Continuous renal replacement therapy without anticoagulation in high-risk patients: predictors of circuit life

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1. Study Purpose and Rationale

Acute renal failure (ARF) is a common condition in the intensive care unit (ICU) and approximately 4% of such patients require renal replacement therapy [1]. Continuous renal replacement therapy (CRRT) is widely adopted in the treatment of severe ARF because of its strength of improved hemodynamic stability and better solute control. However, the main concern with CRRT is the ongoing need for continuous anticoagulation to prevent the activation of coagulation cascade within the circuit. Attempts to run CRRT without anticoagulation generally result in frequent clotting of the circuit. Studies have shown that frequent clotting affects treatment efficacy and increases circuit "down time" which can affect azotemic control [2].

Currently, heparin is the most common choice of anticoagulant given its relative low cost and ease of administration. In a recent large, multi-center, prospective study, bleeding complications in patients on CRRT was approximately 3.3% [1].However, in patients at high-risk of bleeding (from coagulopathies, recent surgery etc.), the reported incidence of bleeding episodes on low dose heparin range from 10-50%. One study found that for every 10 second increase in PTT, the incidence of circuit coagulation was decreased by 25%, but the risk of bleeding increased by 50%[3]. Thus, in the high-risk patients, the need for anticoagulation needs to be balanced against the increased risk of bleeding.

Given the risk of bleeding, several drugs have been used for anticoagulation during CRRT as an alternative to heparin, such as prostacyclin, citrate, hirudin, LMWH, and nafamostat mesilate. However, most of these drugs are costly or require closer monitoring, and the simplest technique in patients at high-risk of bleed is to perform CRRT without any kind of anticoagulation. One prospective observational study showed that there was no significant difference in mean circuit life among high-risk patients undergoing CRRT without anticoagulation compared to patients with low dose heparin anticoagulation who were not at risk for bleed [4]. Another prospective study found that patients at high-risk of bleed who underwent CRRT without anticoagulation had a longer circuit life compared to those who were not at risk and received heparin, possibly as a result of "auto-anticoagulation" from their coagulopathies. Thus, they concluded that CRRT can be safely managed without circuit anticoagulation in high-risk patients [5].

In this study, we hypothesize that CRRT in high-risk patients without anticoagulation yields a comparable circuit life to that of patients undergoing heparin anticoagulation who are not at risk of bleed. Furthermore, we will evaluate what the predictors of circuit life are in patients undergoing CRRT without anticoagulation. This will have important clinical implications as if we are able to identify the predictors of circuit life and as a result, prolong circuit life, we can avoid frequent filter changes and increase treatment efficacy.

2. Study Design and Statistical Analysis

This is a prospective observational cohort study of patients with severe ARF undergoing CRRT. Primary endpoint will be comparing the mean circuit life between the patient undergoing CRRT with heparin anticoagulation and the patients deemed to be high-risk for bleed who will undergo CRRT without anticoagulation. Furthermore, multiple linear progression will be used to identify predictors of circuit life in the high-risk group.

Assuming a mean circuit life of 30 hours with a standard deviation of 10 hours among patients undergoing CRRT with heparin anticoagulation, in order to detect a 5 hour reduction in circuit life with 80% power among the high-risk patients using the t-test, the sample size will be calculated as follows:

$$n=1+16\ (10/5)= 65$$

Thus, we will have 65 patients in each group. The circuit life for each individual will be obtained by averaging the circuit life of 5 consecutive filters. If there is a change in the patient's clinical status and the patient switches from the no-risk group to high-risk group or vice versa, only the data from the first treatment will be used. Circuit life between the 2 groups will be compared using a log-rank (Mantel-Cox) test. A multiple linear progression will be used to identify predictors of circuit life in the high-risk group. In all cases, a p-value less than 0.05 will be considered statistically significant.

3. Study Procedure

Patients with acute renal failure undergoing CRRT will be examined. The following baseline characteristics will be evaluated for all patients:

- Age
- Gender
- APACHE score
- Premorbid renal function
- Blood pressure-MAP
- Contributing factors to ARF
- Reasons for initiation of CRRT
- Duration of CRRT
- Mechanical ventilation
- Inotropic drugs

CRRT includes continuous venonvenous hemofiltration (CVVH), continuous hemodialysis (CVVHD) and continuous hemodiafiltration (CVVHDF). Blood pump flow speed will be kept between 150-300ml/min. Commercially available bicarbonate-buffered solution or lactate buffered solution will be used as dialysate (CVVHD) and/or replacement fluid (CVVHDF of CVVH), and will be infused either precircuit or postcircuit.

Patients who fulfill any of the following criteria will be included in the high-risk patient group: (1) INR>2 (2) Platelets<50,000/ul (3) APTT>60seconds (4) less than 48h post-surgery (5) ongoing bleed or major hemorrhage within the last 48 hrs. These patients will undergo CRRT without heparin anticoagulation. Control patients who are not at high-risk for bleed will be given low-dose heparin (5-10IU of heparin/kg/hr) as standard circuit anticoagulation.

For each circuit, the following data will be obtained in addition to circuit life to evaluate for predictors of circuit life: mode of CRRT, heparin use, blood pump flow rate, ultrafiltrate or dialysate flow rate, type of buffer solution, and timing of fluid infusion. In the high-risk group, these variables along with lab values of coagulation factors and platelets will be assessed to identify factors that predict circuit life.

Routine blood tests will be performed daily in the mornings, which will consist of platelet count, PT-INR, APTT, hematocrit, urea and creatinine. For each circuit, hematocrit, platelet count, PT-INR, and APTT will be defined as the values measured in the morning of the day the circuit was used. If a circuit lasted more than 2 days, averaged values will be used

The criteria adopted for circuit failure will be one of the following: (1) visible clots in the filter (2) two-fold increase in transfilter pressure gradient (difference between circuit pressures pre and post-hemofilter) (3) more than 50% decrease in ultrafiltration rate.

4. Study subjects and method of recruitment

All patients who have ARF requiring treatment with CRRT in the intensive care unit at Columbia Presbyterian Medical Center will be prospectively observed. Prospective collection of data on circuit life is an ongoing quality assurance activity, and requires no intervention other than documentation. Thus, there will be no requirement for informed consent under these circumstances. Subjects will not have to be recruited for this prospective observational study.

-Inclusion criteria: Critically ill patients with severe acute renal failure undergoing CRRT in the ICU, age over 18

-Exclusion criteria: Patients with any dialysis treatment before admission to the ICU or patients with end-stage renal disease on chronic dialysis will be excluded

5. Study Drug

Not applicable.

6. Medical Device

Device for continuous renal replacement therapy will be used.

7. Study Questionnaires

There will be no questionnaires administered to patients.

8. Confidentiality of Study Data

Each study subject will be assigned a unique coding number under which all data will be recorded. These data will be stored in a secure location accessible only to the investigators.

9. Potential Conflicts of Interest

There are no conflicts of interest for the investigators in this study.

10. Study Location

This study will be conducted at New York Presbyterian/Columbia University Medical Center.

11. Potential risks

For patients undergoing CRRT without anticoagulation, there is the possibility of frequent clotting, thus leading to longer “down-time”, and ultimately to compromise of azotemic control. For control patients undergoing CRRT with heparin anticoagulation, there is risk of bleeding (around 3%), thrombocytopenia, vascular thrombosis, and development of heparin induced thrombocytopenia.

12. Potential benefits

For high-risk patients undergoing CRRT without anticoagulation, the risk of bleed is greatly reduced. Identifying predictors of circuit life will help prolong circuit life, which in turn, will help to improve treatment efficacy.

13. Alternative therapies

For patients at high-risk for bleed, there have been alternative therapies looking at safer ways of prolonging circuit life. Regional anticoagulation with heparin and protamine has been looked at with favorable results]; however, there is a risk of rebound anticoagulation, and meticulous dose adjustment and frequent monitoring of coagulation parameters are needed.

Low molecular weight heparin (LMWH) is superior to unfractionated heparin (UFH) in that is causes less platelet activation, has a more constant bioavailability, and a lower incidence of heparin induced thrombocytopenia. A recent, randomized controlled cross over study looking at UFH and LMWH showed a longer circuit life with LMWH with a similar safety profile [10].

Citrate causes anticoagulation by chelation of ionized calcium, and its effects is reversed by the infusion of calcium postcircuit. Citrate has been demonstrated in many studies to prolong circuit life; however there is the risk of metabolic derangements such as hypocalcemia and metabolic alkalosis. Moreover, it requires a special infusion solution which can be costly.

Prostacyclin causes vasodilation and inhibits platelet aggregation which causes anticoagulation. The main concern with prostacyclin is hypotension, and platelet function also needs to be monitored carefully.

Hirudin, a direct inhibitor of thrombin and has no cross-reactivity with heparin or LMWH, and is used as a first line drug in heparin induced thrombocytopenia. This substance is cleared by the kidney.

All of the above drugs are costly, and have never shown to reduce bleeding complications compared to low dose heparin in randomized trials.

14. Compensation to subjects

There will be no monetary compensation for participation in this study.

15. Cost to subjects

There will be no additional costs to the subjects.

16. Minors as research subjects

There will be no minors enrolled in this study.

17. Radiation of radioactive substances

Not applicable.

18. References

1. Uchino S et al. Continuous renal replacement therapy: A worldwide practice survey : The Beginning and Ending Supportive Therapy for the Kidney (B.E.S.T. Kidney) Investigators. Intensive Care Med. 2007 Jun 27

2. Uchino S, Fealy N, Baldwin I, Morimatsu H, Bellomo R. Continuous is not continuous: the incidence and impact of circuit "down-time" on uraemic control during continuous veno-venous haemofiltration. Intensive Care Med. 2003 Apr;29(4):575-8. Epub 2003 Feb 8.

3. Van de Wetering J, Westendorp RG, van der Hoeven JG, Stolk B, Feuth JD, Chang PCl. Heparin use in continuous renal replacement procedures: the struggle between filter coagulation and patient hemorrhage. J Am Soc Nephrol. 1996 Jan;7(1):145-50

4. Uchino S, Fealy N, Baldwin I, Morimatsu H, Bellomo R. Continuous venovenous hemofiltration without anticoagulation. ASAIO J. 2004 Jan-Feb;50(1):76-80.

5. Tan HK, Baldwin I, Bellomo R. Continuous veno-venous hemofiltration without anticoagulation in high-risk patients. Intensive Care Med. 2000 Nov;26(11):1652-7.

6. Morabito S, Guzzo I, Solazzo A, Muzi L, Luciani R, Pierucci A. Continuous renal replacement therapies: anticoagulation in the critically ill at high risk of bleeding. J Nephrol. 2003 Jul-Aug;16(4):566-71.

7. Uchino S, Fealy N, Baldwin I, Morimatsu H, Bellomo R. Pre-dilution vs. post-dilution during continuous veno-venous hemofiltration: impact on filter life and azotemic control. Nephron Clin Pract. 2003;94(4):c94-8.

8. Abramson S, Niles J. Anticoagulation in continuous renal replacement therapy. Curr Opin Nephrol Hypertens. 1999 Nov;8(6):701-7. Review.

9. Amanzadeh J, Reilly RF Jr. Anticoagulation and continuous renal replacement therapy. Semin Dial. 2006 Jul-Aug;19(4):311-6. Review.

10. Joannidis M, Kountchev J, Rauchenzauner M, Schusterschitz N, Ulmer H, Mayr A, Bellmann R. Enoxaparin vs. unfractionated heparin for anticoagulation during continuous veno-venous hemofiltration: a randomized controlled crossover study. Intensive Care Med. 2007 Jun 12;