Use of Saline Flush to Prevent Filter Clotting in Continuous Renal Replacement Therapy without Anticoagulant

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***Objective**: This study aims to compare filter life between saline flushed and non-saline flushed strategies in critically ill patients at high risk of bleeding who are undergoing CRRT without anticoagulation.*
***Material and Method**: A cohort of 121 critically ill patients with severe acute kidney injury (AKI) requiring CRRT in the medical intensive care unit (ICU) and cardiac care unit (CCU) of a tertiary care academic center were included. 78 of them used saline flushed through CRRT circuit.*
***Results**: There was no significant difference between the two groups of treated patients in baseline characteristics, including the extent of coagulopathy and platelet count. Mean circuit survival was 21.2 h for circuits using saline flush and 20.4 h for those using non-saline flush (p = 0.8).The Kaplan-Meier curves revealed no difference in circuit survival time between saline flushed and non-saline flushed groups (p = 0.8).*
***Conclusion**: The use of saline flush into pre-filter site of CRRT circuit does not provide any benefit on circuit clotting prevention in high-risk of bleeding patients requiring CRRT without anticoagulant.*

***Keywords:** Critical illness, Acute renal failure, Acute kidney injury, Hemofiltration, Continuous renal replacement therpy, Anticoagulant*

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Acute kidney injury (AKI) is a common complication in intensive care units[1]. Up to two thirds of intensive care unit patients will develop AKI defined by the RIFLE classification, and approximately 4-5% of general intensive care unit patients will be treated with renal replacement therapy[2]. Continuous renal replacement therapy (CRRT) has recently emerged as the dialysis technique of choice for critically ill patients and is superior to intermittent dialysis for fluid and metabolic control[3]. During CRRT, blood is conducted through an extracorporeal circuit, activating coagulation by a complex interplay of patient and circuit.

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Initiation of clotting in the extracorporeal circuit traditionally has been attributed to contact activation of the intrinsic coagulation system. Activation of tissue factor, leucocytes and platelets play an additional role[4]. Other reasons for premature clotting related to the CRRT technique are repeated stasis of blood flow in tiny filter fibers[5], hemoconcentration, turbulent blood flow and blood air contact in air-detection chambers[6]. Recent international survey on the treatment of critically ill patients with AKI demonstrated that the greatest concerns with CRRT included anticoagulation, dialyzer clotting, nursing workload, lack of standards and cost[7]. Successful application of CRRT depends on adequate filter and extracorporeal circuit life, resulting of appropriate anticoagulation. Anticoagulant management, therefore, is an important aspect of the care of patients receiving CRRT. A major goal of anti-coagulation is to ensure smooth operation of ICU care,

to minimize time spent changing the circuit, to maintain adequate dialysis clearance, and to minimize the costs associated with CRRT. Unfortunately, anticoagulant might be contra-indicated for patients with coagulopathy, ongoing bleeding, and those who have undergone major surgery. Recent study has showed that CRRT without anticoagulant in patients at high risk of bleeding could be safely used with minimal bleeding risks and was associated with an acceptable filter life[8]. In this case, several intensive care units advocate the use of frequent saline flushes to remove pro-coagulant material from the filter on a regular basis, for example, every 30 to 60 minutes. However, this procedure is associated with increased risk of contamination, infection, and nursing workload. This strategy also inevitably provokes 200 to 300 ml of saline added into patients' circulation (Fig. 1) every 1 hour, leading to more difficulty in fluid management in severe AKI patients. In addition, from our experience we have observed that clotting in extracorporeal circuits does not frequently occur in the filter, but it arises in the venous drip chamber (Fig. 1). Saline flushes through the extracorporeal circuit at the pre-filter site might introduce dislodged blood clots from the filter leading to an accumulation of clots in the venous drip chamber (Fig. 1).

There was no information regarding whether we should utilize saline flushes in CRRT without anticoagulation. We, therefore, conducted a retrospective study in order to compare filter life between saline flushed and non-saline flushed strategies in critically ill patients at high risk of bleeding who are undergoing CRRT without anticoagulation. The present study also focused on predictors for the filter survival times in such patients.

Material and Method

Study population

We conducted a retrospective cohort of critically ill patients with severe acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT) in the medical intensive care unit (ICU) and cardiac care unit (CCU) during January 2004-December 2006 at the Siriraj Hospital (a large tertiary care academic center with 1,200 beds in Bangkok, Thailand). The study protocol was approved by the hospital ethics committee. The need for informed consent was waived because the study required no intervention and no breach of privacy or anonymity as such projects are considered quality improvement activities by the Institutional Ethics Committee.

According to the hospital policy, all CRRT treatments in our hospital are performed using continuous venovenous hemofiltration (CVVH) technique. Patients were enrolled only if they received CRRT without the use of anticoagulant. Based on our unit guideline, patients should receive CVVH without anticoagulant if 1) there is ongoing bleeding, 2) there has been a major hemorrhage in the last 48 h, 3) they have had surgery in the last 24 h or 4) they have either an activated partial thromboplastin time (aPTT) more than 60 second, an international normalized ratio (INR) greater than 2 or a platelet count less than 60 x 10^3/mm^3.

Interventions

CVVH was performed using the Aquarius CRRT (Edwards Lifesciences, UK) machine together with 1.4 m^2 synthetic polysulphone filter (APS-650, Asahi, Japan). Blood access was established with a 11.5 Fr central venous hemodialysis catheter. The blood flow rate (Qb) was 150-200 mL/min and the ultrafiltration flow (Quf) was kept between 1,500-2,000 mL/h. Customized bicarbonate-based solution containing Na^+ 140, K^+ 2-4, HCO_3^- 33, and Ca^{2+} 3.3 mEq/L was used as replacement fluid in the pre-dilution mode. The fluid loss rate was set as clinically indicated.

We assessed for the potential benefit of the saline flushed strategy on filter life of critically ill patients undergoing CRRT without anticoagulant. In the saline flushed group, saline flush was carried out by infusing 200 to 300 ml of 0.9% saline into the arterial limb of extracorporeal circuit (Fig. 1) every 1/2 to 1 h. The aims of this strategy are to cleanse the filter and to prevent clotting in filter and CRRT circuit.

Data analysed

The patient data including demographic,

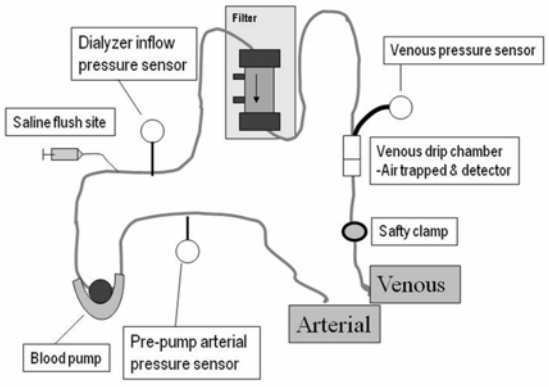

Fig. 1 Standard extracorporeal circuit

physiologic, laboratory and hospital outcome information was retrieved from medical notes or a computer database. The demographic and clinical data included age, sex, serum creatinine and blood urea nitrogen before the CVVH initiation (pre-CVVH creatinine and pre-CVVH BUN), degree of baseline pre-CVVH coagulopathy [aPTT, prothrombin time (PT) and platelet count], use of mechanical ventilator, indication of renal replacement therapy, and intensive care unit (ICU) mortality.

We utilized Sequential Organ Failure Assessment (SOFA) score as an indicator of ICU severity[9].

With regard to CRRT-related data, only the first CRRT circuit used in each patient had the following data collected: circuit life (h), use of saline flush and the reasons for circuit change. According to standard care of patients undergoing CRRT in our hospital, the CRRT circuit is routinely changed every 72 h. The reasons for premature circuit change were divided into 3 categories: (a) clotted; (b) access malfunction; (c) an unrelated patient issue [*e.g.* patient's death, the patient went to the radiology department or operating room, or the patient regained renal function].

Statistical analysis

Statistical analysis and calculations were performed using SPSS statistical package, version 13.0 (SPSS Inc, Chicago,IL). Data are presented either as actual numbers and percentages or mean ± standard deviation (SD) for Normally-distributed data and median (minimal-maximal) for nonnormally-distributed variables. Comparison between saline flushed and non-saline flushed groups was analyzed by using student t-test (normality) and Mann-Whitney U-test (non-normality) numerical values and Chi-square test for categorical data. Circuit survival for both methods was compared using log-rank test with Kaplan-Meier analysis. Circuits were censored for Kaplan-Meier analysis if changed because of access malfunction or unrelated patient issues. A p-value < 0.05 considered statistically significant.

Results

During the studied period, 121 patients admitted in ICU and CCU were treated by CVVH without anticoagulant. The mean age was 62.2 ± 15.3 years and 63 of 121 (52%) were male. Saline flushed strategy was performed in 78 patients (64.5%) and non-saline flushed method was done in 43 cases (35.5%). A summary of the clinical and demographic data for the two groups is presented in Table 1. There was no significant difference between the two groups of treated patients in indication of renal support, and in baseline characteristics except serum creatinine level. Both groups were comparable in the extent of coagulopathy (Table 1). As expected, a

Table 1. Clinical characteristics of critically ill patients undergoing CVVH without anticoagulant according to the use of saline flushed strategy

	Non-saline flush (n = 43)	Saline flush (n = 78)	p-value
Age (years)	58.6 ± 17.4	64.1 ± 13.7	0.06
Gender (M/F)	25/18	38/40	0.42
SOFA score	13.9 ± 2.9	14.0 ± 2.8	0.88
Indication of renal support			0.43
Acidosis	11 (26%)	18 (24%)	
Volume overload	11 (26%)	14 (21%)	
Azotemia	19 (44%)	36 (46%)	
Hyperkalemia	2 (5%)	10 (10%)	
Mechanical ventilation	36 (83.7%)	71 (91%)	0.25
aPTT (second)	48.7 ± 28.5	43.0 ± 22.9	0.23
PT (second)	23.6 ± 12.7	23.4 ± 10.8	0.95
Platelets (x 10^3 /mm^3)	130 ± 79	128 ± 81	0.89
BUN (mg/dl)	82.2 ± 36.4	74.8 ± 36.4	0.29
Creatinine (mg/dl)	5.9 ± 3.6	4.5 ± 2.5	0.02
Survival	11 (25.6%)	13 (16.7%)	0.35

CVVH: continuous venovenous hemofiltration; SOFA: Sequential Organ Failure Assessment; aPTT: activated partial thromboplastin time; PT: prothrombin time; BUN: blood urea nitrogen.

degree of baseline pre-CVVH coagulopathy (aPTT more than 1.5 x normal or INR greater than 1.5 x normal or platelet count lower than 100 x $10^3/mm^3$) was seen in most of patients. Hemofilter lifespan was not significantly correlated with aPTT, INR, or platelet count in either group.

Circuit survival and clotting rates

Mean circuit survival was not different between circuits using saline flush (21.2 $\pm$ 2.0 h) and those using non-saline flush (20.4 $\pm$ 3.1 h, p = 0.8). The reasons for untimely CRRT circuit change are depicted in Fig. 2. Circuit clotting (58%), patient's death (31%), and vascular access problems (4%) were the most common reason to alter the CRRT circuit. The causes of premature circuit change between the two groups were similar.

Of all patients, 8 cases (4 in saline flushed and 4 in non-saline flushed groups) remained using the first set of CRRT circuit until the scheduled change according to hospital policy (at 72 h) (Fig. 2).

As shown in Fig. 3, the survival curves for extracorporeal circuit revealed no circuit survival difference between saline flushed and non-saline flushed groups (p = 0.8). Log-rank analysis demonstrated that 39% of the saline flushed group, and 35% of the non-saline flushed group were functional at the 20th hour. Since vascular access malfunction may also aggravate circuit clotting, we performed an additional Kaplan-Meier analysis where circuits changed for access malfunction were no longer censored for log-rank analysis. CRRT circuits receiving either saline flush or non-saline flush demonstrated similar survival time (p = 0.99)

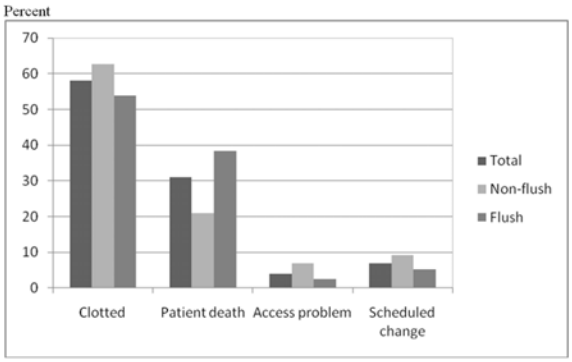

Fig. 2 The percentage of the reasons of CRRT circuit change requirement in studied patients according to the use of saline flushed strategy

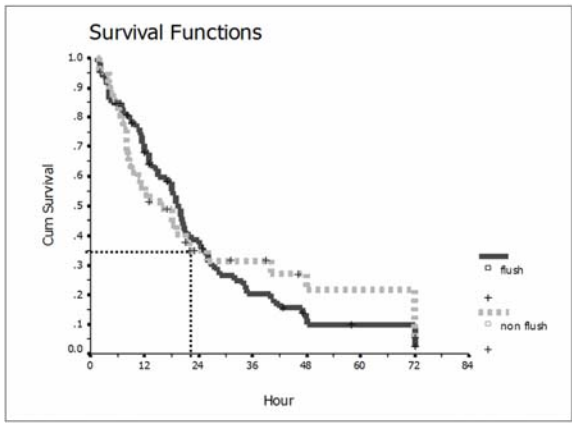

Fig. 3 Kaplan-Meier survival curves indicating CRRT circuit survival times between saline flushed and non-saline flushed groups. The difference in circuit survival between the two groups is not statistically significant (p = 0.8)

Discussion

Acute kidney injury (AKI) commonly develops in critically ill patients. Despite improvement in critical care technology, the mortality rate associated with AKI in the intensive care unit (ICU) have remained relatively high and are extremely higher in severe AKI patients requiring renal replacement therapy (RRT). CRRT has made extracorporeal treatment possible also in critically ill patients, even when they are hemodynamically unstable, in order to balance hypercatabolism and fluid overload. The key success factor of the CRRT is to maintain the patency of the extracorporeal circuit continuously by means of anticoagulant therapy. However, the potential disadvantage of the use of anticoagulant to prevent clotting of the extracorporeal circuit is bleeding complications. The risk of bleeding in critically ill patients is high because of frequent disruption of the vascular wall and coagulopathy.

Unfractionated heparin is the most commonly used anticoagulant worldwide for CRRT because it is inexpensive and user-friendly, but its disadvantages include risk of hemorrhage, heparin resistance and heparin-induced thrombocytopenia. Therefore, clinicians search for alternatives such as CRRT without anticoagulation[8,10-12] increasing natural anticoagulants, minimal systemic anticoagulation, or regional anticoagulation. Of the alternative methods, citrate anticoagulation is gaining wider acceptance. Unfortunately, the simplified and safer protocols for citrate anticoagulation are not yet available in Thailand. In addition, ionized calcium level monitoring is

mandatory and this requirement makes the use of this anticoagulation method not feasible in primary and secondary care hospitals in Thailand. Practically, most critically ill patients with bleeding tendency who require renal support are administered CRRT without the use of anticoagulant. Interval circuit saline flushing has been proposed as an inexpensive, albeit time-consuming and workload-increasing method. It might overcome build-up of cellular and macromolecules constituents of clotting, thereby prolonging circuit lifespan. There has never been a study using this method in patients undergoing CRRT. We therefore, conducted the presented study to validate the potential benefit of saline flushed strategy on filter life and CRRT circuit survival for critically ill patients undergoing CRRT without anticoagulant.

The clinically relevant finding which emerged from our investigation is that the interval saline flushed method provided a similar extracorporeal circuit lifespan to the non-saline flushed method. The mean circuit survivals were approximately 20 hr in both groups. There are several mechanisms potentially responsible for this phenomenon. The first is that patients in both group had similar degree of coagulopathy from low levels of coagulation factors and thrombocytopenia. The second reason is that patients in our study were severely ill as evidenced by their higher SOFA score (14 in both groups) and extremely high ICU mortality (75-85%). Subsequently, a number of patients died while the CRRT circuit was still functioning (Fig. 2) leading to a shorter circuit lifespan in both groups. The last explanation is that by our observations, the clogging of CRRT circuit mostly occurs in the venous drip chamber (Fig. 1), not in the filter. The saline flushed strategy aims to cleanse and prevent the occurrence of clotting in the filter (Fig. 1). On the contrary, small blood clots removed from the filters were washed down and deposited within the venous drip chamber located in the distal part of CRRT circuit. Indeed, the blood-air interface in the venous drip chamber promotes more clotting formation.

We argue that with regard to the risk of microorganism contamination, as well as time and workload consumption, it is not worthwhile to use saline flushed strategy in patients with bleeding tendency who require CRRT. In addition, 200 ml of saline flush every 1 hour will be added into patients' circulation. As a result, we have to remove this amount of fluid (4,800 ml in 24 h) via the ultrafiltrate of extracorporeal circuit leading to more difficulty in fluid management in critically ill patients, who have potential risk to hypotension and fluid overload. Our results indicate that an important determinant of premature circuit clotting is performing CRRT without the use of anticoagulant. The circuit survival of 20 h in our study is not different from that of recent studies. Uchino et al reported the mean circuit survival of 19.3 h in patients requiring CVVH without anticoagulant[12]. The recent study by Normohamed et al. have demonstrated that the median filter life was 12 h in patients undergoing CVVH with no anticoagulant[13]. In contrast, Tan et al have shown that the mean circuit life in patients receiving CVVH without anticoagulation was higher (32 h) than that of our patients. The difference between Tan's study and our study is that they utilized a vascular access with a larger diameter (13.5 Fr) than that used in our study (11.5 Fr). Consequently, their larger dialysis catheter permitted higher Qb (250 ml/min) than Qb set in our CVVH circuit (150-200 ml/min). Premature clotting reduces circuit life and efficacy of treatment and increases blood loss, workload, and costs of treatment. Therefore, improving circuit life is clinically relevant. If use of anticoagulant is contraindicated, we recommend considering alternate measures to prevent circuit clotting such as a use of large bore catheter for achieving the Qb up to 250 ml/min and an increase the rate of pre-dilution replacement fluid. Our study also confirms that the use of saline flushing into the CRRT circuit does not provide any benefit in prevention of filter and circuit clotting.

The present study is limited by the fact that its design is that of a retrospective cohort and the population was relatively small, reflective of only medical ICUs in a single center.

In conclusion, the use of saline flush into pre-filter site of CRRT circuit does not provide any benefit in high-risk of bleeding patients requiring CRRT without anticoagulant.

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Potential conflicts of interest

None.

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การใช้น้ำเกลือนอร์มัลล้างตัวกรองเพื่อป้องกันการอุดตันของตัวกรองในผู้ป่วยที่ล้างไตแบบต่อเนื่องซึ่งไม่ได้รับสารกันเลือดแข็ง

ศิริรัตน์ ปานพันธุ์โพธิ์, เสาวนีย์ เนาวพาณิช, รณิษฐา รัตนะรัต

วัตถุประสงค์*: เพื่อศึกษาความแตกต่างของการใช้และไม่ใช้น้ำเกลือนอร์มัลล้างตัวกรองต่อจำนวนชั่วโมงของการใช้ตัวกรองในผู้ป่วยที่มีความเสี่ยงต่อภาวะเลือดออกซึ่งฟอกเลือดแบบต่อเนื่องโดยไม่ได้รับสารกันเลือดแข็ง*

วัสดุและวิธีการ*: ศึกษาในผู้ป่วยวิกฤติ 121 ราย ที่มีความเสี่ยงต่อภาวะเลือดออกและรักษาโดยการฟอกเลือดแบบต่อเนื่องโดยไม่ได้รับยาต้านการแข็งตัวของเกล็ดเลือด ในหอผู้ป่วย ไอ.ซี.ยู. และหอผู้ป่วย ซี.ซี.ยู. โรงพยาบาลตติยภูมิโดยเป็นกลุ่มที่ไม่ใช้น้ำเกลือนอร์มัล 43 รายและกลุ่มที่ใช้น้ำเกลือนอร์มัล 78 ราย*

ผลการศึกษา*: ข้อมูลพื้นฐานรวมทั้งภาวะ coagulopathy และปริมาณเกล็ดเลือดของทั้งสองกลุ่มไม่มีความแตกต่างกัน ระยะเวลาเฉลี่ยของการใช้ CRRT circuit ในกลุ่มที่ใช้น้ำเกลือนอร์มัลล้างตัวกรอง 21.2 $\pm$ 2.0 ชั่วโมงและในกลุ่มที่ไม่ใช้น้ำเกลือนอร์มัลล้างตัวกรอง 20.4 $\pm$ 3.1 ชั่วโมง ($p = 0.8$) เมื่อเปรียบเทียบโดยใช้ Kaplan-Meier analysis พบว่าไม่มีความแตกต่างใน circuit survival time ระหว่าง 2 กลุ่ม ($p = 0.8$)*

สรุป*: การใช้น้ำเกลือนอร์มัลล้างตัวกรองเพื่อป้องกันการอุดตันวงจร CRRT ไม่มีประโยชน์ในการป้องกันการอุดตันของ CRRT circuit ในผู้ป่วยที่มีความเสี่ยงต่อภาวะเลือดออกซึ่งฟอกเลือดแบบต่อเนื่องโดยไม่ได้รับสารกันเลือดแข็ง*