Comparison of Amino Acid Loss Between Constant Amino Acid Plus Dextrose Infusion and Sequential Dextrose Followed by Amino Acid Infusion During Hemodialysis: A Randomized Crossover Trial

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Abstract

Background: Increasing amino acid loss has been observed in patients receiving intradialytic parenteral nutrition (IDPN). There are two standard protocols for lipid-free formula-IDPN infusion: constant amino acid plus dextrose infusion and sequential dextrose followed by amino acid infusion. However, the difference in amino acid loss between the two infusion protocols has never been explored.

Methods: The present study is a randomized crossover trial performed on ten malnourished chronic hemodialysis patients. They were randomized to receive a constant or sequential infusion protocol. The crossover was performed one week later. Plasma and dialysate amino acid concentrations were determined before and after the hemodialysis session. The changes in blood pressure and capillary glucose concentrations during hemodialysis were also recorded.

Results: The average declines in plasma essential, non-essential, and total amino acid concentrations were comparable between the two infusion protocols. Substantially higher non-essential and total amino acid concentrations were observed in the dialysate from the constant infusion group. In the sequential infusion group, the average capillary glucose level was higher at the 2nd hour and lower at the 4th hour of hemodialysis, and two patients had hypotension.

Conclusion: Constant infusion of amino acid plus dextrose solution during hemodialysis resulted in a more significant loss of amino acids into dialysate than the sequential infusion of dextrose followed by amino acids.

Keywords: dialysis; ESKD; ESRD; kidney failure; malnutrition; protein-energy wasting; PEW

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การศึกษาแบบสุ่มและข้ามกลุ่มเพื่อเปรียบเทียบการสูญเสียกรดอะมิโนระหว่างการฟอกเลือดด้วยเครื่องไตเทียม ระหว่างวิธีการให้สารละลายกรดอะมิโนควบคู่กับเดกซ์โทรส และ การให้สารละลายกรดอะมิโนภายหลังการให้เดกซ์โทรส

ศรินภา อุปริมาตร์, ปรมัตถ์ ธิมาไชย, อุปถัมภ์ ศุภสินธุ์, บัญชา สถิระพจน์, อำนาจ ชัยประเสริฐ, เนาวนิตย์ นาทา, นฤตยา วโรทัย, พามิลา ทรรศนะวิภาส, พิชมณฐ์ อินกอง, ณรงค์ฤทธิ์ ศิริวัฒนสิทธิ์

แผนกโรคไต กองอายุรกรรม โรงพยาบาลพระมงกุฎเกล้าและวิทยาลัยแพทยศาสตร์พระมงกุฎเกล้า

บทคัดย่อ

บทนำ: ในผู้ป่วยที่ได้รับอาหารทางหลอดเลือดดำระหว่างการฟอกเลือดด้วยเครื่องไตเทียม พบว่ามีการสูญเสียกรดอะมิโนเพิ่มขึ้นทางน้ำยาฟอกเลือด ปัจจุบันมีวิธีมาตรฐาน 2 วิธี ในการให้อาหารทางหลอดเลือดดำสำหรับสูตรอาหารที่ไม่มีไขมัน ได้แก่ การให้กรดอะมิโนร่วมกับเดกซ์โทรสพร้อมกัน และการให้เดกซ์โทรสก่อนแล้วตามด้วยกรดอะมิโน อย่างไรก็ตามยังไม่เคยมีการศึกษาถึงความแตกต่างของการสูญเสียกรดอะมิโนทางน้ำยาฟอกเลือด

ระเบียบวิธีวิจัย: การศึกษานี้เป็นการศึกษาแบบสุ่มและข้ามกลุ่มในผู้ป่วยจำนวน 10 คน ที่มีข้อบ่งชี้ของการให้อาหารเสริมทางหลอดเลือดดำ โดยผู้ป่วยจะได้รับการสุ่มเพื่อได้รับกรดอะมิโนควบคู่กับสารละลายเดกซ์โทรสพร้อมกัน หรือ ได้รับสารละลายเดกซ์โทรสก่อนแล้วตามด้วยกรดอะมิโน หลังจากนั้น 1 สัปดาห์จึงมีการสลับวิธีการให้ระหว่างทั้ง 2 กลุ่ม ผลลัพธ์ของการศึกษา คือ ความแตกต่างของความเข้มข้นของกรดอะมิโนในพลาสมาก่อนและหลังการฟอกเลือด และความเข้มข้นของกรดอะมิโนในน้ำยาฟอกเลือด นอกจากนี้ยังมีการเก็บข้อมูลความดันโลหิต และความเข้มข้นของกลูโคสระหว่างการฟอกเลือดด้วย

ผลการวิจัย: ไม่พบความแตกต่างกันของการลดลงของความเข้มข้นของกรดอะมิโนที่จำเป็น กรดอะมิโนที่ไม่จำเป็น และ กรดอะมิโนทั้งหมดในพลาสมาระหว่างทั้ง 2 วิธี อย่างไรพบว่ามีความเข้มข้นของกรดอะมิโนที่ไม่จำเป็น และกรดอะมิโนทั้งหมดในน้ำยาฟอกเลือดสูงกว่าในกลุ่มที่ได้รับกรดอะมิโนและเดกซ์โทรสพร้อมกัน ในกลุ่มที่ได้รับเดกซ์โทรสก่อนกรดอะมิโนพบว่ามีความเข้มข้นของน้ำตาลสูงกว่าในชั่วโมงที่ 2 และต่ำกว่าในชั่วโมงที่ 4 ของการฟอกเลือด และมีผู้ป่วย 2 คนมีความดันโลหิตต่ำ

สรุป: การให้อาหารเสริมทางหลอดเลือดดำโดยวิธีการให้กรดอะมิโนพร้อมกับเดกซ์โทรสระหว่างการฟอกเลือด อาจทำให้มีการสูญเสียกรดอะมิโนในน้ำยาฟอกเลือดมากกว่าการให้เดกซ์โทรสก่อนแล้วตามด้วยการให้กรดอะมิโน

คำสำคัญ: อาหารเสริมทางหลอดเลือด; ขาดอาหาร; ทุพโภชนาการ; ไตวาย; ไตเสื่อม; ฟอกไต

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Introduction

Protein-energy wasting (PEW) is a state of nutritional and metabolic derangements in patients with chronic kidney disease characterized by simultaneous loss of systemic body protein and energy stores.[1] Many contributing causes include increased resting energy expenditure, persistent inflammation, acidosis, multiple endocrine disorders, and the dialysis procedure.[2] Dialysis may contribute to PEW through infectious, inflammatory, and volume-related complications and the loss of nutrients such as protein and amino acids.[3] The previous study showed that the amount of amino acid lost into the dialysate during one dialysis session could range from 6 to 8 gm.[4] In the latter study that prescribed amino acid infusion during hemodialysis, the loss was as high as 28 ± 4 gm. Still, there was a net positive balance, and the plasma concentrations of amino acids increased.[5]

Regarding essential amino acids, branched-chain amino acids (BCAAs), including leucine, isoleucine, and valine, are nutritionally crucial as they cannot be synthesized endogenously and must be obtained through the diet. BCAAs typically decrease following hemodialysis and are essential for protein synthesis and regulating molecular pathways implicated in disease pathophysiology. [6] Decreased plasma BCAA levels, particularly valine, have been reported in chronic kidney disease[7-9], with implications for central and peripheral metabolic functions. [10-12] BCAA depletion during hemodialysis has been linked to fatigue, and normalization of plasma BCAA concentrations has shown improvements in protein metabolism, appetite, and nutritional status.[13]

An intradialytic parenteral nutrition (IDPN) regimen of glucose infusion is aimed at restoring glycogen supply in malnourished patients.[14] In addition, infused glucose may also help prevent the conversion of infused amino acids to energy by suppressing hepatic gluconeogenesis. Moreover, insulin release in response to glucose infusion can also enhance the cellular uptake of amino acids.[15] Glucose and insulin regulate the expression of numerous amino acid transporters in various tissues. Insulin signals rapidly induce the uptake of glucose and BCAAs into the muscle and tissues.[16] In the previous study, intravenous infusion of amino acids and glucose during hemodialysis helped prevent a fall in plasma amino acid and glucose concentrations. Only a slight increase in the losses of free amino acids into the dialysate was detected.[5]

In current clinical practice, the amino acid solution is usually infused during the last 60 to 90 minutes of hemodialysis. This infusion method may have disadvantages, such as undesirable high blood levels of amino acids, less efficient metabolic utilization, and possibly more significant loss during hemodialysis.[17] On the other hand, infusion of amino acid solution plus glucose throughout the hemodialysis session may have potential advantages, including preventing the depletion of amino acid and glucose pools throughout the dialysis session and lowering the risk of intradialytic hypotension from excessive ultrafiltration before the end of hemodialysis. There are two standard methods for lipid-free formula-IDPN infusion: constant amino acid plus dextrose infusion and sequential infusion of dextrose followed by amino acid. The difference in amino acid loss between the two infusion protocols has never been examined.

Materials and methods

Study design and ethics statement

This study was a randomized crossover trial of chronic hemodialysis patients at Phramongkutklao Hospital. Ethics approval was obtained from the Institute Review Board of the Ethics Committee of the Royal Thai Army Medical Department (Approval number R047h/65). This study was registered with the Thailand Clinical Trial Registry (TCTR20230317005). Informed consent was obtained from all patients.

Amino acid solution and infusion protocols

The composition of the amino acid solution is shown in **Table 1.** The two infusion protocols used in the present study were as follows: 1) constant infusion of both dextrose and amino acid solution from the beginning until the end of the hemodialysis session; 2) sequential infusion of dextrose from the beginning until 60-90 minutes before the end of the hemodialysis session followed by infusion of amino acid solution during the last 60-90 minutes of the hemodialysis session.

Table 1 Compositions of amino acid solution

Amino acids	Each 500 ml
L-leucine	7 g
L-isoleucine	4.5 g
L-valine	5 g
L-lysine acetate	3.55 g
(L-lysine equivalent)	2.53 g
L-threonine	1.75 g
L-tryptophan	1.25 g
L-methionine	1.5 g
L-phenylalanine	2.5 g
L-cysteine	0.5 g
L-tyrosine	0.25 g
L-arginine	2.25 g
L-histidine	1.75 g
L-alanine	1.25 g
L-proline	1.5 g
L-serine	1.5 g
L-aspartic acid	0.5 g
L-glutamic acid	0.5 g
Total free amino acids	36.025 g
Essential amino acids	26.025 g
Non-essential amino acids	10.00 g
Total nitrogen	5.00 g

Patients and randomization

The inclusion criteria were age >20 and receiving thrice-weekly maintenance hemodialysis. The exclusion criteria were as follows: 1) volume overload; 2) sepsis; 3) hypotension from a cardiac cause; 4) advanced malignancy; 5) advanced liver disease; 6) blood flow rate during hemodialysis <250 mL/min. A block of 4 randomization randomly assigned patients to either constant amino acid plus dextrose infusion or sequential dextrose followed by amino acid infusion. Five patients were randomized to the constant infusion protocol, and the other five were randomized to the sequential one. The two groups were crossed to the other infusion method one week later **(Figure 1)**.

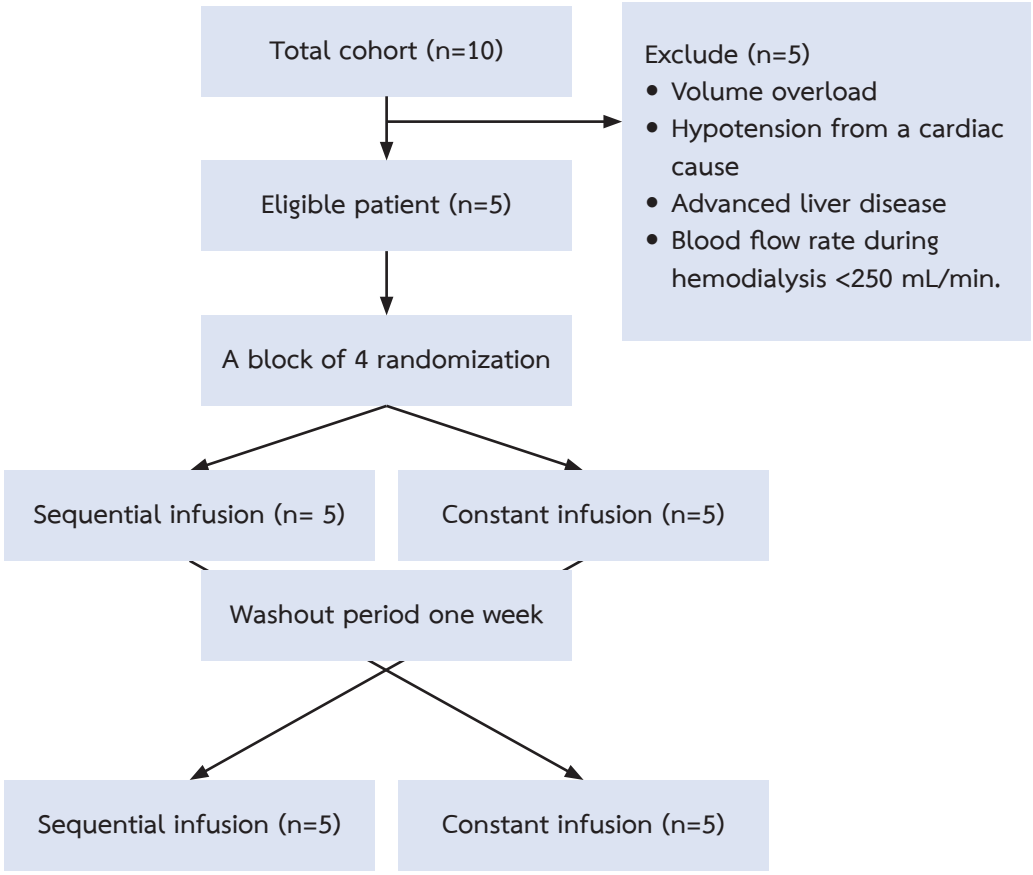

Figure 1 Study flow diagram

Outcomes

The outcomes of the present study were differences in the changes in plasma amino acid concentrations after hemodialysis and amino acid loss in dialysate between the two infusion protocols.

Determination of amino acid concentrations in plasma and dialysate

Plasma samples were obtained from the arterial bloodline before and after hemodialysis, and the dialysate was collected at the end of the hemodialysis to determine amino acid concentrations. Biofluid samples were prepared by denature technique. Most abundant proteins from human plasma were removed by crashing solvent using acetonitrile with a 1:1 ratio followed by centrifugation at 14,000 rpm for 10 minutes, yielding clear supernatant. The supernatant was then filtered through a 0.2 µm cellulose acetate syringe. The prepared supernatant was injected into a high-performance liquid chromatography system (model SHIMADZU Nexera LC-40 series).

Statistical analysis

Data are expressed as mean ± standard deviation or median (interquartile range). Differences between the two groups were analyzed using an unpaired T-test or Mann-Whitney U test. Differences within groups were analyzed using paired T-test, or Wilcoxon Signed Ranks test. Statistical significance was defined as a P-value <0.05.

Results

Baseline characteristics

Ten patients were enrolled in the study **(Table 2)**. The mean age was 63 years, and 50% were male. 60 % had hypertension, and 30% had type 2 diabetes. The mean pre-dialysis serum albumin and creatinine were 3.91 ± 0.49 g/dL and 7.9 ± 2.86 mg/dL, respectively.

Table 2 Baseline characteristics of all patients

Parameters	All participants (n=10)
Age, years	63 ± 15
Male	5 (50)
Body mass index, kg/m^2	23.14 ± 5.46
Underlying diseases • Type 2 diabetes mellitus • Hypertension • Heart disease • Cerebrovascular disease	 3 (30) 6 (60) 1 (10) 2 (20)
Medications • ACEI/ARBs • Beta-blockers • Diuretics • Calcium channel blockers • Statins	 3 (30) 6 (60) 4 (40) 3 (30) 5 (50)
Dialyzer • High flux dialyzer • Surface area 1.3 m^2 • Surface area 2.0 m^2 • Surface area 2.1 m^2	 10 (100) 2 (20) 6 (60) 2 (20)
Blood flow rate, mL/min	375 5 ± 4.01
Dialysate flow rate, mL/min	740 ± 126.49
Pre-dialysis systolic blood pressure, mmHg	141.8 ± 7.22
Pre-dialysis diastolic blood pressure, mmHg	70.6 ± 14.71
Pre-dialysis albumin, g/dL	3.91 ± 0.49
Pre-dialysis creatinine, mg/dL	7.9 ± 2.86

Data were presented by n; number (%, percentage), mean ± SD (standard deviation)

ACEI, Angiotensin-converting enzyme inhibitors; ARB, Angiotensin-receptor blocker; SD standard deviation

Changes in plasma amino acid concentrations

Median plasma amino acid concentrations are shown in Table 3. In the sequential infusion protocol, the average plasma essential amino acid concentration decreased substantially at the end of the dialysis session (7,223.56 vs. 5,281.44 mcg/mL, p-value 0.028). There was no significant change in the concentration of non-essential amino acids. In the constant infusion protocol, the average plasma essential amino acid concentration was also significantly lower at the end of the dialysis session (6,183.67 vs. 4,626.43 mcg/mL, p-value 0.022). There was no significant change in the concentration of non-essential amino acids. Between-group changes in essential, non-essential, and total amino acid concentrations were insignificant **(Figure 2)**.

Regarding individual amino acids, plasma valine and leucine levels increased substantially after hemodialysis in the sequential protocol, but between-group changes were not statistically significant **(Supplementary Tables 1 and 2).**

Table 3 Plasma amino acid concentrations pre- and post-dialysis between the two infusion protocols

Types of amino acids	Mean Difference (95% Confidence interval)		p-value
	Sequential infusion	Constant infusion	
Essential amino acids (mcg/mL)	-1,389.53 (-3,429.37, -418.96)	-1,484.33 (-2,484.7, -606.11)	0.821
Non-essential amino acids (mcg/mL)	-1,330.24 (-4,375.61, 1,583.98)	-1,372.22 (-4,647.27, -882.61)	0.705
Total amino acids (mcg/mL)	-3,211.45 (-6,485.29, 1,487.38)	-3,630.36 (-5,253.38, -2,104.91)	0.705

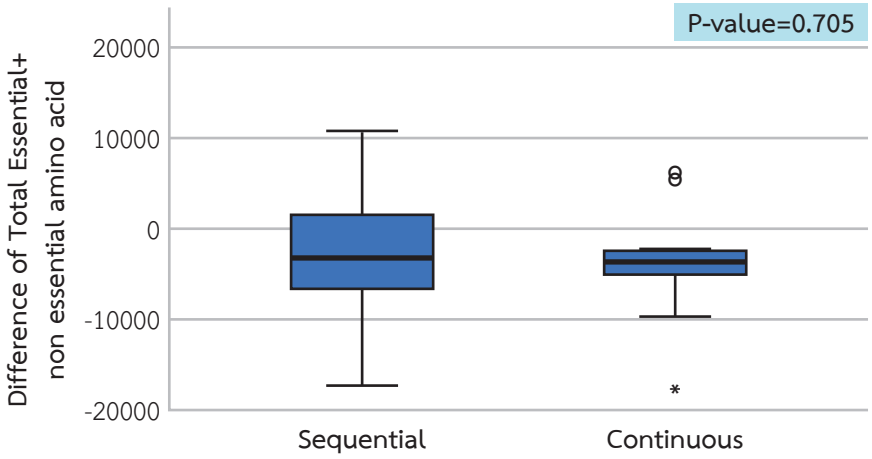

Figure 2 The changes in total plasma amino acid concentrations

Amino acid loss in dialysate

Dialysate amino acid concentrations were analyzed at the end of the hemodialysis session. The changes in dialysate amino acid concentrations are shown in **Table 4.** The loss of essential amino acids during hemodialysis was similar for both infusion protocols **(Figure 3)**. However, the losses of non-essential amino acids **(Figure 4)** and total amino acids **(Figure 5)** were substantially higher in the constant infusion protocol.

Changes in capillary blood glucose and blood pressure

The changes in capillary blood glucose and mean arterial blood pressure are shown in **Table 5**. In the sequential infusion protocol, capillary blood glucose rose at mid-dialysis and was higher than the constant infusion protocol. The mean capillary blood glucose declined at the end of hemodialysis and became lower than the constant infusion protocol. The mean arterial pressure at baseline, mid-dialysis, and the end of dialysis were comparable between the two infusion protocols. Intradialytic hypotension was observed in two patients in the sequential infusion protocol and none in the constant infusion protocol.

Table 4 The concentrations of amino acids in dialysate at the end of the hemodialysis session

Amino acids	Sequential infusion	Constant infusion	Mean Difference (95% Confidence interval)	p-value
Essential AAs (mcg/mL)	4,747.06 ± 540.11	4,621.11 ± 198.74	125.96 (-274.25, 526.16)	0.495
Non-essential AAs (mcg/mL)	5,056.36 ± 1,997.34	7,769.65 ± 2,571.06	-2,713.29 (-4,936.77, -489.81)	0.022*
Total AAs (mcg/mL)	9,803.42 ± 2,516.44	12,390.75 ± 2,684.09	-2,587.33 (-5,093.48, -81.18)	0.044*

Data were presented by mean ± SD (standard deviation)

AA, amino acids

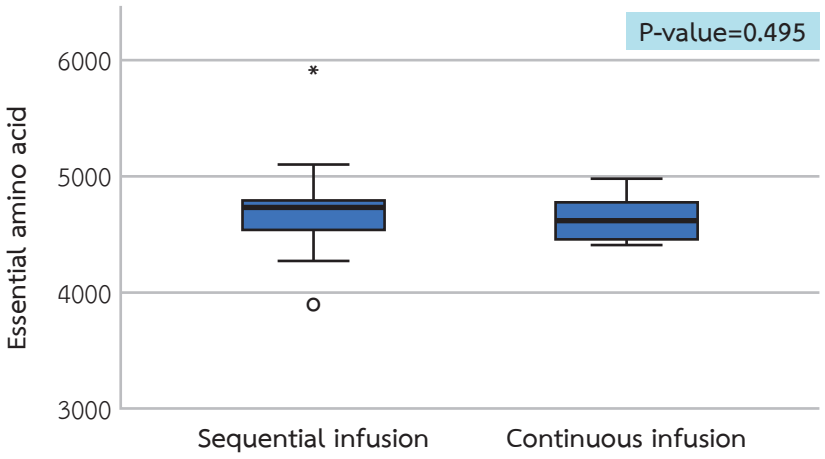

Figure 3 Essential amino acid concentrations in dialysate

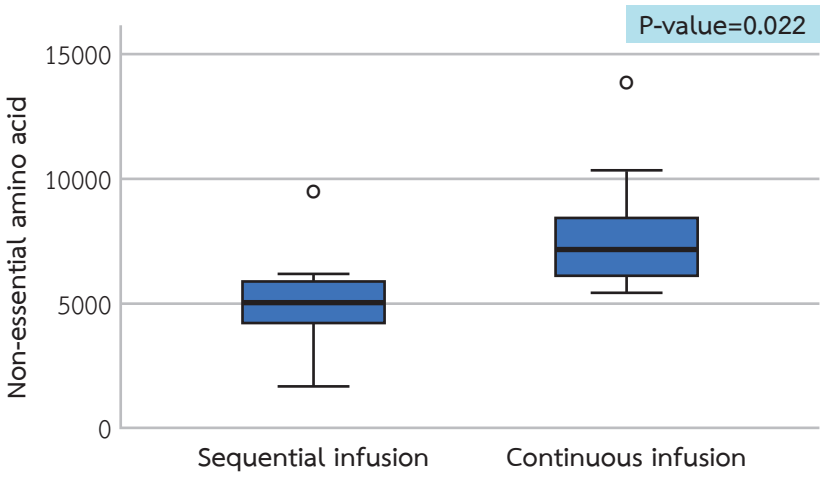

Figure 4 Non-essential amino acid concentrations in dialysate

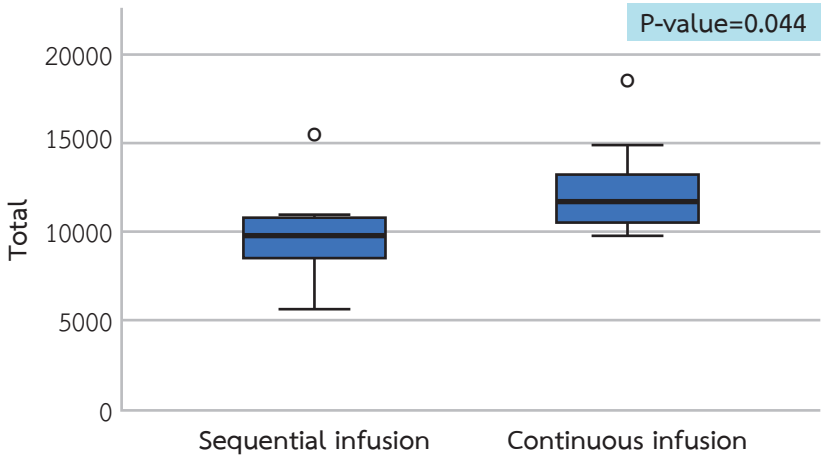

Figure 5 Total amino acid concentrations in dialysate

Table 5 Capillary blood glucose and blood pressure during a hemodialysis

Parameters	Sequential protocol Mean change	Constant protocol Mean change	p-value
Capillary blood glucose (mg/dL)			
Pre-dialysis	184.7 ± 84.75	183.7 ± 83.16	0.939
2 -hour	274.4 ± 52.54	229.9 ± 51.93	0.008*
4-hour	130.33 ± 43.62	191 ± 68.41	0.039*
Blood pressure (mmHg)			
Pre-MAP	96.93 ± 20.09	90.27 ± 12.39	0.575
MAP at 2-hour	92.33 ± 11.99	89.33 ± 5.66	0.333
MAP at 4-hour	91.73 ± 17.05	93.17 ± 13.69	0.878
Hypotension	2 (20)	0	1

Data were presented by n; number (%, percentage), mean ± SD (standard deviation)
MAP, mean arterial pressure

Discussion

The present study revealed a reduction in plasma amino acid levels post-hemodialysis in both infusion protocols, with no significant differences observed between the constant and sequential infusion groups concerning the decline in essential, non-essential, and total amino acid concentrations. However, the constant infusion group had a more pronounced loss of non-essential and total amino acids in the dialysate. Additionally, the sequential infusion group experienced a higher incidence of hypotensive episodes. The estimated amino acid loss in the constant infusion group was 12.39 g/L over a 4-hour hemodialysis session. Although the total dialysate volume was not recorded, elevated amino acid concentrations in the dialysate implied a more substantial loss in the constant infusion group. In the previous study[17], patients were given an infusion containing 39.5 g of amino acids and 200 g of d-glucose at a constant rate, which also revealed the loss of 12.6 ± 3.6 gm of amino acids, comparable to the present study. More significant loss

of amino acids into the dialysate in the constant infusion method might result from a longer period of high blood amino acid levels or less efficient metabolism of these nutrients.

Regarding amino acid quality, our study demonstrated no statistically significant difference in the mean change in plasma essential amino acid levels and dialysate amino acid concentrations between the constant and sequential infusion protocols. Both protocols exhibited comparable reductions in amino acid levels post-infusion. These findings suggest effective amino acid uptake with both protocols, given the positive amino acid input in malnourished patients. This contrasts with the previous report,[17] which indicated that infusate composition influenced plasma amino acid levels, showing increases in most amino acids except tyrosine and histidine. This underscores the importance of carefully selecting infusate composition to optimize nutritional outcomes. Maintaining and enhancing plasma levels of essential amino acids, particularly branched-chain amino acids (BCAAs), in malnourished dialysis-dependent patients could improve their nutritional status and clinical outcomes.

The complications associated with intradialytic parenteral nutrition infusion, particularly the higher frequency of hypotensive episodes in the sequential infusion group, could be attributed to excessive ultrafiltration towards the end of the hemodialysis session.

The study's results highlight the necessity for tailored nutritional strategies during hemodialysis to mitigate amino acid loss and effectively address the metabolic needs of these patients. By carefully selecting and adjusting the composition of the infusate, clinicians can enhance nutritional outcomes and improve the clinical status of malnourished dialysis-dependent patients. This approach is crucial for optimizing the balance between providing adequate nutrition and minimizing the loss of vital amino acids during hemodialysis sessions.

Although the study showed the statistical significance of amino acid loss, there is no data of clinical significance. Given the advantages and disadvantages of sequential and constant infusion regimens, clinicians should carefully tailor their approach based on individual patient characteristics. We propose that a sequential infusion of dextrose followed by amino acids is preferable for malnourished patients with well-controlled blood glucose levels and minimal risk of intradialytic hypotension, as it effectively provides both calories and protein during the intradialytic infusion period. Conversely, a constant infusion of amino acids with a dextrose solution is recommended for patients with a history of hypotension or those requiring high ultrafiltrate volume removal, as it compensates for the significant loss of amino acids into the dialysate. Regardless of the chosen regimen, meticulous blood pressure and glucose monitoring before, during, and after intradialytic parenteral nutrition therapy is imperative.

This study has several strengths. It is the first to delineate the differential concentration of amino acid loss between sequential and continuous amino acid infusion in patients undergoing chronic hemodialysis. Using a cross-over design ensured that participants' characteristics were self-controlled, enhancing the reliability of the findings. Additionally, including patients with indications for intradialytic parenteral nutrition reflects real-world clinical practice. However, the study has limitations, including the absence of recorded total dialysate volume, lack of data on nitrogen balance and oral intake before dialysis sessions, no data on amino acid uptake, and a short follow-up period, which limited the assessment of long-term nutritional status outcomes. Future research should address these limitations to provide a more comprehensive evaluation.

Conclusion

The constant infusion of amino acids plus a dextrose solution during hemodialysis resulted in a more significant loss of amino acids into dialysate than the sequential infusion of dextrose followed by amino acids.

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