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SHORT COMMUNICATION

Safety and intestinal tolerance of high-dose enteral antioxidants and glutamine peptides after upper gastrointestinal surgery

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Objective: Safety and intestinal tolerance of an early high-dose enteral administration of antioxidative vitamins, trace elements, and glutamine dipeptides.
Design: open intervention trial.
Setting: Two university teaching hospitals.
Patients: A total of 14 patients requiring jejunal feeding (64 ± 14 y).
Intervention: A measure of 500 ml/day Intestamin® (FreseniusKabi: 250 kcal/1.050 kJ, 300 μg selenium, 20 mg zinc, 400 μg chromium, 1500 mg vitamin C, 500 mg vitamin E, 10 mg β-carotene, 30 g glutamine) for 5 days beginning 6 h after surgery. Parenteral/enteral nutrition was provided to achieve energy target (25 kcal/kg/day).
Assessments: Intestinal complaints, plasma nutrients, and glutathione.
Results: Only minor signs of nausea, hiccups, flatulence (3/14). Plasma micronutrients (except β-carotene) postoperatively decreased and increased to normal on day 5. Extracellular glutamine remained low (preop: 520 ± 94; d1: 357 ± 67; d5: 389 ± 79 μmol/l); total glutathione decreased (d1: 9.4 ± 3.8; d5: 3.6 ± 2.5 μmol/l).
Conclusion: Study feed is well tolerated and metabolically safe representing a valuable tool for targeted pharmaconutrient supply.
Sponsorship: The trials were carried out with the local University's human resources; Fresenius Kabi (Bad Homburg, Germany) partially supported the trial by financing the analytical determination and providing the supplementation solutions.
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Introduction

Low circulating concentrations of exogenous nutrients (selenium, zinc, ascorbic acid, tocopherols, β-carotene, glutamine) and endogenous metabolites (glutathione) may result in a decreased antioxidative defence which may impair gut integrity and GALT function (Shenkin, 1995; Wernerman & Hammarqvist, 1999; Fang *et al*, 2002; Stehle, 2003). A 'targeted' early postoperative enteral supplementation with high amounts of these pharmaconutrients might essentially contribute to counteract gastrointestinal complications (Berger *et al*, 2002). The goals of the present clinical study in postoperative patients were, thus, to assess the safety and the intestinal tolerance of an early high-dose enteral administration of antioxidative vitamins, trace elements, and glutamine as precursor of endogenous glutathione.

Methods

Study design: Approved open trial after major upper gastrointestinal tract surgery for oesophageal and gastric malignancies in two University teaching hospitals (Kiel, Germany,

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Lausanne, Switzerland) in 14 patients (64 ± 14 y, BMI 24.4 ± 4.6 kg/m^2) requiring enteral feeding for 4 days or longer within a 1-year period. Only esophagus or stomach was resected, and the small bowel was used for anastomosis, leaving absorption capacity unaltered.

Exclusion criteria: contraindication for enteral nutrition, hepatic failure (Child A or worse), severe renal failure (serum creatinine >150 μmol/l), acute pancreatitis, patient weight <50 kg or >100 kg.

Study feed: The application of the new supplement (Intestamin®, Fresenius Kabi, Bad Homburg, Germany) was started within the first 6 h after surgery using continuous infusion via a naso-jejunal or percutaneous tube and was given for 5 consecutive days (500 ml/day: 250 kcal/1.050 kJ, 300 μg selenium, 20 mg zinc, 400 μg chromium, 1500 mg vitamin C, 500 mg vitamin E, 10 mg β-carotene, 30 g glutamine as dipeptides).

Beginning with postoperative day 2, the patients were additionally nourished (combined parenteral and/or enteral supply) to cover energy and protein needs (glutamine-free standard nutrient solutions). The energy target was set at 25 kcal/kg/day.

Metabolic safety: In addition to routine clinical chemistry, assessment was based on analyses of plasma concentrations in comparison with safety ranges published. Blood samples were collected preoperatively, and then on days 1, 3, and 5 after surgery (0700 h). Plasma vitamins C, E, and β-carotene (Erhardt *et al*, 1999), glutamine (Fürst *et al*, 1990) and total reduced glutathione (GSH) (Kuhn *et al*, 2000) were analysed by HPLC. Chromium, selenium, and zinc were determined using atomic absorption spectrophotometry (AAS, graphite furnace). CRP was determined by nephelometry.

Intestinal tolerance: Throughout the study, frequency of aspiration, nausea/vomiting, hiccups, bloating, flatulence, constipation, diarrhoea (three liquid stools per day), and clinical evolution were recorded.

Statistics: Data are presented as means ± s.d. Blood concentration changes over time were analysed by one-way ANOVA (significance level $P<0.05$). Clinical data were evaluated descriptively.

Results

Surgical procedures and clinical treatment as well as duration of surgery (4. 7 ± 0.8 h) were comparable in all patients. Mean blood losses were 620 ± 475 ml. Four patients received packed erythrocytes as partial replacement of blood losses > 500 ml; none received fresh frozen plasma. One patient received by error 560 mg of ascorbic acid, and 132 μg selenium intravenously on day 1 and was excluded from the analysis of those two micronutrients. The test feed was fully delivered (500 ml daily). Additional parenteral/enteral nutrition support was given according to protocol (total energy delivery: 30 ± 8 kcal/kg/day).

Adverse effects occurred in two patients: one anastomotic leakage due to surgical reasons and one subileus and bronchopneumonia, which resolved rapidly, both not being related to enteral supplementation and feeding. Clinical chemistry including routine hepatic tests (ASAT, ALAT, γ-GT, TP) stayed within references (data not shown).

Only minor signs of intestinal intolerance were observed in 3/14 patients with nausea, hiccups, and flatulence. Between days 1 and 5 after surgery, the patients had 2.5 bowel movements as a mean (0–5).

The course of plasma concentrations of vitamins and trace elements are shown in Figures 1 and 2, respectively. Vitamins C and E as well as selenium and zinc postoperatively decreased below reference ranges ($P<0.01$). With the exception of β-carotene, plasma concentrations of the supplemented micronutrients increased between postoperative days 1 and 5 ($P<0.01$) approaching preoperative normal values.

Mean plasma glutamine concentrations (μmol/l) were below reference ranges preoperatively (520 ± 94), and further decreased on day 1 after surgery (357 ± 67). The mean level increased modestly thereafter, remaining low on day 5

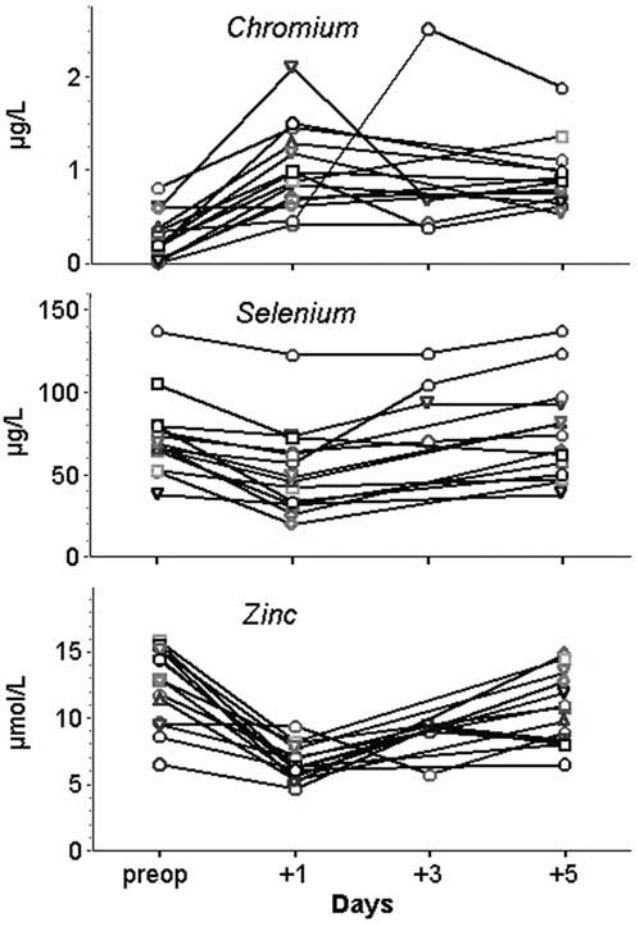

Figure 1 Individual time courses of plasma concentrations: chromium, selenium, and zinc. Reference ranges: chromium 0–10 μg/l, selenium 50–150 μg/l, zinc 10–18 μmol/l.

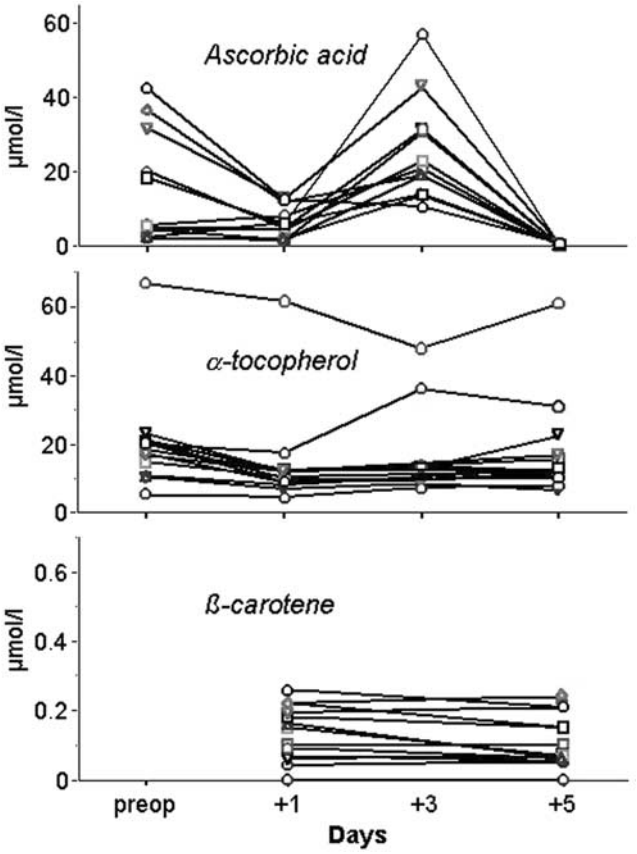

Figure 2 Individual time courses of plasma concentrations: ascorbic acid, α-tocopherol, β-carotene. Reference ranges: ascorbic acid 20–50 µmol/l, α-tocopherol 15–40 µmol/l, β-carotene 0.20–0.50 µmol/l.

(389±79). Total GSH (µmol/l) was elevated preoperatively (9.42±3.76, ie three times the normal reference ranges, which are 2.88–3.25), decreasing to 3.64±2.50 on day 5 ($P<0.01$).

An elevation of circulating CRP (mg/l) above preoperative values (17±28) was observed in all patients after surgery (57±60) and was still significantly higher by day 5 (119±50; $P<0.01$ from preoperative).

Discussion

As planned, gut feeding started in all patients within 6 h after surgery. Only minor signs of gastrointestinal symptoms in three patients confirm satisfactory tolerance of the study feed.

The expected initial decrease of plasma micronutrient concentrations (except chromium and β-carotene;Figures 1 and 2) presumably due to a stress-dependent redistribution of micronutrients to organs such as the liver and the reticuloendothelial system (Shenkin, 1995) and/or losses of micronutrients (haemorrhage and drains) progressively reverted to preoperative values during supplementation. It can be, thus, assumed that the enterally delivered substrates are effectively taken up. Extracellular levels did not exceed physiological levels confirming the metabolic safety of high-dose enteral micronutrient application.

The low plasma response compared with an intravenous and/or an nasogastric application of selenium and α-tocopherol (Berger *et al*, 2001a, b) may be explained by the restoration of intracellular pools in the deprived enterocytes. This hypothesis is strengthened by the observation of decreased total GSH values on day 5. Consequently, the present approach may specifically contribute to maintain gut integrity and, thus, prevent bacterial translocation.

Synthetic dipeptides have been proven to restore stress-induced extracellular glutamine levels after enteral or parenteral administration (Quade *et al*, 2001). Owing to the only moderate increase in plasma glutamine in our study, it can be assumed that after peptide uptake the majority of liberated glutamine was directly used as energy/nitrogen fuel by the gut mucosa (Haisch *et al*, 2000).

The findings of the present clinical study indicate that an early gut feeding with high amounts of micronutrients and glutamine dipeptides is well tolerated and metabolically safe. This novel approach can be seen as a valuable clinical tool for targeted pharmaconutrient supply in postoperative patients counteracting micronutrient deprivation.

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References

Berger MM, Baines M, Wardle CC, Cayeux C, Henry H, Shenkin A & Chioléro R (2001a): Influence of early trace element and vitamin E supplements on the plasma antioxidant status after major trauma: a controlled trial. *Nutr. Res*. **21**, 41–54.

Berger MM, Reymond MJ, Shenkin A, Rey F, Wardle C, Cayeux M, Schindler C & Chioléro RL (2001b): Influence of selenium supplements on the post-traumatic alterations of the thyroid axis—a prospective placebo controlled trial. *Intens. Care Med.* **27**, 91–100.

Berger MM, Goette J, Stehle P, Cayeux MC, Chiolero R & Schroeder J (2002): Enteral absorption of a solution with high dose antioxidants and glutamine early after upper gastrointestinal surgery. *Clin. Nutr.* **21** (Suppl), 17 (abstract).

Erhardt JG, Heinrich F & Biesalski HK (1999): Determination of retinol, antioxidant vitamins and homocysteine in skin puncture blood. *Int. J. Vit. Nutr. Res.* **69**, 309–314.

Fang YZ, Yang S & Wu G (2002): Free radicals, antioxidants, and nutrition. *Nutrition* **18**, 872–879.

Fürst P, Pollack L, Graser TA, Godel H & Stehle P (1990): Appraisal of four pre-column derivatization methods for the high-performance liquid chromatographic determination of free amino acids in biological materials. *J. Chromatogr.* **499**, 557–569.

Haisch M, Fukagawa NK & Matthews DE (2000): Oxidation of glutamine by the splanchnic bed in humans. *Am. J. Physiol.—Endocrinol. Metab.* **278**, E593–E602.

Kuhn KS, Krasselt AI & Fürst P (2000): Glutathione and glutathione metabolites in small tissue samples and mucosal biopsies. *Clin. Chem.* **46**, 1003–1005.

Quade J, Manhart N, Herzog B, Stehle P, Zumtobel V & Senkal M (2001): Enteral and parenteral glutamine dipeptide supply comparably restores plasma glutamine in post-operative patients. *Clin. Nutr.* **20** (Suppl), 44 (abstract).

Shenkin A (1995): Trace elements and inflammatory response: implications for nutritional support. *Nutrition* **11**, 100–105.

Stehle P (2003): Nutrition support in critical Illness. In: *Nutrition and Critical Care*, eds Cynober L & Moore F, Nestlé Nutriton Workshop Series, Vol 8, S. Karger AG, Basel. pp. 57–66.

Wernerman J & Hammarqvist F (1999): Modulation of endogenous glutathione availability. *Curr. Opin. Clin. Nutr. Metab. Care* **2**, 487–492.