

# Safety verification of a new peripheral intravenous catheter placed in the upper arm vein for administration of drugs with high irritant potential

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**SUMMARY** Despite the widespread use of peripheral intravenous catheters, unscheduled catheter failure before completion of treatment occurs frequently. If a large vein is selected, catheter failures may be prevented despite administering a highly irritant drug. In this study, we attempted to use a catheter that can be placed in a large upper arm vein. The new catheter was 88 mm long but had no guidewire to reduce contamination risk. This study aimed to evaluate the safety of the first-in-human trial for the new catheter with the administration of highly irritant drugs. This study was conducted at a university hospital in Tokyo, Japan. Eight Japanese adults were hospitalized adults with planned administration of non-cancer drugs with high irritant potential using a peripheral catheter. A trained nurse catheterized with the new catheter in the upper arm using ultrasonography. The catheterization site was monitored by staff and a research nurse once every 24 hours for up to 7 days. No adverse events or catheter failure occurred and the catheter placement success rate was 100%. In two patients, a temporary occlusion alarm of the infusion pump occurred, possibly due to the flexion of the catheter base. The new peripheral intravenous catheter did not interrupt medical treatments as is common after placement, but safety administered the irritant drugs. However, because this catheter may be easily affected by the contraction of the muscle at the fixation position, the position and method of catheter fixation in the upper arm need to be carefully considered.

**Keywords** adverse event, device malfunction, first-in-human trial, irritant infusates, peripheral intravenous catheter failure

## 1. Introduction

Peripheral intravenous catheters (PIVCs) are widely used. Almost 70% of hospitalized patients worldwide require a PIVC to secure the venous route for infusion therapy (1). In Japan, only a short peripheral catheter (SPC) has been approved as a medical device, while midline catheters and long peripheral intravenous catheters (LPCs) are not available. Physicians and general nurses can choose only a short catheter to secure the peripheral venous route for infusion in Japan.

Despite the widespread use of PIVCs, unscheduled catheter failure (CF) before completion of treatment occurs in up to 69% of patients, even in cases of

successful catheter placement (2-4). In adult inpatients at a university hospital in Japan, 18% of placed catheters were removed because of CF (5). The major reasons for discontinuation of using indwelling catheters are the appearance of symptoms and signs, such as redness, swelling, pain, and induration along the vein, and catheter occlusion and insufficient infusion volume. These signs and symptoms are often observed as early symptoms of complications, such as catheter-related bloodstream infection or thrombophlebitis (6), potentially leading to bacteremia, sepsis, and even death (7). Preventing CF would not only prevent complications but also reduce the burden due to repeated punctures by needles on the patients.

Contributing factors to complications related to CF can be classified as biological, mechanical, and chemical factors (8). In our previous study, we identified the following factors associated with reduced risk of CF: (i) selection of a vessel with a large diameter (at least 3.3 times the external diameter of the catheter) (9), (ii) successful insertion on the first attempt (10), (iii) securing the catheter tip in a non-stimulatory position on the vessel wall (11,12), and (iv) use of a catheter made of soft materials such as polyurethane rather than polytetrafluoroethylene (13). To meet these requirements, a long catheter that can be safely and easily placed in the upper arm vein, that can reach in the vicinity of the axillary vein, and which has a large blood flow, is required.

Although midline catheters and LPCs are PIVCs meet these requirements (14,15), they have several drawbacks mainly associated with the insertion procedure. Existing long catheters (length is 80 mm or over) require a guidewire for insertion which also requires aseptic non-touch technique for additional manipulation of the guidewire. This technique requires more time and effort for catheter placement, and the risk of infection is increased owing to the complicated guidewire procedures (16). Furthermore, the inserter needs to use both hands and cannot hold the US probe for catheter insertion.

To improve the ease of catheterization in this study, we used a new indwelling PIVC catheter (new PIVC) that can be placed in an upper arm vein. It does not necessitate a guidewire even though the catheter length is 88 mm. This study is the first-in-human trial to verify its safety in Japan. This study aimed to evaluate the safety of the new PIVC in patients undergoing administration of drugs with high irritancy other than anticancer drugs by assessing the occurrence of adverse events. The adverse events evaluated in this study included catheter-related bloodstream infection and device malfunction at the time of puncture, during the indwelling period, at the time of removal, and up to approximately 24 hours after catheter removal.

## 2. Methods

### 2.1. Study setting and samples

This exploratory research was conducted in the hematology and oncology department at The University of Tokyo Hospital in Tokyo, Japan, between August and December 2020. All participants read a description of the study and signed a consent form. The study protocol was approved by the Research Ethics Committee of the Graduate School of Medicine and Institutional Review Board, The University of Tokyo (2019016SP). The study protocol was registered and published in the Japan Registry of Clinical Trials: jRCT (protocol number: jRCTs032200076).

### 2.2. Inclusion criteria

Participants were male and female patients over 20 years old who had planned administration of hyper-stimulant drugs, such as those with an osmotic pressure ratio 3 higher, or irritant or vesicant drugs, excluding anticancer drugs, for longer than 24 hours using a PIVC.

### 2.3. Exclusion criteria

We excluded patients who could not maintain the position with the shoulder joint abducted and the elbow joint externally rotated, those who had skin disorders at the puncture site, those with peripheral neuropathy, those with a history of vasovagal reflex due to puncture, those with a history of thrombosis, those with stage  $\geq$  G3a chronic kidney disease, and those with an abnormal blood coagulation ability or a bleeding tendency (prothrombin-international normalized ratio  $\geq$  1.5; activated partial thromboplastin time of  $\geq$  36.1 seconds, and taking anticoagulant or antiplatelet drugs). Patients scheduled to undergo invasive procedures were also excluded (*e.g.*, endoscopy and bronchoscopy). Furthermore, other patients judged by the physician in charge to be inappropriate for participation in this study were excluded.

### 2.4. Sample size

The incidence of adverse events with the new PIVC was unknown, including nerve injury, arterial puncture, vasovagal reflex, skin damage due to echo jelly, hematoma formation due to deep vascular injury, catheter-related bloodstream infection, and venous thrombosis. Adverse events might occur not only with the new PIVC but also with the conventional SPC. Additionally, the frequency of a device malfunction was unpredictable. We set 10 cases as the sample size because this survey was an exploratory study to determine the frequency of adverse events for subsequent validation. The exact one-sided 95% confidence interval of the probability of occurrence was calculated to be 0%-25.9% when the number of cases is 0 of 10 for each event. Therefore, at least one event with a true probability of occurrence  $>$  25.9% was identified with a probability of  $\geq$  95% in this study.

### 2.5. Outcomes and patients' characteristics

The primary outcomes were the incidence of adverse events: nerve injury, arterial puncture, vasovagal reflex, skin damage due to echo jelly, hematoma formation due to deep vascular injury, catheter-related bloodstream infection, and venous thrombosis, from the time of puncture to 24 hours after catheter removal and the frequency of a device malfunction

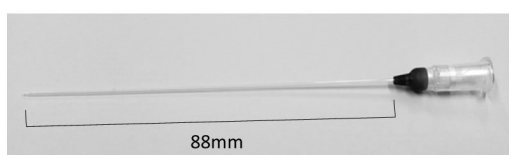
by the time of catheter removal or up to a maximum of day 7. Nerve injury, arterial puncture, hematoma, and venous thrombosis were recorded by an interview, macroscopic observation, and ultrasonography with two-dimensional linear-array transducers (6-13 MHz, FC1-X VA; Fujifilm, Tokyo, Japan) to observe blood vessels and subcutaneous tissues. Bacterial culture tests were applied for removed catheters and the skin surface around the catheter insertion point. The visual analogue scale (100 points: maximum pain) was used to evaluate pain. Photographs of the removed catheter were taken immediately after its removal, and then the angle of the base of the catheter was measured using image-J software (NIH) because this could be related to device failure.

The secondary outcomes were the catheter placement success rate, the incidence of CF, and subjective assessment of catheter placement on the upper arm. CF was defined as premature catheter removal before completion of planned fluid therapy, excluding self-removal and accidental removal. CF and catheter removal were determined by physicians and nurses based on interviews and macroscopic observations. Ultrasonography was additionally used to confirm the subtypes of CF (*e.g.*, catheter dislodgement, thrombus formation in the vein, and subcutaneous edema formation) by a trained researcher. Subjective assessment of catheter placement was confirmed by original questionnaires.

The patients' characteristics (diagnosis, medical history, oral medication, age, sex, and body mass index), blood test data (total protein, albumin, hematocrit, platelet count, white blood cell with differential count, C-reactive protein, prothrombin time, prothrombin-international normalized ratio, activated partial thromboplastin time, and fibrinogen), length of hospital stay, rate and dosage of the infusate, infusion pump use, and performance status were collected by chart review.

## 2.6. Features of the new PIVC

The length of the catheter was 88 mm to enable approaching the peripheral vein in the upper arm and inserting the catheter tip into the vicinity of the axillary vein (Figure 1). The catheter size was 22 gauge (outer diameter: 0.9 mm) and made of polyurethane. There was no guidewire, and catheter insertion was performed by the inserter pushing in the "controlling element"



**Figure 1. New peripheral intravenous catheter.** The length of the catheter is 88 mm. The catheter size is 22 gauge (outer diameter: 0.9 mm) and it is made of polyurethane.

with their finger in the punctured hand, allowing a one-handed catheter insertion operation. This catheter has a backflow prevention valve which can help to protect against blood exposure. Ultrasonography was necessary in order to guide catheter puncture and insertion.

## 2.7. Research procedure

The patients were admitted to the department, and consent for participation in the study was obtained. Informed consent was obtained in accordance with the Declaration of Helsinki and the Clinical Research Act (Japan). Eligibility was confirmed simultaneously, and then a trained nurse catheterized the new PIVC in the upper arm using ultrasonography under the direction of a physician. Standard infection precautions were applied, with 1% chlorhexidine alcohol as skin antisepsis, and the insertion site was covered with dressing film. The catheterization site was monitored by staff and a research nurse at least once every 24 hours. The catheter was removed after being placed for up to 7 days.

## 2.8. Statistical analysis

The incidence of adverse events or device malfunction (%) was calculated as the number of catheters with adverse events or device malfunction/the number of placed catheters. The success rate of indwelling catheters (%) was calculated as the number of successful indwelling catheters/the number of punctures. The incidence of CF (%) was calculated as the number of catheters in which CF occurred/the number of placed catheters. Descriptive statistics were used for the patients' characteristics and the points of the visual analogue scale. Qualitative analysis was used for answers by an open-ended questionnaire. Data were analyzed with the Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, ver. 22.0; IBM Corp., Armonk, NY, USA).

## 3. Results

### 3.1. Participants

The number of patients who agreed to participate in this study was nine. All of them were enrolled in the study and underwent insertion of the new PIVC and infusion. After catheter removal, one participant was excluded from the analysis because the activated partial thromboplastin time value on the day before placement was prolonged beyond the inclusion criteria. One participant withdrew consent after the initiation of infusion, and removed catheter before completion the study, in which subsequent participation to the study was refused but use of data already collected so far was allowed. Therefore, the number of subjects for analysis was eight.

### 3.2. Baseline characteristics

Of the eight participants, four were men. The median age was 51.5 years. The mean of the body mass index was 21.6 kg/m<sup>2</sup>. The mean of the length of the hospital stay was 32.3 days (Table 1). The performance status score on admission was zero in four patients, 1 in two patients, and 2 in three patients. Table 2 shows the blood test data before catheter placement.

Seven patients were administered BFLUID<sup>®</sup> injection: amino acid and glucose injection with electrolytes and vitamin B1 (Otsuka Holdings Co., Ltd., Tokyo, Japan), one patient was administered tazobactam/piperacillin hydrate, and three patients were administered vancomycin hydrochloride (Table 3). All

patients used an infusion pump for the administration of these irritant drugs.

### 3.3. Outcome measures

No predefined adverse events were observed during puncture, at the indwelling period, at the time of removal, and up to approximately 24 hours after catheter removal. The culture test results of all removed catheters and the skin surface around the catheter insertion site were negative.

A temporary occlusion alarm of the infusion pump, possibly due to flexion of the catheter base, occurred in two of eight (25%) patients. Actually, under the magnification of two catheters, a linear line was observed at the base of the catheter. In one patient, the catheter was used until the completion of the treatment, and the other patient hoped to remove the catheter the next day. Table 4 shows the characteristics of the patients, the vessel where the catheter was placed, and details of the catheter according to catheter malfunction. The body mass index was relatively low, and the depth of the vessel was relatively shallow in patients with catheter malfunctions than in those without catheter malfunction. The angle of the base of the removed catheter was smaller in patients with catheter malfunction than in those without catheter malfunction.

According to the visual analog scale, the mean

**Table 1. Participants characteristics**

Age (years): median	51.5 (range: 29-76)
Sex	male: 4; female: 4
BMI (kg/m <sup>2</sup> ): mean (SD)	21.6 (3.3)
Length of hospital stay: mean (SD)	32.3 (18.1) days
Diagnoses (n)	acute myeloid leukemia (2) mycosis fungoides (2) acute lymphoclastic leukemia (1) lymphoplasmacytic lymphoma (1) acute undifferentiated leukemia (1) mantle cell lymphoma (1)

BMI, Body Mass Index.

**Table 2. Blood test values**

Blood test items	Patients' values <sup>a</sup>	Reference values <sup>b</sup>
Total protein (g/dL)	5.50 (4.40-6.40)	6.6-8.1
Albumin (g/dL)	3.00 (2.30-3.60)	4.1-5.1
Hematocrit (%)	23.40 (19.20-28.10)	Men: 40.7-50.1, Women: 35.1-44.4
Blood platelet count (×10 <sup>4</sup> /μL)	7.35 (1.60-35.60)	15.8-34.8
White blood cell count (×10 <sup>3</sup> /μL)	4.45 (0.20-47.80)	3.3-8.6
C-reactive protein (mg/dL)	1.82 (0.20-5.88)	< 0.3
Prothrombin (%)	92.85 (80.0-100.0)	86.0-124.1
PT-INR	1.05 (0.93-1.13)	—
APTT (seconds)	27.50 (25.30-30.10)	24.0-34.0
Fibrinogen (mg/dL)	421.00 (253.0-700.0)	168-355

Values are median (range). <sup>a</sup>Blood test values on the closest day before catheter placement. <sup>b</sup>Reference values of blood testing by The University of Tokyo Hospital. PT-INR: prothrombin-international normalized ratio; APTT: activated partial thromboplastin time.

**Table 3. Total volume of administered irritant drugs**

Patient ID	PIVC dwelling time (days)	Irritant drug administration (total)
201	7	BFLUID <sup>a</sup> 6631 mL
301	4	BFLUID 2265 mL
801	7	BFLUID 6880 mL, VCM 14 g
401	7	BFLUID 3668 mL, KCL 60 mEq
901	7	BFLUID 5850 mL, KCL 60 mEq
501	7	BFLUID 7000 mL, VCM 21 g, KCL 70 mEq
601	7	BFLUID 3500 mL, TAZ/PIPC 49.5 g
701	1 (withdrawal)	VCM 4 g

<sup>a</sup>BFLUID (amino acid and glucose injection with electrolytes and vitamin B1) was infused intravenously. PIVC: peripheral intravenous catheter; VCM: vancomycin; KCL: potassium chloride; TAZ/PIPC: tazobactam/piperacillin hydrate.

**Table 4. Characteristics of the patients, catheter, and vessel**

Items	Total (n = 8)	Without catheter malfunction (n = 6)	With catheter malfunction (n = 2)
Body mass index	21.6 (3.4)	22.3 (3.7)	19.8 (1.2)
Distance between the elbow joint and the puncture point	91.3 (24.2)	88.3 (11.7)	100.0 (56.6)
Vein diameter at the puncture point*	4.4 (1.0)	4.0 (0.6)	5.9 (0.3)
Vein diameter at the catheter tip	5.7 (1.5)	5.3 (1.3)	6.9 (2.0)
Vein depth	7.3 (2.8)	8.4 (2.1)	4.2 (2.1)
Angle of the base of the removed catheter	17.4 (4.4)	18.2 (5.0)	15.1 (0.6)

Data are mean (SD). \*Vein diameter = [major axis + minor axis]/2.

pain scores were < 40 at all the time points, including at insertion and removal. Despite the invasive nature of the needle puncture, there was no incidence of an inability to puncture owing to pain or premature removal during indwelling.

A secondary endpoint, the catheter placement success rate, was 100% in all eight patients. The incidence of CF was 0% at all time points. Regarding the subjective assessment of catheter placement, there were no complaints of hindered activities of daily living due to indwelling and fixation of the catheter in the upper arm.

#### 4. Discussion

To reduce the risk of CF occurrence, we used a new PIVC in the upper arm vein without a guidewire despite it being 88 mm long. In this first-in-human trial to verify its safety, no adverse events or CF occurred. The catheter placement success rate was 100%; it allowed no device malfunction occurred at the catheter placement.

In our previous study, the incidence of CF using SPCs was 29% in the control group compared with 11% in the intervention group, where a care bundle was implemented that used ultrasonography to place the catheter in a larger vessel and secure it in the appropriate position in the vessel during SPC placement (12). To further reduce CF, a PIVC needs to be placed near the axillary vein in the upper arm, which has a larger diameter and higher blood flow rate than those in the forearm veins (17). PIVCs placed near the axillary vein in the upper arm could avoid CF caused by chemical factors due to administering irritant drugs. In fact, a previous study reported an incidence rate of complications of 2.7% with using a catheter that was placed in the upper arm for vancomycin administration (18). However, most existing upper arm PIVCs need a guidewire, which is associated with an increased risk of contamination because it can reach in the vicinity of the axillary vein (16). A catheter inserter has to perform many steps for inserting the catheter; the skill is complex, the process is time-consuming, and the medical cost involved in maximal sterile

barrier precaution is higher than that with the standard precaution. Catheters that can be inserted into the upper arm without a guidewire are expected to reduce the burden on the medical staff and diminish the risk of CF. In this study, we verified the safety of the new PIVC.

A systematic review of studies using LPCs (6-15 cm in length) showed that the insertion success rate ranged from 86% to 100%, and the CF rate in adult patients ranged between 4.3% and 51.5% (16). In the current study, no adverse events occurred during the catheterization in all eight patients, the success rate of the first puncture attempt was 100%, and there was no device malfunction in operation during the puncture. There were no interruptions in the catheter placement due to complaints of pain. There were also no adverse events or CF after placement, and no suspected infectious organisms were detected. Our findings suggest that the new PIVC is as safe as a 80 mm LPC with a guidewire.

The patients in this study generally had low blood platelet count because of their underlying hematological diseases or exposure to cytotoxic chemotherapy, making them susceptible developing subcutaneous hemorrhage upon puncture. In our analysis, no patients developed subcutaneous hemorrhage, possibly because the mean diameter of the vessel at the puncture point was 4.4 mm, and the diameter of the catheter tip position was 5.7 mm, which was approximately five times larger than the catheter outer diameter. It leads to an increased puncture success rate and avoids the mechanical stress to the vessel wall. Additionally, the catheter was sufficiently long to prevent dislodgment, even though the mean depth of the vessel was 7.3 mm.

The cause of a temporary occlusion alarm of the infusion pump in our study is unclear. Between the catheter hub and the skin puncture, the base of the catheter could have been temporarily bent, resulting in occlusion, supported by an emergence of a linear line at the base of the catheter observed under magnification. Patients whose alarms went off had a lower average body mass index and shallower blood vessels than those whose alarms did not go off. The subcutaneous fat layer seemed to be relatively thin in these subjects. It was reported that the subcutaneous adipofascial tissue was

made up of two adipofascial layers; the superficial layer forms a solid structure. It is thought to protect against external forces and the deep layer forms a mobile layer and is thought to lubricate the musculoskeletal movement (19). So that means, contraction of the muscle leads to movement of the epidermis along with the subcutaneous tissue, furthermore, thinner subcutaneous fat layer may allow the skin surface to move easily. Therefore, the positional relationship between the catheter hub fixed to the skin surface and the vessel puncture site may have expanded and contracted under the influence of contraction of the underlying muscles. We need to consider the position and method of catheter fixation in the upper arm, considering that the catheter is easily affected by muscle contraction at the fixation position. Taking into consideration these countermeasures may help prevent catheter malfunction.

In summary, our novel PIVC was safe and beneficial for the administration of irritant drugs. Furthermore, this catheter is user-friendly, because it does not need a guidewire. Further studies, including a randomized controlled trials are warranted to further evaluate the effectiveness of the new PIVC.

## 5. Conclusions

A new catheter without a guidewire did not interrupt medical treatments after placement. The catheter placement success rate was 100%, thus resulting in no device malfunction at the catheter placement. Furthermore, no adverse events, including catheter-related bloodstream infection and CF, occurred. According to the results of the first-in-human trial to verify the safety of the new PIVC, this new catheter without a guidewire is safe for catheterization and administering drugs with a high potential for irritancy. In the case of a temporary occlusion alarm of the infusion pump, the causal relationship is unclear. We consider that the new PIVC is easily affected by the muscle contraction at the fixation position. Therefore, the position and the method of catheter fixation in the upper arm need to be considered.

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