Management of Paediatric Burns:

Current Strategies and Future Perspectives

DOCTORAL (PHD) THESIS

Aba Lőrincz, MD.

Pharmacology and Pharmaceutical Sciences Doctoral School,
Translational Medicine Program

Doctoral School Leader: Erika Pintér MD., PhD., DSc.

Program Leader: Péter Hegyi MD., PhD., DSc.

Supervisors: Gergő Józsa MD., PhD.

András Garami MD., PhD.

Department of Thermophysiology, Institute for Translational Medicine

Medical School, University of Pécs, Pécs, Hungary

Pécs, 2022

INTRODUCTION

1. Second-degree thermal injuries in children.

Combustion is coagulative necrosis of the skin, or deeper tissues, which heat effects can cause – 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 is a dynamic pathology. After inadequate care, burns are accompanied by the permanent death of the reversibly damaged stasis zone between the central coagulated and peripheral hyperaemic tissues [1].

Nearly one hundred thousand children annually suffer a lethal injury from preventable, generally flame-related burn traumas (~93%). The likelihood of a non-fatal injury is presumed to be at least ten times raised (i.e., 1-7,000,000/year). Due to the shortage of fruitfully orchestrated prevention, treatment or rehabilitation policies, almost half (49%) experience permanent disability after the burn [2]. Attributable to these combustions, a high degree of scarring, contractures, and other function deterioration can occur, which the children may face throughout their life. Complications like massive contractures and amputations constitute physical impairments, but even a minor scar or the recollection of the trauma can incite lifelong psychological conditions [3 4]. In addition, after orthopaedic, psychological and aesthetic difficulties resulting from combustion, they are often left out of employment [5]. These are especially true of burns during infancy due to secondary contractures and growth deformations.

Children younger than five are at the maximum risk for a thermal injury because their balance and reflexes improve. 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 [6]. Therefore, by pulling hot liquids onto themselves and touching hot surfaces, children severely injure critical parts: upper limbs, head and neck, and lower limbs in 51, 39, and 26% of all cases, respectively [7].

The severity and prognosis of a wound are decided by the injury's depth, area and location, along with the patient's health and age. Burns are often characterised by mixed depth in a map-like pattern; thus, evaluating their exact severity still constitutes a challenge [8]. In second-degree or partial-thickness combustions (PT or II), the skin's dermis layer has been disturbed, and it can be further sorted into two subcategories.

Superficial partial-thickness thermal injuries (II/A) the papillary stratum of the dermis. In II/A wounds, spontaneous recovery takes 7-10 days on average, and long-term pigmentation changes may occur. Straw-yellow bullae and – after their removal – painful, moist, bright pink wound beds with intact epidermal appendages describe this condition.

In contrast, deep PT burns (II/B) damage the stratum reticulare. As a result, the wound bed transforms numb and desiccated with a blotched pale, white, or purple colour and the demise of all epidermal appendages. In addition, spontaneous recovery often results in extensive hypertrophic scar development and contractures.

2. Management of paediatric partial-thickness burns.

Advances in medicine have steered the development of numerous therapeutic options to cure children with PT burns. However, many questions remain unanswered concerning their optimal use and effectiveness. The various interventions were primarily intended for the chronic wounds of adult patients, while paediatric burn injuries possess different remedial qualities, inflammatory status and exudation [8]. In addition, some dressing materials may be better suited for treating burns in younger patients because of their distinctive burn aetiology, physiology, and evolving nature.

In case of delayed or inadequate medical interventions, the complications' frequency, severity, and duration are increased, resulting in extended hospital stay, higher use of anaesthetic and analgesic drugs, and the total cost of care. Consequently, a swift and effective therapeutic reply is crucial in these severe burns (i.e., II/B, III) [9]. Simultaneously, the lack of current evidence-based treatment policies makes it hard to determine which materials should be favoured for a specific type of injury.

Management of paediatric PT burns entails primary care (e.g., cooling, painkillers, fluid resuscitation and transportation), cleaning and disinfecting the wound, and removing the necrotic tissue. Afterwards, the surgeon must restore the damaged skin barrier to protect the patient from fluid loss and infections. The wound is first covered in a conservative approach with dressings and topical ointments. Next, surgery is performed by sewing a skin graft onto the injury site and then applying a conservative dressing [9 10]. The ideal temporary skin replacement retains absorbent and antimicrobial traits. It can be quickly and painlessly changed - so it must not stick to the wound bed - and stays in place during the healing. It should also be transparent - to monitor the injury - and affordable without causing irritation or toxicity. Recent studies confirmed that a moist environment benefits burned tissue regeneration [11]. Regrettably, such ideal dressing, which fulfils all these criteria, does not yet exist, but specific interventions' qualities are closer to the idyllic model than others.

Formerly, the gold standard for the topical treatment of paediatric PT burns was the soft, white, and water-soluble silver sulphadiazine (SSD) 1% cream. It is offered under many product names like Dermazin®, Flamazine®, Silvadene® or Silvazin® [12-23]. It is still the most regularly administered intervention in many countries, allowing wounds to heal without surgeries. Thus, we chose this cream as a comparator since most papers reported their results associated with SSD due to its historical relevance. However, several studies revealed numerous disadvantages to using SSD, which led to developing a wide range of alternative treatments. Unfortunately, these new options' efficacy in managing paediatric PT burns remains largely unclarified.

AIMS

Many pieces are still missing from the grand portrait of paediatric partial-thickness burn therapies. This thesis' and meta-analysis' fundamental goal was to summarise our current knowledge on the subject, whereas the observational studies were meant to explore uncharted regions. Key topics are discussed 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 complication rates.

2. Our review showed the beneficial effects of zinc-hyaluronan gel or silver foam dressings in PT burns. However, no data was available on combination treatments' impact on severely burned, skin-grafted children. Therefore, we performed a cohort study on patients suffering deep (II/B-III) combustions treated with Aquacel Ag foam® (ConvaTec Ltd., Deeside, UK) and Curiosa gel® (Richter Gedeon Plc., Budapest, Hungary).
3. We measured the success of the zinc-hyaluronan gel alone in paediatric facial II/A thermal injuries with a cohort study - since our literature search concluded that its efficacy had not been investigated in facial burns of children.
4. Case reports on managing paediatric electrical finger injuries and a unique late-onset complication were written. We have also evaluated using Lavanid gel (Polyhexamethylen biguanide (PHMB) or Polyhexanide; SERAG-WIESSNER GmbH & Co. KG, Naila, Germany) in the burn therapy of children, which has not been detailed before.

MATERIALS AND METHODS

1. Meta-analysis and systematic review

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. 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.

1.2. Data synthesis

An expert biostatistician performed analyses using the methods recommended by the working group of the Cochrane Collaboration. 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. 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.

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. The 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).

2.1. 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. Additionally, the number of anaesthesia and dressing changes after STSG was assessed.

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

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. The injured regions associated with facial burns were also examined as a unique outcome.

3. Case reports

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.

3.2. 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.

RESULTS

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 compared with amnion membrane (AM) [16 24 25], biosynthetic dressings (Biobrane, EzDerm, Transcyte) [14 17 18 26-28], and Biobrane only [14 17 18 26 27]. Additionally, the efficacy of silver foam bandages (Acticoat, Aquacel Ag, Mepilex Ag) [29-34], Acticoat only [29-32 34], and negative pressure wound therapy (NPWT) [23 35 36] were demonstrated in our meta-analysis.

Each intervention's attributes were calculated, such as autografts [25 37], Tilapia [12], and Silvasorb [21], which were evaluated via the systematic review. Adjuvant remedies (viz., bFGF [38], rhEGF [39], rhGM-CSF [40], collagenase [15], heparin [41] and vitamins E + C + Zinc [42], and wIRA [43]) together with combined treatments (Biobrane + Recell [27], Acticoat + Biobrane [22 34], Acticoat + Mepitel [29-31 36] and Acticoat + Mepitel + NPWT [36]) were also investigated there.

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 (ranging from 4 to 145 with an average of 30 participants /trial) from 17 RCTs were included in the meta-analysis of TTRE. 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**.**

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.

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

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.

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.

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.

DISCUSSION

SSD's advantages are mainly its applicability, low cost and famous 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 unease. Still, its known side effects include argyria, allergic reactions, and neutropenia [44]. Meanwhile, the wound bed is discoloured, hindering wound evaluation and depth determination [45].

Data analysis showed a tendency for quicker recovery times and reduced complication rate linked to silver foam, biosynthetic and AM dressings. Fewer mean dressing changes correlated with minor discomfort, anaesthesia and handling duration.

Among the most advanced burn dressings are the hydrofiber families, specially developed for hydroregulating combustions. Amid 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. In addition, silver ions released from the dressing inhibit the realisation of infections. With its use in mixed-depth burns, more reversibly damaged tissue survives by strengthening the microcirculation [46-49].

Our meta-analysis primarily studied silver foam dressings on minor burns (<5 TBSA%) [29-34]. Regrettably, the wound's TBSA% and TTRE 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 few dressing changes (n=1.0) and 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.

The study, called "Paediatric deep burn management after split-thickness autologous skin transplantation", compared the concomitant utilisation of Aquacel Ag foam and Curiosa gel with the traditional dressings used at our clinic. Applying the combined intervention, 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 following approach, titled "Management of paediatric facial burns with zinc-hyaluronan gel", studied the characteristics of II/A thermal injuries after using only Curiosa. Most frequently, infants were facially injured (30.4% of the patients were below one year), and 47.8% had additional areas damaged, most frequently the left upper limb (30.4%). In all cases, wound cultures revealed standard bacterial growth, and follow-up examinations found no complications. In brief, paediatric facial II/A burns treated with zinc-hyaluronan resulted in rapid wound closure (TTRE: 7.9 days) and low complication rates, which were accountable for the moderate hospitalisation (LOS:2 days). Besides the gel's ease of application and spontaneous separation, these advantages are connected 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. The grafts adhered completely, in addition to the closure of the burn wounds. 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 growth plate in children, which may cause secondary deformities. For example, in one child, the ulnar deviation of the distal digit was observed throughout the follow-up examinations. Another showed a radial deviancy on the thumb. Additionally, X-rays confirmed the distal phalanx base's bone atrophy and the IP joint's deterioration. Therefore, planning for a long-term follow-up of these patients is necessary to identify and treat these late-onset complications.

To summarise our results, our primary recommendation for investigators is that children's II/A and II/B burns 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. A single, internationally acknowledged scar and pain assessment standard in paediatric burns would significantly enhance this process. Additionally, investigators should abide by the CONSORT principles.

While every intervention could facilitate the recovery of II-degree paediatric burn 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 in paediatric PT burns, physicians should deliberate treatments with little need for dressing reapplication. Such an alternative could be silver-foam dressings alone or combined with zinc-hyaluronan gel, 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. Burn severity classifications were extensively researched with machine learning (ML) [50]. For example, a program was developed to assort burn depths into different groups from digital photographs [51]. It already outperforms clinicians (77%) [52], but its accuracy (83%) [53] is lower than AI-backed infrared thermography's (96%) [54]. In addition, a novel method was reported in 2020 that could approximate burn depth via ultrasound images is an accessible and relatively cheap alternative to physical examination [55].

ML can help by pinpointing sepsis [56], acute kidney injury [57] or other rare complications of severe burns. In addition, by identifying and monitoring at-risk patients' specific parameters (e.g. lactate or GFR), further complications or even death can be avoided. However, existing models remain in the early stages, and additional studies are needed to assess their clinical feasibility.

CONCLUSIONS

Due to their frequency and severe preventable complications, it is essential to care for childhood combustions optimally, so the principles of burn management must be 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 its application and removal were painless compared to traditional bandages used at our clinic. 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, avoiding their side effects. Moreover, wearing it proved to be a convenient, effective and child-friendly option because it required less intervention 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. As the number of interventions, complications, and LOS decreased, the cost of therapy was roughly halved. The excellent functionality substantiates favourable wound healing conditions and cosmetic results experienced.

Although the findings presented in this thesis will get more accurate over time, we aimed to highlight currently unclear parts in our understanding 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. Furthermore, a particular emphasis should be on researching pharmacological possibilities of different burn depths, areas and demographic groups for the optimal future use of combustion dressings. Finally, implementing state-of-the-art diagnostic tools in burn medicine could facilitate this process by objectively describing wounds or predicting and alerting for rare complications.

ACKNOWLEDGMENTS

I profoundly appreciate and respect Gergő Józsa MD., PhD. and András Garami MD., PhD. In addition, to their extensive and pioneering activities, they have always found time to answer my questions and fine-tune this thesis - like several other shared works. I am proud to have had such unprecedentedly passionate research and pediatric surgery mentors. At the same time, I will forever be grateful for permanently sticking enough professional enthusiasm to me.

Péter Hegyi, MD., PhD., DSc. deserves my sincerest gratitude for his resilience, inspiring discourses, and for providing me with the opportunity to research in the Translational Medicine doctoral program.

Likewise, I would like to express appreciation to all the employees of the Department of Thermophysiology and Paediatric Surgery, Medical School, University of Pécs, Pécs, who immediately took me in and helped me with unlimited kindness, making the time spent together unforgettable.

Furthermore, last but not least, I thank my beautiful wife and son, my family and friends for their endless love, their persistent trust in me, for their willingness to laugh at my jokes that have gone wrong - even after all these years -, and for trying to decipher these never-ending sentences.

REFERENCES

1. Kaddoura I, Abu-Sittah G, Ibrahim A, Karamanoukian R, Papazian N. Burn injury: review of pathophysiology and therapeutic modalities in major burns. Ann Burns Fire Disasters 2017;**30**(2):95-102.
2. Forjuoh S, El-Oteify M, Macpherson A, van Nieker, A, Peck, MD, Villaveces A. World report on child injury prevention. In Peden, J. Branche, C. (Ed.), https://apps.who.int/iris/bitstream/handle/10665/43851/9789241563574_eng.pdf;sequence=1: World Health Organisation, 2008:79-101.
3. Arno AI, Gauglitz GG, Barret JP, Jeschke MG. Up-to-date approach to manage keloids and hypertrophic scars: A useful guide. Burns 2014;**40**(7):1255-66 doi:10.1016/j.burns.2014.02.011.
4. Ohgi S, Gu S. Pediatric burn rehabilitation: Philosophy and strategies. Burns Trauma 2013;**1**(2):73-9 doi: 10.4103/2321-3868.118930.
5. Marino M, Soley-Bori M, Jette AM, et al. Measuring the Social Impact of Burns on Survivors. Journal of Burn Care & Research 2017;**38**(1):e377-e83 doi: 10.1097/bcr.0000000000000398.
6. Visscher MO, Carr AN, Narendran V. Premature infant skin barrier maturation: status at full-term corrected age. Journal of Perinatology 2021;**41**(2):232-39 doi: 10.1038/s41372-020-0704-3.
7. Dewar DJ, Magson CL, Fraser JF, Crighton L, Kimble RM. Hot Beverage Scalds in Australian Children. The Journal of burn care & rehabilitation 2004;**25**(3):224-27 doi: 10.1097/01.Bcr.0000124821.22553.24.

8. Shupp JW, Nasabzadeh TJ, Rosenthal DS, Jordan MH, Fidler P, Jeng JC. A review of the local pathophysiologic bases of burn wound progression. Journal of burn care & research : official publication of the American Burn Association 2010;**31**(6):849-73 doi: 10.1097/BCR.0b013e3181f93571.
9. Passaretti D, Billmire DA. Management of pediatric burns. J Craniofac Surg 2003;**14**(5):713-8 doi: 10.1097/00001665-200309000-00021.
10. Schiestl C, Meuli M, Trop M, Neuhaus K. Management of burn wounds. Eur J Pediatr Surg 2013;**23**(5):341-8 doi: 10.1055/s-0033-1356650.
11. Johan P.E. Junker RAK, E.J. Caterson,Elof Eriksson. Clinical Impact Upon Wound Healing and Inflammation in Moist, Wet, and Dry Environments. Advances in Wound Care 2013;**2**(7):348-56 doi: 10.1089/wound.2012.0412.
12. Lima Junior EM, de Moraes Filho MO, Forte AJ, et al. Pediatric Burn Treatment Using Tilapia Skin as a Xenograft for Superficial Partial-Thickness Wounds: A Pilot Study. Journal of Burn Care & Research 2020;**41**(2):241-47 doi: 10.1093/jbcr/irz149.
13. Caruso DM, Foster KN, Blome-Eberwein SA, et al. Randomised clinical study of hydrofiber dressing with silver or silver sulfadiazine in the management of partial-thickness burns. Journal of Burn Care and Research 2006;**27**(3):298-309 doi: 10.1097/01.BCR.0000216741.21433.66.
14. Barret JP, Dziewulski P, Ramzy PI, Wolf SE, Desai MH, Herndon DN. Biobrane versus 1% silver sulfadiazine in second-degree pediatric burns. Plastic and Reconstructive Surgery 2000;**105**(1):62-65 doi: 10.1097/00006534-200001000-00010.
15. Ostlie DJ, Juang D, Aguayo P, et al. Topical silver sulfadiazine vs collagenase ointment for the treatment of partial thickness burns in children: a prospective randomised trial. Journal of Pediatric Surgery 2012;**47**(6):1204-07 doi: 10.1016/j.jpedsurg.2012.03.028.
16. Mostaque AK, Rahman KB. Comparisons of the effects of biological membrane (amnion) and silver sulfadiazine in the management of burn wounds in children. Journal of burn care & research : official publication of the American Burn Association 2011;**32**(2):200-9 doi: 10.1097/BCR.0b013e31820aad94.
17. Kumar RJ, Kimble RM, Boots R, Pegg SP. Treatment of partial-thickness burns: A prospective, randomised trial using transcyte™. ANZ Journal of Surgery 2004;**74**(8):622-26 doi: 10.1111/j.1445-1433.2004.03106.x.

18. Lal S, Barrow RE, Wolf SE, et al. Biobrane improves wound healing in burned children without increased risk of infection. Shock (Augusta, Ga.) 2000;**14**(3):314-18; discussion 18-19 doi: 10.1097/00024382-200014030-00013.
19. Gotschall CS, Morrison MI, Eichelberger MR. Prospective, randomised study of the efficacy of Mepitel on children with partial-thickness scalds. The Journal of burn care & rehabilitation 1998;**19**(4):279-83 doi: 10.1097/00004630-199807000-00002.
20. Bugmann P, Taylor S, Gyger D, et al. A silicone-coated nylon dressing reduces healing time in burned paediatric patients in comparison with standard sulfadiazine treatment: a prospective randomised trial. Burns 1998;**24**(7):609-12 doi: 10.1016/s0305-4179(98)00095-3.
21. Glat PM, Kubat WD, Hsu JF, et al. Randomised Clinical Study of SilvaSorb (R) Gel in Comparison to Silvadene (R) Silver Sulfadiazine Cream in the Management of Partial-Thickness Burns. Journal of Burn Care & Research 2009;**30**(2):262-67 doi: 10.1097/BCR.0b013e318198a2e8.
22. L.Cullingworth AM. A Prospective Single-Centre Randomised Controlled Study to Compare the Time to Healing of Partial Thickness Burn Wounds Treated with Versajet, Biobrane and Acticoat to Conventional Therapy. Global Journal of Medical Research 2015
23. Zheng XP, Chen J, Chen TS, et al. Preliminary effect observation on the application of micro-negative pressure in children with small-area deep partial-thickness burn. Chinese journal of burns 2019;**35**(10):720-25 doi: 10.3760/cma.j.issn.1009-2587.2019.10.004.
24. Branski LK, Herndon DN, Celis MM, Norbury WB, Masters OE, Jeschke MG. Amnion in the treatment of pediatric partial-thickness facial burns. Burns 2008;**34**(3):393-99 doi: 10.1016/j.burns.2007.06.007.
25. Omranifard M, Ansari M, Jazebi N, Rouzbahani R, Akbari M. The comparison between long-term results of treatment with amnion graft and skin graft in children second degree burn wounds. Journal of Isfahan Medical School 2011;**29**(126)
26. Cassidy C, Peter SDS, Lacey S, et al. Biobrane versus Duoderm for the treatment of intermediate thickness burns in children: A prospective, randomised trial. Burns 2005;**31**(7):890-93 doi: 10.1016/j.burns.2005.04.029.
27. Wood F, Martin L, Lewis D, et al. A prospective randomised clinical pilot study to compare the effectiveness of Biobrane® synthetic wound

dressing, with or without autologous cell suspension, to the local standard treatment regimen in paediatric scald injuries. Burns 2012;**38**(6):830-39 doi: 10.1016/j.burns.2011.12.020.
28. Healy CM, Boorman JG. Comparison of E-Z Derm and Jelonet dressings for partial skin thickness burns. Burns, including thermal injury 1989;**15**(1):52-4 doi: 10.1016/0305-4179(89)90072-7.
29. Gee Kee E, Stockton K, Kimble RM, Cuttle L, McPhail SM. Cost-effectiveness of silver dressings for paediatric partial thickness burns: An economic evaluation from a randomised controlled trial. Burns 2017;**43**(4):724-32 doi: 10.1016/j.burns.2016.09.018.
30. Gee Kee EL, Kimble RM, Cuttle L, Khan A, Stockton KA. Randomised controlled trial of three burns dressings for partial thickness burns in children. Burns 2015;**41**(5):946-55 doi: 10.1016/j.burns.2014.11.005.
31. Gee Kee EL, Kimble RM, Cuttle L, Stockton KA. Scar outcome of children with partial thickness burns: A 3 and 6 month follow up. Burns 2016;**42**(1):97-103 doi: 10.1016/j.burns.2015.06.019.
32. Brown M, Dalziel SR, Herd E, Johnson K, She RW, Shepherd M. A Randomized Controlled Study of Silver-Based Burns Dressing in a Pediatric Emergency Department. Journal of Burn Care & Research 2016;**37**(4):E340-E47 doi: 10.1097/bcr.0000000000000273.
33. Karlsson M, Elmasry M, Steinvall I, Sjoberg F, Olofsson P, Thorfinn J. Superiority of silver-foam over porcine xenograft dressings for treatment of scalds in children: A prospective randomised controlled trial. Burns 2019;**45**(6):1401-09 doi: 10.1016/j.burns.2019.04.004.
34. Hyland EJ, D'Cruz R, Menon S, et al. Biobrane™ versus acticoat™ for the treatment of mid-dermal pediatric burns: A prospective randomised controlled pilot study. International Journal of Burns and Trauma 2018;**8**(3):63-67
35. Shen CA, Chai JK, Tuo XY, et al. Efficacy observation on application of negative pressure therapy in the treatment of superficial partial-thickness scald wound in children. Chinese Journal of Burns 2013;**29**(1):14-17 doi: 10.3760/cma.j.issn.1009-2587.2013.01.005[.
36. Frear CC, Cuttle L, McPhail SM, Chatfield MD, Kimble RM, Griffin BR. Randomised clinical trial of negative pressure wound therapy as an adjunctive treatment for small-area thermal burns in children. British Journal of Surgery 2020 doi: 10.1002/bjs.11993.
37. NunezGutierrez H, CastroMunozledo F, KuriHarcuch W. Combined use of allograft and autograft epidermal cultures in therapy of burns.

Plastic and Reconstructive Surgery 1996;**98**(6):929-39 doi: 10.1097/00006534-199611000-00001.
38. Hayashida K, Akita S. Quality of pediatric second-degree burn wound scars following the application of basic fibroblast growth factor: Results of a randomised' controlled pilot study. Ostomy Wound Management 2012;**58**(8):32-36
39. Liang ZQ, Li HM, Meng CY. Repair of second degree facial burns in children using recombinant human epidermal growth factor. Journal of Clinical Rehabilitative Tissue Engineering Research 2007;**11**(10):1974-75
40. Jiaao Y, Kai S, Hua JZ, et al. Treatment of deep second-degree facial burns in pediatric population with recombinant human GM-CSF hydrogel. Wound Repair and Regeneration 2011;**19**(2):A29 doi: 10.1111/j.1524-475X.2010.00670.x.
41. Venkatachalapathy TS. A Comparative Study of Paediatric Thermal Burns Treated with Topical Heparin and Without Heparin. Indian Journal of Surgery 2014;**76**(4):282-87 doi: 10.1007/s12262-012-0674-6.
42. Barbosa E, Faintuch J, Machado Moreira EA, et al. Supplementation of Vitamin E, Vitamin C, and Zinc Attenuates Oxidative Stress in Burned Children: A Randomised, Double-Blind, Placebo-Controlled Pilot Study. Journal of Burn Care & Research 2009;**30**(5):859-66 doi: 10.1097/BCR.0b013e3181b487a8.
43. Hartel M, Illing P, Mercer JB, Lademann J, Daeschlein G, Hoffmann G. Therapy of acute wounds with water-filtered infrared-A (wIRA). GMS Krankenhaushygiene interdisziplinar 2007;**2**(2):Doc53-Doc53
44. Lockhart SP, Rushworth A, Azmy AA, Raine PA. Topical silver sulphadiazine: side effects and urinary excretion. Burns, including thermal injury 1983;**10**(1):9-12 doi: 10.1016/0305-4179(83)90121-3.
45. Fuller FW. The side effects of silver sulfadiazine. Journal of burn care & research : official publication of the American Burn Association 2009;**30**(3):464-70 doi: 10.1097/BCR.0b013e3181a28c9b.
46. Józsa G, Tóth E, Juhász Z. New dressing combination for the treatment of partial thickness burn injuries in children. Ann Burns Fire Disasters 2017;**30**(1):43-46
47. Jozsa G, Vajda P, Garami A, Csenkey A, Juhasz Z. Treatment of partial thickness hand burn injuries in children with combination of silver foam dressing and zinc-hyaluronic gel: Case reports. Medicine 2018;**97**(13):e9991 doi: 10.1097/md.0000000000009991.

48. Castellano JJ, Shafii SM, Ko F, et al. Comparative evaluation of silver-containing antimicrobial dressings and drugs. International Wound Journal 2007;**4**(2):114-22 doi: 10.1111/j.1742-481X.2007.00316.x.
49. Barnea Y, Weiss J, Gur E. A review of the applications of the hydrofiber dressing with silver (Aquacel Ag) in wound care. Therapeutic Clinical Risk Management 2010;**6**:21-27
50. Allaire F, Mallet V, Filippi JB. Emulation of wildland fire spread simulation using deep learning. Neural Networks 2021;**141**:184-98 doi: 10.1016/j.neunet.2021.04.006.
51. Zhang B, Zhou J. Multi-feature representation for burn depth classification via burn images. Artificial Intelligence in Medicine 2021;**118**:102128 doi: 10.1016/j.artmed.2021.102128.
52. Phelan HA, Holmes IV JH, Hickerson WL, Cockerell CJ, Shupp JW, Carter JE. Use of 816 Consecutive Burn Wound Biopsies to Inform a Histologic Algorithm for Burn Depth Categorization. Journal of Burn Care & Research 2021;**42**(6):1162-67 doi: 10.1093/jbcr/irab158.
53. Huang S, Dang J, Sheckter CC, Yenikomshian HA, Gillenwater J. A systematic review of machine learning and automation in burn wound evaluation: A promising but developing frontier. Burns 2021;**47**(8):1691-704 doi: 10.1016/j.burns.2021.07.007.
54. Wang P, Li P, Yin M, Li Y, Wu J. Burn wound assessment system using near-infrared hyperspectral imaging and deep transfer features. Infrared Physics & Technology 2020;**111**:103558 doi: 10.1016/j.infrared.2020.103558
55. Lee S, Rahul, Ye H, et al. Real-time Burn Classification using Ultrasound Imaging. Scientific Reports 2020;**10**(1):5829 doi: 10.1038/s41598-020-62674-9.
56. Tran NK, Albahra S, Pham TN, et al. Novel application of an automated-machine learning development tool for predicting burn sepsis: proof of concept. Scientific Reports 2020;**10**(1):12354 doi: 10.1038/s41598-020-69433-w.
57. Rashidi HH, Sen S, Palmieri TL, Blackmon T, Wajda J, Tran NK. Early Recognition of Burn- and Trauma-Related Acute Kidney Injury: A Pilot Comparison of Machine Learning Techniques. Scientific Reports 2020;**10**(1):205 doi: 10.1038/s41598-019-57083-6.

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 supracondylar 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.*