**Title**

Challenging the distal-to-proximal cannulation technique for administration of anti-cancer therapies: a prospective cohort study

**Authors**

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**Conflicts of Interest:**

The authors declare that they have no conflicts of interest.

**Abstract:**

**Background:** Distal-to-proximal technique has been recommended for anti-cancer therapy administration. There is no evidence to suggest that a 24-hour delay of treatment is necessary for patients with a previous uncomplicated venous puncture proximal to the administration site.

**Objectives:** This study aims to identify if the practice of 24-hour delay between a venous puncture and subsequent cannulation for anti-cancer therapies at a distal site is necessary for preventing extravasation.

**Methods:** A prospective cohort study was conducted with 72 outpatients receiving anti-cancer therapy via an administration site distal to at least one previous uncomplicated venous puncture on the same arm in a tertiary cancer centre in Australia. Participants were interviewed and assessed at baseline data before treatment and on day 7 for incidence of extravasation/phlebitis.

**Results:** Of 72 participants with 99 occasions of treatment, there was one incident of infiltration (possible extravasation) at the venous puncture site proximal to the administration site and two incidents of phlebitis at the administration site.

**Conclusions:** A 24 hour delay is unnecessary if an alternative vein can be accessed for anti-cancer therapy after a proximal venous puncture.

**Implications for practice:** Extravasation can occur at a venous puncture site proximal to an administration site in the same vein. However, the nurse can administer anti-cancer therapy at a distal site if the nurse can confidently determine the vein of choice is not in any way connected to the previous puncture site through visual inspection and palpation.

**Introduction:**

Extravasation is a toxic local reaction caused by a drug or solution leaking into surrounding tissues, usually at the infusion site[1]. This is a serious complication of cytotoxic/vesicant therapy, often causing severe local pain and ulceration; which may progress to tissue destruction that requires corrective surgery[2-4]. Extravasation is relatively uncommon, occurring in around 0.01-6.5% of cytotoxic infusions[3, 5]. They may be under-reported due to the delayed nature of some reactions[6]. This low incidence rate makes testing of interventions preventing extravasation with randomised controlled trials challenging and unrealistic. Risk factors associated with extravasation include poor vein quality, obesity, co-morbid conditions such as diabetes and circulatory disorders; impaired sensory perception, use of rigid cannulae, and clinicians' lack of knowledge/skills[7].

The distal-to-proximal technique is the recommended clinical practice for preventing extravasation. This practice evolved from guidelines suggesting that intravenous anti-cancer therapies should not be administered in a limb where proximal venous punctures have occurred within the previous 24 hours[8]. Although the guidelines suggest that the preferred site for anti-cancer treatment administration is "proximal to venous puncture sites established within the preceding 24 hours"[1], and that practitioners should "avoid a vein that has been used for venous access in the previous 24 hours to prevent leakage"[3], the evidence on which these recommendations have been made is unclear. Sauerland and colleagues asserted that non-adherence to the distal-to-proximal technique increases the risk for extravasation injury[8].

However, most patients attending cancer care ambulatory units require phlebotomy for various tests before the administration of anti-cancer therapies. The cubital fossa is

the preferred site for phlebotomy, often occuring within several hours of a patient's anti-cancer treatment[9]. In most cases, this is not a problem; the anti-cancer infusion may be administered through the alternate arm. However, a proportion of patients do not have this option, due to lymphatic surgery, peripheral neuropathy (grade 4) or poor venous access or other reasons. Therefore, treatment may be delayed and the patient required to return on the following day. Apart from patient inconvenience, which may be significant, there are also some concerns that delaying anti-cancer therapy may compromise the efficacy of treatment, particularly in a curative intent setting[10, 11]. The inefficiencies within the treatment suite and additional stress experienced by patients and their families have led us to attempt to validate the guidelines. Our prospective cohort study is the first to investigate the incidence of extravasation associated with anti-cancer therapies at the infusion site distal to a previous puncture.

## Methods

### Study Design

A prospective cohort design with consecutive sampling was used in this study. Potential participants were recruited from a cancer care ambulatory unit of a tertiary cancer centre in Australia. Before the study began, the usual practice in our institution was that, no infusions were to be given at a site distal to a previous venous puncture within 24 hours. Over the study period, patients were administered anti-cancer therapies at a site distal to a previous venous puncture (phlebotomy or venous cannulation) if a proximal site could not be used. To our knowledge, there is no national guideline or policy that particularly informs practice in this area in Australia.

Patients receiving anti-cancer therapy with a proximal venous puncture (whether due to phlebotomy or cannulation attempts) to the anti-cancer infusion site within the previous 24 hours were eligible for inclusion. Patients were excluded if they were expected to have venous access (in the same limb) for the administration of other drugs, fluids or blood products within seven days; had a patent central venous access device (CVAD); were without access to a phone; or did not speak English. The study was approved by the Human Research and Ethics Committee at the Royal Brisbane and Women's Hospital, and patient consent was obtained before data collection. A set of questionnaires were administered on the day of anti-cancer therapy before drug administration and on day 7 post administration by a research nurse with an extensive experience in the administration of anti-cancer therapy. To facilitate the telephone interviews, patients were given a copy of the day 7 interview questionnaire including all the assessment scales and the Venous Puncture Assessment Tool (VPAT). Due to the cyclic nature of anti-cancer therapies, participants could be recruited on multiple occasions if they remained eligible for the subsequent presentations.

**Procedures**

The research nurse approached all eligible participants to explain the study. Participants were then consented. The consent could occur before or after cannulation for treatment as long as the participant fit the inclusion criteria of the study. At recruitment, the research nurse completed a baseline questionnaire. This included information about demographics and risk factors related to the development of complications, and the locations of venous punctures associated with anti-cancer therapy. On day 7 (+/- 24 hours), participants were advised to return to the clinic to be assessed by the research nurse. At the time of assessment, participants were asked about the condition of the infusion site and any other venous puncture sites above or

below the infusion site. Patients who could not return on day 7 were interviewed by phone. For those who returned to the clinic, both patient subjective assessment and nurse face-to-face assessment were carried out for inter-rater reliability. As part of routine clinical care, all patients were educated by their nurses to report any concerns immediately, or as soon as they identify any signs and symptoms associated with extravasation, even before day 7. The research nurse used an interview guide to ensure the consistency of speech across all interviews. All participants received an exact copy of the assessment tools to assist with the interview process via the phone.

**Intruments**

For the assessment of venous complications, the Vein Assessment Tool (VAT) [12], the Infusion Nurses Society Standards of Practice Infiltration Scale (INS- SPIS) [13], and the Infusion Nurses Society Standards of Practice Phlebitis Scale (INS-SPPS) [13, 14] were used. The scoring for VAT ranges from 0-2, with 0 indicating good vein quality, 1= fair vein quality, and 2= poor vein quality[12]. The scoring for the INS-SPIS ranges from 0-4, with 0 indicating no symptoms and 4 indicating the most severe symptoms associated with infiltration/ extravasation[13]. The scoring for the INS-SPPS ranges from 0-4, with 0 indicating no symptoms and 4 indicating the most severe symptoms of phlebitis. A diagnosis of extravasation required a review and confirmation by a medical officer. In this study, a new assessment tool, the Venous Puncture Assessment Tool (VPAT) including the anterior and posterior views of the both arms, was developed in collaboration with the Herston Multimedia Unit, Royal Brisbane and Women's Hospital to identify all puncture and administration sites (see Fig 1). The aim of the VPAT was to assist participants and the nurse to easily identify where previous puncture sites were on follow-up.

INSERT FIGURE 1

**Data analysis**

Data were entered and analyzed using SPSS®, version 17.0. The sample is described using frequencies for categorical data (such as gender and type of cancer/ anti-cancer therapy) and means/standard deviations for continuous data (such as age and haemoglobin). Using the number of participants enrolled in the study as the denominator and the total number of these participants who develop either an extravasation or phlebitis as numerators, we planned to calculate the proportion of participants developing an injury following administration of a cytotoxic infusion and their 95% confidence intervals. Rating between the research nurse and participants for extravasation and phlebitis were analysed using intraclass correlation coefficient.

**Results**

**Participant Characteristics**

In total, 3942 patients were screened for eligibility at the Oncology Day Therapy Unit. Eighty-two participants were eligible. Of these, 77 (94%) agreed to participate and 72 (88%) completed the study. A total of 99 cannulations occurred among the 72 participants between November 2010 and February 2011. All were for anti-cancer therapy and administered at a site distal to a previous venous puncture (a phlebotomy or failed cannulation attempts) in the same arm. Of the 99 occasions of anti-cancer treatment, 17 (16.83%) included at least one vesicant in the treatment protocol. In 66 cannulations, participants had at least one venous puncture at a proximal site due to phlebotomy. For phlebotomy, 21 gauge needles were used. For cannulation, 22 gauge and 24 gauge needles were used. The number of cannulation attempts required for anti-cancer therapy ranged from one to seven in the same arm. The total number of

venous puntures including phlebotomy ranged from two to eight in the same arm (see Table 4).

The demographic characteristics, medical and treatment information for the 77 participants are summarised in Table 1-3. The mean age was 58.4 (SD=17.7). The majority of participants were male (n=44, 62.1%). The mean vein access score was 0.5 (SD=0.7), indicating good to fair vein quality. The intraclass correlation coefficient for the rating of extravasation and phlebitis between the research nurse assessment and the participants was 1. Five participants could not be contacted for day 7 interview and were lost to follow up.

INSERT TABLE 1

INSERT TABLE 2

INSERT TABLE 3

INSERT TABLE 4

**Incidence of complications**

Of the 99 occasions of treatment, one infiltration was reported in one participant immediately at completion of the anti-cancer therapy. The infiltration occured at the proximal venous puncture site, which was complicated by a failed cannulation attempt. A 22 gauge needle was used during the failed cannulation attempt. The participant who developed an infiltration was  a 30 year-old obese woman with no other known risk factors. The participant had a diagnosis of squamous cell carcinoma of the cervix, (stage IIB), receiving 80mg cisplatin at 40mg/$m^2$/dose, over 60 minutes. This participant also received 1 litre of Normal Saline (0.9% Sodium Chloride) for both pre- and post-hydration over 1 hour each. This incident occurred after regular

working hours and the participant was not reviewed by a medical officer. Furthermore, it was unable to be determined whether the infiltration was caused by the chemotherapy or post-hydration fluid. The immediate assessment identified an infiltration score of 2: skin blanched, gross odema (2.5-15 cm), cool to touch, without pain. As a matter of precaution, extravasation management as per local policy was implemented. The patient was instructed to apply cold compresses for 15-20 minutes four times a day over the next 48 hours. The participant was also advised to return the next day to the clinic for follow up assessment, however the participant did not return. On day 7 follow-up, the participant presented with an an infiltration score of 1 with odema <2.5 cm persisting at the proximal venous puncture site. The vein where a previous puncture for cannulation occurred and the distal infusion site was determined to be the same vein through palpation and visual inspection. This participant was the only one who received treatment at a site distal to a previous venous puncture in the same vein.

**Phlebitis**

Of the 99 occasions of treatment , there were no incidence of phlebitis at the venous puncture sites proximal to the anti-cancer therapy administration site. One participant, who received 1640mg gemcitabine at 1000mg/$m^2$/dose over 30 minutes, developed phlebitis on two occasions between day 0 to day 7. The phlebitis was located within the vein in which the anti-cancer therapy was administered, between the distal administration site and the previous proximal venous punctures on each occasion. There were no signs of phlebitis at the previous venous puncture sites (phlebotomy sites).

**Discussion**

There is a lack of evidence underpinning the clinical practice of a 24-hour delay if the distal-to-proximal technique is not followed. Our study is the first to investigate the implications of administering anti-cancer therapies (including a range of vesicant and non-vesicant solutions) via a site distal to a previous venous puncture. All of the participants in this study received their anti-cancer therapy via an administration site distal to at least one previous venous puncture on the same arm, without any evidence of extravasation. In preparation for this study, a new instrument, the Venous Puncture Assessment Tool (VPAT) was developed (Fig 1); in collaboration with the multimedia unit at our institution. Using the VPAT, the participants and the nurse were able to identify all prior puncture sites during the telephone interview. It was easy to use by both the nurse and participants, and we believe it will be a useful addition to those involved in intravenous assessment practice and research.

The participants in this study had reasonably good vein access as measured by the VAT instrument. However, an average of three cannulation attempts proximal to the site for therapy administration were required. The usual practice in our institution was that the administration nurse could have two cannulation attempts. After two attempts, the nurse was to refer to a more experienced clinician (a nurse or a doctor). There was no specific policy with regards to the criteria for CVAD insertion in patients with numerous failed attempts at our institution. Therefore, patients were referred for CVAD insertion at the discretion of their treating clinicians. The participants in this cohort were mild or moderately unwell, recording, on average at least one comorbidity, which is probably consistent with the general cancer population.

Although an incident of extravasation could not be confirmed in this case, the finding of this study did support the claim that a leakage of fluid can occur within 24 hours at

a proximal venous puncture site if the same vein is used. In other words, the distal-to-proximal technique should still be considered when an alternative vein in the same arm cannot be accessed for anti-cancer therapy.

**Limitations**

The sample size in this study is relatively small. However, this is the first prospective study investigating a very important clinical question of interest. The incidence rates of extravasation and phlebitis were low and consistent with the literature. This may be due to high venepuncture skill levels among the experienced cancer care nurses involved in the trial. However, anti-cancer therapies are generally administered in units where high skill levels are available, so there is no reason why our findings may not be generalised to those units where staff are well trained in venepuncture procedures. It is also noteworthy that there were no patients with low platelet counts in this cohort. Participants with thrombocytopenia may need to receive extra caution as they may have delayed clotting and healing at the venous puncture site, which could, potentially increase the risk of extravasation.

**Implications for Practice**

The distal-to-proximal cannulation technique is recommended for anti-cancer therapy administration. While there remains a lack of evidence suggesting that administration at a site distal to the previous venous puncture may increase the risk of extravasation, our study reported that infiltration can occur at a venous puncture site proximal to an administration site in the same vein. However, the nurse can administer anti-cancer therapy at distal site if the nurse can confidently determine the vein of choice is not in any way connected to the previous puncture site through visual inspection, palpation or the use of a radiologic appliance. The nurse must have a good knowledge of the

anatomy of the veins of the arm. Consequently, there may be a case for modifying the guidelines to suggest that a 24 hour delay between a venous puncture and subsequent cannulation may not be necessary if an alternative vein in the same arm is available for use. Unnecessary delay of treatment that can increase the distress level of patients, cause a delay to the treatment regimen, and reduce the efficiency of care in a high volume cancer care ambulatory setting, can be avoided by effective nursing management.

## Conclusion

A 24 hour delay is not necessary if an alternative vein that is not in any way connected to the previous puncture site can be accessed for anti-cancer therapy. However, this study provides evidence that a leakage of intravenous fluid can occur at a previous puncture site proximal to the administration site if the same vein is used.

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Table 1. Sample demographic characteristics

| | *Mean* | *SD* | *Range* |
|---|---|---|---|
| Age | 58.4 | 17.7 | 18-90 |
| Height (cm) | 169.3 | 9.1 | 150-191 |
| Weight (kg) | 82.5 | 24.2 | 42-179 |
| | *Groups* | *Frequency* | *Percentage* |
| Gender | M | 44 | 61.1% |
| | F | 28 | 38.9% |
| Ethicity | Caucasians | 67 | 93% |
| | African | 1 | 1.4% |
| | South Pacific Islanders | 4 | 5.6% |

Table 2. Medical characteristics

| | *Groups* | *Frequency* | *Percantage* |
|---|---|---|---|
| Type of cancer | Haematological | 23 | 31.9% |
| | Head and Neck | 11 | 15.3% |
| | Lung | 8 | 11.1% |
| | Gynaecological | 8 | 11.1% |
| | Breast | 7 | 9.7% |
| | Genitourinary | 7 | 9.7% |
| | Gastroenterology | 6 | 8.3% |
| | CNS | 1 | 1.4% |
| | Sacoma | 1 | 1.4% |
| Metastasis | Yes | 22 | 65.3% |
| | No | 50 | 34.7% |
| | *Mean* | *SD* | *Range* |
| Haemaglobin (g/L) | 125.3 | 17.0 | 80-182 |
| White cells count ($x10^9$) | 7.6 | 4.8 | 2.7-32.7 |
| Platelets ($x10^9$) | 254.1 | 116.6 | 111-692 |
| Neutrophils ($x10^9$) | 5.3 | 4.5 | 0.9-29.6 |
| Number of comorbidities | 1.0 | 1.2 | 0-4 |
| Number of prior venuous punctures | 3.1 | 1.2 | 2-8 |
| Vein Assessment Tool (VAT) | 0.5 | 0.7 | 0-2 |

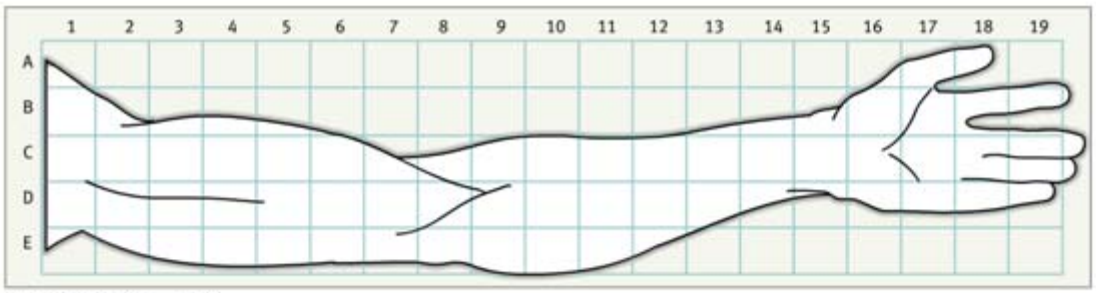
Table 3. Drug classification and number of cycle

| *Drug classification* | *Count* |
|---|---|
| Alkylating agent | 15 |
| Antimetabolite | 14 |
| Antitumour antibiotic | 14 |
| Bisphosphonate | 1 |
| Mitotic inhibitor | 12 |
| Miscellaneous | 2 |
| Monoclonal antibody | 17 |
| Platinum compound | 27 |
| Taxanes | 14 |
| Topoisomerase I Inhibitors | 1 |

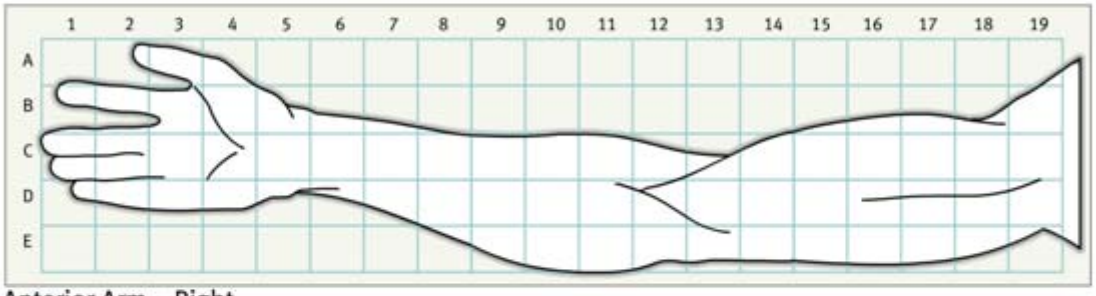
| | *Mean* | *SD* | *Range* |
|---|---|---|---|
| Number of cycle | 4.6 | 5.4 | 1-34 |

Table 4. Number of cannulation attempts required for anti-cancer therapy in the same arm and total number of venous punctures in the same arm

| *Number of cannulation attempts* | *Count* |
|---|---|
| One | 51 |
| Two | 20 |
| Three | 20 |
| Four | 6 |
| Five | 1 |
| Seven | 1 |
| *Total number of venous punctures (including cannulation attempts and phlebotomy)* | *Count* |
| Two | 62 |
| Three | 20 |
| Four | 11 |
| Five | 4 |
| Six | 1 |
| Eight | 1 |

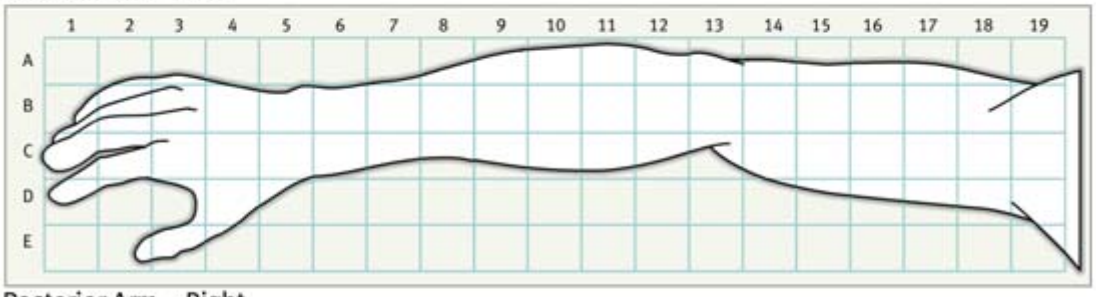



Anterior Arm - Left




Anterior Arm - Right


Posterior Arm - Left




Posterior Arm - Right

| | |
|---|---|
| 1. First attempt blood collection | a. First attempt cannulation |
| 2. Second attempt blood collection | b. Second attempt cannulation |
| 3. Third attempt blood collection | c. Third attempt cannulation |
| 4. Forth attempt blood collection | d. Forth attempt cannulation |

Figure 1. Venous Punctures Assessment Tool (VPAT)