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Total Parenteral Nutrition With Glutamine Dipeptide After Major Abdominal Surgery

A Randomized, Double-Blind, Controlled Study

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Objective
To assess the efficacy of glutamine (Gln) dipeptide-enriched total parenteral nutrition (TPN) on selected metabolic, immunologic, and clinical variables in surgical patients.

Summary Background Data
Depletion of Gln stores might lead to severe clinical complications. Recent studies indicate that the parenteral provision of Gln or Gln-containing dipeptides improves nitrogen balance, maintains the intracellular Gln pool, preserves intestinal permeability and absorption, and shortens hospital stay.

Methods
Twenty-eight patients (age range, 42–86 years, mean 68 years) undergoing elective abdominal surgery were allocated, after randomization, to two groups to receive isonitrogenous (0.24 g nitrogen $kg^{-1}day^{-1}$) and isoenergetic (29 kcal/122 kJ $kg^{-1}day^{-1}$) TPN over 5 days. Controls received 1.5 g of amino acids $kg^{-1}day^{-1}$, and the test group received 1.2 g of amino acids and 0.3 g of L-alanyl-L-glutamine (Ala-Gln) $kg^{-1}day^{-1}$. Venous heparinized blood samples were obtained before surgery and on days 1, 3, and 6 after surgery for routine clinical chemistry and for the measurement of plasma free amino acids. Lymphocytes were counted and the generation of cysteinyl-leukotrienes from polymorphonuclear neutrophil granulocytes was analyzed before surgery and on days 1 and 6 after surgery. Nitrogen balances were calculated postoperatively on days 2, 3, 4, and 5.

Results
No side effects or complaints were noted. Patients receiving Gln dipeptide revealed improved nitrogen balances (cumulative balance over 5 days: -7.9 ± 3.6 *vs.* -23.0 ± 2.6

g nitrogen), improved lymphocyte recovery on day 6 (2.41 ± 0.27 *vs.* 1.52 ± 0.17 lymphocytes/nL) and improved generation of cysteinyl-leukotrienes from polymorphonuclear neutrophil granulocytes (25.7 ± 4.89 *vs.* 5.03 ± 3.11 ng/mL). Postoperative hospital stay was 6.2 days shorter in the dipeptide-supplemented group.

Conclusion

We confirm the beneficial effects of Gln dipeptide-supplemented TPN on nitrogen economy, maintenance of plasma Gln concentration, lymphocyte recovery, cysteinyl-leukotriene generation, and shortened hospital stay in surgical patients.

The metabolic response to trauma is characterized by negative nitrogen balance and typical changes in extra- and intracellular free amino acid patterns.[1,2] Profound intracellular glutamine (Gln) depletion is a typical feature of hypercatabolic states. It appears that its extent is unrelated to the magnitude of trauma and the depletion is little influenced by conventional dietary measures.[3]

Gln is the most abundant free amino acid in the body[4] and is synthesized in practically all tissues.[5] It acts as a precursor for protein synthesis and serves as a preferential energy source for rapidly proliferating immune and mucosal cells. In addition, it is an important intermediate in a large number of metabolic pathways.[3,5–7]

Commercially available amino acid solutions do not contain free Gln because of pharmaceutical considerations during manufacture; thus, provision of such a solution does not prevent Gln depletion. Recent studies indicate that administration of free Gln[8] or Gln-containing dipeptides[10] improves nitrogen balance and maintains the intracellular Gln pool.

Consequently, there is a theoretical case for administering parenteral Gln supplements in an attempt to influence recovery and metabolism. In this study, we investigate whether total parenteral nutrition (TPN) supplemented with a synthetic Gln-containing dipeptide, L-alanyl-L-glutamine (Ala-Gln), improves nitrogen economy and immune status and whether the hospital stay is shortened.

PATIENTS AND METHODS

Twenty-eight patients (12 males, 16 females; age range, 42–86 years, mean 68 years) admitted for elective resection of carcinoma of the colon or rectum were randomly allocated to either a test group or a control group. Demographic and clinical data for all patients are summarized in Table 1. As historical controls, the mean lengths of hospitalization were assessed in 68 patients with similar diagnoses and operations. Patients with manifest metabolic diseases (*e.g.*, diabetes mellitus, hyperthyroidism) or chronic renal or liver disease were excluded. The study was approved by the ethical committee of the medical faculty of the Ruhr-University of Bochum, and the procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 1989. Voluntary informed consent of the patient was obtained before commencement of the investigation.

All patients received 5 days of TPN given continuously over 24 hours with 0.24 g of nitrogen (isonitrogenous) and 122 kJ/kg daily (isoenergetic) via a central venous catheter. Fifty-five percent of the nonprotein energy came from glucose (20%), 45% from a fat emulsion (Lipovenös 20%; Fresenius AG, Bad Homburg, Germany). The control group received 1.5 g of amino acids $kg^{-1}d^{-1}$ (Aminosteril KE 10%; Fresenius AG), and the peptide group received 1.2 g of amino acids $kg^{-1}d^{-1}$ supplemented with the dipeptide Ala-Gln, 0.3 g per $kg^{-1}d^{-1}$ (Dipeptiven; Fresenius AG). The amino acid solution was prepared by clinical pharmacists not involved in patient treatment, and the possible difference in volume between the two regimens was corrected by adding water for injection to safeguard the double-blind, randomized design of the study.

Urine was collected throughout the study, the completeness of collection being monitored by the daily creatinine output.[11] Nitrogen content was measured by an automated chemiluminescence method.[12] The apparent nitrogen balance was calculated without taking losses in stool or skin into account. In this calculation, day 1 was not taken into account because of the known initial postoperative oliguric phase and subsequent fluid retention.

Venous heparin blood samples were obtained before surgery and on days 1, 3, and 6 after surgery for routine clinical chemistry and for measurement of plasma free amino acids. Selected routine biochemical measurements were assessed by standard methods.

Free amino acids were determined by using an automated online high-pressure liquid chromatography system with precolumn derivatization (ortho-phtaldialdehyde–3-

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Table 1. CLINICAL DATA FOR PATIENTS ADMITTED TO THE STUDY

Group	Age (yr)	Sex	Height (cm)	Weight (kg)	Condition
Control	62	M	178	82	Carcinoma of the descending colon
	71	F	164	73	Carcinoma of the colon
	85	F	157	55	Carcinoma of the cecum
	42	M	179	75	Perforation of the sigmoid colon
	77	F	154	64	Polyposis of the large bowel
	63	M	169	73	Carcinoma of the sigmoid colon
	52	F	168	63	Carcinoma of the sigmoid colon
	74	M	156	62	Carcinoma of the rectum
	80	F	160	48	Carcinoma of the ascending colon
	74	M	172	70	Carcinoma of the sigmoid colon
	67	M	174	84	Carcinoma of the sigmoid colon
	82	F	145	56	Carcinoma of the sigmoid colon
	58	F	180	86	Carcinoma of the rectum
n = 13 (mean ± SD)	68.2 ± 12.5		165.9 ± 10.9	68.5 ± 11.8	
Ala-Gln	80	F	157	65	Carcinoma of the ascending colon
	80	F	160	58	Carcinoma of the descending colon
	57	F	161	62	Carcinoma of the ascending colon
	73	M	174	63	Carcinoma of the rectum
	44	M	183	81	Carcinoma of the ascending colon
	80	F	150	48	Diverticulitis of the sigmoid colon
	65	F	157	48	Carcinoma of the rectum
	60	F	155	60	Carcinoma of the sigmoid colon
	74	F	164	67	Perforation of the rectum
	52	M	168	100	Carcinoma of the sigmoid colon
	68	M	168	75	Carcinoma of the sigmoid colon
	72	M	166	60	Carcinoma of the sigmoid colon
	65	M	172	70	Carcinoma of the ascending colon
	62	F	159	77	Carcinoma of the sigmoid colon
	74	F	158	67	Carcinoma of the ascending colon
n = 15 (mean ± SD)	67.1 ± 10.7		165.9 ± 10.9	66.7 ± 13.1	

mercaptopropionic acid [OPA-3-MPA]) and norvaline as the internal standard. The reproducibility of the method was 0.4% to 2.2% (coefficient of variations) and the error of the method was 1.0% to 4.7% (coefficient of variations).[13,14]

Isolation and stimulation of polymorphonuclear neutrophil granulocytes (PMNs) and analysis of generated cysteinyl-leukotrienes (cys-LTs) was performed as described.[15]

The data are expressed as mean ± standard error of

Table 2. AMINO ACIDS IN PLASMA AND LYMPHOCYTE COUNT

	Group	Preoperatively	Day 1 After Operation (pre-TPN)	Day 3 After Operation	Day 6 After Operation
Glutamine	Control	526.27 ± 48.5	356.78 ± 16.6	446.87 ± 21.7*	426.92 ± 27.0†
	Ala-Gln	488.20 ± 19.1	365.32 ± 26.3	531.24 ± 38.0	542.62 ± 28.5
Alanine	Control	267.23 ± 34.6	247.89 ± 17.6	325.46 ± 24.1	282.20 ± 26.4
	Ala-Gln	261.80 ± 19.0	200.03 ± 23.3	313.41 ± 41.8	356.76 ± 26.5
Glutamate	Control	30.26 ± 6.3	26.44 ± 2.4	36.85 ± 4.6	37.24 ± 3.0
	Ala-Gln	30.32 ± 4.9	27.64 ± 4.1	35.38 ± 12.5	42.45 ± 3.8
Lymphocytes	Control	1.75 ± 0.19		1.16 ± 0.24	1.52 ± 0.14
	Ala-Gln	2.05 ± 0.23		1.82 ± 0.20*	2.41 ± 0.17†

Values are mean ± SEM: plasma (nmol/mL) and lymphocyte count (nL).
* $p < 0.05$.
† $p < 0.01$.

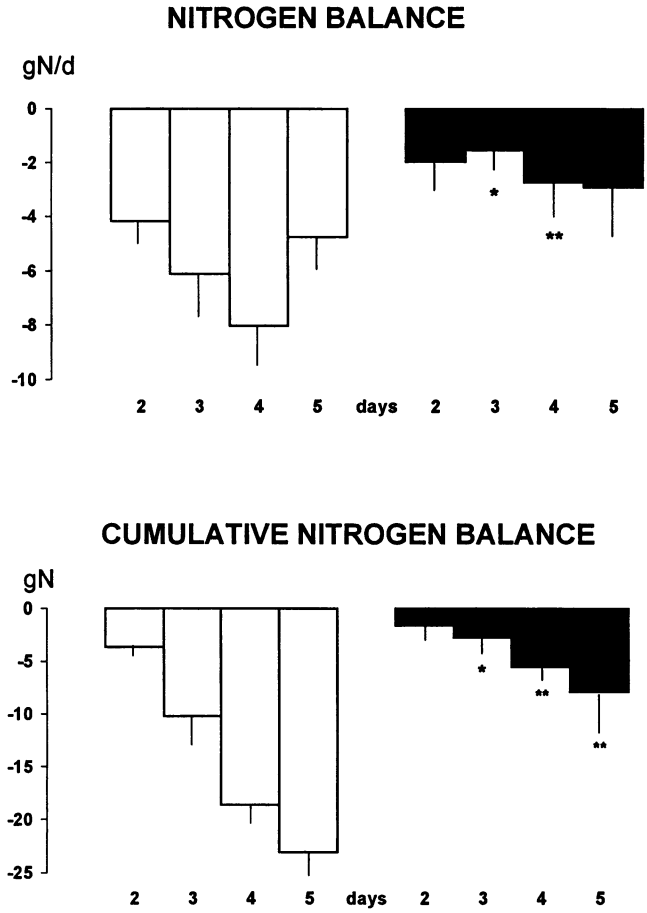

Figure 1. Day-to-day and cumulative nitrogen balance in patients receiving TPN supplemented with L-alanyl-L-glutamine (black columns) or conventional TPN (open columns). Mean ± standard error of the mean, significant between groups: *p < 0.05, **p < 0.01.

the mean. Using a statistical software program (SPSS; Chicago, IL), the one-tailed Mann-Whitney U test, the Wilcoxon test for paired comparisons, and Fisher's Exact test were used as appropriate. Any p values <0.05 were considered significant.

RESULTS

The peptide-containing solution had no side effects, and postoperative recovery was normal in all patients. Plasma protein concentrations and routine clinical biochemical indices did not differ appreciably between the groups.

On postoperative days 3 and 4, nitrogen balances were significantly better in the patients receiving Gln dipeptide (Fig. 1). Mean daily nitrogen balance over the 4-day study period with Ala-Gln was −2.31 ± 0.55 g, better than in the control group (−5.73 ± 0.69 g, $p < 0.001$). The cumulative nitrogen balances on the fifth postoperative day were −7.44 ± 4.04 and −23.04 ± 2.62 g nitrogen, respectively ($p < 0.01$) (see Fig. 1).

Ala-Gln was not detectable in plasma. Plasma free concentrations of glutamate and the constituent amino acids did not differ between the test and the control group (Table 2). The number of lymphocytes declined in the control group on the third postoperative day. It remained low in the control group, whereas normal values were found on days 3 and 6 in patients receiving the dipeptide (see Table 2). Cys-LT concentration in isolated PMNs revealed an immediate drop in both groups; the concentration was restored with Ala-Gln on day 6 but further decreased in the control group (Fig. 2).

The mean length of stay was 21.7 ± 2.8 days in the control group, well comparable to that in the historical controls (22.1 ± 1.54). In patients receiving the dipeptide, hospitalization was considerably shorter (15.5 ± 0.72; $p < 0.05$).

DISCUSSION

Depletion of Gln stores might lead to severe complications, such as infection, poor wound healing, impaired immunity, increased intestinal permeability, and finally multiple organ failure.[16,17] Recently, several clinical studies have shown benefits of specialized feedings enriched with Gln or Gln dipeptides in nutrition support.[18,19] Improved nitrogen retention and maintenance of intracellular Gln concentrations were observed simultaneously with

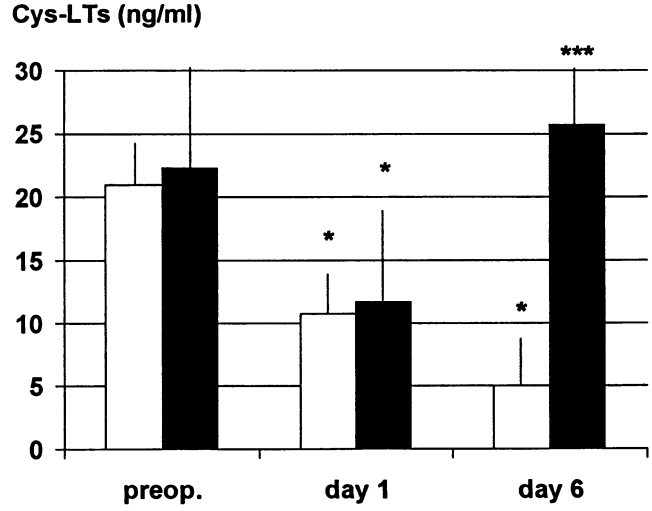

Figure 2. Generation of cysteinyl-leukotrienes (sum of LTC4, LTD4, LTE4) from human polymorphonuclear neutrophil granulocytes after stimulation with Ca-ionophore A23187 (5 μM). Patients receiving TPN supplemented with L-alanyl-L-glutamine (n = 5; black columns) or conventional TPN (n = 5; open columns). Mean ± standard error of the mean, significant between groups: ***p < 0.001; significant with preoperative day: *p < 0.05.

enhanced muscle protein synthesis. Preserved intestinal permeability and absorption capacity were reported in severely ill patients receiving Gln dipeptide-supplemented TPN, as well as enhanced lymphocyte recovery, shortened hospital stay, and markedly reduced hospital cost, after bone marrow transplantation (BMT).[19,20]

Infusion of the Ala-Gln dipeptide solution was free of any side effects, no complaints were noted, and postoperative recovery was normal in all patients. There is a reasonable concern that elevation of blood glutamic acid concentration may occur with Ala-Gln supplementation and thus lead to neural toxicity. We found no increase in circulating glutamic acid levels during this study. Our results are in agreement with previous studies in adult patients[9,21,22] and in premature infants.[23,24] Similar observations showing a very poor *in vivo* conversion of Gln to glutamic acid have been made previously.[25,26] Similarly, the "carrier" amino acid alanine did not accumulate in plasma, and the levels were within the normal range throughout the study.

In this study, we were able to confirm the beneficial effects of Gln dipeptide-supplemented TPN on nitrogen economy (see Fig. 1), maintenance of plasma Gln concentration, lymphocyte recovery (see Table 2), and hospital stay. Patients in the control group lost slightly less than 6 g of nitrogen, or about 36 g of protein daily, well within the range of previous results in similar patients.[27–29] Administration of the Gln dipeptide diminished this loss considerably to yield only 14 g of protein a day, which concurs with the value after major surgery and dipeptide supplementation.[9] This would mean a saving of about 600 g of muscle mass over the 4-day postoperative period.

This extent of protein saving is about the same as achieved with combined therapy with free Gln, growth hormone, and special diet in short bowel patients[30] and exceeds that attained with free Gln in BMT patients,[21] in surgical patients with a combination of TPN and growth hormone,[31] or in patients given synthetic Gln dipeptide.[9] Indeed, the amount of nitrogen lost in this study is comparable to that in the report by Stehle et al.[9] However, comparing the nitrogen loss in the control patients in both studies, our controls showed more negative values. These results suggest that our patients are more catabolic. This is why the protein-saving effect of the Gln dipeptide supplementation was more pronounced in this study.

The nitrogen retained exceeds the quantity of nitrogen provided by Gln. This observation confirms the proposed anabolic effects of Gln and underlines the claim that Gln acts as a conditionally essential amino acid. Recently, cellular hydration has been proposed as an important determinant of protein catabolism. Indeed, cell swelling acts as a potent protein-anabolic signal, whereas cell shrinkage is protein-catabolic. Gln plays an important role in this process and leads to cell swelling.[32] It is well conceivable that the provision of Gln in the catabolic state stimulates intracellular anabolic processes and thereby improves whole body nitrogen balance. A reduction of the inflammatory stress response to an elective operation by Gln is unlikely because Gln has evident immunostimulatory effects. Indeed, there are numerous reports emphasizing the immunostimulatory role of supplemental Gln.[7,18] In recent reports, Gln supplementation was associated with increased counts of circulating total lymphocytes and enhanced T-cell lymphocyte synthesis compared with Gln-free TPN.[7,21,33] Accordingly, Gln dipeptide supplementation in the present surgical patients maintained the total circulating lymphocyte count, in contrast to the profound decline (20%) observed in the control group (see Table 2). Importantly, no effects of Gln dipeptide supplementation were observed in total leukocyte or neutrophil number, suggesting that therapeutic Gln predominantly influences lymphocyte metabolism.[7,21,33]

A novel finding in the present work is the striking influence of supplemental Gln on cys-LT metabolism (see Fig. 2). Cys-LTs are potent lipid mediators and contain the antioxidant glutathione molecule, or a part of the glutathione molecule. It is emphasized repeatedly that diminished release of lipid mediators, especially those of cys-LTs, is accompanied by an attenuated endogenous host defense.[34] The fact that supplemental Gln normalized cys-LT concentration might strongly support its postulated essential role in promoting immune response during catabolic stress.

Hospital stay after surgery was 6.2 days shorter in the Gln-supplemented group. Hospital stay ended when the patient was no longer receiving acute medical therapy and could safely be discharged to home without additional nursing care. The discharge was ordered by the attending surgeon. Although no major complications were observed in the patients studied, patients receiving the Gln dipeptide-supplemented TPN began oral feeding 1.8 days earlier than controls; this difference, however, did not reach statistical significance.

Although not assessed by protocol, an intensive review of the nursing notes revealed obvious improvements in mood and general well-being in the Gln dipeptide-supplemented patients. Improved mood has been described before in patients receiving intravenous Gln.[35] Future studies evaluating the beneficial effects of Gln might include an assessment of mood and well-being of the patients.

The decreased length of hospitalization observed in the present study agrees completely with studies of BMT patients[21,22] (7 and 6 days, respectively). This reduction of hospital stay markedly diminished hospital costs, primarily as a function of reduced charges for room and board.[36] A decreased length of hospital stay of the magnitude seen in our study and the studies cited above has significant implications for patient care and economics.

However, a distinction between surgical patients in the

present study and BMT patients should be made. Indeed, BMT patients are probably the most suitable candidates for Gln supplementation. They are immunosuppressed, their gastrointestinal function is attenuated, and their antioxidative capacity is decreased (glutathione depletion). Certainly, exogenous Gln infused in excessive amounts ($0.54\ g\ kg^{-1}d^{-1}$) exerts a beneficial effect on each of these components. Surgical patients, as reported in our study, may need considerably less Gln, chiefly to counteract intracellular Gln depletion and to satisfy the increased demand for metabolic fuel of the intestine and immune cells. According to previous calculations, the required amount of Gln in similar patients corresponds to about 12 g of exogenous Gln or 20 g of dipeptides per day.[9]

This line of reasoning would imply that there are distinct priorities concerning Gln use during stress. The immune system should receive the first preference. The tentative requirement may be 2 to 6 g per day, depending on the severity of the condition. The second priority might be the increased demand of the intestinal tract and would require about 10 to 20 g Gln per day. The third priority might be given to the replenishment of the intracellular Gln pool. During catabolic stress, the estimated Gln consumption of the intracellular pool is 6 to 12 g. Considering a muscle Gln efflux of 8 to 14 g of Gln per day, the daily additional requirement can be estimated to yield approximately 12 g per day in surgical trauma and approximately 25 g per day in severe trauma and infection.

It is assumed that patients suffering from catabolic stress have a decreased antioxidative capacity, moderate during surgical trauma and excessive in severe trauma and infection.[37] In recent experimental studies, Gln supplementation preserved hepatic glutathione and increased tissue concentrations.[38,39] In another report, combined therapy with vitamin E and Gln was successful in the treatment of severe glutathione depletion-induced venoocclusive disease of the liver after BMT.[40] It is thus conceivable that Ala-Gln supplementation counteracts free radical-induced cellular injury by contributing to replenishment of depleted glutathione stores, certainly minute in surgical patients but considerable during severe injury and infection. Indeed, these protective mechanisms, combined with benefits to the immune system,[7,41] may play a major role in influencing morbidity and outcome.

In accordance with other investigators,[42,43] we believe that omission of Gln from conventional TPN and its subsequent supplementation should be considered as a replacement of a deficiency rather than a supplementation. It might thus be conceivable that the beneficial effects observed with Gln nutrition result simply from the correction of disadvantages produced by an inadequacy of conventional amino acid solutions. The availability of stable Gln dipeptide-containing preparations will certainly facilitate Gln nutrition in the routine clinical setting.

In conclusion, this paper is only one of a growing number of similar reports suggesting that administration of parenteral dipeptide is associated with obvious improvements in the clinical status of patients suffering from catabolic stress, and especially during critical illness. In a current double-blind randomized study, Gln-supplemented TPN significantly improved survival,[42] indicating that early Gln dipeptide-containing TPN, when used as a therapeutic measure, is beneficial after trauma and severe illness.

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