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Original Article

One percent chlorhexidine-alcohol for preventing central venous catheter-related infection during intensive chemotherapy for patients with haematologic malignancies

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ABSTRACT

A central venous catheter (CVC) is a catheter placed into a large vein, and is used for chemotherapy administration. However, there is little confirmatory data on which antiseptic—such as chlorhexidine or povidone-iodine (PI) —is more protective against CVC-related infectious complications in patients receiving intensive chemotherapy. We aimed to compare the effectiveness of 1% chlorhexidine gluconate in 70% alcohol (CH) vs. PI for skin disinfection before CVC insertion in patients receiving intensive chemotherapy. Methods We used either CH or 10% PI as skin antiseptics before CVC insertion, and assessed which agent was more protective against CVC-related infection. The participants were 112 patients with haematologic malignancies who underwent chemotherapy; a total of 292 CVCs were inserted over this period. Blood cultures were obtained when febrile neutropenia occurred. The CVC was removed and the catheter-tip qualitatively cultured when catheter-related infection was suspected. The cumulative incidence of febrile neutropenia, microbial growth from blood or catheter-tip culture, and catheter-related blood stream infection (CRBSI) was evaluated retrospectively. A univariate Cox proportional hazards model showed that CH significantly alleviated infectious complications. Notably, no case of CRBSI occurred in the CH group. Multivariate analysis, adjusted for prolonged neutropenia (>15 days) and older age (>52 years), also showed significant reduction in the cumulative incidence of microbial growth from catheter-tips in the CH group (hazard ratio = 0.146, 95% confidence interval: 0.023–0.502, p = 0.0008). Disinfection using CH, compared with PI, can potentially decrease catheter-related infection without causing adverse skin reactions in patients with haematologic malignancies.

1. Introduction

A central venous catheter (CVC) is a catheter placed into a large vein, such as the internal jugular, subclavian, or femoral vein, and is commonly used to administer chemotherapeutic agents or total parenteral nutrition. We use CVC during chemotherapy administration to prevent the extravasation of vesicant drugs or for the large amounts of transfusion. However, CVC insertion and placement can itself cause several complications, such as artery puncture, hematoma, pneumothorax, and infections. Catheter-related blood stream infection (CRBSI) is a critical complication as it can be lethal [1], particularly during intensive chemotherapy because of the associated leucocytopenia. Hence, we should cautiously consider the risks and benefits of CVC insertion for each patient [2].

To lower the incidence of infectious complications, an antiseptic solution—such as chlorhexidine or povidone-iodine—is always used to clean the skin before insertion of the CVC. Chlorhexidine gluconate (>0.5%) in alcohol provides fast and long-lasting activity.

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It is advocated as the first-line antiseptic solution in some guidelines [3]. Although data from a prospective randomized controlled trial showed the protective effect of CH (vs. 10% povidone-iodine [PI]) for catheter-related infection [4], there is little confirmatory data on which antiseptic is more protective against CVC-related infectious complications in patients receiving intensive chemotherapy [5]. In addition, the optimal concentration of chlorhexidine has not been established. Some guidelines recommend PI as a suitable antiseptic for skin preparation before CVC insertion, provided it is allowed to dry completely [6,7].

Given the controversy, we aimed to compare the effectiveness of 1% chlorhexidine gluconate in 70% alcohol (CH) vs. PI for skin disinfection before CVC insertion in patients receiving intensive chemotherapy. To do this, we retrospectively evaluated the infectious events—febrile neutropenia (FN), microbial growth from blood culture, microbial growth from qualitative catheter-tip culture, and CRBSI—following CVC insertion using either CH or PI for skin disinfection.

2. Materials and methods

2.1. Study design and participants

This single-center, retrospective, observational study included patients who were admitted to the haematology ward in Nihon University Itabashi Hospital and received intensive chemotherapy via a CVC from 1st April 2011 to 31th March 2015 (n = 113). One patient, who underwent allogeneic stem cell transplantation and died because of graft failure, was excluded because we reinserted CVC several times because of non-infectious complications.

In almost all cases, a double-lumen CVC was inserted into the right internal jugular vein by a well-trained physician, one day prior to initiation of chemotherapy. We used maximal sterile barriers and an aseptic technique (including a sterile gown, gloves, and a large drape) for CVC insertion. We checked the vein with ultrasound examination before insertion and used either PI or CH disinfection by the physician's choice. In case of PI disinfection, we inserted the CVC once PI had dried completely. After insertion, we sutured the CVC to the skin to secure it, and used radiography to determine whether it was inserted properly at the insertion site. The insertion site was then immediately covered with a film dressing. The dressing was changed and the insertion site disinfected weekly, using the same aseptic that was used at the time of insertion. The dressing was also replaced if it was either peeling off or dirty.

Two sets of aerobic and anaerobic blood cultures were obtained from peripheral blood and the catheter hub if FN occurred, and broad-spectrum antibiotics were administered in all cases according to the Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenia Patients with Cancer [8]. Coagulase-negative staphylococci cultured from only one of four bottles was regarded as contamination. CVC was removed or reinserted if there is no improvement even after administration of appropriate antibiotics. We also removed the CVC if CRBSI was suspected, i.e., if a patient with a CVC in-situ developed fever or chills or had signs of infection at the CVC insertion site.

The cumulative incidence of FN, microbial growth from blood culture, qualitative culture of bacteria from the catheter-tip, and CRBSI was investigated, and we evaluated the effectiveness of each antiseptic, with data censored at the end of each chemotherapy cycle. CRBSI was diagnosed when the same organism grew from at least one percutaneous blood sample and the catheter-tip sample. This criterion is from Clinical Practice Guidelines for the Diagnosis and Management of Intravascular Catheter-Related Infection by Infectious Disease Society of America (IDSA) [9].

2.2. Statistical analysis

Differences among groups were analyzed using one-way analysis of variance. Receiver operating characteristic (ROC) curves were drawn using logistic regression analysis to determine the cut-off value where Youden's index is maximal, and a Cox proportional hazards model was used to generate a hazard ratio (HR) with confidence interval (CI) for each factor. Finally, each factor whose $P < 0.1$ was adjusted for in the multivariate model. $P < 0.05$ was considered statistically significant.

2.3. Ethical considerations

This study was approved by the local ethics committees (RK-150908-17). Informed consent from each patient were not required for this study because of retrospective observational setting. We posted opt-out notification poster.

3. Results

3.1. Patient characteristics

A total of 112 patients were included in this study. Between them, 292 CVCs were inserted with either CH or PI by the physician's choice from January 2011 to March 2015. The characteristics of the study participants are summarized in Table 1. Owing to the retrospective nature of the study, baseline characteristics differed between the PI and CH groups. The median age was higher in the PI group (54.0 vs. 46.5 years, $P \leq 0.0001$), and the median duration of neutropenia was longer in the PI group (9 vs. 14 days, $P = 0.0015$). Age, disease, and proportion of haematopoietic stem cell transplantations did not differ significantly between the groups.

3.2. Catheter-related infectious complications

The cumulative incidence of infectious complications was analyzed using the log-rank test. Infectious complications—measured until recovery of neutropenia—were significantly lower in the CH group, compared with the PI group, as follows: FN (HR = 0.704, 95% CI: 0.537–0.923, log-rank p = 0.0092) (Fig. 1A), microbial growth from blood culture (HR = 0.563, 95% CI: 0.329–0.961, log-rank p = 0.0474) (Fig. 1B), microbial growth from catheter-tip culture (HR = 0.139, 95% CI: 0.058–0.329, log-rank p = 0.0018) (Fig. 1C), and CRBSI (log-rank p = 0.0034) (Fig. 1. D). There is no incidence of FN and microbial growth from blood culture after CVC removal. Using a Cox proportional hazard model to identify confounding factors, we found a significant unfavorable association between some infectious complications and patients with a longer duration of neutropenia (>15 days) or who were older (age >52 years), as shown in Table 2A–C). Those thresholds were decided according to the ROC curve.

In the multivariate analysis, although the cumulative incidence of FN and microbial growth from blood culture did not differ significantly between the groups, the cumulative incidence of microbial growth from the catheter-tip culture was significantly lower in the CH group, irrespective of the strong influence of neutropenia duration and age (HR = 0.146, 95% CI: 0.023–0.502, p = 0.0008) (Fig. 1C). No episodes of CRBSI were observed in the CH group, whereas 12 episodes occurred in the PI group. Of the 12 episodes, 75% were caused by Gram-positive cocci. The pathogenic microorganisms were as shown in Table 3.

3.3. Adverse skin reactions

In this study, no adverse skin reactions were observed in either group.

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