Original Article

DOI: 10.5582/ddt.2024.01029

Subcutaneous edema as a potential cause of catheter failure in older inpatients receiving peripheral parenteral nutrition

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SUMMARY Malnutrition is a common problem among hospitalized older patients. Peripheral parenteral nutrition (PN) can improve patient outcomes but can also lead to complications that affect future treatment. Older inpatients, in particular, are expected to be prone to these catheter-related complications. However, the impact of peripheral PN on older inpatients has been rarely investigated. In the current study, the impact of PN on short peripheral catheters (SPCs) was evaluated by comparing signs and symptoms at the time of catheter removal between 22 patients with PN and 27 without. In addition to external clinical assessment, sonographic investigations of the SPC site were performed. The prevalence of external signs and symptoms of complications was similar between the patients (all $P > 0.05$). However, subcutaneous edema was found by ultrasound in > 80% of patients with PN, compared with 55.6% of those without PN ($P = 0.051$). Unlike cases without PN, all patients with PN who presented with external signs and symptoms developed subcutaneous edema ($P = 0.022$). Multivariate analysis demonstrated that administration of PN was independently associated with subcutaneous edema (adjusted odds ratio = 6.88, 95% confidence interval = 1.083-75.486, $P = 0.040$). For several decades, phlebitis has been the primary focus of complications related to peripheral PN in clinical settings. However, our results imply that peripheral PN causes subcutaneous edema, which can lead to catheter failure in older inpatients. This study contributes to understanding the etiology of catheter failure during peripheral PN in this population.

Keywords Subcutaneous edema, ultrasonography, phlebitis, etiology, catheter-related complications

1. Introduction

Malnutrition is a common problem among hospitalized older patients (*1*). A low level of serum albumin, which is an indicator of malnutrition (*2*), is a prognostic factor for mortality (*3-5*). Its inverse relation to the development of complications and the mean length of stay in hospital for acute patients has also been identified (*3-5*).

Parenteral nutrition (PN) is an effective method of providing nutritional support to patients when oral or enteral nutrition is not possible, insufficient, or contraindicated (*6*). PN can be delivered through either peripheral access, such as short peripheral or midline catheters, or midline venous access, such as peripherally inserted central catheters or nontunneled central venous catheters inserted directly into the superior vena cava or right atrium (*7*). Although peripheral access is only recommended for short-term use (up to 10-14 days), it has advantages over midline venous access, including ease of placement, cost-effectiveness, and lower risk of fatal infection (*6,8*). Therefore, peripheral access is commonly used for PN in older inpatients (*9*), and short peripheral catheters (SPCs) are often selected, especially for older inpatients in Japan.

PN can improve patient outcomes but can also lead to complications that may have a negative impact on outcomes. Securing SPCs, aging, and high osmolarity of PN fluids are independent risk factors for catheter-related complications (*10-12*), which shows that older patients are particularly vulnerable to such complications during PN. The association between PN and catheter-related complications has been studied previously (*9,13,14*), and phlebitis is a well-known complication related to peripheral access (*7,8,15*).

However, no studies to date have focused on the impact of peripheral PN on older patients. Given that age-related physiological changes occur in the integumentary, venous, and immune systems (*16-18*), the prevalence

of complications and their signs and symptoms in older patients might differ from those among other adults. Thus, this study aimed to elucidate the impact of PN on SPCs, particularly in older hospitalized patients.

2. Methods

2.1. Study design, setting, and selection of participants

This was a cross-sectional observational study conducted at a medical and surgical ward in a municipal hospital with 180 beds in a regional district in Japan. Data were obtained from May to September 2023. The researchers recruited patients in whom an SPC had been placed. The exclusion criteria were age < 64 years, current or past treatment with chemotherapy, and unstable medical conditions. Verbal and written informed consent was obtained from all participating patients or their families prior to enrollment. The study was approved by the Ethics Review Board of the authors' affiliated university (reference No. 10H230001, 10 April 2023), and conformed to the provisions of the Declaration of Helsinki (revised in 2013).

2.2. Outcome measures

The impact of PN on SPCs was evaluated by analyzing the time to removal (dwell time), sonographic findings, and assessing the presence of external signs and symptoms of complications at the insertion site at the time of SPC removal.

2.3. Study procedure

The researchers remained on call in the ward from 08:00 to 16:00 h on weekdays, and nurses notified the researchers when the SPCs were to be removed. The researchers performed external clinical assessment and sonographic investigations of the SPC site just before catheter removal because of premature failure, for routine replacement, or after completion of intravenous therapy. Cases where the cannulation was solely for the purpose of undergoing surgery, and the catheter was removed the day after surgery, were excluded from the analysis.

The following demographic and clinical data were reviewed from the patients' electronic medical records: age, gender, admission diagnosis, body mass index, oral intake restrictions, presence or absence of peripheral PN administration, length of hospital stay, and the most recent blood test results for albumin and C-reactive protein. The admission diagnosis was classified according to the International Classification of Diseases, 10th revision. The length of hospital stay was calculated from the day of admission to SPC removal. Patients were divided into two groups based on whether or not they received PN.

The SONIMAGE HS2 ultrasound machine (Konica Minolta, Tokyo, Japan) was used for all sonographic investigations and measurements, with an 18-MHz linear-array transducer. The focal range and image depth were set at 1 and 2.5 cm, respectively. To obtain clear images of superficial veins, we used the HS1/MX1 acoustic coupler (Konica Minolta) to set the ultrasonic focus on the vein of interest. The SPC and surrounding tissue were scanned in both the transverse and longitudinal axes. All images throughout the investigations were obtained by one particular experienced researcher.

The vein size and depth were measured using images stored in the ultrasound machine. The vein-to-catheter ratio was calculated by dividing the vessel inner diameter by the outer diameter of the catheter cannula placed in the vein. The outer diameters of the 20-, 22-, and 24-gauge cannulas were 1.1, 0.9, and 0.7 mm, respectively.

The presence or absence of subcutaneous edema was determined as described previously (*19,20*). Sonographically, subcutaneous edema was defined as a cobblestone pattern in the subcutaneous fat layer adjacent to the vein of interest, reflecting the presence of fluid in the interstitium.

During external clinical assessment, intravenous catheter function and the following clinical signs and symptoms of SPC complications were evaluated: erythema, pain, swelling and induration. The presence of phlebitis was assessed according to the Infusion Nursing Society guidelines (*21*). Additionally, data related to SPC placement were recorded, including the anatomical site of insertion, catheter gauze, infusion administration method, and all fluids administered through the catheter.

2.4. Statistical analysis

The data were expressed as the mean and standard deviation if normally distributed, and as median with interquartile range if skewed. Categorical variables were presented as frequencies with percentages in parentheses. If a second or subsequent SPC removal occurred in the same patient, only one event was randomly selected for analysis. Patient demographics, SPC characteristics, and external signs and symptoms at the time of catheter removal were compared between the patients with and without peripheral PN. The χ^2 test was used for comparison of categorical variables, and Student's *t*-test or Wilcoxon rank sum test for continuous variables depending on the distribution. The researchers generated multivariate/adjusted models to confirm the association between external signs and symptoms and PN. Only signs and symptoms that showed $P < 0.1$ in the difference between groups were entered into the model as dependent variables. Only variables that showed an association with $P < 0.2$ in the univariate logistic analysis were entered into the multivariate/adjusted model as independent variables. Associations between candidates were tested using the χ^2 test. Only one of the variables

was included if P was < 0.05. Results were presented as odds ratio with corresponding 95% confidence interval (95% CI) and P values in univariate and multivariate/adjusted analyses. Effects were determined through likelihood ratio tests. $P \leq 0.05$ was considered statistically significant. All statistical analyses were performed with JMP11 software (SAS Institute Japan Ltd., Tokyo, Japan).

3. Results

3.1. Demographics and characteristics of SPC insertions

We observed 66 catheter removal events; 17 of which occurred in the same patient. Thus, a total of 49 events from 49 patients were analyzed. Twenty-two patients (44.9%) received peripheral PN compared with 27 (55.1%) who did not. All peripheral PN administered was BFLUID® (Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan) with an osmolarity of ~460 mOsm/L. Patient demographics and clinical data are reported in Table 1. A significant difference was found in the ratio of nil per os between the group of patients with and without peripheral PN (P = 0.017). Otherwise, patient demographics and clinical data were similar between the groups (P > 0.05). The patients' median age was 82.0 (75.0-90.5) years, and 59.2% were female. Fifteen (30.6%) patients had a gastrointestinal disease, 12 (24.5%) a neoplastic disease and nine (18.4%) a respiratory disease. The mean plasma albumin level was 2.9 ± 0.8 g/dl. The median length of hospital stay was 6 (4-13.5) days.

Characteristics of SPC insertions at the time of removal were similar between the groups (all P > 0.05) (Table 2). The most common catheter size was 24-gauge (51.0%, n = 25), followed by 22-gauge (36.7%, n = 18). Most SPCs were inserted in the forearm (75.5%, n = 37). The median vein-to-catheter ratio was 2.86 (2.18-3.43).

3.2. Impact of PN on SPCs

The signs and symptoms at the time of SPC removal were compared between the groups with and without PN (Table 3). Most catheter removals occurred within 72 h in both groups. Sixteen patients (72.7%) with peripheral PN and 18 patients (66.7%) without presented with signs and symptoms at the time of SPC removal (P = 0.647). The prevalence of each sign and symptom was similar between the groups (all P > 0.05). However, different trends were observed in the ultrasonographic detection of subcutaneous edema, which was found in 18 (81.8%) patients with PN compared with 15 (55.6%) without PN (P = 0.051).

In patients with PN, all 16 who presented with external signs and symptoms developed subcutaneous edema. In patients without PN, 13 (72.2%) who presented with external signs and symptoms developed subcutaneous edema, while the remaining five (27.8%) did not. There was a significant difference between patients with and without PN who presented with external signs and symptoms and subcutaneous edema (P = 0.022). In both groups, there were two patients who had edema although signs and symptoms could not be confirmed externally.

Phlebitis was seen in 12 patients (60.0%) with PN and in 13 (48.2%) without PN (P = 0.421). Three cases (12.0%) presented with pain or erythema, and 22 cases (88.0%) had two of the following symptoms: pain, erythema and swelling.

Subcutaneous edema was included in the multivariate/adjusted model as a dependent variable. Table 4 shows the univariate and multivariate analyses for subcutaneous edema. Logistic regression analysis, unadjusted for other

Table 1. Characteristics of patients with and without peripheral PN

	Total (n = 49)	Patients with PN (n = 22)	Patients without PN (n = 27)	P value
Age (yr), median (IQR)	82 (75.0-90.5)	82 (76.0-86.8)	76 (72.0-92.0)	0.801
Sex, n (%)				0.551
Male	20 (40.8)	10 (45.5)	10 (37.0)	
Female	29 (59.2)	12 (54.6)	17 (63.0)	
Admission diagnosis, n (%)				0.417
Neoplasms	12 (24.5)	8 (36.4)	4 (14.8)	
Digestive system	15 (30.6)	7 (31.8)	8 (29.6)	
Respiratory system	9 (18.4)	3 (13.6)	6 (22.2)	
Urinary system	3 (6.1)	0 (0.0)	3 (11.1)	
Circulatory system	2 (4.1)	1 (4.6)	1 (03.7)	
Others	8 (16.3)	3 (13.6)	5 (18.5)	
Nil per os, n (%)	22 (44.9)	14 (63.6)	8 (29.6)	0.017
Plasma albumin level, mean (SD), g/dl	2.9 (0.8)	2.8 (0.9)	3.0 (0.7)	0.437
C-reactive protein, median (IQR), mg/dl	3.3 (0.7-7.7)	3.8 (0.6-7.6)	2.6 (0.7-8.3)	0.825
Body mass index, mean (SD)	20.8 (3.3)[a]	20.3 (2.9)[b]	21.3 (3.7)[c]	0.301
Hospital stay[d] (d), median (IQR)	6.0 (4.0-13.5)	7.5 (4.0-14.3)	6.0 (3.0-13.0)	0.607

Data are presented as n (%), mean (SD) or median (IQR). [a]n = 45, [b]n = 21, [c]n = 24, [d]Number of days from admission to the day of short peripheral catheter removal. IQR, interquartile range; PN, parenteral nutrition; SD, standard deviation.

Table 2. Characteristics of SPC insertions in patients with and without peripheral PN

	Total (n = 49)	Patients with PN (n = 22)	Patients without PN (n = 27)	P value
Characteristics of in-place SPCs				
Catheter size				0.343
24 gauge	25 (51.0)	9 (40.9)	16 (59.3)	
22 gauge	18 (36.7)	9 (40.9)	9 (33.3)	
20 gauge	6 (12.2)	4 (18.2)	2 (7.4)	
Location of SPC				0.796
Forearm or upper arm	37 (75.5)	17 (77.3)	20 (74.1)	
Others[a]	12 (24.5)	5 (22.7)	7 (25.9)	
Vein-to-catheter ratio[b], Median (IQR), mm	2.86 (2.18-3.43)[c]	2.89 (2.44-3.86)[d]	2.69 (1.93-3.33)[e]	0.205
IV infusate administration				
Antibiotics				0.181
Yes	23 (46.9)	8 (36.4)	15 (55.6)	
No	26 (53.1)	14 (63.6)	12 (44.4)	
Methods of administration				
Automated infusion pump				0.961
Yes	18 (36.7)	8 (36.4)	10 (37.0)	
No	31 (63.3)	14 (63.6)	17 (63.0)	
Intermittent infusion				0.215
Yes	18 (36.7)	6 (27.3)	12 (44.4)	
No	31 (63.3)	16 (72.7)	15 (55.6)	

Data are presented as n (%) or median (IQR). [a]Including antecubital fossa, wrist, hand, and foot. [b]14 cases missing; the target vein was undetectable because of tissue changes caused by subcutaneous edema. [c]n = 35. [d]n = 15. [e]n = 20. IQR, interquartile range; IV, intravenous; PN, parenteral nutrition; SPC, short peripheral catheter.

Table 3. Outcome measures: signs and symptoms at the time of short peripheral catheter removal

	Patients with PN (n = 22)	Patients without PN (n = 27)	P value
Time to removal[a]			0.650
< 72 h	15 (68.2)	20 (74.1)	
≥ 72 h	7 (31.8)	7 (25.9)	
External clinical assessment			
Fluid dripping/functioning	(n = 22)	(n = 25)	0.175
No	2 (9.1)	6 (24.0)	
Yes[b]	20 (90.9)	19 (76.0)	
Signs and symptoms of complications			
Presence of signs and symptoms			0.647
Yes	16 (72.7)	18 (66.7)	
No	6 (27.3)	9 (33.3)	
-Erythema			0.409
Yes	9 (40.9)	8 (29.6)	
No	13 (59.1)	19 (70.4)	
-Pain	(n = 19)	(n = 26)	0.433
Yes	8 (42.1)	8 (30.8)	
No	11 (57.9)	18 (69.2)	
-Phlebitis[c, d]	(n = 20)	(n = 27)	0.421
Yes	12 (60.0)	13 (48.2)	
No	8 (40.0)	14 (51.9)	
-Swelling			0.136
Yes	16 (72.7)	14 (51.9)	
No	6 (27.3)	13 (48.2)	
-Induration			0.882
Yes	1 (4.5)	1 (3.7)	
No	21 (95.5)	26 (96.3)	
Sonographic findings			
Subcutaneous edema			0.051
Yes	18 (81.8)	15 (55.6)	
No	4 (18.2)	12 (44.4)	

Data are presented as n (%). [a]Including time to premature failure, routine replacement, and completion of intravenous therapy. [b]Including the cases with and without a infusion pump. [c]Defined based on Infusion Nursing Society guidelines. [d]Two cases missing; unable to be defined because of lack of related information of pain. PN, parenteral nutrition.

Table 4. Univariate and multivariate analyses for subcutaneous edema

	Univariate		Multivariate	
	OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Characteristics of patients				
Age (yr), median (IQR)	1.007 (0.931-1.057)	0.816		
Gender, *n* (%)				
Male	Reference			
Female	1.750 (0.520-5.985)	0.364		
Admission diagnosis, *n* (%)				
Neoplasms	Reference		Reference	
Others[a]	0.329 (0.046-1.484)	0.156	0.250 (0.024-1.709)	0.163
Plasma albumin level, mean (SD), g/dl	0.953 (0.472-2.338)	0.904		
Body mass index, mean (SD)[b]	1.504 (0.780-1.147)	0.582		
Hospital stay (d), median (IQR)	0.999 (0.924-1.074)	0.986		
Characteristics of in-place SPC				
Location of SPC				
Forearm or upper arm	Reference			
Others[a]	0.960 (0.248-4.175)	0.954		
Vein-to-catheter ratio[c], median (IQR), mm	0.518 (0.879-4.781)	0.103	0.297 (0.072-0.862)	0.024
IV infusate administration				
PN administration				
No	Reference		Reference	
Yes	3.600 (1.017-15.068)	0.047	6.875 (1.083-75.486)	0.040
Antibiotics				
No	Reference		Reference	
Yes	0.390 (0.109-1.306)	0.128	0.401 (0.070-2.069)	0.274
Methods of administration				
Automated infusion pump				
No	Reference			
Yes	0.952 (0.279-3.404)	0.938		
Intermittent infusion				
No	Reference			
Yes	0.435 (0.124-1.486)	0.183		

[a]Including digestive system, respiratory system, urinary system, circulatory system, and others. [b]$n = 45$. [c]$n = 35$. IQR, interquartile.

factors, demonstrated that administration of PN was associated with 3.60-fold greater odds of subcutaneous edema (95% CI = 1.01-15.068, $P = 0.047$). Multivariate analysis demonstrated that PN was independently associated with 6.88-fold greater odds of subcutaneous edema (95% CI= 1.083-75.486, $P = 0.040$).

4. Discussion

To the best of our knowledge, this is the first study to investigate the impact of peripheral PN on SPCs in older patients. The study revealed unique findings that appear to be specific to this population.

Fluids with osmolarity > 350 mOsm/L are considered irritant drugs (*10*). This applies to peripheral PN as well, as fluids can be administered through an SPC at concentrations up to 600 mOsm/L (*6*). Administration of irritant drugs has been shown to increase the risk of catheter-related complications, including phlebitis, infiltration and extravasation (*10,12,22*). However, phlebitis has been the primary focus of complications related to peripheral PN for several decades (*6-9,15*). In that context, the present study showed that > 80% of patients who received peripheral PN developed subcutaneous edema. This is higher than in a previous study, in which 64% of 36 patients receiving PN, with a mean age of 69.7 years, presented with subcutaneous edema at the time of SPC removal (*23*). Additionally, the adjusted odds ratio in the present study was 6.88 compared with 2.68 (95% CI = 1.14-6.33) in the previous study. The small sample size in the present study resulted in a wide 95% CI; nevertheless, the results suggest that the risk of developing subcutaneous edema increases with aging.

A previous prospective observational study demonstrated that ultrasound identified subcutaneous edema prior to external signs of an unresolvable complication. Specifically, edema was identified by ultrasound about 20 h prior to clinical recognition of catheter failure, indicating that subcutaneous edema on ultrasound is a predictor of catheter failure (*24*). Another study showed that the ultrasonographic findings of subcutaneous edema were associated with catheter infiltration confirmed by external clinical examination (*23*). All these previous studies and our own (although not prospectively designed) imply that peripheral PN causes subcutaneous edema, which can lead to catheter failure in older inpatients. Unlike patients with PN, we found that five (27.8%) patients without PN presented with external signs and symptoms

without developing subcutaneous edema. We found a significant difference in subcutaneous edema along with external signs and symptoms between patients with and without PN, which suggests that the cause of catheter failure differs depending on whether PN was administered.

In contrast to subcutaneous edema, the present study found no association between phlebitis and PN administration. This contradicts previous studies that showed an association between PN administration and phlebitis (*7,8,15*). This discrepancy may be partially explained by age-related physiological changes. As individuals age, functional and structural alterations occur in the immune system (*25*). Previous reports have shown that older patients can often manifest atypical symptoms against infection (*26,27*). Furthermore, older adults exhibit a general increase in pain thresholds (*28,29*), and a diminished capacity to perceive sharp, localized pain signals (*30*). While erythema and pain are commonly regarded as indicators of phlebitis, the subtlety or atypicality of symptoms among older patients may have resulted in the dismissal of phlebitis in the current study. Alternatively, catheters may have failed because of infiltration caused by subcutaneous edema before the onset of inflammatory reactions to the fluid osmolarity. Numerous definitions of phlebitis and a lack of consensus on phlebitis measurement might also have contributed to disparities in incidence (*31*).

The present study highlights the importance of focusing on subcutaneous edema as a major problem among older inpatients receiving peripheral PN. Hypertonic solutions disrupt cellular function (*32,33*) and cause a fluid shift from inside venous cells to the interstitial space (*10*), resulting in inadvertent leakage to surrounding tissues (*34*). The etiology of the increased risk of edema with aging can be explained by this fluid shift that occurs in small vessels with poor integrity, which is characteristic of older patients (*12,18*). Ultrasonographic evaluation of subcutaneous edema could be a strong predictor of SPC failure among older inpatients receiving peripheral PN. In addition, slowing the rate of administration and finding a vein with a larger blood flow volume (*22*), including consideration of midline catheters, may prevent inadvertent leakage of fluids into surrounding tissues.

This study had several limitations. The median age was 82.0 years, which matches the average life expectancy in Japan (*35*). However, the study findings may not be generalized to the younger population aged 65-74 years. Patient-specific factors, particularly in patients receiving PN, may affect the development of subcutaneous edema. Although we considered several of these variables, we may not have included all relevant confounders. Additionally, differences in catheter size and site have been found worldwide (*36*), suggesting that factors that determined catheter size and site may have influenced the results. Our study was single center and the findings were based on one specific product with a small sample size. Thus, the findings cannot be generalized to older patients globally. Further research is required in various settings with a wider range of osmolarity of peripheral PN. We did not observe all events that necessitated catheter removal during our study. In some instances, removal occurred during off-hours or without notification to the researchers. Those uncollected data could have influenced the final results. Finally, while peripheral PN was independently associated with subcutaneous edema, dwell time did not significantly differ regardless of the presence of PN. Further research is needed to determine whether managing subcutaneous edema can prolong the longevity of the SPC during peripheral PN in older patients.

In conclusion, our results imply that peripheral PN causes subcutaneous edema, which can lead to catheter failure in older inpatients, which contributes to understanding the etiology of catheter failure during peripheral PN in these patients. The management of subcutaneous edema during peripheral PN needs urgent attention, particularly in light of the aging population.

Acknowledgements

The authors express gratitude to all the patients who participated in the study. We would like to thank Hiroshi Taniguchi, Yoko Aoki, Chikako Kudo, and Akiko Hirayama, and all the clinical staff who supported data collection on the ward. We also thank Ayako Ninomiya, Minoru Kabashima, and Kazuko Tateno of Josai International University for their assistance in the conduct of this study.

Funding: This work was supported in by the JSPS (Grant-in-Aid for Scientific Research (C), JP22K10690, to M.K.).

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received May 9, 2024; Revised June 5, 2024; Accepted June 7, 2024.

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Released online in J-STAGE as advance publication June 15, 2024.