, the preciseness of the older measurements might be questionable, and they were often unverifiable without photo documentation.

The assessed risk of bias was also high in general, largely resulting from the lack of reporting randomisation and blinding as well as the absence of (pre)trial protocols. Furthermore, most of the studies did not follow the CONSORT criteria—which may be one of the reasons behind the cause of missing data—or disclose funding sources and conflict of interests. In those cases when the founders were mentioned, they were usually the manufacturers of the evaluated intervention, which poses further risks for bias.

5. Conclusions

There are still many pieces missing from the grand picture of paediatric partial-thickness burn therapies; this review's main goal was to summarise our current knowledge on the topic. Although the results presented in this article will most probably change over time, we aimed at highlighting currently unclear areas in our understanding and at facilitating further clinical studies in the field. A future network meta-analysis would provide sufficient information to differentiate between the efficacy of individual interventions, but a lot more RCTs are needed before we will be able to properly compare them.

Our primary recommendation for investigators is that superficial and deep second-degree burns in children should be analysed separately due to their significantly different characteristics. Furthermore, researchers should follow the CONSORT criteria and report predetermined outcomes of general interest (e.g., TBSA%, TTRE, T%/T, infection and grafting rates, number of dressing changes and LOS) along with their unique observations. Establishing a single, internationally accepted standard for pain and scar evaluation in paediatric burns would greatly advance this process. Another interesting future aspect could be the analysis of optimal dressing change rates.

While every intervention could facilitate the healing of second-degree paediatric burn wounds, individual data analysis showed remarkable differences in secondary outcomes that could not have been statistically proven because of the aforementioned limitations. When choosing the preferred intervention in paediatric PT burns, physicians should consider treatments with little need for dressing changes because these options require the lowest number of anaesthesias, as well as cause the least pain and discomfort for the children. Moreover, by reducing the reapplication rate, the operating theatres' availability can be increased, and time can be saved for the healthcare providers, the advantages of which may result in a decrease in overall costs.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/life12050619/s1, **Figure S1: Risk of bias assessment**. The RCTs compared paediatric patients with PT burns. **Figure S2: Pooled TTRE of the interventions, adjusted by burn depth**. The groups were II/A, II and II/B injuries in children, and the TTRE was measured in days. **Figure S3: Mean TTRE of the interventions, modified by burn area.** The categories were <5, 5–10, 10–25 TBSA% paediatric PT injuries, and the TTRE was calculated in days. **Figure S4: SSD's mean TTRE stratified by depth.** The classifications were paediatric II/A and II burns and the TTRE was determined in days. **Figure S5: Average TTRE of SSD, modified by burn area**. The area cohorts were <10 and 10–25 TBSA% PT injuries, and the TTRE was defined in days. **Figure S6: The mean TTRE of SSD and Biobrane.** The meta-analysis of TTRE in children with PT was measured in days. **Figure S7: Average grafted percentages.** Treatment groups were paediatric PT patients with SSD, silver foam and biosynthetic dressings. **Figure S8: Mean non-grafted patient ratio with SSD and Biobrane.** The percentage comparison of successful conservative treatment in PT injuries of children. **Figure S9: Average infected population percentages.** Treatment comparison **of** SSD, biosynthetic and silver foam dressings as well as Biobrane only in paediatric PT injuries. **Figure S10: Mean non-infected patients' ratio of SSD compared to Biobrane.** The meta-analysis compares the frequencies of complication-free paediatric PT burn treatments, in percentages. **Table S1: RoB2 analysis. Table S2: Mean TTRE of paediatric II/A treatments.** TTRE values were calculated in days. (II/A = Superficial partial-thickness injury; NA = not applicable; NPWT = negative pressure wound therapy, NR = not reported; SD = standard deviation; SSD = silver sulphadiazine; SUM = the summarized values of the same interventions; TBSA% = burned area of the total body surface; TT = traditional treatment; TTRE = time to reepithelialisation; TBSA%/TTRE= the area of regeneration per day; TTRE red% = the percentage of time reduction, with the addition of the intervention; VIS = visible spectrum light; wIRA = water-filtered infrared A.) **Table S3: The average TTRE in paediatric II/A and MD burns.** The TTRE was measured in days. No description was provided about the TBSA% in these instances, thus the T%/T ratios could not be calculated. (II/A = Superficial partial-thickness injury; MD = mid-dermal burn; NR = not reported; SD = standard deviation; SSD = silver sulphadiazine; SUM = the summarized values of the same interventions; TBSA% = burned area of the total body surface; TTRE = time to reepithelialisation.) **Table S4: Mean TTRE summary of II/B injuries in children.** The TTRE was calculated in days. (II/B = Deep partial-thickness burn injury; AM = amnion membrane; NA = not applicable; NPWT = negative pressure wound therapy; NR = not reported; SD = standard deviation; SSD = silver sulphadiazine; SUM = the summarised values of the same interventions; TBSA% = burned area of the total body surface; TTRE = time to reepithelialisation; TBSA%/TTRE = the area of regeneration per day.) **Table S5: Average percentage of reepithelialisation on the tenth day (day 10 RE%) in paediatric PT injuries.** (II = Partial-thickness burn injury (PT); II/A = superficial PT; AM = amnion membrane; day 10 RE = the fraction of reepithelialisation on the tenth day; NA = not applicable; NPWT = negative pressure wound therapy; NR = not reported; SSD = silver sulphadiazine; TBSA% = burned area of the total body surface; TTRE = time to reepithelialisation; TBSA%/TTRE = the area of regeneration per day.) **Table S6: Mean length of stay.** The time children spent (days) inside the hospital while being treated with different regimens for PT burns. (II = Partial-thickness burn injury (PT); II/A = superficial PT; AM = amnion membrane; LOS = length of hospital stay; NPWT = negative pressure wound therapy; NR = not reported; PMB = polymyxin b; SD = standard deviation; SSD = silver sulphadiazine.) **Text S1: Reviews of the analysed interventions. Text S2: Search keys**. References [16–27,34–51,53,58–87] are mentioned in the Supplementary Materials.

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children

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Article

Management of Pediatric Facial Burns with Zinc-Hyaluronan Gel

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Abstract: Zinc-hyaluronan-containing burn dressings have been associated with enhanced reepithelialization and low infection rates, although their effectiveness has not yet been investigated in pediatric facial thermal injuries. This single-arm, retrospective cohort study assessed the characteristics of 23 children (≤17-year-old) with facial superficial partial-thickness burns and the wound closure capabilities of the applied zinc-hyaluronan gel. Patients were admitted consecutively to the Pediatric Surgery Division in Pécs, Hungary, between 1 January 2016 and 15 October 2021. The mean age of the children was 6.2 years; 30.4% of them were younger than 1 year. An average of 3% total body surface was injured in the facial region and 47.8% of the patients had other areas damaged as well, most frequently the left upper limb (30.4%). The mean time until complete reepithelialization was 7.9 days and the children spent 2 days in the hospital. Wound cultures revealed normal bacterial growth in all cases and follow-up examinations found no hypertrophic scarring. In conclusion, pediatric facial superficial partial-thickness burns are prevalent during infancy and coincide with left upper limb injuries. Rapid wound closure and low complication rates are accountable for the moderate amount of hospitalization. These benefits, along with the gel's ease of applicability and spontaneous separation, are linked to child-friendly burn care.

Keywords: pediatric; facial burn; partial-thickness burn; zinc-hyaluronate

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1. Introduction

Pediatric burns constitute a great challenge to patients, their families, and healthcare providers because of their high incidence rate (1–7 million/year) and frequent complications (49% of all cases) [1,2]. The facial region is assumed to be injured in 39% of all burns and the most common etiology is scalding [3]. Children, especially infants, have thinner skin—compared to adults—while their immune system and defensive reflexes are still in development [4,5]. Also, their experience with the environment is limited, in addition to their natural curiosity towards it. These factors combined are responsible for the substantial likelihood of severe traumatic and burn injuries in the pediatric population. Facial burns can be responsible for lifelong deformities due to scar formation and restriction of the facial structure's growth potential. Later, this may lead to severe functional and psychological consequences, such as blindness, as well as eating, mood, and anxiety disorders [6,7].

Thermal injuries can be categorized by their depth. Superficial burns (also called I degree) only involve the epidermis and they appear as painful and red wounds. The papillary stratum is damaged in superficial partial-thickness thermal injuries (alas II/1 degree), which can be characterized by bullae and painful, moist, pink wound beds. Deep partial-thickness burns (II/2 degree) damage the stratum reticulare as well, while the

wound bed turns numb and dry with a purple or white color [8]. Conservative treatments, involving dressings (such as silver foam, biosynthetic, amnion membrane dressings, or xenografts) and ointments (for example, silver sulfadiazine, silver nitrate, or hydrogels) are recommended in I and II/1 degree burns [9,10], while surgical reconstruction with various skin grafts, tissue expansion, and flaps are necessary for deeper injuries [11,12].

Curiosa® gel's (Richter Gedeon Nyrt., Budapest, Hungary) main component is zinc-hyaluronan, which promotes cell regeneration and has antioxidant effects, therefore, it contributes to faster wound closure. Moreover, zinc has antimicrobial properties and is a vital part of more than 1000 transcription factors and 300 enzymes from every class. Hyaluronan is an essential component in the extracellular matrix, and is able to modify cellular functions, through its hyaluronan receptors and viscoelastic attributes. The gel formulation helps in the application of the treatment while it creates a moist environment, thereby stimulating wound healing. Zinc-hyaluronan gel also relieves adverse effects from the injuries, such as wound pain and tissue inflammation [13].

This trial aimed to assess the effectiveness of a zinc-hyaluronan-containing gel since, in previous studies, rapid reepithelialization and low infection rates have been reported when applying this intervention in adults [14] and as a part of pediatric combined burn treatments [15]. However, its efficacy has not been investigated in pediatric facial thermal injuries according to our literature search.

2. Materials and Methods

2.1. Design

A single-center, non-comparative cohort study was conducted at the Surgical Division, Department of Pediatrics, Medical School, University of Pécs, Pécs, Hungary. Patient data were collected retrospectively from our database, from 1 January 2016 to 15 October 2021.

The clinical application of zinc-hyaluronan gel was accepted and permitted by our medical board of the Hungarian Pediatric Surgery Committee in 2010. Written informed consent to participate and to publish was obtained from the patients' legal guardians.

2.2. Participants

During the study period, 66 children visited our clinic with facial burns. Inclusion criteria were being younger than 18 years old and suffering from a II/1 degree facial burn. Moreover, the children had to be treated in the first 72 h after the injury with zinc-hyaluronan gel, with no other intervention used until the scab's separation from the wound bed—including skin grafting. Furthermore, inclusion required the absence of acute or chronic comorbidity; a burned total body surface area (TBSA) smaller than 10%; and the attendance of the patient on every follow-up examination.

Children were excluded from the study if they had only I-degree burns (10 patients), were treated with other interventions (13 patients), had more extensive burns than 10% TBSA (4 patients), received skin grafts (2 patients), had severe comorbidities (2 patients) or missed the follow-up (12 patients). The relatively high rate of patients not appearing on control examinations was associated with the COVID-19 pandemic.

2.3. Treatment Protocol

The children were transported to our hospital by their guardians or by ambulance after primary care. First, the attending surgeon assessed the patient's medical history, as well as the wound depth and area according to the Lund–Browder diagrams for the appropriate age groups in addition to looking for signs of inhalation injury and eye trauma [16]. Clinical management began with the rinsing of the burn injury using soap and water, which was followed by disinfection of the affected area. Then, bullectomy and debridement of the necrotic tissue were performed under the effects of anxiolytics and local analgesia or general anesthesia, when it was deemed necessary based on the patients' wound

or age (Figure 1A). Next, the zinc-hyaluronan gel was applied to the cleaned burn surface, which was repeated 3–5 times daily until complete reepithelialization. It is important to note that this gel creates a biological membrane on top of the injury, which protects the area from water loss and infections, but it also makes the precise healing assessment difficult until complete wound closure (Figure 1B,C). Subsequent to the scabs' separation from the wound bed, we advised the patients to apply an oily ointment, e.g., Vaseline, on their scars during the daytime, 3–4 times every day (Figure 1D). After showering, the usage of a heparin-sodium, allantoin, and extractum cepae-containing gel (Contractubex® gel, Merz Pharmaceuticals GmbH, Frankfurt, Germany) was advocated due to its loosening and smoothing effect on sprawling or shrunken scar tissue, while reducing the itching sensation and inflammation [17]. Follow-ups were held on the day after the injury, and every 3–5 days thereafter, until wound closure. The children's facial development and the scar tissue were reexamined 1, 6, and 12 months following the accident.

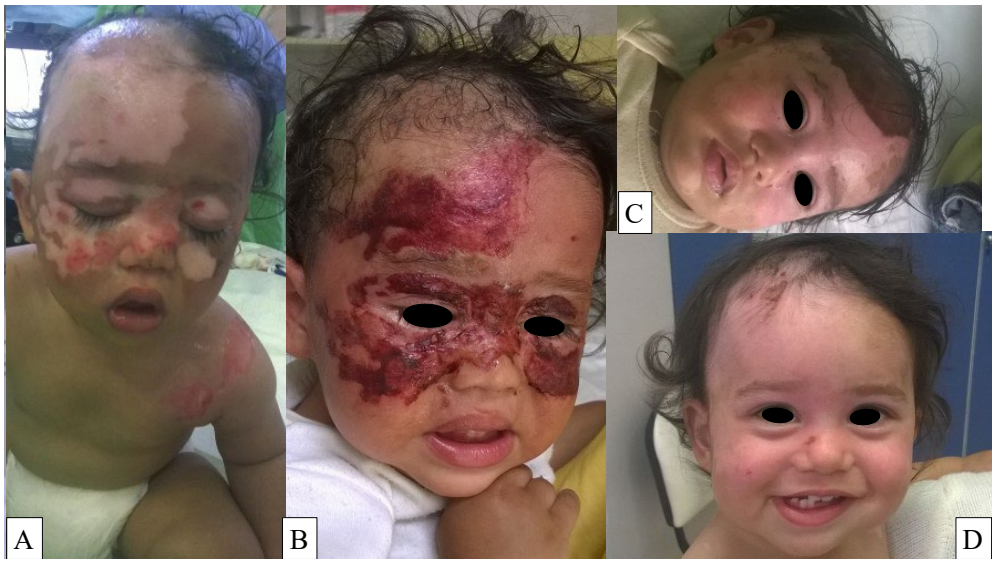

Figure 1. (**A**) A child had bullectomy and debridement performed in general anesthesia on the first day of injury. (**B**,**C**) On the third- and sixth-day control appointment, the patient showed signs of skin regeneration and reduction in wound size, which was covered with the biological membrane. (**D**) The 12-day follow-up revealed almost complete reepithelialization.

2.4. Outcomes and Demographics Measured

Each patient's burn status was documented and photographed before applying the first dressing and thereafter at every control appointment until complete wound closure. The children were evaluated based on nine aspects. We analyzed the patients' demographic data, such as sex and age distribution, the mechanisms and depth of the burns, and the injured TBSA, along with the associated burn regions. The primary outcomes were the average days until the occurrence of a complete, shiny, new layer of epithelium, the total time to reepithelialization (TTRE), the length of hospital stay (LOS), and the complication rates.

2.5. Statistical Analysis

The data on the outcomes were statistically analyzed in Microsoft Excel 2021, while for data presentation Microsoft PowerPoint 2021 (Microsoft Corporation, Redmond, Washington, USA) was used. Means and standard deviations (SDs) were calculated for the evaluated endpoints.

3. Results

During the trial period, 23 children were eligible consecutively to participate in this cohort study. A total of 16 boys (69.6%) and 7 girls (31.4%) had II/1-degree facial burn with an average age of 6.2 years (SD: 5.8; range: 1–17 years). The patients' distribution in the age groups is shown in Figure 2, which draws attention to the increased incidence in the infant population (30.4% of all patients).

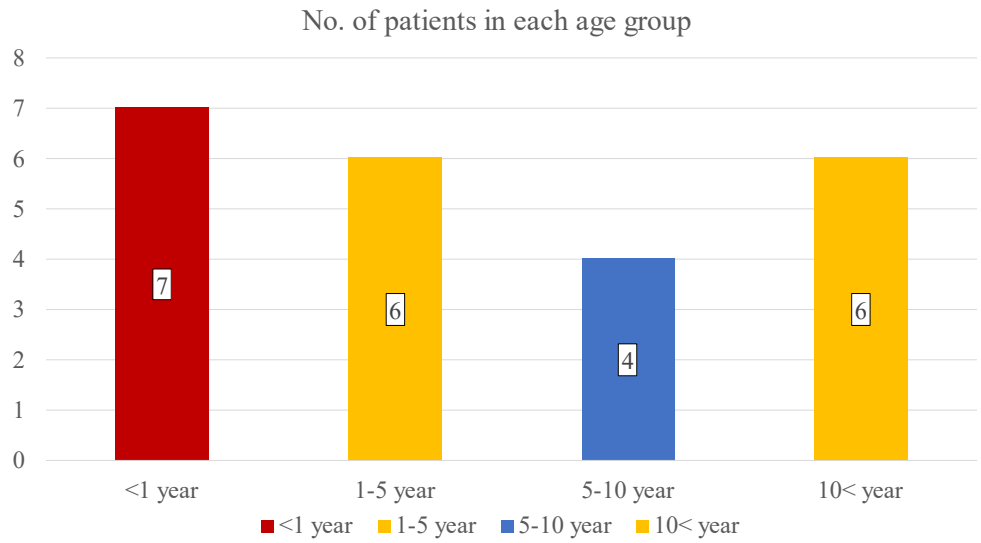

Figure 2. The number of children in four different age groups.

With the analysis of the burn etiologies, we found that all of the traumas were accidental and the most common mechanism was scalding (56.5%), followed by flame (30.4%), contact (8.7%), and chemical injuries (4.3%) (Figure 3). During infancy, the incidence of scalding was 85.7% (6 out of 7 patients), while in teenagers, the risk of flame-caused burns increased to 66.6%.

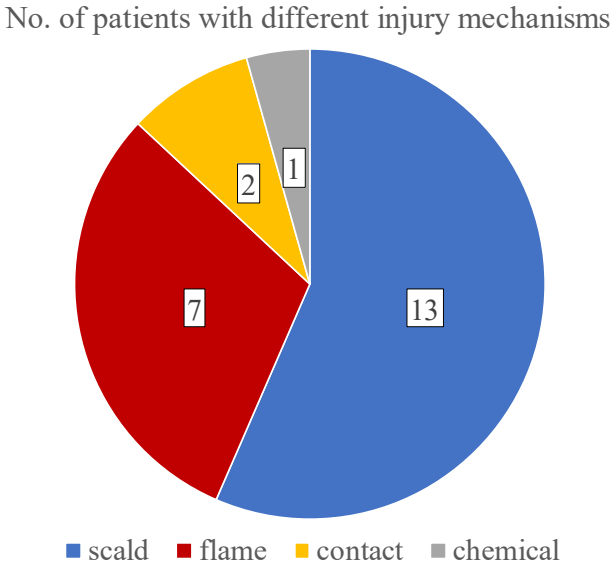

Figure 3. A pie chart showing the distribution of various burn etiologies.

Four children had predominantly I-degree burns, while three patients had II/2-degree thermal injuries, in addition to their II/1-degree burns. Figure 4 shows the distribution of the burned facial areas with a mean of 3% TBSA (SD: 1.0; range: 1–5% TBSA).

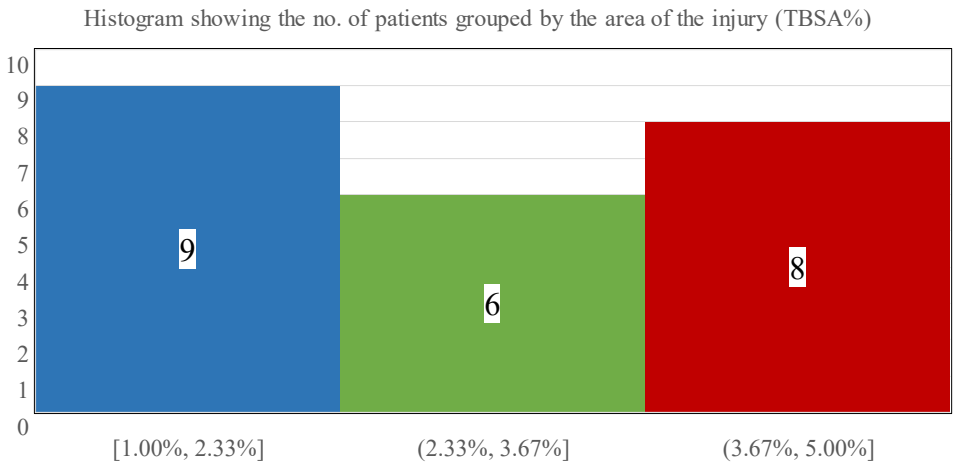

Figure 4. The number of patients stratified via affected burn surface ranges.

The analysis of additional thermal injuries besides facial burns was also conducted, which is presented in Figure 5. Overall, 11 children suffered burns in multiple areas and most commonly (30.4% of all cases) the left upper limb was damaged.

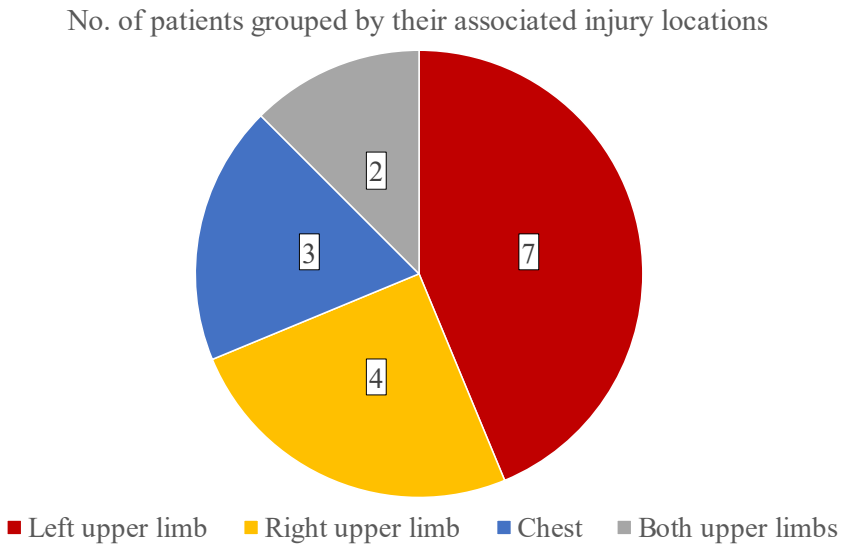

Figure 5. The distribution of burned areas associated with facial combustions.

Our main evaluated endpoint was the days required for complete wound closure or TTRE of zinc-hyaluronan treated facial burns. On average, the children needed 7.9 days until reepithelialization (SD: 2.3; range: 5–15 days). Most patients (52.2%) healed within 5 to 7 days, while 34.4% of the children required 8–10 days (Figure 6). TTRE was more than 10 days in the remaining 13% of the population, who suffered 5 TBSA% injuries in the facial region and had associated burn locations as well.

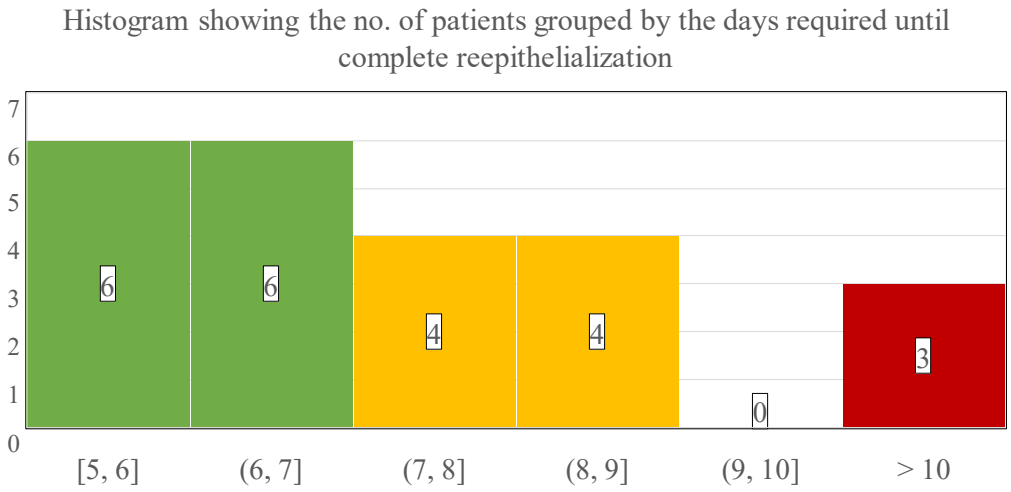

Figure 6. Numbers below the histogram indicate the time interval in days that was necessary for wound closure, while numbers in the bars indicate the number of patients who healed in the corresponding interims.

The evaluation of LOS revealed that 11 children could be treated ambulatory, thus the mean overall hospitalization was notably low, on average 2.0 days (SD: 3.8; range: 0–14 days) *(*Figure 7*)*. When only the inpatient's LOS was estimated, it showed that children who were admitted to our ward required 3.8 days (SD: 3.2; range: 1–14 days) until they could be discharged.

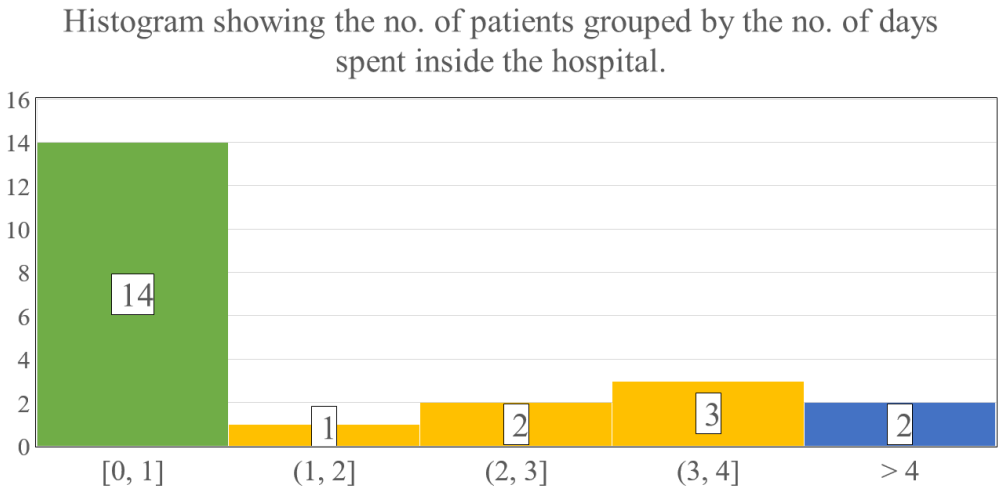

Figure 7. The numbers in the bars show the number of patients, while the numbers below the histogram indicate the time intervals in days spent hospitalized.

Lastly, complication rates were also assessed. Only two children had a fever, which peaked at 38 °C and 40 °C, even though all the wound cultures showed normal bacterial growth. Thus, these instances were attributed to noninfectious systemic inflammatory response syndrome (SIRS), which presumably developed due to the pro-inflammatory cytokine release in large area burn injuries [18]. Furthermore, none of the children showed signs of hypertrophic scarring or contractures, although some of the patients' follow-up examinations are still ongoing.

4. Discussion

The qualities of zinc-hyaluronan gel make it an appropriate match for treating facial burns in children. Its ease of application and spontaneous separation, compared to traditional dressings, achieve wound healing in a painless and child-friendly manner [13]. Biological membranes formed over the injury act as a physical barrier against infection and fluid loss, while also promoting autolytic debridement and reepithelialization by creating a moist environment [14,19]. As a result of the facial region's excellent vascularization, it allows for a more conservative approach even in deeper burns, compared to other parts of the body [20].

Pediatric facial burns still constitute a great challenge to healthcare providers, despite the availability of numerous treatment methods. Their burden is attributable to the presence of essential organs responsible for sensory, breathing, digestive, and communicative functions in this area. In this cohort study, we analyzed the demographic data and outcomes of 23 children whose facial II/1-degree thermal injuries were treated with zinc-hyaluronan gel, during a six-year period. Primarily boys were injured (69.4% of all patients) and the mean age of the patients was 6.2 years. A substantially increased incidence was observed in children who were younger than one year of age (30.4% of all cases). Burn etiology evaluation concluded that the patients were most commonly injured via scalding (56.6% of all children), which was even more predominant during infancy (85.7% of infants), while teenagers were more likely to be injured by flames (66.6% of teenagers). These results further validate the epidemiological observations provided by international trials [21–23].

The average wound area was 3% TBSA in the facial region, and the left upper limb was often burned concomitantly (30.4% of all cases). These thermal injuries epithelialized in 7.9 days on average, and the majority of the patients (52.2%) healed within 5 to 7 days when treated with the zinc-hyaluronan gel. It is critical to highlight that a significant percentage of the children (47.9%) could be treated in an ambulatory manner, thus the actual TTRE might be even lower because the patients' wounds could not be examined each day. None of the children acquired infections and the regenerated skins were an almost perfect color match without any scarring. Moreover, due to the aforementioned reasons, the overall LOS was markedly low with 2.0 days on average. Because of the small TTRE and LOS values combined with the absence of complications, patients could recuperate at home. These factors could be also associated with a reduced total cost of care, shorter time required for dressing changes, and a lower number of anesthesias administered, in addition to decreased need for hospital staff and operating theatre availability. Regrettably, information was not collected about these aspects in a rigorous manner, but further research may prove them superior compared to other conventional approaches.

Research on pediatric facial burn interventions is scarce and there is no internationally accepted "gold standard". Therefore, the choice of treatment mainly depends on the preference of the burn specialist and the customs of the healthcare institute. Similar depth and area injuries in children showed comparable (Mepitel, TBSA: 3.29%, TTRE: 7.58 days) [24] or delayed reepithelialization—related to zinc-hyaluronan—while using EZDerm (TBSA: 4.26%, TTRE: 18.75 days) [25,26], Acticoat (TBSA: 3.23%, TTRE: 14.18 days) [27,28], and Mepilex (TBSA: 2.85%, TTRE: 10.29 days) [26,27] according to the results of our previous meta-analysis [29]. It must be mentioned that these studies did not specifically evaluate facial burns and their application may be difficult in this area. Anesthesia could be necessary during dressing changes, thus a prolonged LOS was also observed with these treatments (EZDerm: 3.36 days, Mepilex: 3.12 days) [26]. The infection rate was also high in the last two interventions (EZDerm: 36.96%, Mepilex: 16.39%) [25–27], while there was no infection observed with Mepitel [24].

As reported by Rogers et al. [30], Biobrane may increase reepithelialization further (TBSA: 6%, TTRE: 10 days), although this alternative also raised the risk for infection (5.7%) and allergic reactions, while the overall LOS was also higher by 3.5 days on average. Other temporary dressings such as amnion membrane allografts (TBSA: 7.39%, TTRE:

13.33 days) [31] and tilapia xenografts (TBSA: 11.13%, TTRE: 10.07 days) [32] showed great healing potential as well, though their acquisition and storage could pose difficulties.

Limitations of this study must also be discussed. The relatively low sample size and single-center design might put into question the generalization of the results. Patients and healthcare providers could not be blinded; thus, the measurements might contain biases. Large population randomized controlled trials (RCTs) would be needed to conclude the efficacy of zinc-hyaluronan on pediatric facial II/1-degree burns. Yet, the findings in this study can be beneficial to outline the objectives and methods for future RCTs.

5. Conclusions

In summary, treating paediatric facial superficial partial-thickness burns with zinc-hyaluronan gel resulted in rapid wound closure and low complication rates, which were accountable for the low amount of hospitalizations. These advantages, in addition to the minimal need for anesthesia, and the gel's ease of applicability and spontaneous separation, are associated with child-friendly burn care.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Surgical Division, Department of Pediatrics, Medical School, University of Pécs.

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Pediatric deep burn management after split-thickness autologous skin transplantation

A comparative study

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Abstract

Treatment of pediatric deep burns remains a challenge for healthcare personnel. After skin grafting, several treatment options are available, but comparative studies of the different options are scarce. Here, we compared the effectiveness of 2 postoperative dressings used to treat deep pediatric burns after split-thickness skin grafting.

At the Department of Paediatrics, University of Pécs, 16 children received skin transplantation after the deep second and third-degree injuries between January 1, 2012 and December 31, 2020 whose results have been analyzed, in this cohort study. We compared the traditionally used Grassolind or Mepitel net and Betadine solution (comparison group) with Aquacel Ag foam and Curiosa gel (intervention group).

Seven children were included in the comparison and 9 children in the intervention group. In the control group, the average number of anesthesia was 6.29, while the number of dressing changes was 4.29. After complete wound closure, the dressing's final removal was on the 13th day, while the mean length of hospitalization was 21.89 days. On average, in the intervention group, 3.56 anesthesia was induced, and 0.66 dressing changes were needed after transplantation. Complete healing (dressing removal) was on the 10th day, and the mean length of hospitalization was 12.38 days.

In the intervention group, the need for anesthesia significantly decreased by 43% ($P = .004$), and they required 84% fewer dressing changes after transplantation ($P = .001$). Moreover, the dressing could be removed 3 days earlier, and the length of hospitalization was reduced by 45% on average.

Abbreviations: DC = dressing changes after transplantation, LOS = length of stay, SD = standard deviation, STSG = split-thickness skin graft, TBSA = total body surface area, TTRE = time to ReEpithelialization.

Keywords: deep pediatric burn, hydrofiber dressing, silver foam, skin graft, Zinc-hyaluronic acid

1. Introduction

Recent studies showed that the incidence of burn injuries in children is increasing in several countries, while pediatric burns still constitute a challenge for healthcare, even in the developed world.[1] In severe forms, burns can also damage deeper tissues besides the skin. Children younger than 5 are at the highest risk because their reflexes are still developing. Furthermore, their skin is thinner than in adults, and they explore the environment without experience with hot subjects and surfaces.[2,3] Without proper therapy, burn injuries can result in lifelong functional, aesthetical, and psychological complications, such as hypertrophic scarring, contractures, or post-traumatic anxiety disorders.[4–6]

In the treatment of thermal injuries, the first 24 to 48 hours are of crucial importance. Missed or inadequate interventions can increase the frequency, severity, and duration of the complications, resulting in an extended hospital stay and a higher cost of care.

Irreversible skin damage in burns is the primary cause of adverse consequences. Therefore, full recovery can only be expected if the integrity of the epidermis has been restored.

The severity and prognosis of a burn are determined by the depth, location, and area of the injury, along with the patient's age and general health.[7,8] Deep partial burns (earlier known as II/2) impact the stratum reticulare in the dermis as well. The

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The datasets generated during and/or analyzed during the presentstudy are available from the corresponding author on reasonable request.

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wound bed is numb with a blotched pale, white, or purple color. Without medical intervention, spontaneous recovery is eventual and often results in extensive hypertrophic scar development. Full-thickness (also known as third-degree) thermal injuries damage the entire skin, which becomes necrotized as well as painless, pale, and pearly. Spontaneous healing does not occur in this condition, and an operative approach is necessary to help the patients.[7] In these severe forms of burns (ie, deep partial and full-thickness), the administration of prompt and effective treatment is of utmost importance.

Earlier clinical trials with the application of either Aquacel Ag foam or Curiosa gel found beneficial effects for each of these treatments individually in second-degree burns.[9–19] However, according to the best of our knowledge, as of today, no data are available on the effect of combining these treatments in pediatric patients with deep second or third-degree burns after skin transplantation. Therefore, in the current study, we present the results obtained from skin grafted children with deep second and third-degree burn injuries treated simultaneously with Zinc-hyaluronic acid gel and a unique silver foam dressing.

2. Materials and methods

2.1. Design

We conducted a nonrandomized, single-center, comparative clinical trial at the Surgical Division, Department of Paediatrics, Medical School, University of Pécs, Pécs, Hungary. The intervention groups' data were collected prospectively between January 1, 2015 and December 31, 2020. The children's characteristics were compared retrospectively with a control group, collected from patients with the same type of injuries who were treated at our clinic from January 1, 2012 to December 31, 2016.

The clinical application of the Aquacel Ag foam and Curiosa gel dressing combination was accepted and permitted by our medical board in 2010. The Hungarian Paediatric Surgery Committee approved the clinical study. Written informed consent was obtained from the patients' guardians in the prospective arm. In the case of the retrospectively collected patient outcomes, permission could not be acquired in every instance; thus, the head of our medical team (GJ) took responsibility for the children's anonymization.

2.2. Participants

Between January 1, 2012 and December 31, 2020, 62 children (younger than 16-year-old) visited our clinic with deep partial or full-thickness burns treated with the combination therapies. Children with comorbidities (6 patients) or more extensive burns than 15% of the total body surface area (TBSA) (9 patients) and those who did not receive skin grafts (16 patients) were not included in the present study. We have excluded 15 patients from our registry due to missing photo documentation, thus, the injuries' depth, grafted area, or wound closure time could not be verified. Attending the short-term (1-month) follow-up was also required for participating in this study, and the mid- and long-term control examinations are still ongoing. Finally, 16 children with deep burns were included in this study, 7 treated with the traditional and 9 with the modern methods. The available data limited the study size because no surgeon at our department could unreservedly apply the conventional dressings after observing the advantages of the contemporary approaches.

2.3. Comparative treatment group

Grassolind gauzes (Hartmann, Germany) are widely used as inexpensive, paraffin impregnated dressings made of open-weave cotton cloth. These dressings are non-medicated and can be safely applied without any sensitizing effects after prolonged use. Their primary function is to create a temporary barrier between the host and the environment, thereby also preventing fluid loss.

Mepitel (Mölnlycke Health Care, Sweden) is a two-sided dressing with a silicone wound contact layer. It was designed to be quick and less painfully removable without causing damage to the regenerating skin. It also seals the wound margins to protect the skin from damaging leaks and maceration, while its perforations allow the exudate to pass through into a secondary absorbent dressing.[20,21]

Betadine (Egis Gyógyszergyár Zrt., Hungary) is an antiseptic solution. Its active ingredient is povidone-iodine, which has a broad-spectrum antimicrobial effect.

These traditionally used dressings are suitable for covering skin defects while treating burn injuries and managing the skin grafts in the post-transplantation phase. However, none of them has any antibacterial properties, which is why they were combined with Betadine in our institution.

2.4. Intervention treatment group

Aquacel Ag (ConvaTec, USA) foam is a Hydrofiber dressing consisting of a superficial polyurethane waterproof layer and a multi-layered absorbent surface containing 1.2% ionized silver. The dressing absorbs the wound secretion as the Hydrofiber layer transforms into a gel, facilitating wound-humidification and closure while protecting against infections.[10,11,13,14,16,18,19]

We have combined this silver-foam dressing with **Curiosa gel** (Richter Gedeon Nyrt., Hungary). Its main component is Zinc-hyaluronic acid that promotes cell regeneration; therefore, it contributes to faster wound closure. Moreover, zinc has antibacterial effects, while the gel formulation helps prevent the adhesion of the silver foam to the base of the burn wound.[9–11]

2.5. Treatment protocol

After the burn injury, each child in the study received primary care before hospital admission. Most patients were transported to our department after their wounds were cooled with running tapwater during first aid, received temporary coverage, and pain medications in the ambulance. All children were assessed by an experienced burn specialist in our department, who also determined further therapeutical steps (Fig. 1A).

After disinfecting and cleaning the burn site (Figs. 1B and 2A), the children required bullectomy and tangential necrectomy (Fig. 1C), which was performed in general anesthesia induced with Calypsol (ketamine – Richter Gedeon Nyrt., Hungary); afterward, we determined their need for transplantation. If we could safely ascertain the depth of the injury after the debridement, we simultaneously performed split-thickness skin graft (STSG) transplantation (Figs. 1D and 2/B). We re-examined the wound's base 2 days later in case of uncertainty, and then we carried out the operation if required.[22] After the transplantation, we applied Grassolind, or Mepitel nets, combined with Betadine solution in the comparison group, whereas Aquacel Ag with Curiosa in the treatment group.

In the comparison group, the application, changing (every other day after the transplantation (Fig. 2C)), and final

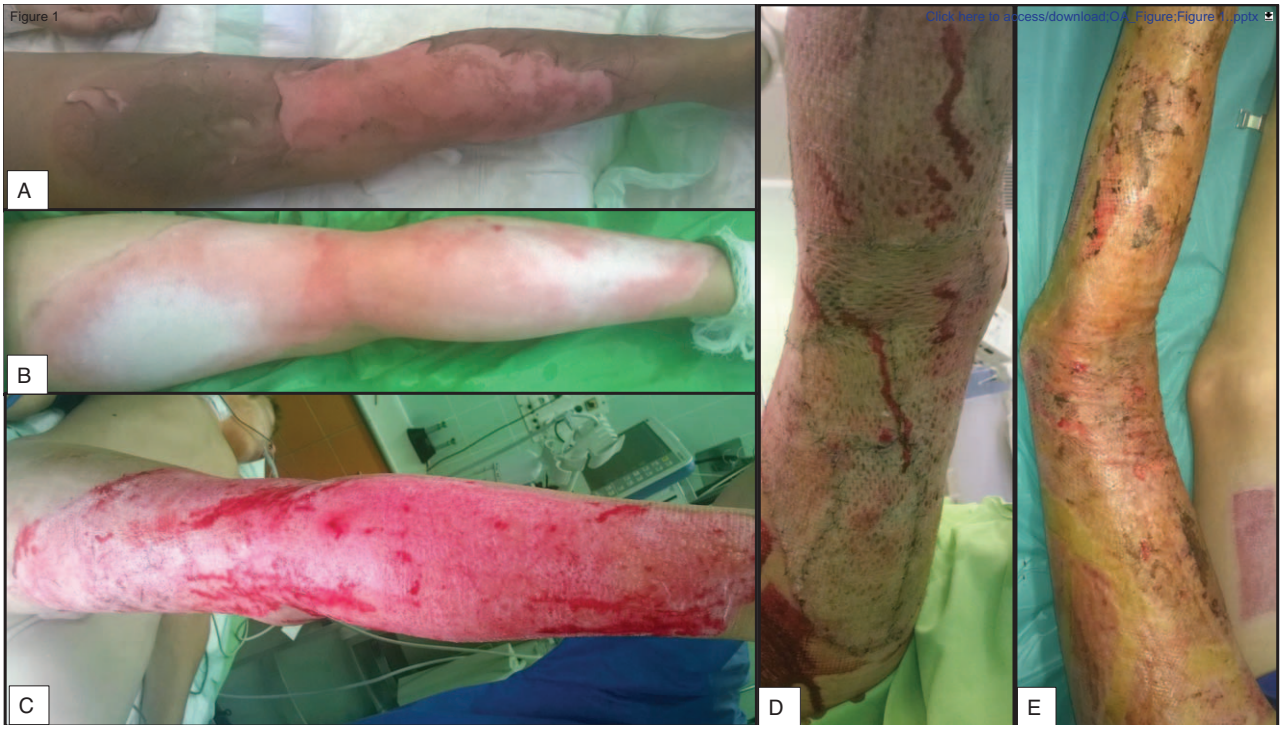

Figure 1. Timeline of an intervention treated burn patient's management. It shows the state of the burn A) upon admission, B) after cleaning the injury, C) following necrectomy, D) subsequent to STSG, and E) at the final dressing removal. STSG = split-thickness skin graft.

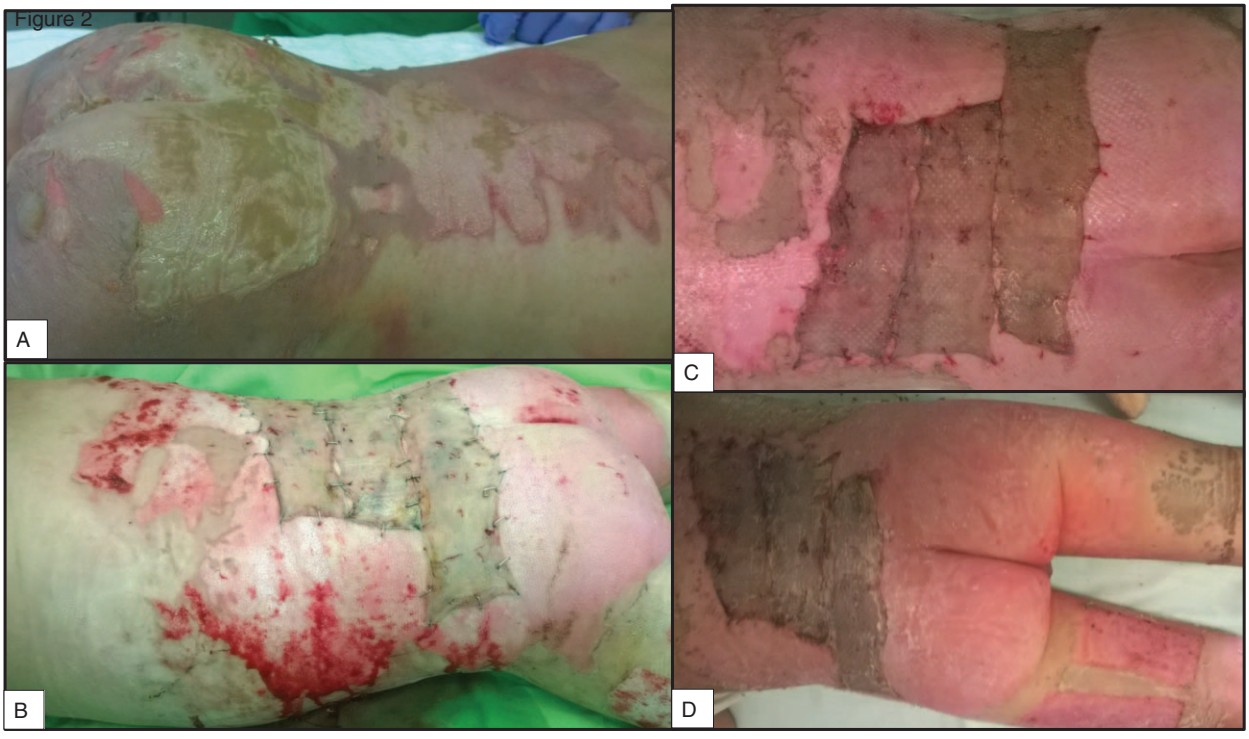

Figure 2. Photo documentation of a control group patient's recovery. A) Admission picture, B) after STSG, C) the state of the injury at a dressing change, and D) discharge photo. STSG = split-thickness skin graft.

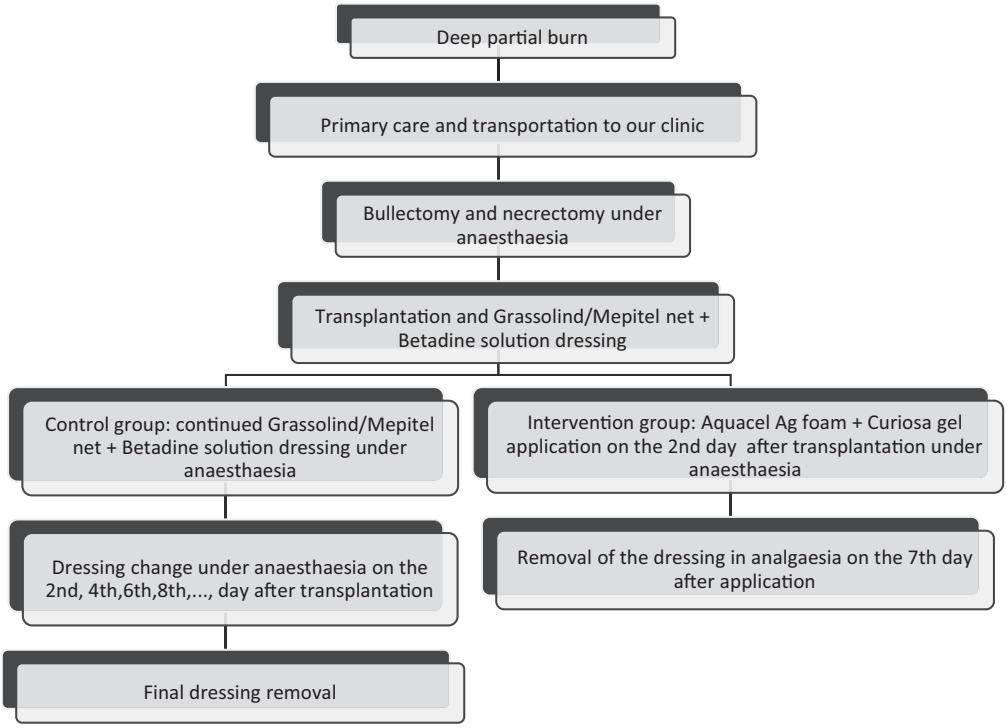

Figure 3. The treatment protocol for the 2 groups in this trial.

removal of the dressings (Figs. 2D and 3) were all made in narcosis. General anesthesia was required due to the common complication of dressing adherence to the wound bed. In these cases, the dressing's removal resulted in the tearing up of the still regenerating epithelium, bleeding, and skin loss. A previous study confirmed that a moist or wet environment is beneficial for the burned skin's healing process.[23] Consequently, these dressings' frequent changes were necessary because povidone-iodine-soaked gauzes were usually dehydrated after 2 days in our clinical experience and lost their antibacterial efficacy.

In earlier studies about pediatric superficial second-degree burns, we have found that the silver foam dressing can be easily removed after complete reepithelialization – it is like the scab's spontaneous separation from the wound bed – therefore, it is painless.[10,15] As a result, we applied only the first dressing under general anesthesia in the intervention group. Narcosis was not necessary afterward, except when the dressing was contaminated or excessive fluid discharge from the wound was observed. Seven days after the initial application, we removed the foam dressings in general analgesia with diclofenac (Cataflam; Novartis Hungaria Kft., Hungary) or under the effects of the anxiolytic midazolam (Dormicum; Egis Gyógyszergyár Zrt., Hungary) or both medications (Figs. 1E and 3).[8,24]

In both groups, the graft donor sites were treated with the control treatment dressings, but only the evaluation of the transplanted areas was done in this study.

A month later, the patients were recalled for a control appointment where their injury was re-examined for possible complications,[4–6] but fortunately, none of the children suffered any (Fig. 4).

2.6. Outcomes and demographics measured

A photograph was taken of every patients' burn before applying the first dressing and after that, at every dressing change until complete wound closure. The children were evaluated based on 9 aspects. We analyzed the patients' demographic data, such as sex and age distribution, etiology, grafted surface area, and the severity of the burns. Our primary outcomes were the average days required until complete healing, the number of required anesthesia and dressing changes after skin transplantation, as well as the total days of hospitalization.

2.7. Statistical analysis

Statistical analyses were performed with Statistics Kingdom calculators available at https://www.statskingdom.com. Welch *t* test was used for continuous variables because of the unequal group sizes and variances, while the Mann–Whitney *U* test was used if the data had discrete variables. With a confidence interval of 95%, probabilities of less than .05 were considered significant. Consultations with a biostatistician were held to confirm our choice of tests.

3. Results

3.1. Distribution by sex

Five boys and 2 girls were included in the comparison group, while 6 boys and 3 girls were in the intervention group (Figure 5). Thus, the ratio of boys was 71.43% in the control, and 66.67% in the intervention, while it was 68.75% in the 2 groups combined.

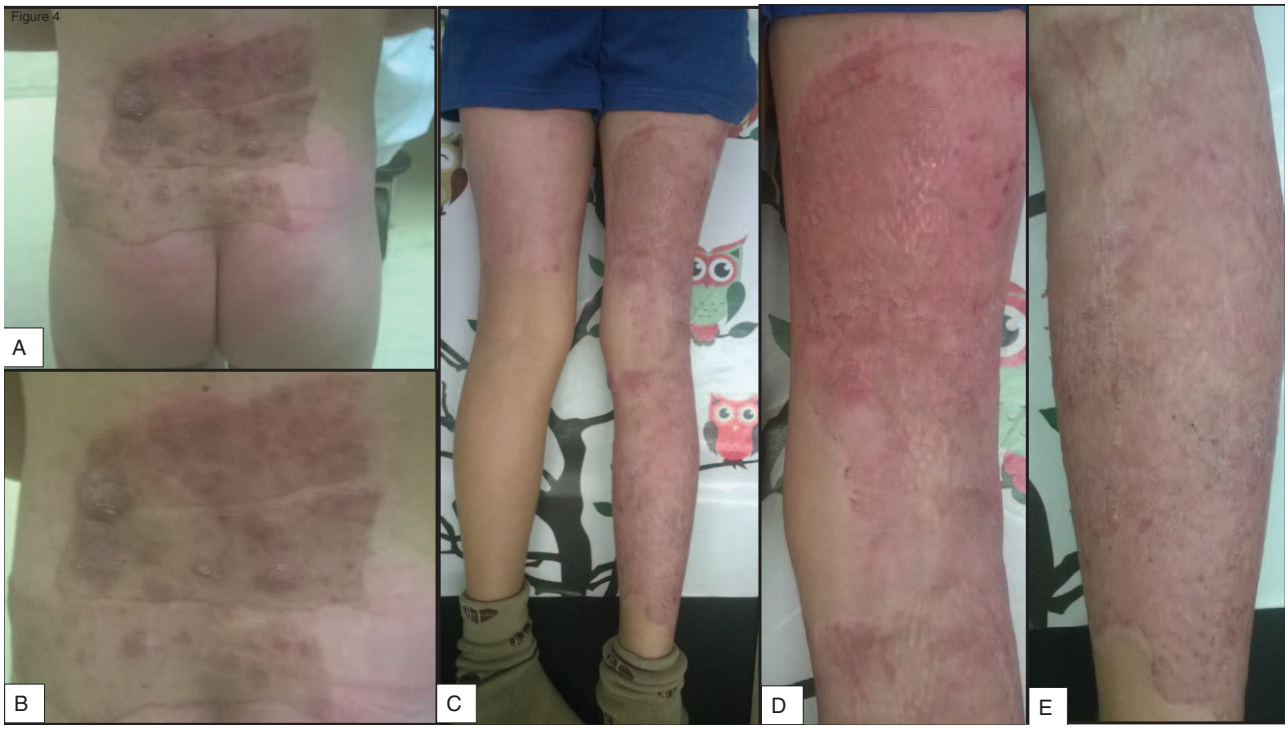

Figure 4. One-month control appointment results of a patient from the (A–B) comparison and (C–E) intervention group.

3.2. Distribution by age

The patients' mean age was 3.00 years (standard deviation, SD: 2.56; range: 1–12 years) at the time of the accident in the control group, while it was 4.88 years (SD: 4.38; range: 1–16 years) in the intervention group. The distribution of the patients' age in the groups; younger than 5, between 5 and 10, and older than 10 years old is shown in Figure 6. Only 1 child was older than 10years in both groups. Children younger than 5 years old had the highest incidence rate for deep burns (68.75% of all cases).

3.3. Distribution by etiology

We also studied the cause of burn injuries. Every case was due to an unintentional accident; the possibility of an intentional insult did not arise regarding any included children. In the comparison group, all thermal injuries occurred due to scalding (Fig. 7). The intervention group included 4 children with scalds (44.44%), 3 with flame (33.33%), and 2 with contact burns (22.22%). Of the latter, 1 was caused by a heater and the other by a household appliance. The most frequent etiology was scalding injury occurring in 68.75% of all patients and 89.89% in younger than 5-year-old children.

3.4. Mean grafted TBSA%

The extent of the burn injuries that received STSG was measured using the Lund–Browder schema,[7,28] based on which we have calculated the percentages of the burned area compared to the TBSA. In the control group, the grafted burn injury's extent was 6.07 TBSA% (SD: 2.44; range: 2–8) and in the intervention group, the grafted TBSA% was 5.27 (SD: 2.64; range: 2–8) (Fig. 8). Although the mean TBSA% of the intervention group is

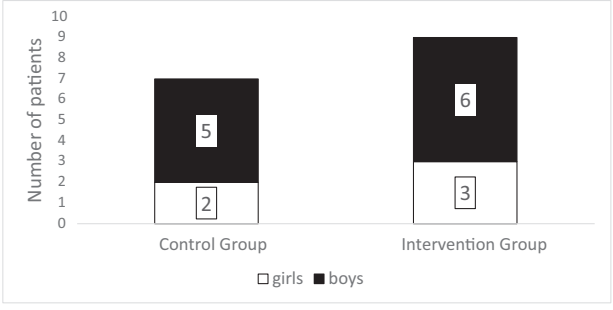

Figure 5. The sex distribution of patients.

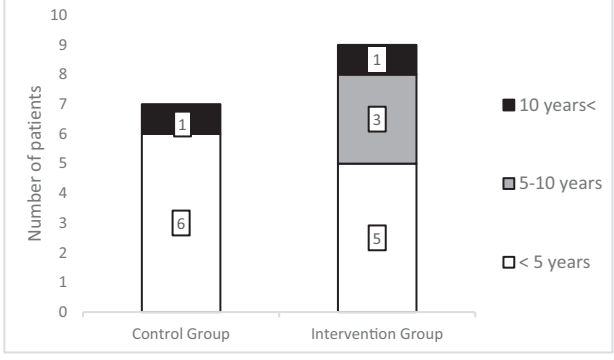

Figure 6. The patient's distribution via their age.

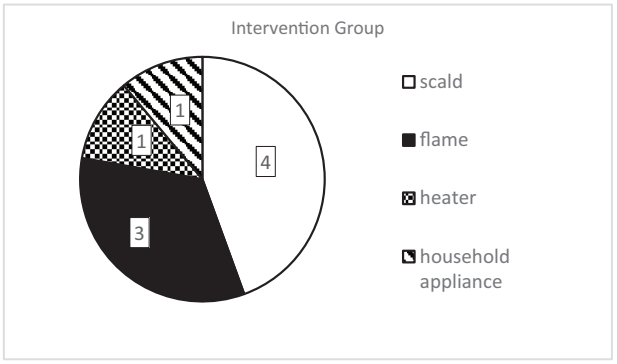

Figure 7. The number of burn injuries based on etiology in the treatment groups.

13.18% lower than that of the comparison group, the difference was not statistically significant ($P = .57$).

3.5. The severity of the burns

We used the American Burn Association classification to determine the burns' severity.[29] Five out of 7 burns were major (71.43%) in the comparison group: 4 suffered more than 10 TBSA%, mostly superficial partial-thickness burns, and 1 had a facial burn injury. In the intervention group, 7 out of the 9 children had major injuries (77.78%). Three had second-degree burns of more than 10 TBSA%, 2 had hand and facial burn injuries, and 2 suffered burns of the feet, with 2 patients having a combined reason for increased severity. The rest of the second-degree burns were moderate in both treatment groups because the affected area was 5 to 10 TBSA%.

We have also compared the ratio between grafted third and deep second-degree burns, and in the comparison group, there was only 1 child (14%) with full-thickness injuries. At the same time, there were 3 children (33%) in the intervention group.

3.6. The mean time to reepithelialization

We defined time to reepithelialization (TTRE) as the average duration from transplantation of the skin graft until the transplanted skin's complete wound closure without wound leakage. Patients in the comparison group needed an average of 13.57 (SD: 4.28; range: 8–18) days until reepithelialization, whereas in the children in the intervention group, TTRE was only 10.44 (SD: 2.27; range: 7–15) days (Fig. 9). Although the difference was not statistically different between the 2 groups ($P = .246$), the healing time was 23% shorter after Hydrofiber silver-foam with Zinc-hyaluronic acid gel dressings than in the comparison group. To adjust for the slight difference in the burned surface area, the healing time by area (TTRE/TBSA%) was calculated to measure how long it takes for a hypothetical 1 TBSA% burn to regenerate. The comparison group required 2.24 days, while the intervention group needed 1.98 days for a 1 TBSA% wound closure, which is an 11.38% time reduction with the intervention treatment.

3.7. The average number of anesthesia required

In the comparison group, the dressing was changed every other day, which required general anesthesia in the operating theatre with an average of 6.29 times (SD: 1.28; range: 4–8).

The Hydrofiber dressings combined with Zinc-hyaluronic acid gel dressing were applied on the second day after the skin graft transplantation under general anesthesia. Afterward, further dressing changes were not needed, except in case of contamination or excessive wound leakage. Seven days later, the dressing was removed in general analgesia or under the effects of anxiolytic or both medications. In the intervention group, anesthesia was needed an average of 3.56 times (SD: 0.83; range: 2–5), which was significantly less than what was required for the comparison group patients ($P = .004$) (Fig. 10).

3.8. The average number of dressing changes after transplantation

A significant difference was found in the average number of dressing changes after transplantation between the treatment groups ($P = .001$). The intervention group only got their dressing combinations first applied 2 days after the transplantation, when the grafts' take was confirmed. Therefore, the reapplication rate was measured in both groups after that moment in the patients' management. There were, on average, 4.29 dressing changes (SD: 1.50, range: 2–6) in the comparison, whereas only 0.66 changes were required (SD: 0.82, range: 0–2) in the intervention group (Fig. 11). Thus, the frequency of dressing changes was reduced by

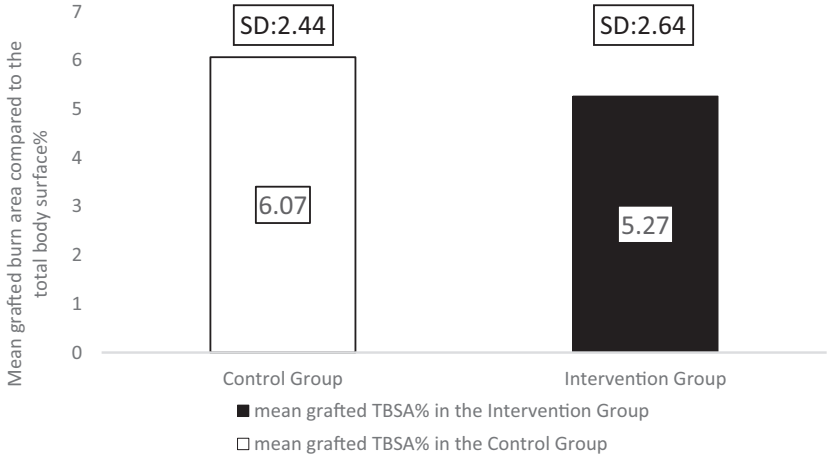

Figure 8. The mean grafted burn areas in the analyzed groups.

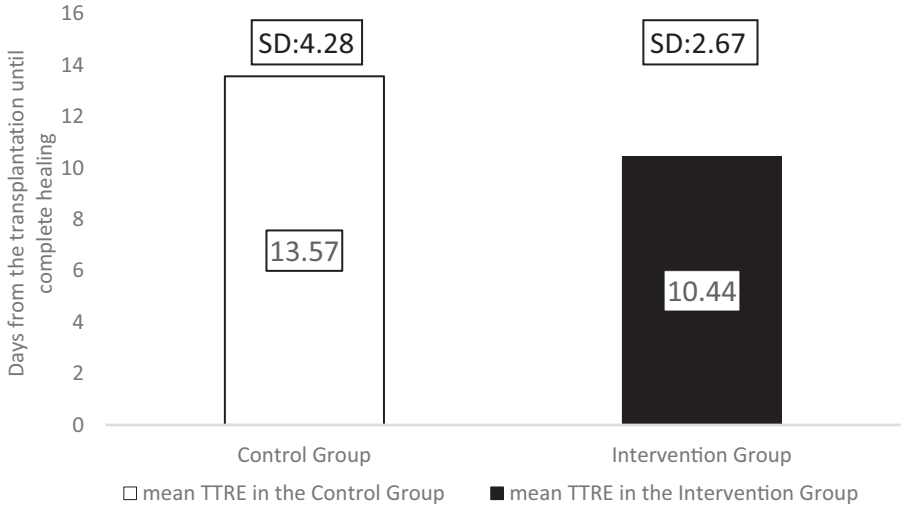

Figure 9. The average TTRE in the 2 groups. TTRE = time to ReEpithelization.

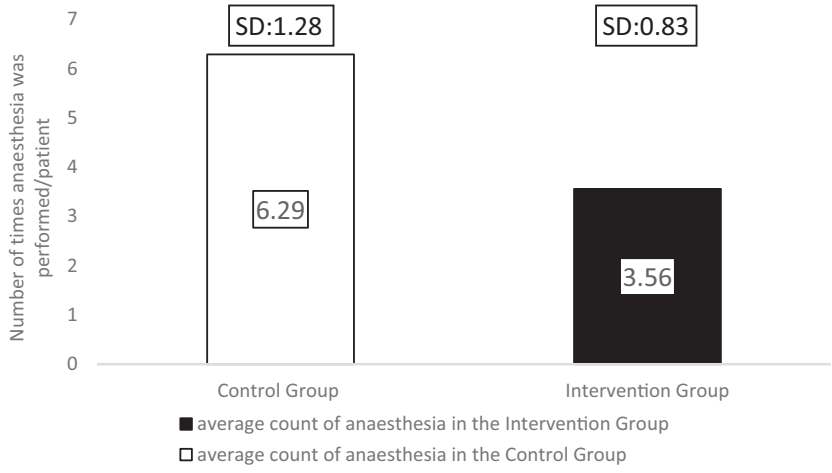

Figure 10. The mean number of times anesthesia in the 2 treatment groups.

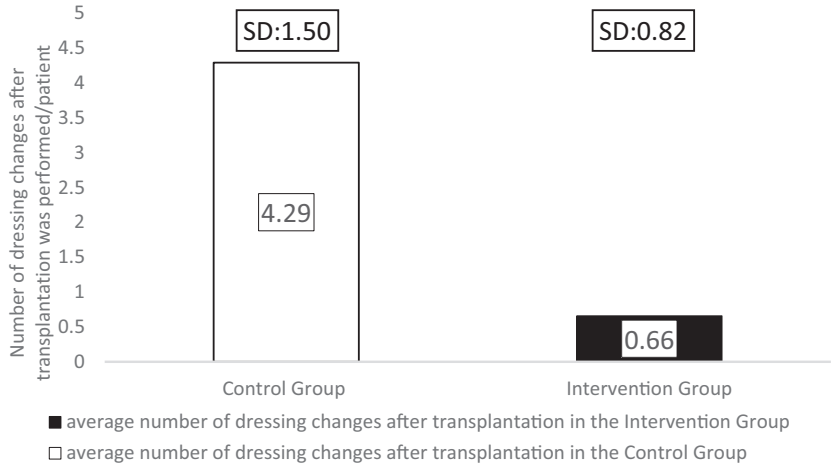

Figure 11. The mean number of dressing changes after transplantation performed in the groups.

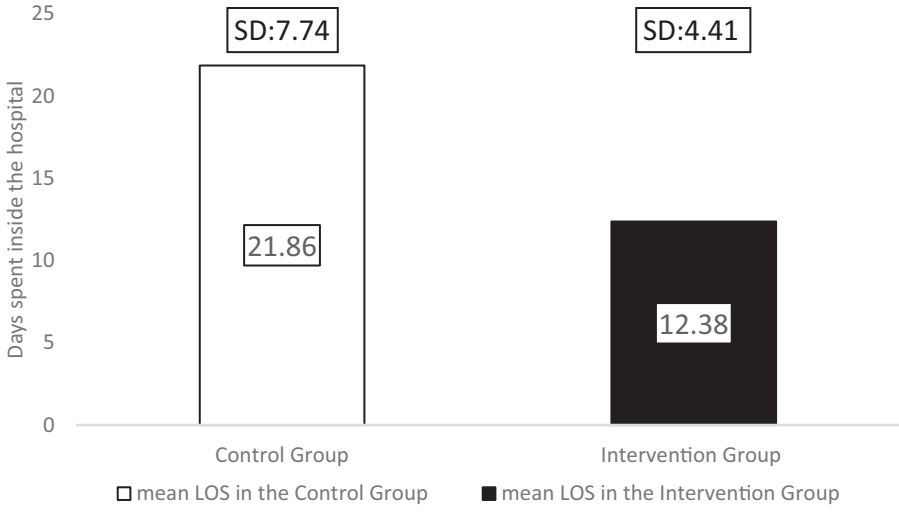

Figure 12. Length of stay inside the hospital, measured in days.

84.34%, resulting in less discomfort for the children. Consequently, the need for healthcare professionals and operating theatres were also reduced.

3.9. Mean length of hospital stay

The duration of time spent inside the hospital is an essential factor for the child, family, and healthcare personnel. Our study compared the 2 treatment options and found a tendency for reduced length of hospital stay (LOS) in the intervention group ($P = .055$). Children in the comparison group spent on average 77% more time in the hospital than intervention group patients. The mean LOS for the comparison group was 21.86 days (SD: 7.74; range: 12–35), while children in the intervention group spent 12.38 days (SD: 4.41; range: 5–19) in hospital (Fig. 12). From this analysis, we had to exclude 1 patient from the intervention group. Even though the child's grafted wounds healed after 13 days, the patient spent 46 days in the hospital due to reasons independent from the burn injury. For clarity, without excluding the patient, the mean LOS in the intervention group would have been 16 days (SD: 10), which is still markedly lower than the LOS in the comparison group.

It is critical to highlight that in the intervention group, we were able to discharge multiple patients before the final dressing removal – after we have instructed the children and their parents on how to protect the dressing.

The summary of our findings is shown in Table 1.

4. Discussion

Predominantly boys suffered burn injuries in our study (68.75%). The grafted burn area was similar in all children (range: 2–8 TBSA%), with an average of 6.07 TBSA% in the comparison and 5.27 TBSA% in the intervention group.

Large population studies found correlations between age and the burn location, and they have discovered age-specific injury mechanisms.[2,5–27] Under the age of 5, the typical causes included pulling hot liquid placed at a height onto themselves and directly touching the heater, while in children older than 10 years, flame-related wounds were dominant. Since young children's withdrawal reflexes are not yet fully developed, a moment of "freezing" is often present after coming in contact with heated surfaces, which increases the duration and severity of the burn.[2,25–27]

In our study, primarily children younger than 5-year-old suffered from deep burns (68.75% of all cases), of which 89.89% had scalding-related accidents. These results are in accordance with the results provided by international trials.[1,25–27]

Table 1

The summary of results.

	Control group			Intervention group	
No. of patients	7			9	
Outcomes	**Mean**	**SD (range)**	***P* value**	**Mean**	**SD (range)**
Age (years)	3	3.7 (1–12)	.398	4.89	4.38 (1–16)
Grafted TBSA(%)	6.07	2.44 (2–8)	.57	5.27	2.64 (2–8)
TTRE (days)	13.57	4.24 (8–19)	.246	10.44	2.27 (7–15)
TTRE/TBSA% (days)	2.24		1.98		
DC (n)	4.29	1.5 (2–6)	.001	0.67	0.87 (0–2)
No. of anesthesia (n)	6.29	1.28 (4–8)	.004	3.56	0.83 (2–5)
LOS (days)*	21.86	7.74 (12–35)	.056	12.38	4.41 (5–19)

TBSA% = total body surface area, TTRE = time to ReEpithelization, DC = dressing changes after transplantation, LOS = length of stay.
* The intervention group only contains 8 children in the LOS analysis.

The Hydrofiber dressing's unique layered design could interact with the wound exudate, and it provided a micro-environment that was optimal for healing for at least a week.[30,31] The silver ions, in addition to zinc and povidone-iodine, facilitated the dressing's antimicrobial effectivity[9,30] because none of the burn sites became infected. Consequently, we have found a significant reduction in the average number of dressing changes after transplantation in the intervention group ($P = .001$). In the comparison group, patients required 4.29 dressings, whereas only 0.66 changes were needed for children with the intervention treatment. The average number of anesthesia was also significantly reduced in the group treated with Hydrofiber dressings combined with Zinc-hyaluronic acid gel ($P = .004$) due to the interventions' lower number of dressing changes and less traumatizing separation from the wound bed. Patients in the Grassolind or Mepitel net and Betadine solution group needed narcosis 6.29 times on average, whereas in the intervention group, it was only required 3.56 times. The TTRE was 13.57 days in the comparison group, while it took only 10.44 days in the intervention group. The faster healing times and fewer dressing changes explain the difference in the LOS; on average, patients spent 21.86 days inside the hospital in the comparison group, whereas only 12.38 days in the intervention group.

Limitations of our study must also be mentioned. We could not collect sufficient data from the patients' pain levels and about the healthcare costs, retrospectively. However, we are confident that the less frequent dressing changes and anesthesia in the intervention group also caused less stress and discomfort to the children. These benefits for the patients, at the same time, can also reduce the need for hospital staff and operating rooms, thereby reducing the costs of healthcare. It must be emphasized that the patient population in our trial was small, and we collected patients' data from a single center. Future trials are needed to confirm our results and ultimately to better treat and improve children's life quality with severe burn injuries.

In conclusion, our results showed that utilizing modern Hydrofiber dressings combined with Zinc-hyaluronic acid gel on children's burn wounds required 84% fewer dressing changes after transplantation compared to the traditionally used dressings at our clinic. Patients treated with the intervention did not require additional narcosis for the dressing changes (after the initial application); therefore, we could reduce the need for anesthesia by 43%. The children in the intervention group also had 23% faster-wound closure; thus, 45% shortened hospital stay, which data further support the benefits of the applied treatment in the intervention group.

Acknowledgments

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Author contributions

AL participated in the data curation, formal analysis, interpretation, and visualization of the data as well as writing the original draft and reviewing and editing the article. GJ was involved in the conceptualization, methodology, investigation, project administration, and supervision processes in addition to reviewing and editing the article. AG took part in project administration, supervision, and reviewed and edited the article. AGL was involved in the investigation, formal analysis, and validation. ZJ reviewed and edited the article was involved in the investigation. All authors read and accepted the final manuscript.

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Case Report

Management of Pediatric Partial-Thickness Burns with Lavanid Gel (Polyhexamethylen Biguanide, Polyhexanide) "Case Reports"

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Abstract

Aim: The evaluation of Lavanid gel (Polyhexamethylen Biguanide (PHMB) or Polyhexanide) in pediatric burn therapy. **Patients and Methods:** The authors present the cases of two children. **Case I:** A 6-year-old boy chemically burned his thighs, consequently necrectomy and autologous split-thickness skin transplantation were performed. The donor and grafted areas were covered with Grassolind net and Polyhexanide gel. **Case II:** Grassolind net and Polyhexanide gel was used as the dressing of a 2-year-old girl's superficial partial-thickness left forearm scald as well. **Results:** During therapy, the transplanted skins adhered completely, in addition to the reepithelialization of the burn wounds. Infection or other complications were not observed. The follow-up of the children is still ongoing, short-term results suggest that the application of Grassolind net with Polyhexanide gel is an effective burn dressing, which creates an appropriate environment for wound healing. **Conclusions:** Based on our initial experiences, the analyzed intervention could be applied in a gentle, child-friendly manner and was associated with favorable burn wound healing capabilities as well as esthetic outcomes.

Keywords: Children; PHMB; Polyhexanide; Partial-thickness burn

Introduction

Burns are the direct or indirect injury of the skin and deeper tissues due to thermal effects. Skin loss is the basis and sustenance of thermal injuries. Complete recovery can only be expected after the reconstruction of the integument's continuity. Burns are often classified by their depth (Figure 1), which depends on the triggering agent's temperature and the duration of heat contact. The severity and prognosis of burns are dependent on the patients' age and general health, along with the injuries' depth, area [1-4].

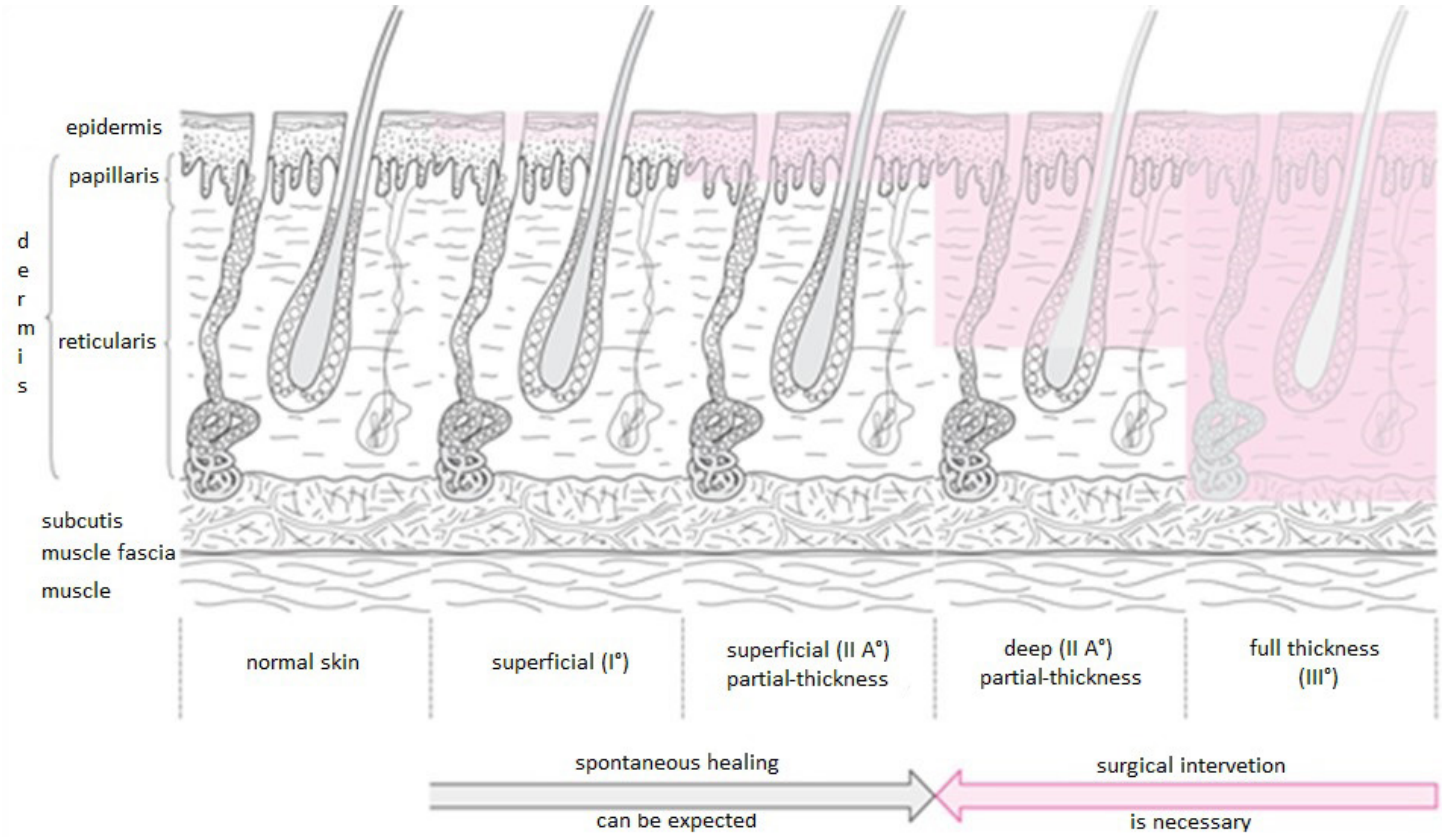

Figure 1: Burn depth classification. It is based on the recommendation of the European Burn Association (EBA) (Juhász I. Thermal Injuries [Termikus sérülések]. In: Gaál Cs. Surgery [Sebészet] Medicina 2016).

Burn Depth

Superficial thickness (I degree) burns damage the epidermis, resulting in severe pain and minimal edema. Upon physical examination, erythema can be observed, without the formation of bullaes. Generally, the triggering factor is sunlight, and they do not require any medical intervention, because healing occurs in 5-7 days without scar formation. Partial-thickness (II degree) injuries affect the dermis and have two subcategories. Superficial partial-thickness (II/1 degree) burns impact the skin's papillary layer, causing straw-yellow bullaes, which are responsible for painful, bright pink wound beds after their removal. On average, II/1 degree burns regenerate within 7-10 days, spontaneously. The reticular layer of the dermis is also involved in deep partial-thickness (II/2 degree) thermal injuries. Subsequent to bullectomy, the wound base is blotched, whitish and numb. Without medical attention, unprompted healing is incidental and slow, often resulting in extensive scarring. Full-thickness (III degree) burns disrupt the subcutis or deeper tissues. Thus, the skin becomes necrotised and painless, with a pearly and pale color. Surgical intervention is necessary for this condition because spontaneous healing should not be expected [2,4].

The Management of Burns

Conservative Therapy

An important step in the conservative treatment is the burn wound's rinsing with a disinfecting agent, then the removal of dead tissues. Thorough debridement causes considerable pain, thus the cleansing and covering of the children's burn wounds were performed under the effects of analgesic and anxiolytic drugs or general anestesia. The healing of the burn wound begins when epithelial cells travel from the healthy to the damaged areas. These cells may originate from the remaining epithelial appendages, like from the sebaceous and sweat glands' ducts' epithelial lining. Conservative treatments must facilitate this epithelialization process. In I degree burns, the therapy is strictly conservative, which can be managed in an ambulatory manner. Regardless of the burn mechanism - such as sunburn or domestic accident - several alternatives are available, like the Fenistil® and Burn Free gels®, or the Irix®, Panthenol®, and Naksol sprays®.

II/1 degree burns can also be effectively treated conservatively. Maintaining a moist environment is of utmost importance, therefore the burn wounds' and the donor and transplanted areas

were covered with saline or other solution soaked gauze sheets or various gels. Burn wounds are prone to infection and conversion, which is the deepening of the injury. Consequently, combining the treatment with antimicrobial compounds is often warranted, where an important expectation from them, is to impede wound healing as minimally as possible.

From the solutions, the usage of Octenisept® and Betadine® are most widespread in Hungary. Betadine® contains povidone-iodine, which has a remarkably wide antimicrobial spectrum; it is bactericide, fungicide and selectively virucide. Although, in our experience, it may cause a stinging feeling in children and cannot be administered to iodine sensitive individuals [4-6]. The benefits of Octenisept® include, that it stings less, and it does not discolor the wound base, thus it simplifies its evaluation. Both international and Hungarian guidelines recommend the silver sulfadiazine containing Dermazin® cream, which is antibacterial and promotes reepithelialization. Its disadvantage is, that it requires daily dressing changes, and creates a yellowish plaque on the burn, which makes depth determination difficult [7,8]. Zinc-hyaluronan (Curiosa® gel) is well-known in wound management for its cell regeneration supporting effect, which results in rapid wound closure.

A Lavanid® (PHMB, Polyhexamethylen biguanide or Polyhexanide) is a sterile, preserved gel, based on Ringer solution and characterized by good tissue tolerance. As a preservative, it contains 0,04% polyhexanide, which is accounted as one of the most popular treatments in chronic wound and burn care. Besides the cleansing and moistening of the injuries, PHMB gel is capable to heal wounds, infected with multiresistant bacteria [9,10].

In addition to the administration of different solutions and gels, wax and paraffine containing nets (Grassolind®, Klinitulle®) are also commonly used in our country, along with silicone (Safe-Tac®), that reduces or prevents the adhesion of the dressing to the wound base. Grassolind® is a woven cotton dressing, and contains paraffine. It is capable to cover large body surfaces, while it does not cause hypersensitive reactions. Meanwhile, Bactigras® dressings contain 0.5% chlorhexidine, besides paraffine. The mesh structured Inadine®'s wide antimicrobial spectrum allows the prevention and management of infected wounds [6,11,12]. Film dressings (OpSite®, Omiderm®, Tegaderm®) are suitable for the treatment of wounds without exsudation. In comparison, hydrogel dressings (Elastogel®, IntraSite® gel, NuGel®) are appropriate for the absorption of wound secretion. Materials that are able to establish the injuries' optimal moisture level are called hydroactive or hydrocolloid dressings (Hydrocoll®, Allevyn Non-Adhesive®). Antiseptic metals are not only contained in liquids and wash-off solutions but in silver impregnated wound coverings as well (Aquacel Ag®, Acticoat®). The most novel dressing type is the hydrofiber, such as Aquacel Ag foam®. It consists of an external polyurethane waterproof film layer and a multilayer absorbent surface, with a silver ion content of 1.2 % by weight. The multilayer cushion contains a sheet of foam and a plate with hydrofiber technology. It absorbs wound secretions, causing the hydrofiber layer to turn into a gel, which helps to keep the wound moist, heals wounds as soon as possible, and prevents infections. Wearing the bandage is comfortable for the patient, while its removal is painless and it does not require anesthesia [7-10,13-19]. In the management of burns, the NPWT (Negative Pressure Wound Therapy) method is becoming increasingly common, which can also improve blood supply to the affected area. It exerts negative pressure (vacuum) to help the wound edges merge, and remove infectious substances [5].

Surgical Treatment

In case of circular, large area, and deep burns, necrotomy (tension reduction incision) is required, which is aimed at improving the circulation of the affected region. In order to prevent compartment syndrome, fasciotomy is also recommended in some cases, for example in the case of electrical burns. Dead tissues are a breeding ground for toxic bacterial infections and should be removed as soon as possible by necrectomy. Tangential excision is often used, during which dead areas are removed in thin layers until a viable, spot-bleeding surface is obtained. This procedure can be performed with an electric dermatome or Humby knife. To restore the barrier function of the skin, the lack of continuity must be eliminated. Allograft and xenograft type coverages are also known, in the latter case we mostly utilize porcine skin, which is used as a temporary covering [9,10].

With the development of biotechnology and tissue culture, a huge number of products have recently been placed on the market to cover wounds. Epidermis type preparations, like Epicel®, are suitable for epidermal type coverage from autograft cultured cells. They are bred from the patient's skin, but also be obtained from allogeneic cultured cells. A dermis type preparation is AlloDerm®, an allogeneic cell-free dermal matrix with intact basal membranes, grown from human skin, which prepares the wound base for proper autograft transplantation. Integra® is an extracellular matrix made up of bovine collagen and other wound healing materials, which helps to develop a new dermis. Combined products of the epidermis and dermis types can also be used. Apligraf® for example, contains bovine keratinocytes, fibroblasts and type I collagen [5].

During an autologous transplant, the burned area is covered with Split-Thickness Skin Grafts (STSG) taken with a dermatome or Humby knife. Donor skin may come from the proximal, medial or lateral surface of the thigh, as well as from many other regions. The donor area is selected based on which region causes the least number of cosmetic problems for the patient later and can be obscured by clothing.

The essence of a meshgraft is that the skin taken from the intact donor area can be stretched into different proportions with the help of mesh dermatome, thus increasing its size. In the case of sheet-like or non-meshed grafts, the donor skin is not stretched, therefore a more beautiful cosmetic result is obtained. Transplantation of full-thickness skin gives the best cosmetic results, but the disadvantage is that it has a higher nutritional need owing to its thickness, therefore graft failure is more common [2,4,5].

Covering the transplanted skin is always necessary, for this, we can use gauze sheets, gels and various dressings soaked in the solutions described in the conservative therapeutic part for the treatment of grade II burns. Currently, keeping the wound moist or wet seems to be the best way to heal wounds.

Case Report I

The combined application of Grassolind net and PHMB gel was performed in a child who received skin transplantation for his II/2 and II/1 degree deep burn injury. The six-year-old boy was admitted to our department due to a chemical burn on his left thigh. The grade II/2 injury necessitated autologous STSGs which were covered with Grassolind net and PHMB gel, along with the donor areas. On the second day, during dressing change, no inflammatory signs or complications were observed. Seven days after transplantation, graft adhesion has been observed (Figure 2).

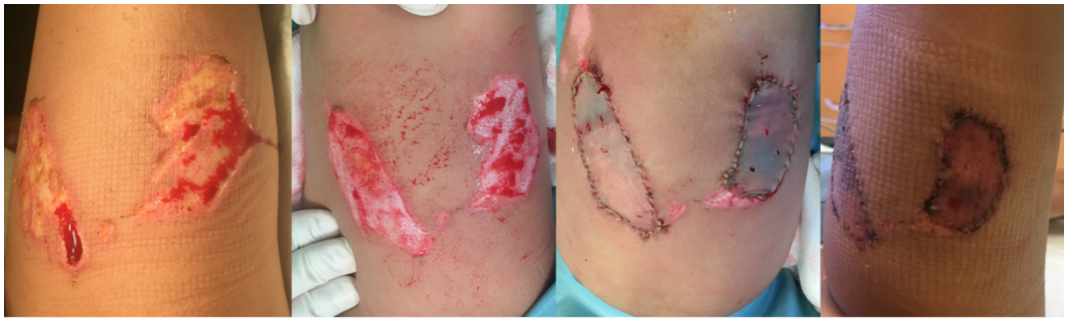

Figure 2: Management of the first patient. The left thigh's ventromedial II/2 degree burn injury, before **(a),** and after necrectomy **(b).** Two days after the transplantation **(c).** On the seventh day of therapy, the take of the STSG was visible **(d).**

Case Report II

A 2-year-old girl's left forearm was covered with Grassolind net and PHMB gel, due to a II/1 degree scalding. Three days after the application of the treatment combination, during dressing change, partially epithelialized areas were observed with minimal fluid leakage. The final removal of the dressing was done 8 days following the injury when complete wound closure was noted. Hereafter, we advised the local application of a greasy ointment. Three weeks after the burn, the control examination revealed scar-free healing with remarkable cosmetic results (Figure 3).

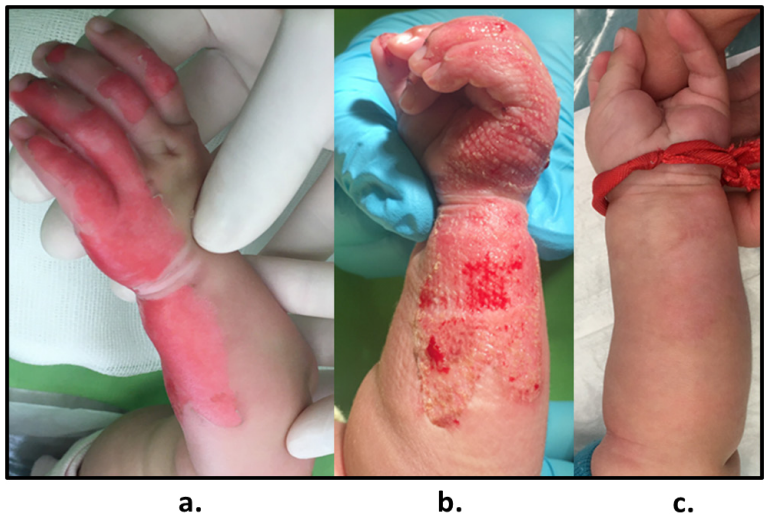

Figure 3: Photodocumentation of the second patient. A II/1 depth injury subsequent to debridement, on the left forearm's ulnar surface and extending to the fingers **(a).** The results of Grassolind net and Polyhexanide gel therapy, after three days **(b).** On the three-week control appointment, the patient presented without scarring and had excellent cosmetic outcomes **(c).**

Discussion

Thermal injuries mainly occur in families, living under inadequate social circumstances, where the risk of infection is high during reepithelialization. The management of mixed-depth burns is a constant challenge for healthcare providers, and the expert opinions are controversial regarding the efficacy of conservative treatments. Contiguous, deep thermal injuries unequivocally necessitate surgical intervention, while in the case of superficial partial-thickness burns, conservative treatment results in favorable outcomes. In the international literature, a vast amount of therapeutic options are well-known and accepted. This article provides the evaluation of an alternative dressing, with promising initial results.

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Gyermekkori, áramégés okozta kézujjsérülések ellátásáról és késői szövődményeiről

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Elektromos áram okozta égési sérülések gyermekkorban ritkán fordulnak elő, az összes égés mindössze 2–10%-át teszik ki. Nehézséget okozhat a sérülés valódi súlyosságának meghatározása a kicsiny ki- és bemeneti sebek miatt. Áramégések során a legtöbb esetben mély necrosis alakul ki. Ilyen sérülések esetén a bőr, a lágy részek, a csontok, illetve fiatal életkorban a növekedési zóna sérülésével is számolni kell, ami növekedési zavart és ezáltal másodlagos deformitásokat okozhat. Jelen esettanulmányunk célja az áramégés során létrejött gyermekkori kézujjsérülések ellátásának és késői szövődményeinek bemutatása. Egy 15 éves fiúgyermek izzócsere közben ráfogott egy vezetékre, ami a jobb mutatóujján égési sérülést okozott. Distalis interphalangealis ízülete felett volarisan 25 × 14 milliméter nagyságú bemeneti, dorsalisan a körömágy lateralis szélén 8 × 7 milliméteres kimeneti áramjegy volt látható fehér, necroticus sebalappal, mely III . fokú égési sérülésnek bizonyult. A mély égési sérülés miatt necrectomia, keresztlebeny-plasztika és az adóterület teljes vastagságú bőrrel végzett transzplantálása történt. A primer rekonstrukciót követően három héttel a lebeny leválasztására került sor. A nyomon követés során a mutatóujj körömperc-deviációja volt észlelhető. A röntgenvizsgálat a körömpercbázis ízfelszínét is érintő csonthiányt igazolt. Egy 2 éves leánygyermek szöggel nyúlt a konnektorba, emiatt hüvelykujján és tenyerén keletkezett égési sérülés. Interphalangealis ízülete felett dorsalisan és volarisan, valamint a hypothenar területén III. fokú égési sérülés volt látható. Necrectomiát követően a hüvelykujj ventralis bőrdefektusának zárása elforgatott lebennyel, a donorterület és a dorsalis bőrdefektus fedése teljes vastagságú bőrrel történt. A gyermek nyomon követése jelenleg is zajlik, rövid távon a csontérintettség okozta végperc-deviáció látható. A gyermekek hosszú távú nyomon követése szükséges a késői szövődmények felismerése és kezelése céljából.
Orv Hetil. 2022; 163(14): 564–568.

Kulcsszavak: áramégés, gyermek, kézujjsérülés, növekedési porc, lágyrész-rekonstrukció

Case reports of pediatric electrical finger burn injuries' management and late-onset complications

Pediatric electrical injuries are rare; they only constitute 2–10% of all burn causes. Determination of their actual severity may be challenging due to their small entry and exit wounds. Deep necrosis develops during electrical burns in most cases. These injuries can damage the skin, soft and bone tissues, and in children, the growth plate, which may cause secondary deformities. The objective of these case reports was the presentation of paediatric electrical finger injuries' management and late-onset complications. A 15-year-old boy touched an electric wire while changing a lightbulb, which caused a burn injury on his right index finger. During the physical examination, a 25 × 14 mm, third-degree burn was identified volarly, above the distal interphalangeal joint as an entry wound, and an 8 × 7 mm exit site occurred dorsally at the nailbed's lateral edge. Necrectomy and cross finger flap surgery were performed. The cross flap was separated three weeks after the primary reconstruction. Throughout the follow-up examinations, the ulnar deviation of the distal digit was observed. X-ray confirmed the bone atrophy of the distal phalanx base. A 2-year-old girl inserted a nail into the power outlet, causing third-degree burns on her thumb around the interphalangeal

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joint and hypothenar region. After necrectomy, the thumb's skin defect was reconstructed with a rotated flap, while the donor site received full-thickness skin graft transplantation. The follow-up of the child is still ongoing. Long term follow-up of these patients is necessary to identify and treat late-onset complications.

Keywords: electrical burn, child, finger injuries, growth plate, soft tissue reconstruction

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Áramégés során gyakran sérül a kéz és az ujjak [1], ami megkésett vagy helytelen kezelés esetén számos, akár egy életen át tartó funkcionális, pszichés és kozmetikai szövődménnyel járhat [2–4]. Az égési seb mélysége függ az áramerősségtől, a hőfoktól, az ellenállástól és a behatás időtartamától egyaránt [5]. Gyermekkorban a növekedési porc sérülése is bekövetkezhet, amely hosszú ideig rejtve maradhat, és évekkel később okozhat látható következményeket.

Módszer és eredmények

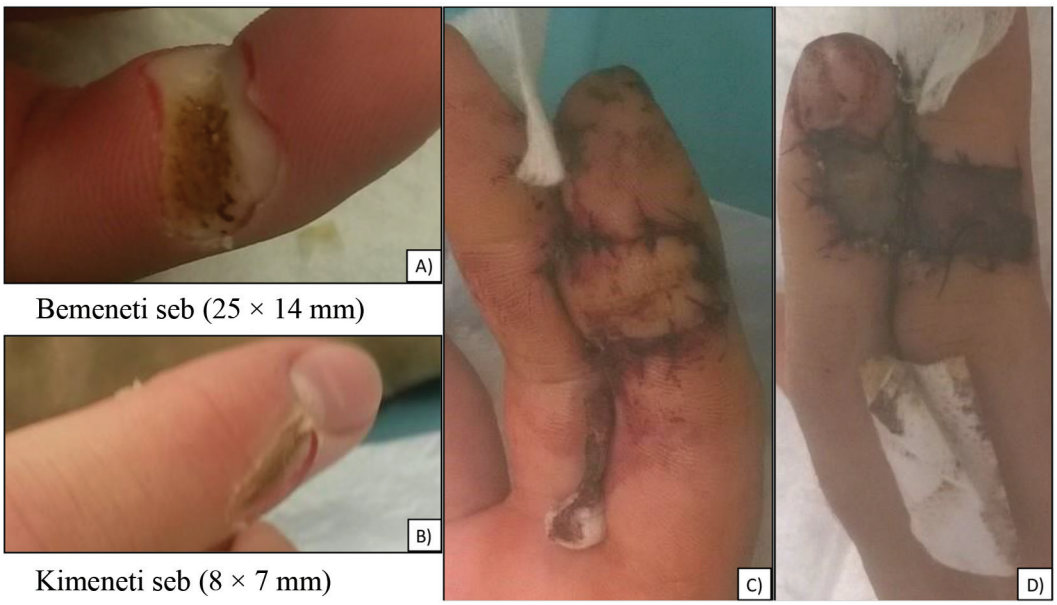
Első eset

Egy 15 éves fiúgyermek izzócsere közben ráfogott egy vezetékre, ami a mutatóujján égési sérülést okozott.

Klinikánk Sürgősségi Osztályára való felvételekor belszervi és neurológiai statusában kórjelző eltérés nem volt, valamint az EKG-vizsgálat kóros eltérést nem igazolt. A gyermek jobb mutatóujján, distalis interphalangealis ízülete felett volarisan 25 × 14 mm nagyságú bemeneti áramjegy volt látható fehér, necroticus sebalappal, mely III. fokú égési sérülésnek felelt meg *(1/A ábra)*. A kimeneti jegy dorsalisan a körömágy lateralis szélén 8 × 7 mm-es nagyságú volt, mely kevert mélységű II. fokú égésnek látszott *(1/B ábra)* [6]. Az ujj keringése, beidegzése megtartott maradt, distalis interphalangealis ízületét aktívan flektálta és extendálta a gyermek. Kezdetben az égési sebalap feltisztulása érdekében antibakteriális, 0,25%-os ezüst-nitrát-oldatos kötés felhelyezése történt [7]. A megfigyelési időszakban láz, keringési zavar nem alakult ki. A lokalizáció és a sérülés súlyossága miatt égésplasztikai, illetve kézsebészeti konzílium is történt, amelyek alapján az elhalt szövet kimetszését és keresztlebeny-plasztika elvégzését javasolták.

Általános érzéstelenítésben és antibiotikumvédelemben necrectomia, utána keresztlebeny-plasztika, valamint az adóterület teljes vastagságú, Wolfe–Krause-bőrrel való fedése történt *(1/C és 1/D ábra)* [8]. A posztoperatív szakban amoxicillin- és klavulánsav-tartalmú oralis antibiotikumkezelést alkalmaztunk. A kötéscserék során a lebeny jó vérellátásúnak bizonyult, a sebek reakciómentesek voltak.

A primer rekonstrukciót követően három héttel, általános érzéstelenítésben a középső ujj dorsalis felszínén



1. ábra A) A jobb mutatóujj distalis interphalangealis ízületénél látható bemeneti és B) kimeneti áramjegy. C) Volar és D) dorsal irányból készített, keresztlebeny-plasztika utáni felvételek

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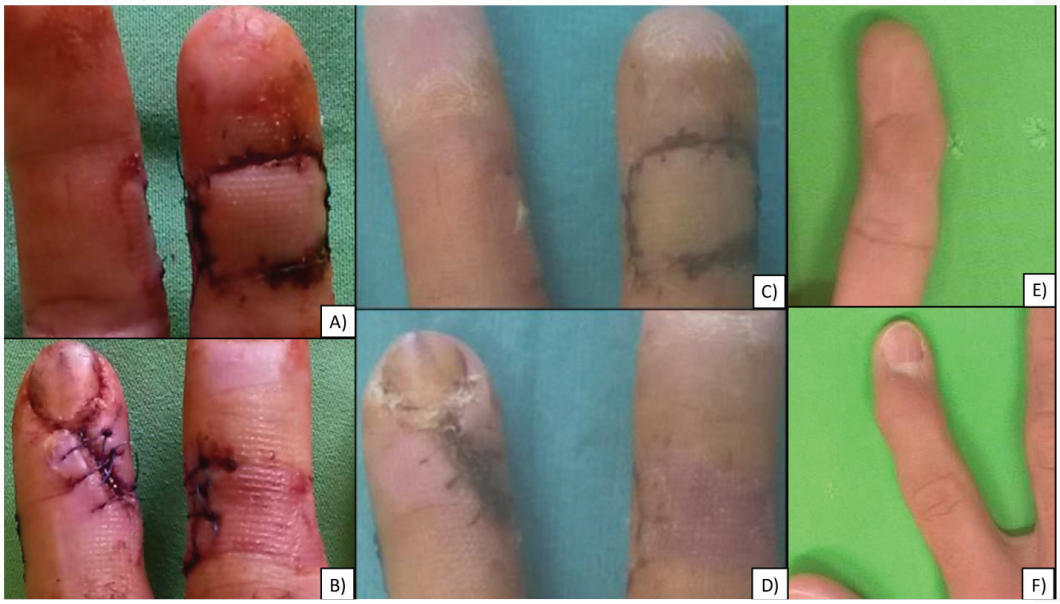
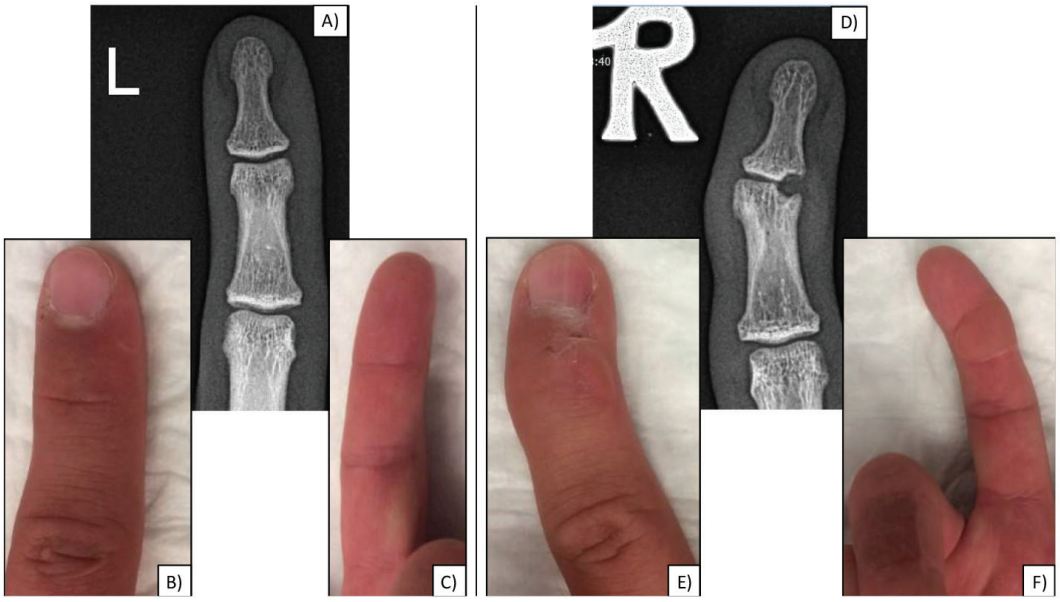


2. ábra A) Palmaris és B) dorsalis nézet a keresztlebeny-leválasztás utáni állapotról. C) és D) Három héttel később, a varratok eltávolítása után. E) és F) A tíz hónapos kontrollvizsgálaton észlelt ulnaris deviáció a jobb mutatóujj distalis interphalangealis ízületében



3. ábra A) Röntgenfelvétel, valamint B) fizikális kép dorsalis és C) tenyéri oldalról az ép bal kéz mutatóujjáról. D) Röntgenképen a jobb mutatóujj distalis percének proximalis epi-, illetve metaphysise és a középperc distalis metaphysisének lateralis peremén éles szélű, 6 × 4 mm-es csonthiány látható, zárt epiphysis mellett. A distalis perc lateralis és ventralis irányban deviál. E) Fizikális kép dorsalis és F) volaris aspektusból a jobb mutatóujjon észlelhető ulnaris deviációról

kialakított keresztlebeny leválasztása történt *(2/A és 2/B ábra)*. A keresztlebeny keringése a leválasztás után is megtartott maradt. A mutatóujj körömpercén a bőrgraft megtapadt dorsoradialisan, az áramkimeneti jegynél; gyulladásos jelek nem voltak. Két héttel később történt a varratok eltávolítása, szövődményt ekkor nem tapasztaltunk *(2/C és 2/D ábra)*.

A tíz hónapos nyomon követés során a mutatóujj-körömperc ulnaris deviációja volt észlelhető *(2/E és 2/F ábra)*. A röntgenvizsgálat a körömpercbázis ízfelszínét is érintő csonthiányt igazolt, amely az áramégés következtében kialakuló csontkárosodásra utalt *(3/A és 3/D ábra)*. Három évvel a sérülés után a deviáció progrediált, de funkcionális károsodást továbbra sem okozott *(3/B, 3/C, 3/E és 3/F ábra)*.

Második eset

Egy 2 éves leánygyermek szöggel nyúlt a konnektorba, emiatt áramégési sérülés keletkezett a hüvelykujján és a tenyerén. A primer ellátás során az EKG-vizsgálat ritmuszavarra utaló eltérést nem igazolt.

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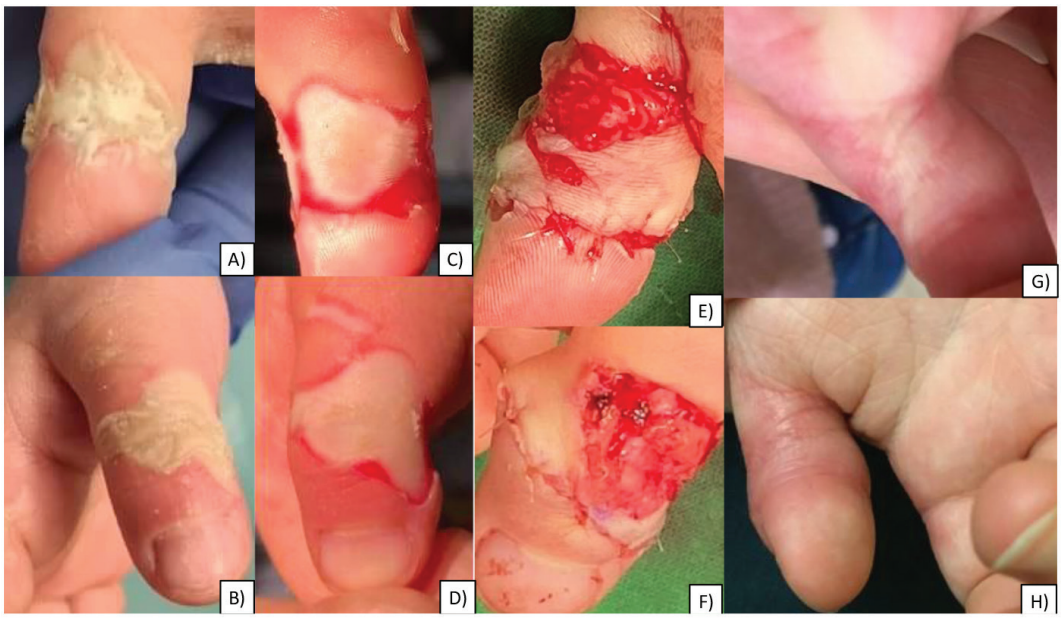
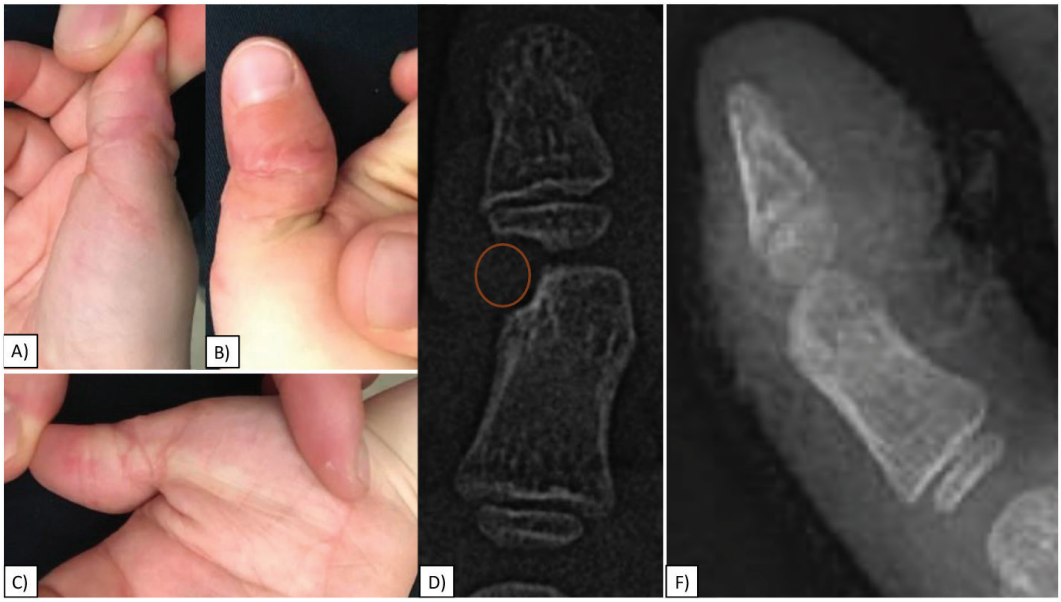


4. ábra A jobb hüvelykujj interphalangealis ízületének III. fokú égési sérülése A) radialis és B) dorsalis irányból. C) és D) Necrectomia előtti felvételek. E) és F) Elforgatott lebenyplasztika után, a fennmaradó bőrhiányos területek Wolfe–Krause-grafttal való transzplantációja történt. G) Négy héttel a műtét utáni kontrollvizsgálat palmaris és H) radialis irányból



5. ábra A hat hónapos kontrollvizsgálat a jobb kéz hüvelykujján látható radialis deviációról, A) radialis B) dorsalis és C) palmaris irányból készített felvételeken. D) A hat hónapos röntgenfelvételen az interphalangealis ízület csontdefektusát a piros kör jelzi, amely a F) primer röntgenképen nem volt észlelhető

Fájdalomcsillapítás és parenteralis folyadékpótlás mellett szállították sebészeti ambulanciánkra. A jobb hüvelykujj interphalangealis ízülete felett dorsalisan és volarisan, valamint a bal kéz hypothenari területén áramjegy volt látható fehér, necroticus sebalappal, amelyek mély (II. és III. fokú) égési sérüléseknek feleltek meg. Az ujjak keringése, beidegzése megtartott volt. A primer röntgenvizsgálat a kéz csontjain eltérést nem mutatott. A sebek fedése antibiotikummal impregnált hálóval történt *(4. ábra)*.

Másnap általános érzéstelenítésben, necrectomiát követően a hüvelykujj ventralis bőrdefektusát elforgatott lebennyel pótoltuk [9]. A donorterület és a hüvelykujj dorsalis bőrhiányának fedése teljes vastagságú bőrrel történt. A bal kéz hypothenari területén lévő égési sebet kimetszettük és *per primam* zártuk, ezután a műtéti területeket antibiotikummal impregnált hálóval fedtük.

A posztoperatív szakban az ujjakon keringészavar nem volt észlelhető. A műtétet követő negyedik napon narcosisban kötéscserét végeztünk, melynek során a teljes vas-

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tagságú bőr megtapadását, valamint az elforgatott lebeny jó keringését diagnosztizáltuk.

Hat hónappal a rekonstrukciót követően a kontrollvizsgálat során a hüvelykujj radialis deviációját tapasztaltuk, teljes funkció mellett *(5. ábra)*.

Megbeszélés

A gyermekkori áramégések bár ritkák, gyakran érintik a kezet, és annak súlyos károsodásait okozhatják [1, 2]. A kis méretű ki- és bemeneti áramjegyek miatt a sérülések pontos súlyosságát nehéz megítélni, a legtöbb esetben azonban mély necrosissal járnak [3]. Kezelésüket az égés mélységéhez, lokalizációjához és kiterjedéséhez kell igazítani. Esettanulmányunkban az alkalmazott terápiák mellett maradandó elváltozást igen, míg funkcionális károsodást nem tapasztaltunk. Esztétikailag és pszichésen nem jelentett kifejezett terhet a betegeknek a minimális hegesedés, valamint az ízületi deviáció. A deformitás korrekciós műtétjét mérlegeltük, de egyelőre nem hajtottuk végre, annak lehetséges komplikációi és a várható csekély életminőségbeli javulás miatt [10]. Az első esetismertetésben bemutatott gyermek növekedése befejeződött, további progresszió nem várható. A fiatal felnőtt számára az ujj deviációja nem zavaró, amellett hogy az érintett ízület funkciója teljes, emiatt korrekciós műtétet nem szeretne. A második gyermek nyomon követése jelenleg is zajlik, a további növekedésből adódó funkcionális állapotromlás megelőzése és kezelése érdekében.

Következtetés

Az áramégések során gyakran mély necrosis alakul ki. Ilyen sérülések esetén nemcsak a bőr és a lágy részek károsodásával kell számolni, hanem a csont, illetve fiatal életkorban a növekedési zóna sérülésével is. Ez növekedési zavart és ezáltal másodlagos deformitásokat okozhat.

A primer ellátás során a röntgenfelvétel készítése megfontolandó, a kezdeti állapot rögzítése és a későbbi összehasonlítás miatt. A késői szövődmények felismerése és kezelése céljából szükséges a gyermekek hosszú távú nyomon követése.

Anyagi támogatás: A közlemény megírása, illetve a kapcsolódó kutatómunka anyagi támogatásban nem részesült.

Szerzői munkamegosztás: L. A.: Közreműködött a vizsgálat végrehajtásában, megírta az első kéziratot, és utána felülvizsgálta, javította, valamint részt vett az adatok vizualizálásában és a végső validálásban. Cs. Zs.: Hozzájárult az adatok rendszerezéséhez, feldolgozásához, valamint ellenőrizte és elfogadta a végső közleményt. M. T.: Részt vett a koncepcionalizálásban, a metodológia kidolgozásában és a tanulmány szerkesztésében, validálásában. O. Zs.: Közreműködött a vizsgálatok végrehajtásában, felügyeletében, valamint a publikáció korrekciójában és végső változatának elfogadásában. G. A.: Részt vett a vizsgálat felügyeletében, adminisztrációjában, szerkesztésében és validációjában. J. G.: Hozzájárult az esettanulmány koncepcionálásához, metodológiájának kidolgozásához, a vizsgálatok kivitelezéséhez, az adatgyűjtéshez és a vizualizációhoz, a projekt adminisztrációjához, felügyeletéhez, valamint szerkesztette és validálta a végső közleményt. A cikk végső változatát valamenynyi szerző elolvasta és jóváhagyta.

Érdekeltségek: A szerzőknek nincsenek érdekeltségeik.

Köszönetnyilvánítás

Hálás köszönetet mondunk a pécsi Gyermekklinikán és Transzlációs Medicina Intézetnél hivatásukat fáradhatatlan odaadással végző munkatársaknak, szerető családjainknak, valamint a folyamatos szakmai fejlődésében érdekelt Olvasónak.

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