trace element supplementation modulates pulmonary infection rates after major burns: a double-blind, placebo-controlled trial

Mette M Berger, François Spertini, Alan Shenkin, Catherine Wardle, Lucie Wiesner, Charles Schindler, and René L Chiolero

ABSTRACT Infections remain the leading cause of death after major burns. Trace elements are involved in immunity and burn patients suffer acute trace element depletion after injury. In a previous nonrandomized study, trace element supplementation was associated with increased leukocyte counts and shortened hospital stays. This randomized, placebo-controlled trial studied clinical and immune effects of trace element supplements. Twenty patients, aged 40 ± 16 y (x ± SD), burned on 48 ± 17% of their body surfaces, were studied for 30 d after injury. They consumed either standard trace element intakes plus supplements (40.4 μmol Cu, 2.9 μmol Se, and 406 μmol Zn; group TE) or standard trace element intakes plus placebo (20 μmol Cu, 0.4 μmol Se, and 100 μmol Zn; group C) for 8 d. Demographic data were similar for both groups. Mean plasma copper and zinc concentrations were below normal until days 20 and 15, respectively (NS). Plasma selenium remained normal for group TE but decreased for group C (P < 0.05 on days 1 and 5). Total leukocyte counts tended to be higher in group TE because of higher neutrophil counts. Proliferation to mitogens was depressed compared with healthy control subjects (NS). The number of infections per patient was significantly (P < 0.05) lower in group TE (1.9 ± 0.9) than in group C (3.1 ± 1.1) because of fewer pulmonary infections. Early trace element supplementation appears beneficial after major burns; it was associated with a significant decrease in the number of bronchopneumonia infections and with a shorter hospital stay when data were normalized for burn size. Am J Clin Nutr 1998;68:365–71.

KEY WORDS Burns, nutrition, copper, selenium, zinc, trace element deficiency, infection, immunity, supplementation, critically ill patients

INTRODUCTION

Patients with major burns suffer many unresolved metabolic, endocrine, and immune alterations. Infectious morbidity remains the leading cause of mortality after major burns (1), and its origin is multifactorial. The immune system is depressed overall (2). Some of these changes can be ascribed to alterations in trace element metabolism. Some trace elements, especially copper, selenium, and zinc, are indeed involved in both humoral and cellular immunity (3, 4). Antibody production, T cell proliferative response to mitogens, neutrophil function, and natural killer cell activity are decreased in trace element deficiency (5).

Altersations of trace element metabolism have been described repeatedly in burns (6–8). Plasma copper, iron, selenium, and zinc concentrations are severely depressed for prolonged periods and urinary excretion of selenium and zinc is increased. These authors concluded that patients with major burns suffer acute trace element deficiencies. Using the balance study technique, our team showed that part of this deficiency is related to large exudative losses through the burned areas (9, 10). During the first week after injury, patients with burns covering 30% of their body surfaces lose 20–40% of their body copper content and 10% of their selenium and zinc contents. The large urinary copper, selenium, and zinc losses that occur for many weeks are much smaller than the cutaneous losses.

Burn patients have increased energy expenditure and subsequent increased nutritional requirements (11). Their complex endocrine and cytokine alterations are associated with impaired effectiveness of nutrition. They frequently have infections and delayed wound healing, which are complications of malnutrition. The combined alterations resulting from increased trace element losses and malnutrition are likely to induce some of the immune changes observed after burns. Indeed, in a previous open study in which early trace element supplements were used, our team showed that specific trace element supplements were associated with earlier normalization of serum concentrations, increased leukocyte counts, and shorter hospital stays (12). The present trial studied trace element metabolism, immune defense, and clinical evolution in severely burned patients receiving identical early enteral nutritional support and then either the usually recommended parenteral trace element supplies or additional large supplements.

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TABLE 1

Patient characteristics

<table>
<thead>
<tr>
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<th>Group C</th>
<th>Group TE</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>43 ± 14</td>
<td>39 ± 16</td>
<td>40 ± 16</td>
</tr>
<tr>
<td>BSA (%)</td>
<td>45 ± 10 (35–65)</td>
<td>52 ± 22 (30–86)</td>
<td>48 ± 17</td>
</tr>
<tr>
<td>Tobiasen index</td>
<td>15.46 ± 2.6</td>
<td>14.64 ± 3.5</td>
<td>15.04 ± 3.0</td>
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<tr>
<td>APACHE II score</td>
<td>10 ± 5</td>
<td>13 ± 2</td>
<td>11 ± 4</td>
</tr>
<tr>
<td>Number with inhalation injury</td>
<td>5</td>
<td>2</td>
<td>7</td>
</tr>
</tbody>
</table>

**Note:** SD, range in parentheses. *n = 10 in each group.* Group C, control group; group TE, trace element–supplemented group; BSA, burned body surface area; Tobiasen index, enables calculation of a survival probability (13); APACHE II score, Acute Physiology and Chronic Health Evaluation (14); MV, mechanical ventilation. There was no significant difference between groups for any variable.

SUBJECTS AND METHODS

The study was designed as a double-blind, placebo-controlled supplementation trial. With the approval of the Institutional Ethics Committee and informed consent from patients or their close relatives, 20 patients admitted to the Burns Centre between February 1992 and November 1995 were enrolled in the study. The patients had thermal burns covering > 30% of their body surface areas. The study period was from the day of injury, called day 0, to day 30 postinjury. On admission, patients were randomly assigned to 1 of 2 groups (Table 1).

The severity of the burn injury was assessed by using the total body surface area burned and the Tobiasen scoring index, which is based on age, sex, body surface area burned, inhalation injury, proportion of deep burns, and location of injuries (13). The Tobiasen scoring index enables the calculation of a survival probability. The severity of the physiologic alterations was assessed by using the APACHE II score (14). Patients with suspected inhalation injury had a bronchofibroscopic examination on admission.

**Intervention**

The patients were randomly assigned to 2 groups. Both groups received standard amounts of trace elements, consisting of 1 vial Addamel N (Pharmacia, Stockholm) daily given intravenously as a separate infusion (15). Group TE, the intervention group, received additional supplements of copper, selenium, and zinc in a 0.9% NaCl infusion from day 0 to day 8 [8 infusions using copper gluconate, sodium selenite, and zinc gluconate (Aguettant, Lyon, France)] (Table 2). Group C, the control group, also received a placebo 0.9% NaCl infusion. The intervention solutions were initiated as soon as possible after admission.

The decision to supplement the patients for only 8 d was based on our observation of decreasing trace element losses over 7 d in the balance study in relation to surgical wound closure (10). Because the aim of the supplementation was to substitute for losses, it was decided to stop the supplementation after day 8 for safety reasons (the balances thereafter remain unknown).

**Blinding**

The trace element solutions were transparent, colorless, prepared by the pharmacist, and identified by a numeric code. The addition of trace elements was undetectable to the clinical team. After day 8 all patients continued to receive the recommended trace element supplements for 2 wk. All intravenous and enteral intakes were recorded from day 0 to day 8 to calculate actual trace element intakes; cumulative delivery was calculated by using our previous balance study database (9, 10). The cumulative intakes include those provided by intravenous crystalloids, albumin solutions, blood transfusion, fresh frozen plasma, and enteral nutrients (Table 2).

**Timing**

Patients were admitted to the intensive care unit (ICU) within 1.5 h of injury on average, and a basal sample (day 0) was taken within 2.4 h of injury (range: 30 min to 5 h). The trace element infusion (or placebo) was started within 1.5 h of day 0 sampling (range: 20 min to 3 h) and infused over 10–12 h. The day 1 sample was drawn at 0600, ~6 h after the end of the first trace element infusion (range: 0–12 h). Blood samples were collected on days 5, 10, 15, 20, and 30 at 0600. Interleukin 6 (IL-6) and trace elements were not measured on day 1 in the first 9 patients (5 in group C and 4 in group TE); because values for 7 other patients are missing for day 30, day 30 is not included in the statistical analysis. Serum, plasma, and erythrocytes were separated within 2 h of sampling and stored at −50°C until analyzed.

**Nutritional management**

Enteral nutrition was started within 12 h of injury by using standard high-energy and high-protein enteral formulas.
During the final 18 h of culture was measured as described (16). The mean measured resting energy expenditure on day 2 was 10 176 ± 2604 kJ (2423 ± 620 kcal).

In addition to the micronutrients contained in the enteral diet, the patients received daily intravenous vitamin supplements from day 1 until resumption of oral nutrition: 1 vial Cernevit (Clinitec, Plessis, France) containing 3500 IU retinol, 220 IU cholecalciferol, 10.2 mg α-tocopherol, 125 mg ascorbic acid, 5.67 mg riboflavin, 5.5 mg pyridoxine, 6 μg cyanocobalamin, 0.414 mg folic acid, 16.15 mg dexamphenol, 69 μg biotin, 46 mg nicotinamide, and 500 mg ascorbic acid as Redoxon (Roche, Basel, Switzerland).

Analyses

Plasma copper, selenium, and zinc were analyzed by atomic absorption spectrophotometry; total proteins, albumin, and C-reactive protein (CRP) were analyzed by nephelometry; and IL-6 was analyzed by enzyme-linked immunosorbent assay (R and D Systems, Abingdon, United Kingdom). For clinical purposes, albumin and CRP were also measured in all patients on day 2. Peripheral leukocyte counts (Coulter counter; Coulter Electronics, Hialeah, FL) were determined every day until day 20. The area under the curve for leukocytes was calculated at day 20 by using the trapezoid method.

Immunologic variables (days 10 and 20)

For measurement of peripheral blood mononuclear cell (PBMC) proliferation, PBMCs (2 × 10⁷/well) from each patient were isolated on a Ficoll gradient (Pharmacia and Upjohn, Uppsala, Sweden) and cultured in triplicate on 96-well round-bottom plates (Nunc, Roskilde, Denmark) in 10% AB+ serum (Swiss Red Cross, Bern, Switzerland) in RPMI medium with appropriate concentrations of mitogens (10 mg phytohemagglutinin/L, 10 mg pokeweed mitogen/L, 10 mg concanavalin A/L, or 25 μg phorbol myristate acetate/L mixed with 0.1 μmol ionomycin). Incorporation of [³H]thymidine (DuPont NEN Products, Boston) into DNA during the final 18 h of culture was measured as described (16).

For measurement of neutrophil chemotaxis, cells were isolated on a dextran gradient (17). Neutrophil migration in 1% agar gel was measured against FLMP (Sigma, St Louis) as the chemotactic agent (16).

Lymphocyte subpopulations were analyzed by flow cytometry (Epics Profile II; Coulter) (17). Expression of cell surface adhesion molecules was performed by flow cytometry with use of antibodies from Coulter (18).

Ten healthy subjects from the medical and nursing staffs served repeatedly as controls for the measurement of immunologic variables. Blood was drawn from the control subjects at the same time as from the patients.

Clinical endpoints

Length of stay in the specialized burn unit and in the hospital were recorded. Infectious complications were recorded during the first 30 d after injury; these were defined, according to consensus of the Society of Critical Care Medicine, as the association of leukocytosis (>10000 cells/mm³ or >15% young forms), fever (temperature <35.5°C or >38.5°C), increased CRP, and infection: pneumonia (purulent sputum, microorganisms at bronchialalveolar lavage, or new infiltrate on chest X-ray), microorganisms in urine (≥10⁵ on urine culture), skin infection (>10³ organisms on biopsies), or bacteremia (2 positive blood cultures) (19). The number of days of antibiotic treatment was recorded. The perioperative antibiotic 48-h prophylaxis was not included in the antibiotic count. Respiratory complications were recorded and acute respiratory distress syndrome (ARDS) was defined as days with acute lung injury with a ratio of arterial oxygen pressure to fraction of inspired oxygen (PaO₂/FiO₂) <200. The number of episodes as well as days with ARDS and days of mechanical ventilation were recorded.

Statistical analysis

Results are expressed as means ± SDs. Between-group comparisons were carried out using chi-square or Mann-Whitney tests where appropriate (JMP version 3.1; SAS Institute Inc, Cary, NC). Analysis of variance (ANOVA) was calculated on the first 20 d (6 determinations) for trace elements, proteins, and leukocytes (? patients did not complete the study until day 30). Plasma concentrations were analyzed by using two-way ANOVA for repeated analysis (time effect and intergroup comparison). Post hoc analysis for difference between groups was done by the Dunnett method. Differences were considered significant at the level of P < 0.05.

RESULTS

The characteristics of the patients in the 2 groups were similar (Table 1). Severity of injury did not differ between groups, with a probability of survival of 0.63 and 0.69 in the C and TE groups, respectively. There were 7 cases of inhalation injury, 5 in group C and 2 in group TE: 6 patients with mucosal erythema and soot deposition and 1 patient with severe inhalation injury (group TE), with mucosal sloughing and subsequent bronchial stenosis. This latter patient died on day 41 in acute respiratory failure after transfer to another hospital. One patient in group C with acute renal failure required continuous hemodiafiltration for 13 d (from day 13 to day 30).

Nutrition

Early enteral nutrition was carried out in all patients. There were no differences in energy and nitrogen intakes between the groups: a large inter- and intrapatient variability was observed in relation with surgery. The patients received 3220 ± 2280 kJ (766 ± 543 kcal) during the first day postinjury; intake increased to 7905 ± 5050 kJ on day 5 and stabilized around 9025 ± 4840 kJ (2150 ± 1150 kcal) by day 7. Protein intakes were 42 ± 30 g during the first day, increased to 94 ± 60 g on day 5, and stabilized at 107 ± 46 g by day 7. As expected, the cumulative intravenous trace element intakes from day 0 to day 8 were much larger in the trace element–supplemented group (Table 2).

Plasma concentrations

Trace elements

Mean plasma copper concentrations were below the reference range in both groups until day 20; there was no significant difference between groups (Figure 1). Mean plasma selenium con-
centrations were below the reference range in group C until day 10 but stayed within normal ranges in group TE (*P < 0.03 on days 1 and 5). Mean plasma zinc concentrations decreased significantly more in group C on day 1 than in group TE and remained below the reference range until day 20 in both groups.

In the analysis of the percentage change over time from baseline plasma concentrations (day 0), the largest deviations were observed on day 1 for copper and zinc. The decrease was −51 ± 9% in group C compared with −35 ± 25% in group TE for copper (NS between groups) and −45 ± 10% in group C compared with −9 ± 30% in group TE for zinc (*P = 0.05), with zinc plasma concentration decreases of −29 ± 28% compared with +24 ± 50%, respectively, on day 5. For selenium, the largest changes from baseline were observed during the first 10 d in group C: on day 1, −21 ± 17% for group C compared with −3 ± 26% for group TE (NS); on day 5, −34 ± 20% for group C compared with +13 ± 14% for group TE (*P = 0.005); on day 10, −24 ± 17% for group C compared with +12 ± 33 for group TE (*P = 0.03).

Proteins

Hemoglobin and hematocrit were elevated on admission (157 ± 13 g/L and 0.45 ± 0.6, respectively), which is common early after major burns; the lowest values were reached between days 10 and 20 (98 ± 8 g/L; NS between groups) as a result of hemodilution, surgical losses, and inflammatory response. Albumin concentrations were strongly depressed in both groups until day 30, being lowest on day 1 (Figure 2). IL-6 concentrations were highest on day 1 and CRP peaked between days 2 and 5 in both groups; the difference between groups was significant on day 1 for IL-6 (*P < 0.001) and on day 2 for CRP (*P < 0.05), values being higher in the control group.

Leukocyte counts

Although total leukocyte and neutrophil counts were high when subjects were admitted because of the above-mentioned hemocoagulation, both counts decreased in both groups consecutively to the hemodilution related to fluid resuscitation (Figure 3; lowest mean value reached on day 2). Thereafter, there was a parallel increase in total leukocyte and neutrophil counts in both groups (data not shown). There was a tendency for leukocytes to increase more in group TE, the difference between groups being significant only on day 15 (highest mean leukocyte count on day 14). The area under the curve calculated (for days 0–20) tended to be larger in group TE than in the group C (*P = 0.08). In contrast, the groups did not differ in total lymphocyte counts during this period.

Immunologic variables

Neutrophil chemotaxis was unchanged compared with that of healthy controls, without differences between groups (Figure 3). There were, however, striking differences in T lymphocyte proliferation to mitogens compared with in healthy controls; T lymphocyte proliferation was decreased by ≈60% in burned patients, with no significant difference between groups. None of the usual lym-
Infections per patient 3.1 ± 1.1 (2–5) 1.9 ± 0.9 (1–4) 2.5
Cutaneous 9 10 19
Pulmonary 15 3 18
Bacteremia 4 4 8
Urinary 3 2 5
Antibiotic treatment (d) 21 ± 7 14 ± 7 18
ICU stay (d) 39 ± 13 (18–58) 30 ± 12 (14–46) 34
Hospital stay (d) 66 ± 31 (24–129) 54 ± 27 (26–94) 60
ICU (d/BSA) 0.9 ± 0.3 0.6 ± 0.2 4 0.7
Hospital stay (d/BSA) 1.5 ± 0.7 1.1 ± 0.7 1.3

1 x ± SD; range in parentheses. n = 10 in each group. Group C, control group; group TE, trace element–supplemented group; ICU, intensive care unit; BSA, body surface area burned.

DISCUSSION

Nutritional support of burned patients is focused mainly on energy, nitrogen, and vitamin intakes (11, 20). There is no specific recommendation in the literature regarding trace element supplementation. It is established that trace elements play a key role in a series of metabolic and immune pathways. Many authors described alterations of trace element metabolism in burns, such as low serum concentrations and increased urinary excretion (8). More recently, our group showed large cutaneous losses leading to acute deficiency states (9, 10). The mean cumulative losses during the first week postinjury were close to 33 mg for copper (520 μmol), 2.5 mg for selenium (32 μmol), and 190 mg for zinc (2910 μmol). This constitutes extensive losses...
approaching 20–40% of body content for copper and 10% of body content for selenium and zinc. In a subsequent nonrandomized supplementation trial, the supplements were calculated to substitute for the cutaneous losses (12). The results showed clinical evidence of beneficial effects of early trace element supplements on wound healing (better graft take), immune response with higher leukocyte counts between days 7 and 12 postinjury, and reduced hospital stays.

The present investigation provides further evidence of the role of specific and separate trace element supplements in such patients, because the changes observed in the intervention group could not be due to global nutrition problems in the control group because both groups were managed identically. Early enteral nutrition was provided to all patients, and energy and protein intakes were similar in both groups. The study confirms that trace element supplements achieve a pharmacologic effect, with earlier normalization of plasma selenium and zinc concentrations, as we suggested previously (12), the changes being most visible for selenium (Figure 1). A trend toward higher leukocyte counts persisted. Moreover, the trace element supplements resulted in a significant decrease in the number of bronchopneumonia infections, an important clinical benefit after major burns.

Infections remain the main cause of morbidity after major burns (1). The number of pulmonary infections was significantly reduced in the trace element–supplemented patients, with 15 episodes of bronchopneumonia in 8 patients in group C compared with only 3 in 3 patients in group TE (P = 0.016). Part of this difference may have been related to inhalation injury, which causes mucosal injury and facilitates pulmonary infections. However, analysis of bronchopneumonia occurrence in patients without inhalation injury showed the same positive effect. This reduction is clinically relevant because pneumonia is the most frequent infection in burn patients today (1). Other types of infections were unaffected by trace element supplementation.

Immunity is affected in 2 ways by major burns (3), with alterations of 1) nonspecific defenses including physical barriers (skin disruption), cytokine production, phagocytosis, and complement production, and 2) antigen-specific responses with antibody production and cell-mediated immunity (5). Cell-mediated immunity (proliferation and cellular differentiation), cytokine production with low IL-1 and IL-2 production, and phagocyte function of neutrophils and macrophages are very sensitive to zinc deficiency (4, 21). Copper deficiency produces neutropenia and impaired phagocytosis (22). Selenium is involved in one of the main antioxidant defense systems of the body with the glutathione peroxidase family; selenium deficiency reduces neutrophil phagocytosis (23) and favors emergence of virulent viruses (24). Deficiency of any of these elements, but especially of selenium and zinc, reduces resistance to several microorganisms and increases rates infection from bacteria, fungi, parasites (5), and viruses (24, 25). Supplementation of populations with either borderline status or well-established deficiencies is associated with improved immune defense and reduction of infection rates. This has been shown in elderly people (26, 27) and also in general populations with endemic deficiencies (25). To our knowledge, our study is the first to show that infectious complications in critically ill patients can be reduced with trace element supplementation.

After observing the differences in infection rates, it was important to reexamine whether the 2 patient groups were really comparable. Although the groups were apparently similar with respect to the Tobiasen severity index, the total burned surface and the APACHE II scores were slightly higher, although not significantly so, in the TE group. The most severe burns were included in the TE group (2 patients with burns covering 80% and 87% of body surface area and the most severe inhalation injury). However, the trace element–supplemented patients were slightly younger (NS), explaining the similar Tobiasen index in more severe burns. Despite this trend toward more severe burns, the trace element–supplemented patients had shorter lengths of stay in the ICU and fewer pulmonary infections.

Compared with our previous open trial, the differences between the groups were not so great regarding trace element concentrations and total leukocyte and neutrophil response. This could be explained by the fact that the difference in cumulative trace element intakes between groups was smaller in this study than in our previous study (12), which was due to the systematic prescription of standard supplements (1 vial of Addamel N daily) to all patients from admission onward. Length of treatment may also have been too short; the persistent low plasma trace element concentrations support the view that supplementation could have been continued beyond day 8. Nevertheless, the supplementation was associated with a trend toward higher total leukocyte and neutrophil counts during the second week after injury compared with control subjects; this finding agrees with our first supplementation trial, although the differences between groups are less significant. However, there was no obvious effect of the supplements on cell-mediated immunity. T cell alterations were described in burns (2, 28, 29), and T cell responses to mitogen were markedly depressed in both groups, although this was not improved by the trace element supplements. Taken together, the data suggest that trace element supplements directly affect neutrophil function and peripheral neutrophil counts, possibly through associations with changes in neutrophil trafficking. Because T cell proliferation in response to mitogens was unchanged, the significant reduction in number of infections is consistent with the main effect of trace elements being on the nonspecific immune defenses mediated by the neutrophils, with a protective effect against bacterial aggression.

Burn patients are characterized by an intense inflammatory response, and IL-6 is massively increased after burns (30), peaking during the first day after injury as observed in our control group. The peak IL-6 concentrations were lower in the trace element–supplemented patients, possibly as a result of a blunting of the inflammatory response. This finding is strengthened by the observation of subsequent lower peak CRP concentrations, suggesting an effect of very early trace element provision on the inflammatory cascade. In this context, it is of interest that selenium, through the glutathione peroxidases, is involved in the down-regulation of the nuclear transcription factor κB, which is a key to the production of proinflammatory cytokines such as IL-6 (31). Usually, during an acute phase response, plasma selenium concentrations decreases, probably in response to cytokine production. Critically ill patients are characterized by low plasma selenium concentrations and increased urinary excretion (32), the changes being even more marked in trauma patients (33) and after burn injury (6, 9). Free radical production is increased in many critical illnesses, and selenium is part of the endogenous antioxidant defense mechanism as a constituent of the glutathione peroxidase family. In animals with reperfusion injuries, which are characterized by an increased free radical load, antioxidant status has been successfully reinforced with selenium supplements (34). Burn injury is also characterized by
a steep and prolonged increase of free radical production (35), and administration of antioxidants has been attempted. Selenium supplementation appears logical when considering the acute deficiency and the associated glutathione peroxidase dysfunction. Selenium plasma concentrations were maintained within normal ranges in the trace element–supplemented patients. The effect of this change on glutathione peroxidase activity remains to be determined.

Overall, these data indicate that trace element supplementation with quantities larger than standard trace element supplements has a favorable effect on pulmonary infections after burns and contributes to a reduction in the length of ICU stay when data are normalized for the burned surface area. A better understanding of the effects of trace elements on neutrophil function and the acute phase response is warranted in future studies. We realize that the study of neutrophil chemotaxis, immune cell phenotyping, and PBMC modification assays are gross approaches to the study of the alterations in immunity of burned patients. Trace element supplementation may modulate immunity by subtle modifications of cell physiology such as respiratory burst or cell signaling. This will require more complex biochemical studies of neutrophil and T cell function, which are already in progress in our laboratory.

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REFERENCES