Surgical management and hypermetabolic modulation of pediatric burns
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Chapter 7

EARLY BURN WOUND EXCISION IN THE FIRST 24 HOURS MODULATES THE INFLAMMATORY AND CATABOLIC RESPONSE IN SEVERELY BURNED CHILDREN

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SUMMARY

Severe burns and major trauma are associated with an acute and profound hypermetabolic response characterized by an increased circulation of catabolic hormones and acute phase proteins. One of the principles of modern burn treatment is early burn wound excision and grafting. Whether this surgical approach increases this response remains in debate. In order to study the real effect of burn excision on the postburn hypermetabolic response, 35 severely burned children were studied. Twenty patients received immediate burn wound excision and fifteen conservative topical treatment and delayed excision. Data compiled included oxygen consumption, acute phase proteins, IL-1 Beta, IL-6, IL-10, TNF-alpha, and anabolic hormones (GH, IGF-1). Immediate burn wound excision abrogated the hypermetabolic response in pediatric burn patients. Patients treated with conservative treatment had a significantly higher inflammatory status at the same time interval and significantly lower levels of anabolic hormones, suggesting a benefit of the surgical approach versus conservative treatment. Immediate burn wound excision is a safe therapeutic approach that modulates the hypermetabolic response after burn injury. It should be considered in all severe full thickness burns.
INTRODUCTION

Severe burns and major trauma are associated with an acute and persistent hypermetabolic response characterized by hyperdynamic circulation and increased circulating levels of catabolic hormones. Increases in catecholamine, glucagon, and cortisol levels raise the energy requirements. The development of postinjury insulin resistance with alteration of glucose transport and futile cycling of triglycerides diverts amino acids to fuel production, resulting in muscle wasting and nitrogen imbalance.\(^1,2\)

One of the main components of this response is the acute inflammatory response that is regularly seen in this kind of patients. There is an increase in acute-phase proteins soon after the onset of the trauma; which is usually mediated by the pro-inflammatory cytokines with a concomitant depression of the anti-inflammatory component of this response.\(^3\) Elevated levels of pro-inflammatory cytokines and acute-phase proteins have been associated with the induction of anorexia, weight loss, tissue wasting associated with malignancy, chronic diseases such as rheumatoid arthritis, sepsis-induced proteolysis and multiple organ dysfunction syndrome.\(^4-5\) In addition to this increase in catabolic hormones and acute phase proteins, a reduction in anabolic hormones, including growth hormone and insulin-like growth factor type I is observed after a thermal injury.\(^6\) Several studies in severely burned patients have showed that nutritional support and pharmacological intervention with anabolic agents such as growth hormone, insulin, and insulin-like growth factor I alone or combined with its principal binding protein IGFBP-3 abrogate muscle wasting.\(^7-10\) The treatment of burned children with recombinant human growth hormone showed an attenuation of elevated tumor necrosis factor alpha, which was consistent with the beneficial effect that growth hormone has on the acute-phase response.\(^11\)

Early burn wound excision is regarded as the main factor in the decline of invasive burn infection and in the improvement of burn survival.\(^12\) Although programs of early burn wound excision are widely accepted, there are still many who question its benefits. It has been pointed out that the surgical trauma may increase the severity of the acute phase response, which can damage another systems, such as the lungs, in a second hit phenomenon.\(^13-14\)

The real effect of immediate burn wound excision on the acute phase and metabolic response is unclear. We hypothesize that immediate burn wound excision and grafting abrogates the acute phase response and the hypermetabolic response after burn injury.
MATERIAL AND METHODS

**Patient Population**

Twenty severely burned pediatric patients were prospectively studied to determine the effects of early burn wound excision on the inflammatory and metabolic response. Patients younger than 15 years of age with > 40% total body surface area (TBSA) burn without evidence of organ failure were enrolled. Informed consent in accordance with the Institutional Review Board of the University of Texas Medical Branch at Galveston was obtained from all patients and/or parents.

Resuscitation given immediately after burn was guided by the Galveston formula of 5000 ml/m² TBSA burned + 2000 ml/m² TBSA lactated Ringer’s solution given in increments over the first 24 hours. All patients underwent total burn wound excision on admission and the wounds were closed with available autograft and allograft skin. Donor sites were treated with fine mesh gauze impregnated in scarlet red. Sequential staged surgical procedures for repeated grafting were undertaken until the wounds were completely closed. All patients received nasoduodenal feedings with Vivonex TEN (Sandoz Nutrition, Minneapolis, MN), an elemental formula containing 82.3% carbohydrate, 3%fat (linoleic acid), and 14.7% protein. Caloric intake was given at a rate calculated to deliver 1500 kcal/m² TBSA burned + 1500 kcal/m². This feeding regimen was started at admission and continued at a constant rate until the wounds were 95% healed. None of the patients received recombinant human growth hormone or other recombinant growth factors during the study.

**Study Design**

After admission, patients were studied to determine cytokine production in serum/plasma, acute phase proteins and metabolic rate. The same determinations in serum and plasma were made 24 hours after the operation and 5 days after the operation to determine the effect of early burn wound excision on the inflammatory and metabolic response. Blood samples were collected for cytokine and hormone determinations. Indirect calorimetry was performed to determine any changes in substrate utilization.

**Methods**

Resting energy expenditure and respiratory quotient were calculated from O₂ and CO₂ concentrations in expired gases. A metabolic cart calorimeter (Sensormedics, Yorba Linda, CA) and standards equations were used.

Serum glucose, electrolytes, C-reactive protein, C-3 complement, and α₁-acid glycoprotein were determined using a Behring nephelometer (Behring, Deerfield, IL). Serum IGF-I, IGFBP-3, and GH were determined by RIA (Nichols Inst. Diagnostics, San Juan Capistrano, CA.).

Serum TNF-α was determined by an ultra sensitive human ELISA (Endogen, Woburn, MA.). Standard curves for quantification of human TNF-α was linear from 0 to 1000 pg/ml on a logarithmic scale. Serum IL-1β was determined by ELISA
 Early burn wound excision modulates the acute-phase response

(Endogen, Woburn, MA.). Standard curves for quantification of human IL-1β was linear from 0 to 400 pg/ml on a logarithmic scale. Serum IL-6 was determined by ELISA (Endogen, Woburn, MA.). Standard curve for quantification of human IL-6 was linear from 0 to 3000 pg/ml on a linear scale. Serum IL-10 was determined by ELISA (Endogen, Woburn, MA.). Standard curve for quantification of human IL-10 was linear from 0 to 600 pg/ml on a linear scale.

**Control-matched group comparison**

In order to compare the effect of burn wound excision with the traditional topical treatment with 1% silver sulfadiazine, a control group of 15 patients that were treated for 5 days with this topical treatment before subsequently transferred to our institution was used. On admission, cytokine, acute phase proteins, and hormones were determined and compared to those found on patients on postoperative day 5.

**Statistical Analysis**

Comparisons of metabolic and cytokine data were made with paired t-test and repeated measures ANOVA. Comparisons between the study group and control group were made with unpaired t-test. Ordinal data was studied with Fisher’s exact test. Significance was accepted at p<0.05. Data are presented as means ± SEM.

**RESULTS**

**Patient Demographics**

The mean age of all enrolled pediatric patients was 6 ± 0.8 years, with burn sizes of 59 ± 4 % TBSA. Patient demographics are summarized in Table 1. No deaths occurred, and patients did not present with septic episodes during the study. All patients could be discharged home when all burn wounds were covered.

| TABLE 1 |
| Patient Demographics (n=20) |
| (Early burn excision group) |

| AGE (years) | 6 ± 0.8 |
| SEX (Male/Female, %) | 45/55 |
| TBSA Burned (%) | 59 ± 4 |
| TBSA Full thickness burns (%) | 55 ± 4 |
| % WEIGHT CHANGE (Admission-Discharge) | -0.5 ± 1.5 |
| INHALATION INJURY (%) | 40 |
| LENGTH OF HOSPITAL STAY (days) | 39.5 ± 5 |
**Caloric Intake and Indirect Calorimetry**

There were no differences in the caloric intake of protein, carbohydrate, and fat before and after early excision and grafting. No differences could be demonstrated for oxygen consumption or respiratory quotient (see Table 2), indicating there were no significant changes in substrate utilization after excision and grafting.

**TABLE 2**

Effects of immediate burn wound excision on oxygen consumption and respiratory quotient

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>Postoperative</th>
<th>5 days postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen Consumption</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(kcal/day)</td>
<td>1630 ± 265</td>
<td>1625 ± 305</td>
<td>1645 ± 295</td>
</tr>
<tr>
<td>Respiratory Quotient</td>
<td>1.0 ± 0.03</td>
<td>0.97 ± 0.02</td>
<td>0.98 ± 0.02</td>
</tr>
</tbody>
</table>

**Serum Glucose, Electrolytes, and Acute Phase Proteins**

No hyperglycemia, hypoglycemia, or electrolyte imbalance could be found during the study. Acute phase proteins did not change significantly during the first 24 hours after the operation. Serum levels of C-reactive protein significantly decreased five days after the operation (p<0.05), whereas the rest of acute phase proteins showed a progressive decline (see Figure 1).

**Serum IGF-I, IGFBP-3, and GH**

There were no significant changes in serum concentrations of IGF-I, IGFBP-3, or GH throughout the study period. Serum concentration did increase slightly, although this change did not show statistical significance. Serum concentrations of these anabolic hormones are shown in Table 3.

**Serum Cytokines**

There were no significant differences in serum levels of IL-1β, TNF-α, IL-6, and IL-10 before or 24 hours after the operation. Five days after the operation, however, all patients showed a significant decrease in all pro-inflammatory cytokines tested, indicating a decrease in the inflammatory status of the patients despite the surgical trauma (p<0.05, Figure 2). The anti-inflammatory cytokine IL-10 decreased slightly after the operation, and returned to the pre-operative level 5 days after the operation. (Figure 2).
Early burn wound excision modulates the acute-phase response

Figure 1
Acute phase proteins showed a progressive decline and did not increase after surgical excision of the burn wound, showing that surgical intervention do not increase the inflammatory state of burn patients

TABLE 3
Serum concentartions of IGF-I, IGFBP-3, and GH before and five days after the operation

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>5 days postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-1 (µg/ml)</td>
<td>89 ± 8</td>
<td>109 ± 12</td>
</tr>
<tr>
<td>IGFBP-3 (µg/ml)</td>
<td>1.3 ± 0.2</td>
<td>1.4 ± 0.2</td>
</tr>
<tr>
<td>GH (µg/ml)</td>
<td>3.2 ± 1.0</td>
<td>3.4 ± 0.5</td>
</tr>
</tbody>
</table>

(*) *p*<0.05 repeated measures ANOVA, Five days postoperative vs. 24 hours post-operative and pre-operative
Control-matched group comparison

Demographics for the control group are shown in Table 4. There were no significant differences when compared to the study group. Patients treated with 1% silver sulfadiazine for 6 days showed levels of IGF-1, IGFBP3, and GH that were significantly lower than patients treated with prompt surgical excision. Furthermore, all cytokine and acute phase proteins determinations were significantly higher than the study group. Oxygen consumption and respiratory quotient were also significantly higher when compared with the study group (p<0.01). Therefore, patients treated with conservative treatment showed a more acute hypermetabolic response to burn trauma than patients treated with early surgical intervention. All data is summarized in Table 5 and Figures 3 and 4. Three patients died in the control group (one from sepsis and two from respiratory distress).

(*) p<0.05 repeated measures ANOVA, Five days postoperative vs. 24 hours postoperative and pre-operative

Figure 2
All proinflammatory cytokines significantly decreased five days after burn wound excision. Levels of antiinflammatory cytokine IL-10 decreased after the operation, but returned to preoperative levels after five days.
Early burn wound excision modulates the acute-phase response

**TABLE 4**
Patient Demographics Control Group (Topical treatment group)

<table>
<thead>
<tr>
<th></th>
<th>Control (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>7.2 ±1.3</td>
</tr>
<tr>
<td>Sex (Male/Female)</td>
<td>8/7</td>
</tr>
<tr>
<td>TBSA Burned (%)</td>
<td>54 ± 3</td>
</tr>
<tr>
<td>TBSA Burned full thickness (%)</td>
<td>48 ± 6</td>
</tr>
<tr>
<td>% Weight Change</td>
<td></td>
</tr>
<tr>
<td>(Admission-Discharge)</td>
<td>-2.3 ± 2.5</td>
</tr>
<tr>
<td>Inhalation injury (%)</td>
<td>65</td>
</tr>
<tr>
<td>Length of Hospital Stay (Days)</td>
<td>45 ± 6</td>
</tr>
</tbody>
</table>

TBSA = Total body surface area
Data shown as mean ± SEM

(*) p<0.05, unpaired t-test, Conservative Group vs. Immediate excision group

**Figure 3**
Patients treated conservatively showed higher levels of acute phase proteins compared to patients on day five postoperatively after burn wound excision.
Chapter 7

**TABLE 5**
Comparison of hormones between the study group and control group

<table>
<thead>
<tr>
<th></th>
<th>Immediate burns excision group (Day 5) n=20</th>
<th>Conservative treatment group (Admission day 6) n=15</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-1 (µg/ml)</td>
<td>109 ± 12</td>
<td>77 ± 8 (*)</td>
</tr>
<tr>
<td>IGFBP-3 (µg/ml)</td>
<td>1.4 ± 0.2</td>
<td>1.2 ± 0.3</td>
</tr>
<tr>
<td>GH (µg/ml)</td>
<td>3.4 ± 0.5</td>
<td>2.8 ± 0.4</td>
</tr>
</tbody>
</table>

(*) p<0.05 unpaired t-test

(*) p<0.05, unpaired t-test, Conservative Group vs. Immediate excision group

**Figure 4**
TNF-alpha and IL-6 had higher levels in patients treated conservatively five days after the injury. Levels of IL-1 Beta and IL-10 had similar levels.
DISCUSSION

An acute hypermetabolic and inflammatory response is often observed following major illness or trauma, such as a severe burn. Increases in acute phase proteins, proinflammatory cytokines, and catabolic hormones raise the energy requirements resulting in muscle wasting, nitrogen imbalance, and futile substrate cycling of glucose and triglycerides. When this acute posttraumatic response prolongs in time, it yields to a multiple organ dysfunction syndrome, and eventually to death. The common denominators of the acute phase response are the activation of the immune system, with overproduction of proinflammatory cytokines and depression of the antiinflammatory cytokines, and associated changes in neurological, metabolic and endocrine functions irrespective of the diverse underlying pathological conditions. Most endocrine cells are directly affected by all cytokines that are released during the acute-phase response and profound changes in the hormonal balance accompany this response. This acute response of inflammation is associated with increased tissue needs of nutrients that are required for the augmented demands related to increased substrate oxidation due to fever and to tissue remodeling and repair. Circulating cytokines contribute to this beneficial response by stimulating hormones and cellular processes that increase substrate uptake, mobilization, cellular transport and metabolism. In contrast, prolonged elevations of cytokines may contribute to the development of insulin resistance and other catabolic responses mediated by abnormal release of hormones. There is evidence that cytokines induce strong inhibitory hypothalamic signals for GH secretion. Interleukin 1 stimulates Somatostatin release, which in turn inhibits GH release. This stimulating effect on Somatostatin is shared with TNF-α and IL-6, with a synergism between TNF-α and IL-1. At the level of the pituitary, IL-6 has been reported to have a positive effect, which may explain the elevated levels of GH in patients with inflammatory diseases or experimental endotoxemia. However, in clinical experience growth retardation usually follows prolonged periods of infection and inflammation, suggesting that the acute phase response may cause resistance to GH and IGF-1. Together with the former systemic response, the long term paracrine effects of synergistically acting proinflammatory cytokines secreted in high local concentrations in tissues infiltrated by inflammatory cells may alter or inhibit the normal function of mesenchymal and endothelial cells and in some cases even cause cell destruction.

Different interventions and treatments have proved to be efficient in modulating the acute phase response and the hypermetabolic response following burn injury. When room temperature is increased from 25 Celsius degrees to 33 Celsius degrees, the mean metabolic rate of patients affected of 40% TBSA burns significantly decreases. Another intervention that has been universally accepted is nutritional modulation through nutrition supplementation via the enteral route, which, if applied as soon as possible, will help prevent weight loss. Lately, hormonal modulation has opened a new horizon in the treatment of the hypermetabolic and acute phase response. The administration of growth hormone (GH) to burn patients produced beneficial
metabolic effects and improved wound healing. In prospective randomized clinical trials GH increased protein turnover with synthesis exceeding breakdown\textsuperscript{8,25}, and improved wound healing, with a significant acceleration of skin graft donor site wound healing\textsuperscript{26}. Other anabolic agents that have been tested and proved effective with fewer side effects are insulin growth factor 1 with its binding protein number 3 (IGF1-BP3)\textsuperscript{30,27}, and oxandrolone\textsuperscript{28}.

Although all former treatments have proved to be effective in the modulation of the inflammatory and hypermetabolic response, the treatment that most has changed survival and outcome in burn injuries is surgery. Treatment of full thickness burns by awaiting spontaneous separation and subsequent skin grafting is a prolonged process associated with much pain and suffering, severe metabolic derangements, multiple septic episodes, and lengthy hospitalization. Prompt wound closure has been shown repeatedly to improve survival\textsuperscript{29}, decrease length of hospital stay, and curb metabolic expenditure for burn patients of all ages\textsuperscript{30,31}. It is now unusual for a child to succumb to burn injury of any size\textsuperscript{32}, and older patients have been shown also to benefit from an early surgical approach\textsuperscript{33}. Benefits of immediate burn wound excision were also proved in the present study. Burned children who were treated with this approach showed a significant decrease in the inflammatory response. All proinflammatory cytokines had lower levels after excision of all full thickness burns, and acute phase proteins showed also a progressive decline. On the other hand, levels of anti-inflammatory cytokine IL-10 returned to preoperative levels (which were still lower than normal), and levels of anabolic hormones did not change. Changes in oxygen consumption were also minimal, which corroborated that early surgical intervention do not augment oxygen and caloric demands. All patients survived their injuries and there were no adverse effects related to the surgery. This was also our experience and others in previous studies\textsuperscript{34,35}. When patients treated with immediate burn wound excision were compared to patients that received for the same period of time topical treatment with silver sulfadiazine, this second group of patients presented with a significantly profound inflammatory and catabolic response. Acute phase proteins and proinflammatory cytokines had significantly higher levels, whereas levels of IGF-1 were significantly lower. Conservative topical treatment of burn injuries is associated with significant higher levels of burn contamination and infection\textsuperscript{31,36}, which in turn raise the inflammatory response and the caloric requirements. Early surgical intervention reduces the bacterial load in all burn wounds, and, as proved in the present study, modulates the hypermetabolic response without collateral effects. Furthermore, three patients died in the control-matched group whereas none in the study group. Even though the difference was not statistically significant, probably due to the small size of groups, it provides the insight of the benefits of immediate surgical intervention. In previous experience of immediate surgical intervention, results showed that this surgical approach is very safe, shortening length of stay and decreasing complications without significant side effects\textsuperscript{34,37}.

In summary, immediate burn wound excision is a safe therapeutic approach that is associated with minimal side effects. It does not increase the caloric demands and
Early burn wound excision modulates the acute-phase response. Immediate excision of full thickness burns modulates the inflammatory response, decreasing the levels of acute phase proteins and cytokines, while preserving the levels of anabolic peptides. When compared to matched-controls, immediate surgical intervention proves to be superior to conservative topical treatment and delayed excision. Immediate burn wound excision should be considered as the treatment of choice for full thickness burns.

REFERENCES

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