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Prevention of central venous catheter occlusion by saline with or without heparin in intensive care unit after surgical intervention: a double-blind, randomized trial

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ABSTRACT

Heparinized saline is used to prevent catheter obstruction; however, it is associated with concerns regarding the incidence of heparin-induced thrombocytopenia and the accuracy of the blood test results. This study compared the impact of saline with and without heparin on central venous catheter occlusion rates in post-surgical intensive care unit patients using a prospective, double-blinded, randomized, controlled design. Patients aged 20–90 years planned to experience central venous catheter insertion and postoperative intensive care unit admission were enrolled and were randomly assigned to either the heparin group (administered normal saline with heparin) or the control group (administered normal saline alone), based on a 1:1 ratio. Nurses blinded to patient allocation performed the occlusion assessment (every 24 h). The Kaplan–Meier curve was used to assess the time to occlusion or removal of each catheter. Central venous catheter insertion results of 136 patients showed no significant variation in occlusion rates between the heparin and control groups within the first 3 days. There was no significant difference between normal saline with and without heparin in preventing central venous occlusion in the intensive care unit up to 3 days post-surgery. The results of this study suggest that it is not necessary to use normal saline with heparin in the management of central venous catheter occlusion, at least when moving from the operating room to the intensive care unit.

Keywords: central venous catheter, heparin, occlusion management

Abbreviation:
CVC: central venous catheters

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INTRODUCTION

In intensive care units (ICUs), critically ill or postoperative patients frequently receive care through the use of central venous catheters (CVCs). Central venous systems are accessed through CVCs for administering fluids, medications, parenteral nutrition, blood products, and monitoring central venous pressure.[1,2] Normal saline containing heparin has been used for the prevention of occlusion of the catheter in daily clinical practice in Japan. The use of heparin has been shown to decrease the risk of CVC occlusion and prolong the average duration of use of the CVC line.[3-5] However, heparin treatment can cause complications including heparin-induced thrombocytopenia (0.5–5.0%), leading to bleeding despite low-dose administration.[6-9] Some studies indicate the saline solution and heparinized solution are equivalent.[10-12]

Normal saline enhances coagulation test accuracy, shields patients from heparin risks, and boosts patient safety. However, an optimal method for the prevention of CVC line obstruction in the immediate postoperative ICU remains to be established. Heparinized saline or saline bolus injections are administered at the discretion of the anesthesiologist during transfer from the operating room (OR) to the ICU for the prevention of CVC occlusion. This study compared catheter occlusion rates during jugular venous catheter management between saline- and heparinized-saline groups in ICU surgery patients using a prospective, double-blinded, randomized, controlled design. It was hypothesized that using heparin for CVC management might lower catheter occlusion rate more effectively than saline alone.

MATERIALS AND METHODS

Study design

This study, approved by institutional review board (IRB) #2018-0330 of our institution, was conducted with informed consent from all participants. The University Hospital Medical Information Network registered the trial (UMIN 000033713) before patient enrolment. Patients aged 20–90 scheduled for CVC insertion in the OR and ICU admission between February 2019 and August 2019 were screened for eligibility. The following individuals were excluded: those requiring continuous ICU heparin administration, those with pre-existing blood coagulation disorders, those unable to continue participation, those hypersensitive to heparin, those requiring more than two insertion attempts, those requiring anticoagulant or fibrinolytic medications, those concurrently participating in another study, and those with a history of coagulopathy and a platelet count below 50,000/mm^3. The exclusion criteria after the initiation of the trial were as follows: requirement for continuous administration of heparin or anti-coagulation therapy after initiating the study.

Randomization

After obtaining informed consent and recording demographic data, patients were randomly assigned (using a computer program) to receive either heparinized saline or normal saline. An independent operator prepared the allocation sequence without involvement in the trial. An optimal balance was achieved using an age-stratified permuted block method, with strata for those aged 20–55 and 56–90 years. Dedicated study personnel assigned patients to one of the two groups at a 1:1 ratio in a separate environment. The group allocation was known solely to the pharmacists who prepared the drugs.

Blinding

Five mL of either saline or heparin (5000 IU/5 mL) was dispensed by pharmacists into clean vials labeled with the study ID, following randomization. The vials contained indistinguishable, colorless and transparent drugs. Each patient's room received the prepared medications. All involved in the procedure, including surgeons, nurses, anesthesiologists in the OR and ICU, and patients, were unaware of the treatment groups. The prepared drugs and recorded data of each group were managed using unique identification codes. The anesthesiologists responsible for the surgical interventions and the ICU were not involved in the processing of the syringes, randomization, or postoperative evaluation, thereby ensuring double blinding.

CVC management and evaluation

An anesthesiologist inserted the CVC (Arrow quad-lumen central venous catheterization kit, Cardinal Health KK, Japan, Tokyo)[13] in the OR, and blood collection, connection of infusion routes, and establishment of a closed circuit were performed using the following equipment: Sure-plug AD, TERUMO Co, Japan, Tokyo.[14] A negative pressure type plug was used in this study such that the drug solution in the lumen of the CVC moves to the syringe side when the syringe is operated. A blue part (Fig. 1) with slide locks was used to seal each lumen.[13] One of the four lumens of the CVC was used to evaluate occlusion. Based on the group allocation, 1 mL of the flushing solution was diluted 10-fold with normal saline (10 mL normal saline or 100 UI/mL of heparin). The lumen of the CVC was evaluated using a syringe with natural force after admission to the ICU to confirm the ability to aspirate blood immediately, and 10 mL of the diluted solution was administered through the evaluation lumen. The lumen was locked using the blue part, and the syringe was retracted. The patency of the CVC was considered to be preserved if blood could be aspirated using a syringe with natural force. Patency was assessed once immediately after admission to the ICU and thereafter, once daily from the following day, ie, at the end of the nurse's day shift or during the removal of the CVC. Patency was confirmed immediately before the CVC was removed at the time of discharge from the ICU, and this was

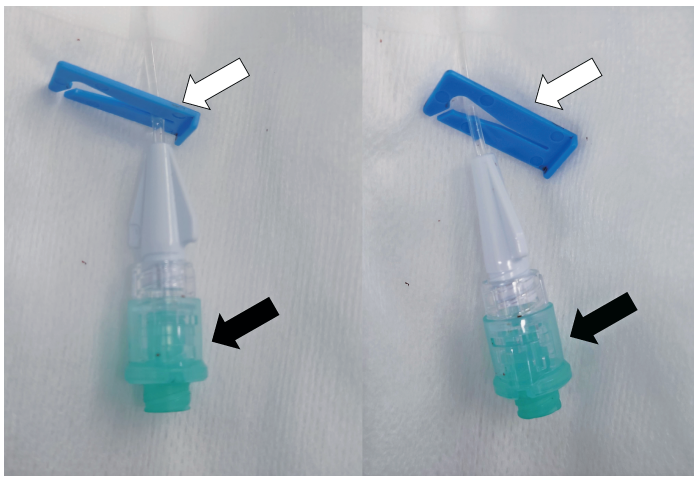

Fig. 1 A blue part with slide lock and connection part
Left: a lumen is locked by a blue part (white arrow).
Right: a lumen is not locked using a blue part.
Black arrow: connection part.[14]

regarded as the patency time. One nurse carried out the procedure while two nurses conducted the assessment. The time to occlusion, removal of the catheter, or discharge from the ICU was defined as patency time.

Statistical analyses

The sample size for demonstrating equivalence between two proportions was estimated using the Makuch and Simon method.[15] We assumed a 20% CVC occlusion rate in the control group, considered differences in proportions insignificant if they were ≤20%, set alpha at 0.05, and aimed for 80% statistical power. Sixty-five catheters would be required in each group, assuming no loss of follow-up.[16] Seventy-five patients were added to each group as contingency for potential dropouts and heightened variance. Kaplan–Meier curves were used to depict the occlusion rates, which were compared using the log-rank test. Qualitative variables and demographic data, including age, weight, height, and body mass index, were compared using the *t*-test. Pearson's chi-square test was used to analyze categorical data. A *p*-value of <0.05 was considered statistically significant. The statistical analysis was carried out via SAS version 9.4 (SAS Institute Inc, Cary, NC, USA) and Stata 16 MP (StataCorp, College Station, TX, USA).

RESULTS

Among the 246 patients who were assessed for eligibility between February 2019 and August 2019, 75 were excluded and 21 declined. Thus, 150 patients were randomly allocated two groups, each containing 75 patients. Fourteen patients, comprising six from the heparin group and eight from the control group, were excluded after applying the exclusion criteria (requirement for anti-coagulation therapy) after starting the trial. Thus, the data from 136 patients (study group, n = 69; control group, n = 67) were included in the final analysis (Fig. 2).

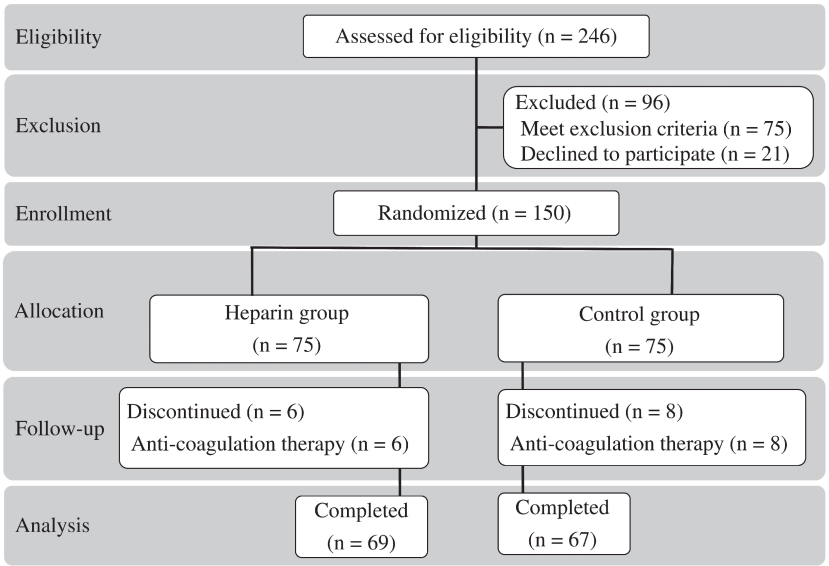

Fig. 2 Consort diagram

Table 1 Demographic and surgical characteristics

	Central venous catheter*		
	Study group (n = 69)	Control group (n = 67)	*p*-value#
Age (years)	66.3 ± 14.6	65.5 ± 14.3	0.75
Height (cm)	160.8 ± 9.3	160.0 ± 15.4	0.70
Body weight (kg)	59.4 ± 12.3	58.5 ± 12.1	0.68
Body mass index (kg/m²)	22.8 ± 3.3	23.8 ± 12.1	0.54
Male:Female	44:25	39:28	0.51
Catheter insertion site (n)			
Internal jugular vein	69	67	NS
Surgical characteristics (n)			
Gastroenterological surgery†	26	30	NS
Cardiac surgery	21	20	NS
Vascular surgery‡	10	10	NS
Brain surgery	7	3	NS
Urological surgery	3	3	NS
Oral surgery	0	0	NS
Head and neck surgery	0	1	NS
Respiratory surgery	0	0	NS
Orthopedic surgery	1	0	NS
Gynecological surgery	1	0	NS

Data are presented as mean ± standard deviation or number (of patients), as appropriate.
NS: not significant

* The patients were allocated to one of the following two groups using a computer-generated randomization program: the study group (normal saline with heparin) and the control group (normal saline without heparin).

Statistical significance of the differences between the two groups was assessed using two-tailed *t*-test and chi-square test. A *p*-value of <0.05 was considered statistically significant.

† Gastroenterological surgery includes esophageal, gastrointestinal, hepatobiliary, and pancreatic surgery.

‡ Vascular surgery includes Y-grafting, lower limb vascular surgery, and thoracic and abdominal endovascular aortic repair.

Sufficient cases were included to provide the desired statistical power. Analysis of the patients' data (age, height, body weight, sex) and surgical characteristics revealed no significant differences between the groups (Table 1). The primary outcomes of the study are presented in Figure 3. The Kaplan–Meier curve displays the time from ICU admission to the occlusion of each catheter or removal of the catheter before discharge from the ICU (Fig. 3). No significant between-group differences were observed in the occlusion rate (p = 0.61). No adverse or unintended effects were observed in either group (Table 2).

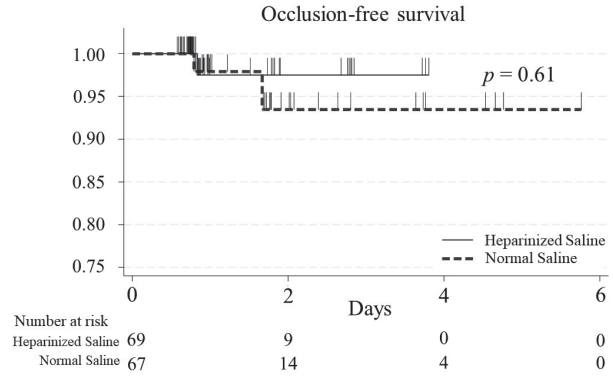

Fig. 3 Kaplan–Meier curves at removal
The Kaplan–Meier curves depict the time from admission to the intensive care unit to the occlusion or removal of the central venous catheters.

Table 2 Unintended results of the study

	Central venous catheter group*		
	Study group (n = 69)	Control group (n = 67)	*p*-value
Patient death (n)	0	0	NS
Re-examination of blood collection due to abnormal test values (n)	0	0	NS
Reasons for removal (n)			
For leaving intensive care unit	49†	46†	NS
Patient removal	0	0	NS
Occlusion	0	0	NS
Reasons for occlusion (n)			
Natural catheter occlusion	2	1	NS

Data are presented as mean ± standard deviation, interquartile range, or as number (of patients), as appropriate.
NS: non-significant
* Patients were allocated to one of the following 2 groups using a computer-generated randomisation program: study group with central venous catheter (normal saline with heparin), control group with central venous catheter (normal saline without heparin).
# Statistical significance of the differences between the 2 groups was assessed using two-tailed *t*-test and chi-square test. A *p*-value of <0.05 was deemed to indicate statistical significance.
† The central venous catheter that was not removed at the time of discharge from the intensive care unit was also used in the general ward.

DISCUSSION

This study contrasted catheter occlusion rates during CVC management in post-surgical ICU patients between normal saline with and without heparin. The present study revealed that the patency of the CVC line was retained for the first 3 days with the use of normal saline alone or in combination with heparin in patients admitted to the ICU after surgery, thereby rejecting the null hypothesis. The results of this study can be used to prevent CVC occlusion during transfer from the OR to the ICU and during short-term ICU stay.

The use of heparin for the prevention and management of catheter blockage has been a subject of debate and disagreement. A recent Cochrane Review reported no significant difference in the incidence of CVC obstruction in pediatric patients following saline and heparin flushing.[17] However, it must be noted that the studies included in this systematic review were heterogeneous owing to differences in the types of cancer, heparin concentrations, frequency of flushing the CVCs, and methods for evaluating occlusion. A 2022 Cochrane Review of adults also concluded that it is unclear whether the incidence of CVC obstruction after intermittent locking with heparin is less than that after intermittent locking with saline, and low-certainty evidence suggested that heparin may have little or no effect on catheter patency duration.[18]

Previous reviews have provided insufficient evidence to justify the use of saline-only for the management of obstruction in daily practice at our hospital. Therefore, this study was conducted in a clinical setting at our hospital to determine whether catheter occlusion management with open flushes every 24 hours results in different occlusion rates in a surgical ICU where postoperative patients are admitted only for a short period of time, and to evaluate whether it is tolerated. The majority of patients included in this study were discharged from the ICU by day 3 and had the CVC removed. Thus, this study did not examine the long-term prevention of obstruction. However, the results of this study can be used to prevent CVC occlusion during transfer from the OR to the ICU and during short-term ICU admission. Upon admission to the ICU, blood sampling immediately after cleansing the CVC lumen with heparinized saline may affect the results of blood sampling for coagulation function tests and may cause heparin-induced thrombocytopenia. Our data show that it is not necessary to use heparinized saline when transferring patients from the OR to the ICU, as there is no advantage in terms of the CVC obstruction rate.

The features of the drip route connection of the CVC are an important consideration. When a syringe is connected to a negative pressure plug, the drug fluid in the CVC line flows back into the plug from the patient side and blood flows back into the CVC line. In contrast, a positive pressure plug has a structure in which the drug solution is extruded when a syringe is connected to the plug. In the former circumstance, without a part to clamp each lumen (Fig. 1), the patient's blood may flow back into the CVC line and clot when the syringe is inserted or removed. In this study, a difference in the occlusion rate was avoided, possibly because great attention was paid to maintaining patency of the CVC line. Therefore, in facilities with no positive pressure plugs, patients should be closely monitored to minimize cases of CVC line occlusion.

The limitations of this research are noted. Patients in good condition, who underwent scheduled surgery and were admitted to the short-term ICU, were the study subjects. These results may not be suitable for long-term management in patients with severely deteriorated conditions. Second, the observation period may have been insufficient because most patients left the ICU on day 2; therefore, the log-rank test originally assumed might have been inappropriate. Third, the incidence of rare adverse events, such as heparin-induced thrombocytopenia, was not recorded as only patients with short ICU stays were included in this study. Finally, the estimated sample size was based on an expected occlusion rate of 20%; however, the actual occlusion rate was only 2–3%. Further, there may have been differences in the prevalence of thrombophilia, stemming

from factors such as racial predisposition and patient backgrounds. Nonetheless, we believe our results provide a foundation for the design and sample size estimation of larger, prospective studies involving patients with long-term stays in the ICU. Effective clinical outcomes warrant further investigation through well-designed trials assessing heparin with normal saline.

In conclusion, the use of normal saline with heparin or normal saline alone for the management of the CVCs resulted in no differences in the occlusion rate in patients admitted to the ICU for a short duration after surgical intervention. The results of this study suggest that it is not necessary to use normal saline with heparin for the prevention of CVC occlusion, at least when moving from the OR to the ICU.

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CONFLICT OF INTEREST

The authors have no conflicts of interest in relation to this work.

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