Surgical management and hypermetabolic modulation of pediatric burns
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Chapter 9

SUMMARY, ADDRESS TO THE AIMS, CLOSING REMARKS
AND FUTURE PERSPECTIVES
Although burn injuries are frequent in our society, many surgeons feel uncomfortable in managing patients with major thermal trauma. With an overall incidence of more than 800 cases per 100000 person/year, only motor vehicle accidents cause more accidental deaths than burns. During the past century, many lessons were learnt regarding the initial management, resuscitation, infection control and local treatment of burns. Early in the 1960s, it was becoming plain that burn care is a complex enterprise involving many professional disciplines and that, from a logistic point of view, it was sensible to concentrate the severely burned in the same ward so that an experienced team could be developed to provide ongoing care, both medical and psychosocial. Soon after, the development of new and more effective resuscitation formulas, and the synthesis of silver sulphadiazine opened a new era in burn treatment. Severe burned patients were no longer doomed to succumb to burn shock or burn wound sepsis. A new challenge, however, appeared in the horizon of burn care. Surgeons were faced with patients who survived beyond the initial phase of their injury, and definitive care of the burn wound began to be the main focus of all clinical and research efforts. Previously, nearly all large, deep burns were treated expectantly: eschar was permitted to slough spontaneously, and open wounds were left to granulate. Split-thickness skin grafts were then applied, in a process that lasted weeks or, frequently, months before permanent wound closure could be achieved. The former was recognized as being contrary to the fundamental principle in the treatment of other traumatic wounds which had been learned during the two World Wars: the prompt excision of all devitalized tissue. The debate remained hypothetical because of numerous practical clinical constraints until many other advances, such as the development of new powered dermatomes and mesh-expanding techniques, and sophisticated intraoperative and critical care monitoring occurred. Above all, pediatric burn patients have benefited most from this new era of early excision and grafting. Children present with the best survival rate among burn patients, with an excellent psychosocial adaptation to normal living.

Currently, the approach most used in many burn centers throughout the world is the staged surgical wound closure. In this approach, unequivocally deep burns are excised at intervals of approximately 7 days, with immediate coverage of all exposed areas by autologous skin grafts. The timing of the first surgical procedure is dependent on physiologic status and on the clinical estimate of burn depth. Burns that are left non-excised are usually treated with cerium nitrate sulfadiazine. Early or immediate total excision has emerged as an alternative to staged surgical wound closure. This approach requires an experienced team, and is logistically demanding of both personnel and resources. It has been claimed that this aggressive approach may increase catabolism and the inflammatory response, without real gains in patient survival. Moreover, it is generally believed that a short delay in surgical therapy is not harmful. Consequently, in this thesis all arguments against immediate burn wound excision are addressed. A general introduction to the pathophysiology of burns, burn diagnosis and burn treatment is presented in chapter 1. In the subsequent chapters, the aims outlined in the scope of the thesis are addressed in a step-wise manner.
AIMS

1. What are the exact consequences of immediate burn-wound excision and massive blood transfusion in severe pediatric burns related to postoperative complications and to morbidity and mortality?

In chapter 2 the safety and efficacy of total burn wound excision in the first 24 h post-injury were studied. A cohort of 30 consecutive pediatric patients affected with massive burns (Total body surface area burned > 60%) were included in the study. All patients were admitted and surgically treated in the first 24 hours after the injury. Resuscitation was initiated on admission and continued during the operation subtracting the fluid losses of the operation and careful monitoring of the urine output. All full thickness burns were excised and the wounds were covered with available autografts and the rest of the wounds covered with homografts. Patients included in the study were very young (mean age 6 ± 1 years) and affected of massive burns (Total body surface area burned 80 ± 2 %). There were no intra-operative deaths or complications. Resuscitation was completed without problems in all patients, and there were no septic episodes in the acute postoperative period. Half of the patients, however, had septic episodes during their hospital course, but only 10% (3 patients) died. Length of stay in the hospital was 67 ± 8.8 days, i.e., 0.83 ± 0.2 days per 1% burned.

Extensive bleeding is common during burn surgery. Massive transfusions have been related to cardiovascular instability, postoperative coagulopathy, pulmonary dysfunction, metabolic abnormalities, and increase incidence of infection. In chapter 3 twenty consecutive pediatric burned patients were studied to determine the effect of massive transfusion of reconstituted whole blood. Only patients admitted within 24 hours after the injury and affected of burns of more than 60% total body surface area were included. All patients received total burn wound excision on admission. Blood was transfused during the operation as reconstituted whole blood (1 unit of packed red cells + 1 unit of fresh frozen plasma) to maintain the hematocrit in a range between 30 and 35%. Minimal crystalloids were infused during the operation (governed by the urine output, which was maintained at 1 ml/kg per hour). The patients’ estimated circulating volume was 1694 ± 308 ml, and blood transfused during the operation was 4133 ± 1692 ml, which consisted of more than a double-exchange transfusion per patient. A significant decrease of white blood cells and platelet count (p<0.001) occurred in all patients. The depressed values returned to normal within 48 hours without treatment. Coagulation parameters did not change after surgery and remained stable. Only one patient had bleeding complications, which was related to concomitant acute renal failure. There were no reintubations during the first 7 days after the operation nor clinical evidence of cardiogenic or noncardiogenic pulmonary edema. Survival was 100% in this cohort of patients. High amounts of crystalloids administered during the resuscitation correlated with depressed clinical and laboratory respiratory parameters whereas the amount of re-
constituted whole blood did not affect respiratory function.

We concluded that total burn wound excision in the first 24 hours post-injury is a safe technique that can be extended to any kind of pediatric patient and burn size. Even though during total burn excision massive transfusion may occur, this transfusion practice with reconstituted whole blood does not compromise hemostasis nor is associated with and increased rate of septic episodes or pulmonary complications.

2. What is the impact of burn wound excision on bacterial colonization and invasion?

A change in the epidemiology of burn wound infections has been evidenced in the last two decades. The development of new and more potent topical antimicrobials and early burn wound excision are regarded as the main impact in such decline in invasive burn infection. In chapter 4 twenty consecutive pediatric patients were studied to assess the efficacy of burn wound excision in decreasing burn colonization and invasion. Patients were divided in two groups: patients admitted within 24 hours after the injury and patients transferred from another unit on day 7 postburn. On admission, all full thickness burns were excised and covered with auto- and homografts. Wound biopsies were collected from the burn self and from the excised wound bed. Quantitative bacteriology was performed in both biopsies to assess the effect of burn wound excision. Rate of infection, sepsis and graft take were also studied to determine the clinical outcome. Surgical excision significantly reduced the colonization of the wound in both groups of patients an average of 10^2 colonies/gram tissue (p<0.05). Patients treated with surgical excision in the first 24 hours had bacterial counts significantly lower than patients treated conservatively (10^4 colonies/gram of tissue vs. 10^6 colonies/gram of tissue, p<0.05). Quantitative bacteriology in the excised wound showed similar differences (10^2 colonies/gram of tissue vs. 10^4 colonies/gram of tissue, p<0.001). None of the patients treated on day 1 postburn had graft loss or infection, whereas three of the patients treated on day 7 postburn had graft loss and infection and 2 patients presented with sepsis postoperatively (p<0.05). We concluded that conservative topical treatment has a higher incidence of infection and graft loss than early excision and grafting. Delaying burn wound excision increases bacterial load and increases gram-negative colonization. When such colonization reaches 10^6 colonies/gram of tissue in the burn eschar, they should be considered at risk for developing invasive burn wound infection even when the wounds are excised. Burn wound decreases an average of 10^2 colonies/gram tissue; therefore excision of the burn eschar should be performed as soon as possible to prevent reaching the threshold of invasive burn wound infection and sepsis.

3. Are all pediatric patients candidates for immediate burn wound excision?

Survival after massive burn injury has improved dramatically over the last two decades. The question of when futility of treatment has been reached, however, is
still to be determined. In *chapter 5* patients with burns in 98% total body surface area or more were examined in order to determine whether survival after this major traumatic insult is feasible in children. Resuscitation and enteral nutrition was initiated on admission, and immediate total excision of all full thickness burns was performed in the first 24 hours after the injury. Six patients were treated with burns over 100% of total body surface area with a component of more than 98% of full thickness burns in a period of 10 years expanding from January 1989 to January 1999. The survival rate for this group of patients was 50%. Causes of death included burn shock, septic shock, and respiratory distress syndrome. The three patients who survived remained in hospital $126 \pm 50$ days, and required $13 \pm 3$ operations to achieve complete wound closure. We conclude that pediatric burns involving 100% total body surface area present with acceptable survival. Currently, all pediatric burn patients are candidates for survival following thermal injury, with the exception of anoxic brain injury and brain death after inhalation injury.

4. **What are the impact and the efficacy of Cultured Epidermal Autografts in massive pediatric burns?**

Paucity of donor sites in massive burns makes the use of expanded skin of paramount important. In general, should an unlimited amount of autologous, bioengineered skin be available at the time of surgery, the most important problem and limiting factor during major burn excision would be solved. In *chapter 6*, thirty-two patients with full-thickness burns of more than 90% body surface area were studied to assess the efficacy of cultured epidermal autografts (CEA) for closure of burn wounds. Patients grafted with CEA were compared with patients grafted with conventional meshed autografts. Patients treated with CEA had a better quality of burn scars but incurred a longer hospital stay and higher hospital costs. The incidence of sepsis and pneumonia, and the survival rate in both groups was comparable. Conventional meshed autografts proved to be superior to CEA due to the long-term fragility and poor take, therefore, future research should focus on bioengineered dermal templates to produce a bilaminate cultured autograft.

5. **Does immediate burn-wound excision increase the inflammatory and catabolic response after burn injury?**

In *chapter 7* we studied the effect of immediate burn wound excision in the acute phase response and in the hypermetabolic response after injury. Twenty patients younger than 15 years of age with > 40% total body surface area burn without evidence of organ failure were enrolled. After admission, patients were studied to determine cytokine production, acute phase proteins and metabolic rate. The same determinations were made 24 hours after the operation and 5 days after the operation. After immediate burn wound excision and grafting, there were no significant changes in substrate utilization, oxygen consumption or respiratory quotient. Ana-
bolic hormones did slightly increase in the postoperative period, although this change did no show statistic significance. There were no metabolic imbalances after surgery. Acute phase proteins remained stable after the operation and showed a progressive decline in the first 5 days after the operation. Serum levels of C-reactive protein decreased significantly (p<0.05). Serum levels of proinflammatory cytokines IL-1β, TNF-α, and IL-6 remained stable after the operation and significantly decreased during the postoperative period (p<0.05). The antiinflammatory cytokine IL-10 decreased slightly after the operation, and returned to the preoperative level 5 days after the operation. There were no deaths and patients did not present with septic episodes. In conclusion, immediate burn wound excision does not increase the caloric demands and the post-burn hypermetabolic response. It decreases the levels of acute phase proteins and cytokines while preserving the levels of anabolic peptides.

6. Does conservative treatment and delayed burn-wound excision increases the inflammatory and catabolic response in children?

Patients treated with immediate burn wound excision in chapter 7 were compared to a control-matched group in order to compare the effect of burn wound excision against the traditional topical treatment with 1% silver sulfadiazine. Fifteen patients that were treated for 5 days with this topical agent were studied. The same determinations on day 5 were performed and compared to the results in patients treated with immediate burn wound excision. The levels of anabolic hormones (IGF-1, IGFBP3, GH) in the conservative group were significantly lower than levels in the study group (immediate excision). Furthermore, all cytokine, acute phase proteins determinations, and substrate utilization and oxygen consumption were significantly higher. Three patients died in the control group, one from septic shock and two from respiratory distress syndrome. We concluded that immediate surgical intervention proved to be superior to conservative topical treatment and delayed excision.

7. Can pharmacologic intervention abrogate the catabolic response of severe pediatric burns together with immediate burn-wound excision?

In chapter 8, twenty-nine severely burned children were prospectively studied to determine the effects of recombinant human insulin growth factor-1 (IGF-1) complexed with its principal binding protein, IGFBP-3, on skeletal muscle metabolism in severely burned children. Patients were treated with immediate burn wound excision, and were studied before and after treatment with 0.5, 1, 2, or 4 mg/kg/day IGF-1/IGFBP-3, to determine net balance of protein across the leg, muscle protein fractional synthetic rates, and glucose metabolism. Another group was studied in a similar fashion without IGF-1/IGFBP-3 treatment as time controls. To study muscle metabolism, a stable isotope infusion protocol was used. Baseline samples were obtained before the beginning of the infusion. A primed constant infusion of L-[ring-2H3]-phenylalanine was given via a subclavian vein catheter. Biopsies were taken
from the vastus lateralis muscle and arteriovenous blood samples were obtained from the study leg. IGF-1/IGFBP-3 treatment at 1 to 4 mg/kg/day improved net protein balance and increased muscle protein fractional synthetic rates. IGF-1/IGFBP-3 did not affect glucose uptake across the leg or change substrate utilization. In conclusion, IGF-1/IGFBP-3 at doses of 1 to 4 mg/kg/day attenuates catabolism in catabolic burned children treated with immediate burn wound excision.

CLOSING REMARKS AND FUTURE PERSPECTIVES

The research described in this thesis provides evidence that immediate burn wound excision in pediatric patients is a safe and efficacious approach that renders a high survival rate and modulates the post-burn inflammatory and catabolic response. This was supported by the absence of complications in all children treated with this surgical modality and the extreme good tolerance of massive transfusion of reconstituted whole blood. It was also proved that early burn wound excision significantly decreases bacterial colonization and invasion and provides a salutary effect on post-burn inflammation and catabolism. In the present thesis, delaying burn wound excision had significant and harmful consequences: there was a significant colonization and invasion of the burn wound leading to a significant increase of invasive burn infection and sepsis, and the acute phase and hypermetabolic response were significantly increased and prolonged. Children present with limited metabolic reserves and due to fluid shift are very labile. Despite this, they had a perfect outcome, which supports the assumption that immediate burn wound excision can be extended to all sort of patients, with the exception of anoxic brain injury and brain death following smoke inhalation injury.

However, there are still some problems to be solved in order to achieve the best outcome in massive burns. One of the drawbacks of immediate burn wound excision that still exist is that potentially viable tissue can be sacrificed during surgery. New and specific methods to diagnose the viability of burned tissue need to be developed. With such method of diagnosis, surgery would be then limited to clearly dead tissue, minimizing the harm to the patient. Laser Doppler flowmetry, thermography and light reflectance are some of the technologies currently being researched. On-going studies show that these techniques can predict the outcome of the burn (whether the burn would heal or not), but its use has not become standard yet in everyday clinical decision-making (to excise or not to excise).

One of the logistic problems when managing massive burns is the procurement of autologous skin for burn wound closure. For years, homografts (cadaver skin) have been the standard of care. Any new skin substitute or dermal template should imitate the properties provided by cadaver skin. Homografts, either fresh (taken from cadavers and maintained at 4 Celsius degrees) or cryopreserved (-70 Celsius degrees) take and grow on the wound. They provide a physical and biological barrier and modulate the hypermetabolic response and improve the immune system. If left in place, however, are eventually rejected by the host. Different skin substitutes are
in the market, but there is no bilaminar (dermal-epidermal graft) currently available. Dermal templates need the application of a super-thin autograft as a second stage operation; and epidermal grafts, such as culture epidermal grafts, lack the dermal component and a true dermal-epidermal junction. As a mean to overcome the current clinical problems associated with skin substitutes, the most natural step are to employ tissue engineering techniques to develop skin graft substitutes. Should an unlimited source of engineered auto-skin graft became available, one of the main problems of burn surgery would be solved.

Finally, the pharmacologic intervention and modulation of the acute phase and hypermetabolic response with new growth factors and recombinant hormones warrant a continuing evolution. Controlling and modulating the individual response will provide a mean to individualize the treatment of burns and trauma. With a better understanding of the pathophysiology of burns, we will be able to test anabolic drugs and hormones, along with anti-inflammatory and antiadrenergic drugs to determine their role in the management of the acute phase response.

References