Comparison of Plasma Amino Acid Concentrations in End-stage Renal Disease Patients on Hemodialysis and Peritoneal Dialysis.

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Objectives: Recent reports have suggested that patients treated by CAPD have a relatively increased risk of death compared to patients undergoing HD, although the cause of this discrepancy is poorly understood. Protein malnutrition is an important risk factor in ESRD. Also, amino acid concentrations, for which the physiological function differs from that of protein, may be an independent risk factor in ESRD.

There is no doubt concerning the prevalence of low amino acid levels in both HD and CAPD patients. But the difference in plasma amino acid levels between these two groups has not been well defined. The purpose of this study is to compare plasma amino acid levels between patients with ESRD on HD and CAPD.

Methods: A cross sectional study of overnight fasting plasma amino acid concentrations was performed on 12 CAPD and 45 HD patients with ESRD, matched by age, sex and body mass index. The levels of individual plasma amino acid and TAA, EAA, NEAA and BCAA were compared for the HD and CAPD groups. In order to measure losses during HD and CAPD, amino acid and protein concentrations were measured from 10 dialysates obtained from 10 HD patients and 12 peritoneal dialysis solutions from 12 CAPD patients.

Results: All of the measured amino acid concentrations were found to be lower in the CAPD group compared to the HD group. Furthermore, the levels of TAA (2017.3±781.1 vs. 903.3±316.1 \(\mu\) mol/L), EAA (1201.8±492.6 vs. 567.6±223.2 \(\mu\) mol/L), NEAA (815.5±386.6 vs. 335.7±100.2 \(\mu\) mol/L), and BCAA (315.0±146.0 vs. 145.2±65.0 \(\mu\) mol/L) were all lower in the CAPD group than in the HD group. The protein loss was 2.0±0.2 g/L in the peritoneal dialysate but was not detectable in the hemodialysates. TAA loss over a one week period was about 61.8±13.0 mmole for the HD group and 38.0±13.0 mmole for the CAPD group.

Conclusions: Our results show that amino acid concentrations are lower in ESRD patients on CAPD than on HD. It seems likely that protein loss in the peritoneal dialysate is a contributing factor to lowered plasma amino acid concentrations in ESRD patients on CAPD than on HD. We believe that the lowered amino acid concentrations observed in CAPD patients may worsen the clinical outcome compared to HD patients.

Key Words: Amino Acid, CAPD, Hemodialysis, End stage renal disease
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derable amount of amino acid and/or protein loss during replacement therapy, and the amount of amino acid loss varies depending on the type of dialysis. The average loss of free amino acids in the dialysis fluid has been reported to be 5-8 g/dialysis during HD, and 1.2-3.4 g/24 hr during CAPD\(^3\)\(^-\)\(^5\). Substantial loss of protein in the dialysate, which accelerates the decline of plasma amino acid concentrations, is a major drawback for CAPD which is not present for HD.

CAPD treatment, with its basic differences from HD in terms of small and large molecule dialysis profiles, continuous 24-hour-a-day blood purification and cardiovascular and blood chemistry stability may be the preferred replacement therapy for ESRD\(^6\). Since the introduction of CAPD, nephrologists have been questioning the ability of the method to achieve the same results as HD. But, clinical and ethical considerations, including the right of patients to select their preferred dialysis treatment, make such an evaluation impossible in prospective, unbiased studies.

Most early comparative studies failed to show significant differences in overall patient survival between CAPD and HD\(^1\)\(^-\)\(^2\). However, all of these studies were retrospective and limited by the lack of quality case-mix adjustment. Recently, a report appeared suggesting that patients treated by PD had a relatively increased risk of death compared with patients undergoing HD\(^13\). The United States Renal Data System\(^14\) also reported that CAPD patients had a 19% higher mortality rate compared to those receiving HD. The cause of this discrepancy in mortality rates is poorly understood.

The concentration of plasma amino acids reflects disturbances in whole-body protein and amino acid metabolism, even though plasma amino acids constitute only a small portion of the body's free amino acid pool\(^3\). Differences in the structure of amino acids, and amino acid body requirements for amino acids, suggest that individual amino acids may have organ-specific metabolic and pharmacological functions\(^5\). Protein malnutrition is an important risk factor in ESRD. Also, plasma amino acid concentrations for which the physiological function differs from that of protein, may be an independent risk factor in ESRD. Much recent data support the concept that specific nutrients have the capacity to affect clinical outcome\(^15\), independent of their general nutritional effects\(^6\). In this regard, further research is necessary to understand the optimal balance required for each amino acid to support immune, gut and anabolic functions which may influence the mortality rate in patients with ESRD.

There is no doubt about the existence of low amino acid levels in both HD and CAPD patients. However, the difference in plasma amino acid levels between these two groups has not been quantified. The purpose of this study is to compare the plasma amino acid concentrations between patients with ESRD on HD and CAPD matched by age, sex and body mass index.

**MATERIAL AND METHODS**

Patients (Table 1) : 57 ESRD patients who were maintained on CAPD or HD at Soonchunhyang University Chunan Hospital, South Korea, and 30 healthy volunteers (control group) were enrolled in this study. Of the 57 ESRD patients, 12 patients (6 male and 6 female), aged between 40-62 years, were on CAPD (CAPD group) and 45 patients (23 male and 22 female), aged between 31-60 years, were on HD (HD group). All of the HD patients were on regular hemodialysis, 8-12 hours per week using a cellulose acetate hollow fiber (Table 2) and a dialysate characterised in Table 3. Kt/V urea was 0.9-1.2 retrospectively.

The duration of dialysis was 26.0±12.3 months in the CAPD group and 54.1±31.6 months in the HD group. The underlying diseases of the HD group were chronic
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Table 2. Characteristics of the Hemodialyzer

| Membrane       | Cellulose acetate |
|----------------|-------------------|
| Manufacturer   | Baxter            |
| Surface area   | 1.10m² (CA 110)   |
| Wall thickness | 15 Å              |
| Priming volume | 80 ml             |
| Pore size      | 15-35 Å           |
| Ultrafiltration rate | 4.3 ml/min/mmHg |
| Blood flow     | 200-250 ml/min    |
| Dialysate flow | 500 ml/min        |

glomerulonephritis in 20 cases, hypertension in 10 cases, polycystic kidney disease in 3 cases and unknown in 12 cases. Underlying diseases of the CAPD group were chronic glomerulonephritis in 9 cases and hypertension in 3 cases. The control group consisted of 30 healthy volunteers (15 male and 15 female), aged between 25-65 years (mean ± SD: 45 ± 11.5). Routine laboratory tests indicated that serum creatinine and blood glucose levels were normal. The mean height was 161.1 ± 7.6 cm in the HD group, 160.1 ± 6.6 cm in the CAPD group, and 163.3 ± 5.5 cm in the control group.

The mean body weight was 49.7 ± 8.1 kg in the HD group, 50.7 ± 9.9 kg in the CAPD group, and 56.5 ± 9.5 kg in the control group. The mean body mass index was 19.1 ± 2.2 in the HD group, 19.7 ± 2.5 in the CAPD group, and 19.8 ± 7.8 in the control group. Serum albumin and cholesterol levels are summarized in Table 1.

METHODS

A cross-sectional study of overnight fasting plasma amino acid concentrations was performed on fifty-seven patients with ESRD. The levels of individual plasma amino acid and total amino acids (TAA), essential amino acids (EAA), non-essential amino acids (NEAA) and branched chain amino acids (BCAA) were compared between HD and CAPD groups. In order to measure the amount of amino acid and/or protein loss during HD and CAPD, amino acid and protein levels were measured in 10 dialysates obtained from 10 HD patients and 12 peritoneal dialysis solutions from 12 DAPD patients. Efferent dialysate fluid was collected throughout dialysis. The dialysate flow rate, blood flow rate, and total volume of ultrafiltration were 500 ml/min, 200-250 ml/min and 2-3 liter respectively.

Dialysate samplings from CAPD patients: All of the CAPD patients were instructed to have a regular supper composed of more than half a bowl of rice with approximately 50g of cooked meat or fish. Peritoneal dialysate (2.5% Dianeal, 2L) was infused at 23:00-24:00 and drained at 7:00-8:00 the next morning. The volume of dialysate was measured by weighing the bag and subtracting the weight of the empty bag. The drained volume of the peritoneal dialysate was 2120 ± 170 ml. At the end of the draining, venous blood samples were taken for amino acid assay and blood chemistry study. The dialysate to plasma ratio of urea was 0.95-1.0 retrospectively.

AMINO ACID ANALYSIS

The proteins were separated by a centrifugal filter (Ultrafree-MC filter, nominal molecular weight limit: 80,000, Millipore, USA). 20 μl of plasma and standard amino acids were dried in sample tubes under vacuum (supplied by Waters). Derivatization of amino acids was done with 20 μl of a derivatizing solution (7:1:1:1 mixture of methyl alcohol, H₂O, triethylamine, phenylisothiocyanate) for 10 minutes. Amino acids were analyzed by a reverse phase HPLC, performed by the PICO-TOU AMINO ACID ANALYSIS Column (MILLIPORE CO.).

STATISTICS

Results are expressed as mean ± 1 SD unless otherwise specified. Statistical comparisons used the unpaired t-test, the Mann-Whitney U test and linear regression.

Table 3. Composition of the Dialysate for Hemodialysis and Peritoneal Dialysis.

|                      | HD    | PD    |
|----------------------|-------|-------|
| Sodium(mEq/L)        | 140.0 | 132.0 |
| Potassium(mEq/L)     | 2.6   | -     |
| Calcium(mEq/L)       | 3.5   | 3.5   |
| Magnesium(mEq/L)     | 1.5   | 0.5   |
| Chloride(mEq/L)      | 111.0 | 96.0  |
| Acetate(mEq/L)       | 36.6  | -     |
| Lactate(mEq/L)       | -     | 40.0  |
| Glucose(g/L)         | 2.5   | 2.5   |
| Osmolarity(mosmol/L) | 305.3 | 396.0 |

Manufacturer:
HD: Green Cross CO. (HDSol-3), Korea
CAPD: Baxter, Dianeal (PD-2 peritoneal Dialysis Solution)
Table 4. Comparison of Amino acid Concentrations of the Plasma and Peritoneal Dialysis Solution in the PD groups

| Amino acids     | Peritosol | Plasma    | P value |
|-----------------|-----------|-----------|---------|
| Aspartate       | 97.8±22.6 | 36.5±20.1 | 0.0001  |
| Glutamate       | 17.5±10.4 | 22.0±13.2 | -       |
| Serine          | 30.3±10.4 | 28.8±9.2  | -       |
| Glycine         | 172.2±43.8| 121.4±41.3| 0.01    |
| Histidine       | 203.3±6.3 | 23.0±8.5  | -       |
| Arginine        | 123.8±35.5| 43.4±19.6 | 0.001   |
| Threonine       | 42.9±16.7 | 32.1±12.6 | -       |
| Alanine         | 262.0±46.0| 203.3±102.2| -      |
| Proline         | 193.8±44.2| 84.6±31.6 | 0.0016  |
| Tyrosine        | 22.0±4.0  | 18.3±8.9  | -       |
| Valine          | 86.8±31.3 | 76.1±34.6 | -       |
| Methionine      | 26.3±7.9  | 10.0±3.7  | 0.0001  |
| Isoleucine      | 31.4±4.9  | 26.4±12.9 | -       |
| Leucine         | 44.4±5.0  | 42.7±18.5 | -       |
| Phenylalanine   | 53.4±15.1 | 24.3±11.4 | 0.0001  |
| Tryptophan      | 26.0±3.5  | 57.1±19.1 | 0.0001  |
| Lysine          | 93.4±16.2 | 53.4±20.3 | 0.0001  |

Amino acid concentrations: Among 20 amino acids, 17 amino acids were measured, including 10 EAA (valine, leucine, isoleucine, threonine, methionine, lysine, phenylalanine, tryptophan, histidine, arginine) and 7 NEAA (serine, glycine, alanine, proline, tyrosine, aspartate, glutamate).

A. Plasma amino acid concentrations in the control group and HD group (Fig. 1). The concentrations of aspartate (8±4 vs. 75±61 μmol/L) and proline (234±81 vs. 168±36 μmol/L) were higher in the HD group than in the control group. Serine (67±26 vs. 87±42 μmol/L), tyrosine (36±19 vs. 52±22 μmol/L), valine (164±74 vs. 233±107 μmol/L), isoleucine (59±30 vs. 79±39 μmol/L) and leucine (93±48 vs. 137±68 μmol/L) were lower in the HD group than in the control group. BCAl (447±210 vs. 355±146 μmol/L) and EAA (1046±421 vs. 898±369 μmol/L) were lower in the ESRD group but there was no difference between NEAA (1003±371 vs. 1120±445 μmol/L) and TAA (2060±778 vs. 2070±808 μmol/L) for the control and HD group.

B. Comparison of plasma amino acid levels between the CAPD and HD group (Fig. 1): All of the amino acid concentrations were higher in the patients on HD than on CAPD as follows: aspartate (75±61 vs. 36.5±20.4 μmol/L), glutamate (62.5±44.8 vs. 22.0±13.2 μmol/L), serine (66.6±26.2 vs. 28.8±9.2 μmol/L), glycine (277.0±132.9 vs. 12.14±41.3 μmol/L), histidine (68.7±36.2 vs. 23.0±8.5 μmol/L), arginine (76.0±36.5 vs. 43.4±19.6 μmol/L), threonine (93.0±45.3 vs. 32.1±12.6 μmol/L), alanine (568.6±169.7 vs. 203.3±102.2 μmol/L), proline (234.0±81.4...
were higher in the dialysate than in the plasma (p < 0.001).

The concentrations of tryptophan were higher in the plasma (57.1 ± 19.7 μ mole/L) than in the dialysate (26.0 ± 3.5 mmole/L) (p < 0.001).

The levels of TAA (903.3 ± 146.0 μ mole/L), EAA (567.6 ± 223.2 μ mole/L), and NEAA (335.7 ± 100.2 μ mole/L) in the HD group were higher than those in the plasma (p = 0.0001). The levels of BCAA in the plasma (145.2 ± 65.0 μ mole/L) showed no significant difference compared to that in the dialysate (62.6 ± 27.7 μ mole/L).

The amino acid concentrations in the dialysate and those in the plasma were of three types. In type 1: most amino acid concentrations in the plasma and dialysate were very similar (Fig. 4). In type 2: most amino acid concentrations in the plasma and dialysate were higher in the plasma than in the dialysate (p = 0.0001). In type 3: Some amino acid concentrations were higher in the dialysate than in the plasma (Fig. 5).

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C. Comparison of protein concentrations in hemodialysate and peritoneal dialysate: The loss of protein in peritoneal dialysis solution was 2.0 ± 0.2 g/L of peritoneal dialysate but no loss was detected in hemodialysates.

D. Comparison of plasma and dialysate amino acid concentrations in patients on CAPD (Fig. 2): The concentrations of aspartate (36.1 ± 19.0 vs. 8.5 ± 8.9 μ mole/L), tyrosine (26.0 ± 46.0 μ mole/L), and lysine (53.4 ± 16.2 μ mole/L) were higher in the dialysate than in the plasma (p < 0.001).

The concentrations of glutamate (24.3 ± 14.3 vs. 17.5 ± 14.0 μ mole/L), serine (28.4 ± 9.2 vs. 30.3 ± 10.4 μ mole/L), histidine (25.2 ± 8.5 vs. 20.3 ± 6.3 μ mole/L), threonine (23.2 ± 12.6 vs. 42.9 ± 16.7 μ mole/L), alanine (203.3 ± 102.2 vs. 262.0 ± 46.0 μ mole/L), tyrosine (23.0 ± 8.9 vs. 22.0 ± 4.0 μ mole/L), and lysine (53.4 ± 16.2 μ mole/L) showed no difference between the dialysate and the plasma.

The concentration of tryptophan was higher in the plasma (57.1 ± 19.7 μ mole/L) than in the dialysate (26.0 ± 3.5 mmole/L) (p < 0.001).

The levels of TAA (003.3 ± 161.1 vs. 1343.9 ± 144.1 μ mole/L), EAA (567.6 ± 223.2 vs. 757.3 ± 60.0 μ mole/L), and NEAA (335.7 ± 100.2 vs. 586.6 ± 98.4 μ mole/L) were higher in the plasma than in the dialysate (p = 0.0001). The levels of BCAA in the plasma (145.2 ± 65.0 μ mole/L) showed no significant difference compared to that in the dialysate (62.6 ± 27.7 μ mole/L).

The amino acid concentrations in the dialysate and those in the plasma were of three types. In type 1: most amino acid concentrations in the plasma and dialysate were very similar (Fig. 4). In type 2: most amino acid concentrations were higher in the dialysate than in the plasma (Fig. 3). In type 3: Some amino acid concentrations were higher in the dialysate than in the plasma (Fig. 5).
4.4 ± 1.4 μ mol/L, valine; 25.2 ± 4.3 μ mol/L, methionine; 3.2 ± 0.5 μ mol/L, isoleucine; 10.7 ± 1.7 μ mol/L, leucine; 14.6 ± 3.6 μ mol/L, phenylalanine; 8.4 ± 1.1 μ mol/L, tryptophan; 9.5 ± 2.8 μ mol/L, lysine; 11.5 ± 3.1 μ mol/L, TAA; 257.3 ± 49.1 μ mol/L, EAA; 112.0 ± 22.4 μ mol/L, NEAA; 145.3 ± 27.7 μ mol/L.

**DISCUSSION**

In our study, plasma amino acid concentrations were lower in the CAPD group than in the HD group. In agreement with previous reports (3-5), amino acid losses were considerable during dialysis. But amino acid loss during a given time was two to three times greater in the HD group than in the CAPD group. Therefore, lowered amino acid concentrations observed in the CAPD group could not be explained by amino acid loss during dialysis.

The mechanism which induces plasma amino acid abnormalities in ESRD is not linked to a single cause but encompasses a multitude of factors. Many patients experience anorexia, nausea, vomiting caused by intercurrent illness, inadequate dialysis or medication, and a moderate amount of amino acids are lost during each hemodialysis (3-5). In addition, altered lipid metabolism (19), metabolic acidosis (20, 21), decreased muscle mass (22), and insulin resistance (23, 24) may also be closely related to the mechanism inducing plasma amino acid abnormalities in ESRD.

It is not known whether lipid metabolism, metabolic acidosis and insulin resistance differ between patients on CAPD and HD. In order to minimize the effect of diet on the plasma amino acid concentrations, we instructed the patients to have for supper, the evening before the study day, at least half a bowl of rice as the main dish and about 50g of meat and/or fish with some vegetables. Also, there was no difference in the levels of serum cholesterol and albumin. Therefore, a difference in the diet content does not seem to be a contributing factor to the discrepancy in amino acid concentrations between the
CAPD and HD groups.

Kt/V urea was 0.9-1.2 in the HD group, retrospectively. However, we could not match the adequacy of dialysis between the CAPD and HD groups because the dialysis adequacy criteria were not measured for the CAPD group.

There was no difference in the anthropometric measurements between the CAPD and HD groups, suggesting that any difference in the muscle mass does not influence the discrepancy of amino acid concentrations between the two groups.

The BCAA levels were lower in the HD group than in the control group. But there was no difference in the concentrations of the TAA, EAA, and NEAA between the control and HD groups. It is known that BCAA are decarboxylated by the same enzymes, and available evidence indicates that the decrease cannot be accounted for by excessive uptake by splanchnic tissue in ESRD. Compared to the control group, the concentrations of serine, tyrosine, valine, isoleucine, leucine, and lysine were lower in the HD group, but the concentrations of aspartate, arginine, and proline were higher. The concentrations of glutamate, glycine, histidine, threonine, alanine, methionine, phenylalanine, and tryptophan were similar in the control and HD groups. In contrast to a previous report, which showed lowered threonine and higher glycine concentrations in the HD group, no difference in the concentrations between the control and HD group were found. It was both unexpected and interesting to find that all of the plasma amino acid concentrations were significantly lower in the CAPD patients than in the HD patients in our study.

The fact that the amino acid loss during dialysis was greater in the HD group than in the CAPD group, together with the observation of protein loss only in the peritoneal dialysate, indicates that the lowered amino acid concentrations in the patients on PD seem mainly due to protein loss through the peritoneal dialysate.

Investigation of the mechanisms for amino acid loss during peritoneal dialysis could not be performed through this study. But we were able to find that the concentrations of all the plasma amino acids were similar to those in the peritoneal dialysate while, in other cases, some or all of the amino acid concentrations were higher in the peritoneal dialysate than in the plasma. These findings suggest that the mechanism for amino acid loss through peritoneal dialysis differs from case to case.

In conclusion, our results suggest that amino acid concentrations are lower in patients with ESRD on CAPD than on HD. This seems to be due to protein loss through the peritoneal dialysate. We believe that lowered amino acid concentration, frequently observed in the ESRD patients on CAPD, may worsen the clinical outcome for CAPD patients compared to HD patients. Our speculation may be reinforced by the new concept of the so-called "amino acid-based peritoneal dialysis solutions" recently described by other authors.

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