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Original article

Trace element repletion following severe burn injury: A dose-finding cohort study

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SUMMARY

Background & aims: Major burn patients are characterized by large exudative losses of Cu, Se and Zn. Trace element (TE) repletion has been shown to improve clinical outcome. Having increased the TE doses over time, the study aimed at analysing if our repletion protocol corrected TE plasma concentrations and if the necessity for continuous renal replacement therapy (CRRT) might increase the TE needs.
Methods: Retrospective analysis of prospectively collected data in burn patients requiring intensive care (ICU) between 1999 and 2015. Inclusion criteria: Admission on day 1, full treatment, burned surface area (TBSA) ≥20% and ≥1 TE plasma determination during the stay. Four groups were constituted according to protocol changes. Period 1 (P1): 1999–2000, P2: 2001–2005, P3: 2006–2010, P4: 2011–2015. Changes consisted in increasing TE repletion doses and duration. Demographic data, daily TE intakes and weekly plasma concentrations were retrieved for the first 21 ICU-days. Data as median (IQR).
Results: 139 patients completed the criteria, aged 37 (28) years, burned on 35 (25) % TBSA. As a result of prescription, Cu, Se and Zn intakes increased significantly between P1 and P4, resulting in normalization of plasma Cu (16 μmol/l) since P3 and Zn (13.5 μmol/l) since P2. Median plasma Se were above reference range (1400 nmol/l) during P3 and P4. CRRT patients required higher doses of Cu for maintenance within normal ranges.
Conclusion: This dose finding study shows that the latest repletion protocol is safe and normalizes Cu and Zn concentrations. Se doses result in supra-normal Se concentrations, suggesting prescription reduction. CRRT patients are at high risk of Cu depletion and require specific monitoring.

1. Introduction

Trace elements (TE) such as copper (Cu), selenium (Se) and zinc (Zn) play essential physiological roles. As cofactors of multiple key enzymes, they are involved in redox signaling and antioxidant defense (Se and Cu), immune response (Se and Zn), wound healing (Cu, Se and Zn) and regulation of gene expression (Zn) [1,2]. All have been found to be acutely depleted after burn injury [3] and losses are largely explained by the wound exudation [4]. Intravenous repletion of acute TE deficit has been shown to reduce infectious complications and length of stay [5,6]. Additional benefits such as reduced skin protein catabolism [7] and improved antioxidant status were also shown in a randomized controlled trial [3]. These beneficial effects have recently been confirmed in a meta-analysis [8].

Recommendation to replete TE losses have been included in the burn specific guidelines of the European Society of Clinical Nutrition (ESPEN) [9] and the American guidelines (ASPEN) [10]. TE repletion is routinely performed in 92% of American Burn Centers [11], although important variations of the supplements and the doses administered are noted. Recently, we detected specific problems in burn patients with acute renal failure requiring prolonged continuous renal replacement therapy (CRRT) [12]: very large doses of Cu (>10 mg/day I.V.) were required to achieve the lower border of normal Cu reference ranges. Since 1999, the Lausanne burn center feeding protocol has been adjusted over 4

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periods (Table 1) and the TE doses have gradually increased as well as the duration of the repletion.

The aim of the study was to ensure that the repletion strategy which followed a dose-finding logic with progressive increase of TE doses, adequately restored plasma TE concentration and to what extent CRRT would influence needs.

2. Material and methods

2.1. Setting

The Lausanne University Hospital (Centre Hospitalier Universitaire Vaudois) is a 1100 beds quaternary care hospital. The multidisciplinary intensive care unit (ICU) has 33 beds, 5 being dedicated to burns patients.

2.2. Study design and data

A retrospective cohort study, based on prospectively collected data, was performed on consecutive burns ICU admissions between June 1st, 1999 and December 31st, 2015, after Institutional Research Ethics Committee approval. Informed consent was waived. Inclusion criteria were: full treatment, burn injury involving ≥20% body surface (TBSA) (i.e. the threshold for intravenous TE repletion prescription), at least one TE plasma concentration determination during the ICU stay and admission in our institution no more than 24 h after burn injury. Data were recorded until day 21.

Burn injury size and depth were estimated by the plastic surgeons (Wallace's Rule of Nine) and inhalation injury was documented by bronchoscopy [13]. Fluid resuscitation was oriented by the Parkland formula.

The cohort was divided into four groups according to the period defined by the changes in our clinical management protocol (summarized in Table 1): Period 1 (P1): 1999–2001 (n = 11), P2: 2002–2005 (n = 29), P3: 2006–2010 (n = 57), P4: 2011–2015 (n = 42). Patients were further stratified according to burns severity (20–40% and >40% TBSA).

Nutrition protocol: enteral feeding was always encouraged from the admission day. Energy targets were set by indirect calorimetry or Toronto equation estimation [9]. Changes over time consisted mainly in a reduction of caloric targets from 1.3× the measured energy expenditure (MEE) to 1.0× MEE and introduction of protein-enriched enteral feeds and enteral glutamine since 2006 (Intestamin®, Fresenius Kabi, Switzerland).

TE repletion protocol (Table 1): repletion was routinely performed for patients with burns ≥20% TBSA since 1999 using the TE cocktail tested in the randomized trial [4] (Specific burn TE profile: Cu 3.75 mg, Se 375 μg, Zn 37.5 mg). The TE were provided as sodium selenite, copper gluconate and zinc gluconate. The TE doses are indicated as elemental doses.

Since the beginning of P2, patients received an additional TE solution named "stress profile 1" containing one Addamel® vial (Fresenius Kabi AG, Stanz, Switzerland) to which 100 μg Se and 10 mg Zn were added. This TE solution was slightly modified since P3 ("stress profile 2"), when a Decan® vial (Laboratoires Aguettant, Lyon, France) replaced the Addamel® vial: Se dose was maintained and Zn was reduced to 5 mg. This TE solution was not burn-specific, but systematically prescribed for 5 days with a vitamin "cocktail" to highly inflammatory patients, malnourished or on parenteral nutrition (every day of PN). The specific burn TE profile and the stress profiles 1 and 2 were each mixed, diluted in 250 ml NaCl 0.9% and delivered separately via a central vein catheter as a 6–12 h infusion (between 6pm and 6am). Multivitamins were administered separately.

As summarized in Table 1 and based on plasma concentrations, all these modifications led to a gradual increase of the repletion doses (since the beginning of P2) and a prolonged duration of supplementation since the beginning of P4.

Study variables were extracted from the computerized information system (Metavision®, iMDSoft, Tel Aviv, Israel) and included specific burn severity scores, length of mechanical ventilation and ICU stay and requirement of continuous renal replacement therapy (CRRT). Daily intake of Cu, Zn and Se were also extracted and included the sum of intravenous and enteral intakes.

Table 1
Evolution of the ICU's nutritional recommendations.

Variable	Period 1 (99–01)	Period 2 (02–05)	Period 3 (06–10)	Period 4 (11–15)
Initial resuscitation	4 ml/kg/% TBSA burned	4 ml/kg/% TBSA burned	2 ml/kg/% TBSA burned	2 ml/kg/% TBSA burned
Energy target	MEE[a] × 1.3	MEE[a] × 1.2	MEE[a] (or Toronto)	MEE[a] (or Toronto)
Nutritive solution	Standard	Standard	Protein-enriched Low fat	Protein-enriched Low fat
Protein target	Not explicit	Not explicit	1.3–2.0 g/kg	1.3–2.0 g/kg
Enteral glutamine[e] (*Intestamin®*)	None	None	30 g/day for 10 days (TBSA >20%)	30 g/day for 10 days (TBSA 20–60%) 30 g/day for 30 days (TBSA >60%)
Specific burn IV trace element preparation	1 Specific burn TE-flex[b]: 5 days/20–30% BSA 10 days/30–40% BSA 21 days/>40% BSA		1 Specific burn TE-flex[b] 5 days/20–30% BSA 10 days/30–40% BSA 21 days/>40% BSA	1 Specific burn TE-flex[b] 5 days/20–30% BSA 14 days/30–60% BSA 30 days/>60% BSA
Standard ICU IV micronutrient	None	Stress profile 1[c]	Stress profile 2[d]	
Max total daily intravenous TE's intake	Copper 3.75 mg Selenium 375 μg Zinc 37.5 mg	Copper 5.05 mg Selenium 507 μg Zinc 54 mg	Copper 4.23 mg Selenium 545 μg Zinc 52.5 mg	
Max total daily intravenous and enteral TE's intake	No additional enteral intake except minor quantities in enteral feeds		Additional 300 μg Se, 20 mg Zn contained in Intestamin[e]: Copper 4.23 mg Selenium 845 μg Zinc 72.5 mg	

The TE doses are indicated as elemental doses.
[a] **MEE** = indirect calorimetry measured energy expenditure.
[b] **Specific burn TE flex**: Cu 3.75 mg, Se 375 μg, Zn 37.5 mg.
[c] **Stress profile 1** (Indication = parenteral nutrition or acute inflammatory condition): 1 Addamel® N vial (Cu 1.3 mg, Se 32 μg, Zn 6.5 mg and 6 other TE) + 100 μg Se and 10 mg Zn.
[d] **Stress profile 2** (Indication = parenteral nutrition or acute inflammatory condition): 1 Decan® vial (Cu 0.48 mg, Se 70 μg, Zn 10 mg and 7 other TE) + 100 μg Se and 5 mg Zn.
[e] **Intestamin®** 500 ml: Glutamine 30 g, Se 300 μg and Zn 20 mg, (Fresenius Kabi, Switzerland AG).

Analytical methods: Plasma TE concentrations were measured by inductively coupled plasma mass spectrometry (ICP-MS) [14] and were usually checked on a weekly basis. Blood samples were drawn at 6am via an arterial catheter to avoid any contamination by the TE solution. The results were available within 3–4 days after sampling.

Infectious complications were retrieved from the discharge reports, based on microbiological findings and antibiotherapy introduction or rotation. Multiple positive cultures were considered only once when they were related to a unique infectious episode. Concomitant sites of infection, including primary bloodstream infections, were considered as separate episodes of infections. Episodes of infections due to several microorganisms were considered only once. Infections were defined according to the American Burn Association (ABA) criteria [15]. C-reactive protein (CRP) values were also extracted.

Toxicity signs were systematically searched from the start. 1) Copper: gastrointestinal symptoms (vomiting, liver toxicity), cardiomyopathy, and renal failure [16]. 2) Selenium: gastro-intestinal symptoms, alopecia, nail changes, mental status alterations or neuropathy [17,18]. 3) Zinc: gastrointestinal symptoms [19].

2.3. Statistical analysis

Descriptive statistics are presented as medians with interquartile ranges (IQR = p25–p75), as mean (standard deviation) for continuous variables and as frequencies and percentages for categorical variables. Study periods were compared using the χ^2 test, Fisher's exact test, one-way-ANOVA or Kruskal–Wallis tests. For serial measurements, a Bonferroni correction was applied. Plasma TE concentrations were compared between with and without CRRT patients using two sample *t*-test and Wilcoxon rank sum test. Pearson's correlation was analyzed between plasma TE and CRP. Statistical significance was accepted at the probability (p) < 0.05. The statistics and graphics were carried out using STATA 14 software (StataCorp LP, College Station, TX, USA).

3. Results

3.1. Baseline characteristics of patients

Altogether 564 patients were admitted for burns to the ICU between 1999 and 2015, with a median age of 42 years (IQR 22) and a median TBSA burned of 17% (IQR 22): 139 patients completed the inclusion criteria (Fig. 1). Their main characteristics are presented in Table 2. Included patients were younger (37 years, IQR 28) and more severely burned (35%, IQR 25). Baseline characteristics and severity of the patients did not differ through the periods, except for a trend toward an increased ventilation time in P4. Patient's weights did not differ statistically different, with a median value of 72 kg (IQR 22) (trend to higher values in P4 p = 0.114). The number of patients requiring CRRT was significantly increased in P4 (29%, p < 0.05). The majority was treated by CVVH, with a typical dose of 25 ml/kg/h and a mean duration of 38 days (from 1 to 213 days), starting as a median by day 8. The mortality was modestly higher in P4 (17%), but did not reach significance (NS: p = 0.44).

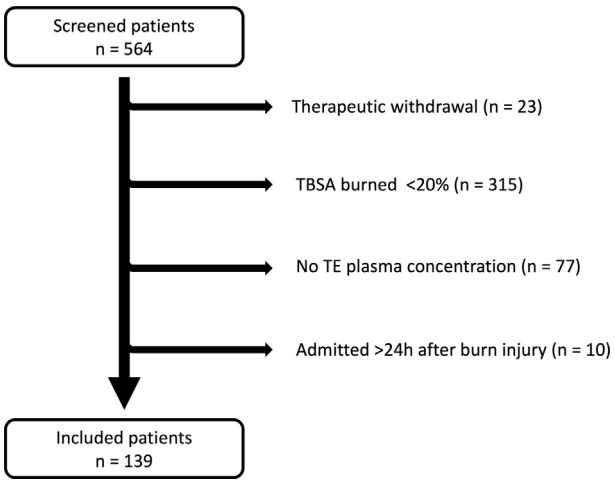

Fig. 1. Consort diagram. Some patients had multiple exclusion criteria.

3.2. Copper, selenium and zinc intakes

As a result of the increasing prescription the daily TE intakes increased in P2, P3 and P4. The daily Cu intake progressed from 3.4 mg (IQR 1.1) in P1 to 4.3 mg (IQR 2.9) in P4 (Fig. 2). The daily Se intake increased from 346 μg (IQR 124) in P1 to 594 μg (IQR 470) in P4. The daily Zn intake increased from 35 mg (IQR 12) in P1 to 70 mg (IQR 41) in P4. The highest daily intakes were provided to the patients with the largest burns, especially during the more recent periods. The results did not differ when expressed as mg/kg/24 h.

3.3. Copper, selenium and zinc plasma concentrations

Plasma Cu was below references ranges in P1 (8.3 μmol/l, IQR 5.2, normal range 12.5–23.6) and normalized since P3 (16.0 μmol/l, IQR 9.1). Plasma Se was also below references in P1 (530 nmol/l, IQR 430, normal range 750–1500 nmol/l) and normalized since P2 (1045 nmol/l, IQR 532). Se median values were close to the top of reference range during P3 and P4, with median values above 1400 nmol/l. Plasma Zn was lowest during P1 (6.7 μmol/l, IQR 3.9, normal range 10.1–17 μmol/l) and normalized since P2 (13.5 μmol/l, IQR 7.2).

Overall, the supplementation protocol, and the increasing doses (see below) allowed normalization of plasma TE concentrations within approximatively one week. The stratification of the patients by severity (Fig. 2) showed that plasma Cu, although within ranges, was still at the lower limit of the reference values for burns ≥40% TBSA. Plasma Se was frequently above reference values after the first week and regardless of the severity of the burns. Plasma Zn normalized independently of severity. Figure 3 shows the TE concentrations in presence or absence of renal replacement therapy. The normalization of plasma TE concentrations among patients under CRRT required significant higher intakes of TE, this phenomenon being particularly obvious for the Cu, and least for Zn (not shown). Plasma Cu, or Se and CRP values were not correlated (r2 < 0.000) and Zn only modestly (r2 = 0.0203).

3.4. Infectious complications

Table 2 shows the mean number of infections per patient during the first 21 days, which was significantly lower since P3 (p < 0.05), with a mean number of 1.7 and 2.0 infections during respectively P3 and P4, compared to a number of 2.3 and 2.6 during P1 and P2. CRP median values were the highest in P1 and the lowest in P3 (p < 0.001).

3.5. Toxicity signs

None of the above described toxicity signs was observed.

4. Discussion

The most important finding was that the repletion protocol in use since 2006 (Table 1) was safe and enabled normalization of

Table 2
Patient characteristics.

Variable	All periods	Period 1 (1999–01)	Period 2 (2002–05)	Period 3 (2006–10)	Period 4 (2011–15)	p-value
Number of patients	139	11	29	57	42	
Number of patients ≥40% BSA	59	5	10	24	20	
Age (years)[b]	37 (28)	50 (37)	31 (24)	37 (25)	38 (30)	0.74[c]
Gender (male)[a]	94 (68%)	7 (64%)	19 (66%)	35 (61%)	33 (79%)	0.33[d]
TBSA burned (%)[b]	35 (25)	38 (32)	35 (23)	35 (19)	36 (35)	0.32[c]
Full thickness burn size (%)[b]	23 (28)	28 (30)	23 (17)	20 (28)	25 (38)	0.36[c]
Inhalation injury[a]	83 (60%)	5 (45%)	19 (66%)	34 (60%)	25 (60%)	0.72[c]
ABSI score[b]	8 (3)	9 (2)	9 (3)	8 (3)	9 (3)	0.42[e]
Ryan score[b]	1 (1)	1 (1)	1 (1)	1 (0)	1 (1)	0.91[e]
Length of stay (days)[b]	31 (35)	34 (14)	31 (37)	29 (34)	30 (35)	0.72[c]
Ventilation time (days) [b]	12 (19)	14 (15)	11 (14)	9 (20)	20 (23)	0.06[c]
Number of infections per patient during 21 days[h]	2.0 (1.2)	2.3 (1.6)	2.6[g] (1.3)	1.7[g] (1.1)	2.0 (1.2)	<0.05[c]
CRP medians (mg/l)[b]	168 (125)	180 (108)	169 (145)	161[g] (114)	172[g] (139)	0.001[e]
Number of patients requiring CRRT[a]	17 (12%)	1 (9%)	1 (3%)	3 (5%)	12 (29%)	<0.05[f]
Mortality[a]	16 (12%)	2 (18%)	2 (7%)	5 (9%)	7 (17%)	0.44[f]

[a] Numbers of patients (%).
[b] Medians (interquartile range): CRP is expressed as the median of all values of the first 21 days.
[c] Kruskal–Wallis.
[d] Chi-squared.
[e] ANOVA.
[f] Fisher's exact.
[g] Bonferroni.
[h] Mean (standard deviation).

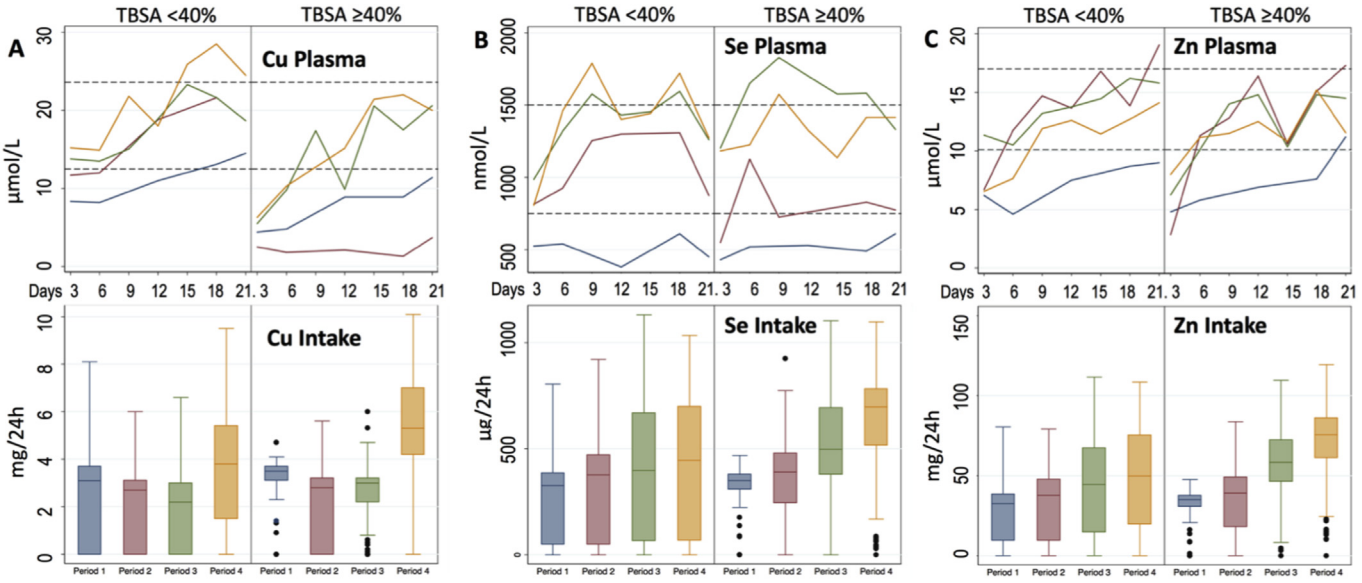

Fig. 2. For copper (A) selenium (B) and zinc (C):

- Median plasma concentrations of TE's concentrations over 21 days and by period, according to burn size (<or ≥40% TBSA burned). The dashed lines represent the reference values. Note the supra-normal selenium values.
- Median daily intakes by period and according to burn size. Note the increased delivery of the three elements.

plasma TE concentrations in most of our major burn patients within 7 days. This safety observation would enable using these repletion doses in centers where TE determination is not available.

Based on the previous studies by the group, plasma concentration was chosen as a surrogate endpoint for assessing adequacy of the repletion dose, despite the limitations associated with this variable. Plasma concentrations are influenced by inflammation (increasing Cu concentrations, lowering majority of other TE), due to cytokine mediated redistribution during the acute phase response. There is usually a positive (Cu) and respectively negative (Se, Zn) correlation between the plasma TE and inflammation measured by CRP. However, although median CRP values differed between periods, the difference was small (about 20 mg/l) enabling comparisons: no correlation between CRP and plasma Cu and Se concentrations was observed, with only a modest negative correlation for Zn. This uncoupling is likely explained by the TE repletion.

The evolution of the Cu repletion dose is particularly interesting. In response to persistent low plasma values, the daily prescription and intake increased steadily, nearly doubling between periods 2 and 4 (Fig. 2). Although the Cu concentrations reverted to normal ranges, the requirement for additional doses especially in the subset of patients with burns ≥40% TBSA, motivated a modest increase of the Cu dose, reason why the daily repletion dose was increased from 4.23 mg to 4.77 mg/day since 2017. These results are consistent with the data of the prospective study of Jafari et al. [14]. Preventing Cu deficiencies is crucial in severely burned patients to prevent

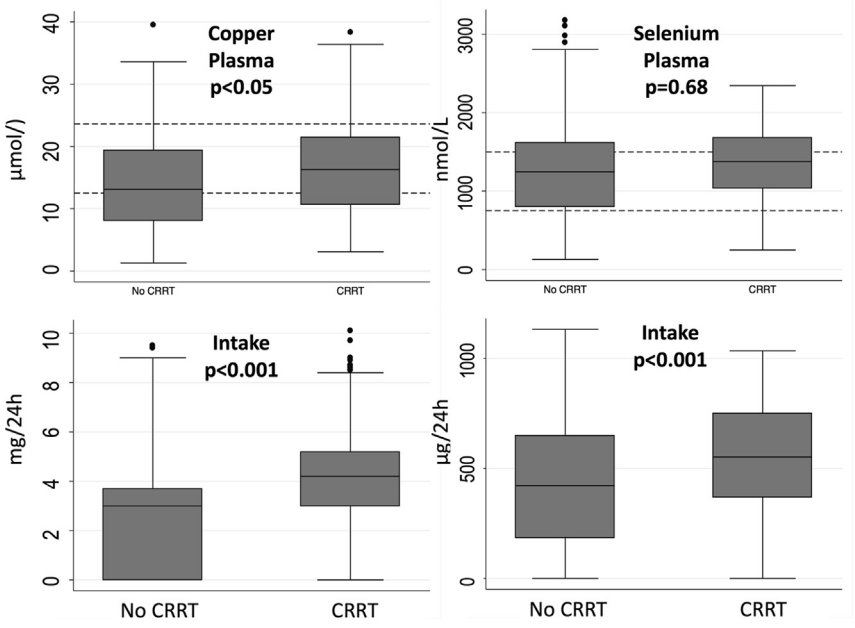

Fig. 3. Comparison of intake and plasma concentrations of copper and selenium over 21 days and by period, with or without CRRT. The dashed lines represent the reference values. The normalization of plasma concentrations was achieved by a significant increase of TEs intake (particularly Cu) in CRRT patients (Mann–Whitney, $p < 0.001$).

immunosuppression, delayed wound closure and cardiac arrhythmias [1,20]. Overdose is easily prevented by a weekly monitoring of Cu plasma and no sign of toxicity was observed over 16 years.

The present study also identified an overcorrection of Se concentrations whatever the burn severity. This occurred as the result of the introduction of an enteral Se+Zn containing glutamine product since 2006 which resulted in a sharp increase of maximal Se intakes (745 µg/24 h). Indeed, the enteral solution contains 300 µg of Se which has an absorption rate of 70–90% [21]. These results prompted us to reduce the intravenous intake of Se from 545 µg/day to 273 µg/day. Selenium is a key component of many enzymes, involved in immune response and wound healing [2], but also in antioxidant defense [22] (glutathione peroxidase family, GPX) and thyroid hormone production. The determination of GPX is unfortunately not available for routine, but results from our previous trial showed that plasma GPX was already normalized with the P2 doses. None of the clinical acute or chronic manifestation of Se toxicity was observed [17,18]. It is unlikely that the prescribed doses were toxic, since doses up to 1000 µg per day have been safely administered to unburned ICU patients for several weeks without apparent side effects [23].

The average absorption of Zn being much lower than Se, around 30% [24,25], and added to its redistribution during inflammation, the blood concentrations of Zn did not increase in the same proportions after the introduction of the enteral Se+Zn containing glutamine product, confirming the dose finding results of Heyland et al. [26]. Plasma Zn concentrations have the particularity not to correlate with tissue concentrations and especially during inflammatory diseases: the skin biopsies of our previous randomized study show nevertheless that the patients receiving Zn repletion normalize tissue concentrations and that this was associated with an increasing trend in plasma [27]. Our results showed that indeed, unlike Cu and Se concentrations, Zn concentrations remained below normal during the first 7 days, with normalization after the 1st week in patients burned at $\geq$ or <40%. Thus, the significant initial decrease of Zn concentrations during the acute phase of burn injury is the result of redistribution of Zn into the cellular compartment, which appears to be mediated by cytokines that modulates the expression of Zinc transporters [28]. Hepatic sequestration, intense leukopoiesis or Zn ion sequestration from the pathogens (nutritional immunity) are other possible mechanisms [27]. It seems therefore not desirable to further increase the Zn intake. Although Zn supplementation has been shown to promote a more rapid wound healing [3]. The therapeutic margin of Zn is important with limited risks of toxicity. Intakes above 100 mg per day may nevertheless lead to digestive disorders and depression of cellular immunity [29]. Very high enteral intakes (>150 mg) can cause Cu deficiency, by competing for absorption, a property which is used to treat Cu overload diseases [19].

Finally, we found a significantly reduction of infectious complications during periods 3 and 4 compared to periods 1 and 2. This confirms the results of our randomized controlled trials showing less infectious complications in the TE intervention groups [3,7,30].

The repletion needs were significantly increased for all TE in patients undergoing CRRT (Fig. 3), but the effect was the greatest on Cu. This emphasizes the importance of monitoring at least the 3 TE and especially Cu, particularly in case of prolonged continuous renal replacement therapy [12]. A significant increase of patients requiring CRRT was observed during the last period. Unpublished data showed that this was related to changes regarding the initial resuscitation of burned patients; patients received lower fluid resuscitation volumes, more propofol, and required more norepinephrine with a rapid increase in creatinine values. By regression analysis, trace element doses were not determinants of renal function. In addition, the plasma TEs concentrations were the same in period 3 and 4 (Fig. 2) and were unrelated to the early increase of CRRT during period 4. Toxic doses of Cu and Se are far higher than those administered in the protocol. Interestingly, analysis of the patients with Se plasma concentrations exceeding 2000 µg/l (18 patients [22 plasma values] in period 3 and 12 patients [13 plasma values] in period 4), identified only one patient in period 3 and two patients in period 4 requiring CRRT.

In summary, these results are consistent with those reported in our most recent trial [14]; TE losses seem lower than initially reported in the historical studies. This might be explained by the faster wound healing we had shown previously [3]. These results prompted us to modify our repletion protocol from January 2017, by reducing substantially the Se doses, increasing slightly the Cu doses and reducing slightly Zn doses. When using the Se+Zn containing enteral glutamine solution, knowing that Zn absorption is at best

30% and Se absorption being 70–90%, we suggest from now the following maximum daily total intravenous intake: Cu 4.77 mg, Se 273 μg and Zn 45.5 mg.

5. Limitations

This study was retrospective and might be considered of less value than prospective trials. Considering the heterogeneity of major burn populations, dose finding and randomization are difficult to conceive. The use of placebo was declared unethical within the center after the positive clinical effects of the 2 randomized trials: such a study might be realized in a larger center where this repletion protocol is not yet in place. The single center study attenuated the heterogeneity issue: a homogeneous cohort study is an advantage, as procedures and treatments were well controlled, and no patient was excluded as is the case in randomized controlled studies [31]. Indeed computerization induces standardization and by making the metabolic data visible, has improved the nutritional monitoring and treatment of our patients [32]. The clinical unavailability of GPX-3 determination is certainly a limitation. Nevertheless the comparison of the Se concentrations with our previous PRCT data enable reasonable conclusions. This burned cohort is the largest cohort to date on which the TEs were studied. Even so, the number of patients included remains limited and some changes may have gone undetected.

6. Conclusion

TE repletion is safe and associated with a decrease of infectious complications. The numbers of determinations enable applying the strategy even without availability of TE determinations. When available, they should ideally be monitored on a weekly basis. When prescribing enteral Se+Zn containing glutamine solution, the supplemental amount of Se should be taken into account due to its high absorption. Patients treated by CRRT should be closely monitored as they need higher repletion doses while on CRRT.

Author contributions

The authors' responsibilities were as follows—OP, MMB: designed the study, wrote the manuscript and analyzed the data; OP, PS, MC, AV: researched the data; OP, MC, PV, MMB: contributed to the discussion; all authors reviewed and edited the manuscript; all authors: read and approved the final manuscript. None of the authors reported a conflict of interest related to the study.

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest. The study was financed by the Service of Adult Intensive Care Medicine and Burns of Lausanne (Switzerland).

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