COMPLICATIONS OF REGIONAL CITRATE ANTI-COAGULATION FOR CRRT: AN OBSERVATIONAL STUDY

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Abbreviations:

- AKI: Acute Kidney Injury
- AEs: Adverse events/effects
- CVVH: Continuous Veno-Venous Hemofiltration
- CVVHD: Continuous Veno-Venous Hemodialysis
- CRRT: Continuous Renal Replacement Therapy
- HDD: Hemodialysis dependency
- HIT: Heparin Induced Thrombocytopenia
- ICU: Intensive Care Unit
- PRBCs: Packed Red Blood Cells
- RCA: Regional Citrate Anticoagulation

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Introduction

Regional citrate anticoagulation (RCA) is the recommended anticoagulation modality for continuous renal replacement therapy (CRRT). RCA was associated with a low rate of complications in randomized controlled trials. However, little is known about the type and rate of complications in real life. We sought to describe complications associated with RCA in comparison with those associated with heparin anticoagulation.

Methods

In our institution, RCA has been the default anticoagulation modality for CRRT in all patients without contra-indications since 2013. We have retrospectively reviewed all consecutive patients who received CRRT between January and December 2016 in our institution. For each CRRT session, we have assessed circuit duration, administered dose as well as therapy associated complications. Those parameters were compared according to whether the circuit was run in continuous veno-venous hemodialysis (CVVHD) mode with RCA or continuous veno-venous hemofiltration (CVVH) mode with heparin anticoagulation.

Results

We analyzed 691 CRRT sessions in 121 patients. Of those 400 (57.9%) were performed in CVVHD-RCA mode and 291 (42.1%) in CVVH-Heparin Mode. Compared with CVVH-Heparin mode, CVVHD-RCA mode was associated with a longer circuit lifespan (median duration 54.9 (IQR 44.6) vs 15.3 hours (IQR 22.4), $p<0.0001$).). It was associated with a higher rate of metabolic acidosis (77 (20.2%) vs 18 (7.2%) ($p<0.0001$), alkalosis 186 (48.7%) vs 43 (17.1%), ($p=0.0001$) and hypocalcemia (96 (25.07%) vs 26 events (10.79%), ($p<0.0001$). However, the majority of these alterations were of benign or moderate severity. Only one possible citrate intoxication was observed.

Conclusions

CVVHD-RCA was associated with a much longer circuit life but an increased rate of minor metabolic complications, in particular acid-base derangements. Some of these complications might have been prevented by therapy adaptation. Medical and nursing staff education is of major importance in the implementation of a RCA protocol.

Introduction

Regional Citrate Anticoagulation (RCA) is the recommended anticoagulation strategy for continuous renal replacement therapy (CRRT) in patients without contra-indications (1). The safety of RCA protocols has largely been addressed in many clinical conditions in several randomized controlled trials (2–4). Together, these studies have demonstrated RCA superiority over systemic heparin anticoagulation in terms of filter lifespan, bleeding complications without increasing the rate of metabolic alkalosis (5). Large, observational studies from centers with extensive experience with RCA (6) confirm these results and report a very low rate of metabolic complications and citrate intoxications in unselected patients undergoing CRRT. RCA might even be safe in patients with severe liver failure (7).

Despite these compelling evidence and the seemingly obvious benefit of the modality, its acceptance and utilization remain relatively low throughout the world. Indeed, in a sub-analysis of the international observational Do-RE-MI-FA study (8), RCA was utilized in less than 20% of circuits while no anticoagulation at all was still frequently prescribed. This seems like a minor increase compared with the BEST KIDNEY cohort in which RCA was utilized in less than 10% of circuits (9). Another (yet unpublished) study from France suggested that, in units with low experience with RCA, filter lifespan was not superior to heparin while the rate of complication was higher. For these reasons, many intensivists throughout the world seem to remain reluctant to introduce RCA in their units as it is seen as *complicated*, *requiring intensive training* and might lead to complex metabolic complications. Real life data, coming from a center with intermediate experience with RCA and outside the context of a randomized trial are therefore needed.

We therefore decided to retrospectively review data from all CRRT sessions performed in our center during the calendar year 2016, 3 years following the introduction of RCA as a default anticoagulation regimen for CRRT. We sought to evaluate the type and rate of complications associated with RCA compared with systemic heparin anticoagulation during CRRT.

Methods

Ethics

The study protocol was approved by the Ethics Committee Vaud (CER-VD 2017-00008). The need for specific individual informed patient consent was waived due to the observational nature of the study. However, patients who declined our institution general consent for data reutilization were excluded from the study.

Study design

This is a monocentric retrospective observational study conducted in the adult intensive care unit (ICU) of the Centre Hospitalier Universitaire Vaudois (CHUV), a tertiary, teaching hospital located in Lausanne, Switzerland. The ICU contains 35 beds and records approximately 2000 admissions per year. All consecutive patients admitted to our ICU between January and December 2016 and who received CRRT were included in the study. As mentioned, patients who declined consent for data reutilization were excluded.

CRRT initiation

Our institutional protocol does not specify strict recommendations for CRRT initiation. All therapies were evaluated on a case-by-case basis by treating physician.

CRRT delivery

All therapies were delivered using Multifiltrate Pro® CRRT generators (Fresenius Medical Care, Bad Homburg, Germany). Therapies were set in a standardized way according to our unit protocol. According to this protocol, RCA represented the default anticoagulation method for CRRT. In patients with contra-indications (PT<40% in the absence of anti-vitamin K therapy (as a marker of severe liver failure), serum lactate level > 4mmol/l and need for >25 μg/min of norepinephrine (as markers of circulatory shock), systemic anti-coagulation with heparin was considered. As per the manufacturer's instruction, circuits were electively replaced after 72 hours of running time.

CVVHD-RCA

CRRT with RCA was delivered in continuous-veno-venous-hemodialysis (CVVHD) mode with standard solutions (CiCa® dialysate and 4% (136 mmol/l) trisodium citrate solution) following an

adapted Fresenius® protocol(10). Dialysate flow rate was adapted according to patients' dry weight aiming for a dose slightly above 25 ml/kg/h. Citrate solution flow was started at 4 mmol per liter of blood and titrated according to post-filter ionized calcium measurements. Calcium reinfusion solution consisted in 100 mmol/l $CaCl_2$ solution infused at a rate of 1.7 mmol/l effluent and titrated according to systemic ionized calcium measurements. Total calcium was regularly monitored throughout the therapy.

CVVH-Heparin

CRRT with systemic heparin anticoagulation was delivered in pre- post-dilution continuous-veno-venous-hemofiltration (CVVH) mode with standard substitution solution (Multibic®). Initial dose was set at 25ml/kg/h with approximately 33% of the dose delivered as pre-dilution. Heparin was administered as a continuous infusion via a separate central or peripheral venous line. Heparin infusion was titrated to aim for an anti-Xa activity between 0.3 and 0.6 IU/ml.

In patients with contra-indications to both RCA and heparin, a similar protocol was followed but with a lower anti-Xa activity target or no anticoagulation at all according to clinician's judgement.

Data Collection

Patients' characteristics and outcomes

All data were manually collected using electronic chart records (Metavision®, IMD Soft, Tel Aviv, Israel) and Soarian® (Cerner, North Kansas City, USA). We collected patients' characteristics on admission as well as ICU and hospital outcomes (survival, length of stay and dialysis dependence). For the purpose of the study, dialysis dependence was defined as the receipt of any form or renal replacement therapy (RRT) within 72hrs of discharge. For patients with multiple ICU stays, only the first was considered for baseline data and the last for outcome data.

CRRT Sessions

For all included patients, we then reviewed all consecutive CRRT sessions. A CRRT session was defined as the period of time during which a single CRRT set was connected to a patient. Temporary disconnections were considered as part of a session (recirculation mode). For each session, we have recorded: therapy modality (CVVH or CVVHD), anticoagulation method, delivered dose, filter lifespan and reason for interruption and complications.

Complications

Electronic medical records were screened for biological alterations occurring during each CRRT session. To assess for complications, we recorded the lowest and highest values of pre-determined parameters during a session and the following 12 hours. The following pre-defined complications were recorded: thrombocytopenia (thrombocyte level <150 G/L), hypothermia (body temperature <35°C), metabolic acidosis (pH < 7.35 and/or BE < -2), metabolic alkalosis (pH > 7.45 and/or BE > 2), hypocalcemia (serum calcium <1.05 mmol/L), hypernatremia (serum sodium >145 mmol/L) and significant hemorrhage (recorded in medical notes and/or >2 red packed cells transfused during sessions). Classifications of alterations are detailed in table 1 of the Appendix. Alterations present on therapy initiation (pre-existing anomaly) or with an obvious alternate explanation were not considered. For CRRT sessions ran in CVVHD-RCA mode, we also collected changes in blood or dialysate pump flow rate as well as total over ionized calcium ratio and need for calcium substitution to assess citrate intoxication. For this part of the study, only filters with a lifespan longer than six hours were considered.

Delivered dose

Delivered dose was estimated as the total of dialysate or pre and post-dilution flow rates. For this part of the study, only filters with a lifespan longer than six hours were considered.

Statistical Analysis

Continuous data with normal distribution are reported as mean (standard deviation) and compared using Student t-test. Non-normally distributed data are reported as median (interquartile range) and compared using Mann–Whitney U test. Ordinal data are reported as number (percentage) and compared by means of Fisher's exact or Chi-square test as appropriate. Kaplan-Meier survival analyses with log-rank test were used to compare circuits' lifespan. A two-sided P value < 0.05 was considered significant. Prism 8.0.1 and SPSS version 25 were used for statistical analyses.

Results

Patients' demographics

During the study period (Fig. 1), 1806 patients (2011 admissions) were admitted to our ICU. Of those, 137 (7.6%) required RRT including 16 who denied institutional consent to participate in research.

Hence, 121 patients (126 stays) were included in this study and analyzed. Their characteristics on ICU admission are presented in table 1. Briefly, 81(66.9%) were males, their median age was 69 years (IQR 11) and median weight 79.9 kg (IQR 25). Median Charlson score was 6.0 (IQR 4.0) and 48 (39.7%) had some degree of pre-existing chronic kidney disease, including 18 (15.1 %) who required chronic hemodialysis. The main reason for ICU admission was sepsis (24.6%) followed by cardiogenic shock (15.9%) and hemorrhagic shock (8.7%).

Outcomes

Among the 121 patients included in the study, 48 (39.7%) died while in ICU and 10 (8.3%) while on the ward (overall in-hospital mortality 47.9%). Median ICU length of stay was 8.9 (IQR 15.1) days, median hospital length of stay was 23.7 (IQR 41.2) days. Among survivors, 44 (59.5%) required RRT on ICU discharge (including 16 with pre-existing ESRD) and 26 (41.3%) required RRT on hospital discharge (including 13 with pre-existing ESRD).

CRRT sessions

Altogether, 691 CRRT sessions were administered to eligible patients for a total duration of 26'055 hours (1'085.6 days). Of those, 400 (57.9%) were performed in CVVHD-RCA mode and 291 (42.2%) in CVVH-Heparin mode. Among all considered ICU admissions, both modalities were sequentially administered in 44 (34.9%) admissions. A single modality was used throughout other admissions, CVVHD-RCA in 51 (40.5%) and CVVH-Heparin in 31 (24.6%).

Filter lifespan

As presented in figure 2, CVVHD-Citrate mode was associated with a longer filter life compared with CVVH-Heparin (median duration 54.9 hours (IQR 44.6) vs 15.3 hours (IQR 22.4), $p<0.0001$). This difference remained even when CVVH-Heparin sessions during with less than 625 UI/h of heparin was administered, were excluded ($p<0.0001$), Fig.1 of the Appendix. As shown in table 2, in CVVHD-RCA mode, only 28 (8.8%) of the sessions were interrupted as a result of filter clotting versus 113 (42.8%) in CVVH-heparin mode ($p<0.0001$). As a consequence, median delivered dose was much higher during sessions in CVVHD-RCA mode: 1.5 (IQR, 1.2) L/kg compared to 0.5 (IQR, 0.7) L/kg in sessions in CVVH-Heparin mode ($p<0.0001$).

Complications

Complications occurring during CRRT were assessed in 636 CRRT sessions with a duration >6hrs (385 CVVHD-RCA, 251 CVVH-Heparin). Main results are presented in Figure 3 and 4.

Electrolytes

Hypocalcemia occurred more frequently during CVVHD-RCA sessions compared with CVVH-Heparin sessions: 96 (25.07%) vs 26 events (10.79%), p<0.0001. However, this difference disappeared when only moderate and severe hypocalcemia (<0.95 mmol/L) were considered (5 (1.3%) vs 3 (1.2%) p=0.99). There was no difference in the rate of observed hypernatremia between the two modalities 13 (3.4%) vs 4 (2.0%) (p=0.44).

Acid-base balance

Overall, metabolic acidosis occurred more frequently during CVVHD-RCA sessions compared with CVVH-Heparin sessions (77 (20.2%) vs 18 (7.2%) (p<0.0001). When only severe (pH<7.20 and/or BE<-6) acidosis was considered, no statistically significant difference was observed between the two groups (16 (4.2%) vs 6 (2.4%) (p=0.27).

Similarly, metabolic alkalosis, was more frequently observed during CVVHD-RCA sessions than during CVVH-Heparin sessions: 187 (48.8%) vs 43 (17.1%), (p=0.0001). This different persisted even when only severe (pH>7.60 and/or BE>6) alteration were considered (54 (14.1%) vs 0 (0%)(p<0.0001).

Therapy adaptations

Blood pump flow was adapted at least once in 53 (13.8%) CVVHD-RCA circuits and dialysate flow in 38 (9.9%).

Citrate intoxication

One patient with severe circulatory shock was diagnosed with citrate intoxication although he did not fulfill all criteria (peak total / ionized calcium ratio 2.40). For this patient, therapy was replaced with CVVH-Heparin and the clinical situation eventually improved.

Another patient had a transient elevated total/ionized calcium ratio (peak 2.53) with no other sign of intoxication. Therapy was maintained with parameters normalization over 48 hours. This situation was therefore not considered as citrate intoxication.

Hematological complications

The incidence of thrombocytopenia was similar during CVVHD-RCA and CVVH-Heparin sessions (6.6 vs 11.1% ($p<0.07$). However, when only severe (<100G/l) alterations were considered, there was less thrombocytopenia in therapies ran in CVVHD-RCA group 3 (0.8%) compared to CVVH-Heparin mode 15 (6.4%), $p<0.0001$.

Clinically significant hemorrhage were observed at a similar rate during CVVHD-RCA and CVVH-Heparin sessions (23 (5.6%) vs 11 (4.4%) ($p=0.47$). Similarly, there was no difference in terms of number of sessions during which >2 PRBC were transfused (35 (9.1%) vs 22 (8.8%), $p=0.99$).

Heparin induced thrombocytopenia (HIT) was diagnosed in one patient while undergoing CVVH-Heparin CRRT.

Other complications

The rate of documented hypothermia (body temperature <35°) was similar during CVVHD-Citrate and CVVH-Heparin sessions (29 (7.5%), 22 (8.8%), $p=0.55$).

Discussion

Summary of key findings

We performed a retrospective observational study on 691 consecutive CRRT sessions to assess the rate and the severity of complications associated with RCA outside the protected setting of randomized controlled trials. We found that, compared with heparin anticoagulation, RCA was associated with an almost fourfold filter lifespan. Such difference was linked to a much lower rate of clotting issues within the circuit. We found that RCA was associated with a higher incidence of electrolyte disorders, in particular acid-base alterations. However, the vast majority of these abnormalities were minor and of unknown significance. In our selected patients group, only one possible citrate intoxication was observed and no major complication was observed.

Comparison with previous studies

The observed longer filter life and lower rate of circuit clotting associated with RCA is largely consistent with previously reported data (5,11–15). In particular, it is similar to that observed in cohorts using a similar protocol (10). Although we did not perform a cost analysis, our data confirm

that RCA introduction should logically translate in important costs savings. In addition, longer filter life translates into lower workload for the nursing staff and improved therapy quality (19).

The reported incidence of metabolic complications associated with RCA is higher than previously reported (11,13,14). This is possibly related to the way our data was collected: indeed, we have elected to report every single, even transient and perhaps insignificant event. However, when only severe alterations were considered, only metabolic alkalosis was more commonly observed during RCA. Their clinical relevance cannot be assessed with our study design since patients' allocation was not random. However, it might also be related to our team's limited experience at the time of the study. Indeed, timely therapy adaptation (changes in blood flow or dialysate rate) might have prevented the occurrence of some moderate or severe acid-base alterations. However, such adaptation were rarely performed. Similarly, the observed hypocalcemia could probably have been avoided by more experience teams.

Several cohorts have reported a lower rate of hemorrhagic complication and (3,4,16–18). We have not observed such difference. This is probably related to the very low rate of hemorrhagic complications in our population. For similar reasons, we have not observed a difference in the rate in HIT (only one case).

Study implications

Our data confirm that, even in a center with intermediate experience with RCA, very long circuit lifespan can be achieved. However, the observed higher rate of complications, and the fact that the majority of these complications could have been prevented with minor therapy adjustments emphasize the importance of education and experience when RCA is applied. Implementation of a RCA in a unit should be associated with a strict protocol and intensive education to minimize therapy associated complications.

Strengths and limitations

This study has several strength. First, our data is based on a large number of observations, close to 700 circuits have been evaluated. Detailed chart review was performed by a single investigator enabling the report of granular data on CRRT practice. Second, we believe that our center is ideal for evaluating RCA complications in real life since it is large (2000 admissions per year) with a large CRRT practice (>100 patients treated per year) but a relatively limited experience with RCA (at the time of

the study) and a large number of nursing staff with an important turn-over. Hence, our findings might apply to many similar sized units and perhaps even to smaller ICUs although this remains to be demonstrated.

However, this study also has several limitations worth discussing. First, as a monocentric observational study, result might be associated with bias. There might be limitations in the quality of the data related to nursing/medical documentation. However, complications that were a priori defined would all be identified by routine nursing surveillance in a patient undergoing CRRT. In particular, temperature, arterial blood gas analyses and electrolyte levels measurement are all part of routine follow-up for such patients in our unit. In addition, our protocol mandate regular monitoring of systemic and total ionized calcium. All data are automatically entered in our electronic chart records system minimizing the risk of data loss.

Second, the allocation of anticoagulation regimen was far from random since, as per study protocol, RCA was considered to be contra-indicated in patients with liver failure (defined as a PT<40%) or circulatory shock (defined as a serum lactate >4 mmol/l or need for noradrenaline at a rate >25 µg/min). In addition, both modalities were used in more than a third of the patients. Therefore, no inference on outcomes and mortality in particular can be made in this study. However, this bias is likely to bias result in favor of CVVHD-RCA circuits. Therefore, the higher rate of complication might be under-evaluated.

Third, we have not accounted for the fact that a given complication might have occurred several times in a given patient in different CRRT sessions. This issue might artificially increase the rate of complications. In addition, we can only report on complications' severity and not their duration. Here again, the method chosen should not bias comparison between two groups. However, both these limitations should not bias group comparisons as it applies to both in a similar way.

Conclusions

In a center with intermediate experience, consistent with randomized controlled studies, regional citrate anticoagulation for CRRT, was associated with a much longer circuit lifespan compared with systemic heparin. However, it was associated with a higher rate of mild metabolic complications in particular metabolic alkalosis. Some of these complications could have been prevented by therapy adaptation. Medical and nursing staff education is of major importance in the implementation of a RCA protocol.

CONFLICTS OF INTERESTS:

NB, MA and EP stated that they had no conflicts of interest to declare.

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Figures and Tables

Patients (n=121)	
Demographics	
Median age - (IQR) - years	69 (11)
Median body weight - (IQR) - kg	79.9 (25)
Male sex - no. (%)	81 (66.9)
Illness severty	
Median Charlson score - (IQR)	6 (4)
Renal function parameters	
Mean baseline creatinine - (SD) - umol/L	93.5 (64.8)
Mean GFR MDRD - (SD) - ml/min/1.72m2	67.9 (48.3)
Co-existing conditions	
Chronic kidney injury - no. (%)	48 (39.7)
Hemodialysis dependancy - no. (%)	18 (15.1)
Diabetes mellitus - no. (%)	39 (32.2)
Chronic hypertension - no. (%)	74 (61.2)
Congestive heart failure stage I (FEVG=40-50%) - no. (%)	10 (8.3)
Congestive heart failure stage II (FEVG < 40%) - no. (%)	20 (16.5)
Peripheral arterial disease - no. (%)	25 (20.7)
ICU admissions (n=126)	
Diagnostic at ICU admission	
Septic shock - no. (%)	31 (24.6)
Cardiogenic shock - no. (%)	20 (15.9)
Hemorrhagic shock - no. (%)	11 (8.7)
Cardiac arrest - no. (%)	10 (7.9)
Acute kidney failure - no. (%)	7 (5.6)
Acute respiratory failure - no. (%)	6 (4.8)
Intoxication - no. (%)	2 (1.6)
Others - no. (%)	39 (31)
Type of admission (2 missing)	
Medical - no. (%)	53 (44)
Surgical - no. (%)	61 (50.4)
Others - no. (%)	10 (8.3)
CRRT modality	
CVVH-Heparin - no. (%)	31 (24.6)
CVVHD-RCA - no. (%)	51 (40.5)
CVVH-Heparin and CVVHD-RCA - no.(%)	44 (34.9)

Table 1: Patients' demographics (n=121) and ICU stays characteristics (n=126).

Circuits (n=690)	CVVHD-RCA	CVVH-Heparin	P values
Renal replacement therapy characteristics			
Total number - no. (%)	**400 (57.9)**	**291(42.2)**	-
Median filter lifespan - (IQR) - hours	54.9 (44.6)	15.3 (22.4)	<0.0001
Median dose delivered - (IQR) - ml/kg	1.5 (1.2)	0.5 (0.7)	<0.0001
Median time between ICU admission and Therapy initiation - (IQR) - hours	45 (77.8)	38.8 (59.8)	<0.0002
Reason for therapy interruption (114 missing)			
Reason for therapy interruption indicated - no. (%)	317 (79.25)	260 (89.34)	<0.0001
Filter clotting - no. (%)	28 (8.8)	113 (43.5)	<0.0001
End of therapy - no. (%)	137 (43.2)	64(24.6)	<0.0001
Time limit of 72h reached - no. (%)	134 (42.3)	22(8.5)	<0.0001
Elevation of transmembrane pressure - no. (%)	18 (5.7)	61(23.5)	<0.0001
Missing Data – no. (%)	83 (20.8)	31(11.742)	-

Table 2: CRRT Circuit parameters and reasons for interruption comparison between CVVHD-RCA and CVVH-Heparin. 690 circuits

RCA: regional citrate anticoagulation

CVVHD: Continuous veno-venous hemodialysis

CVVH: continuous veno-venous hemofiltration

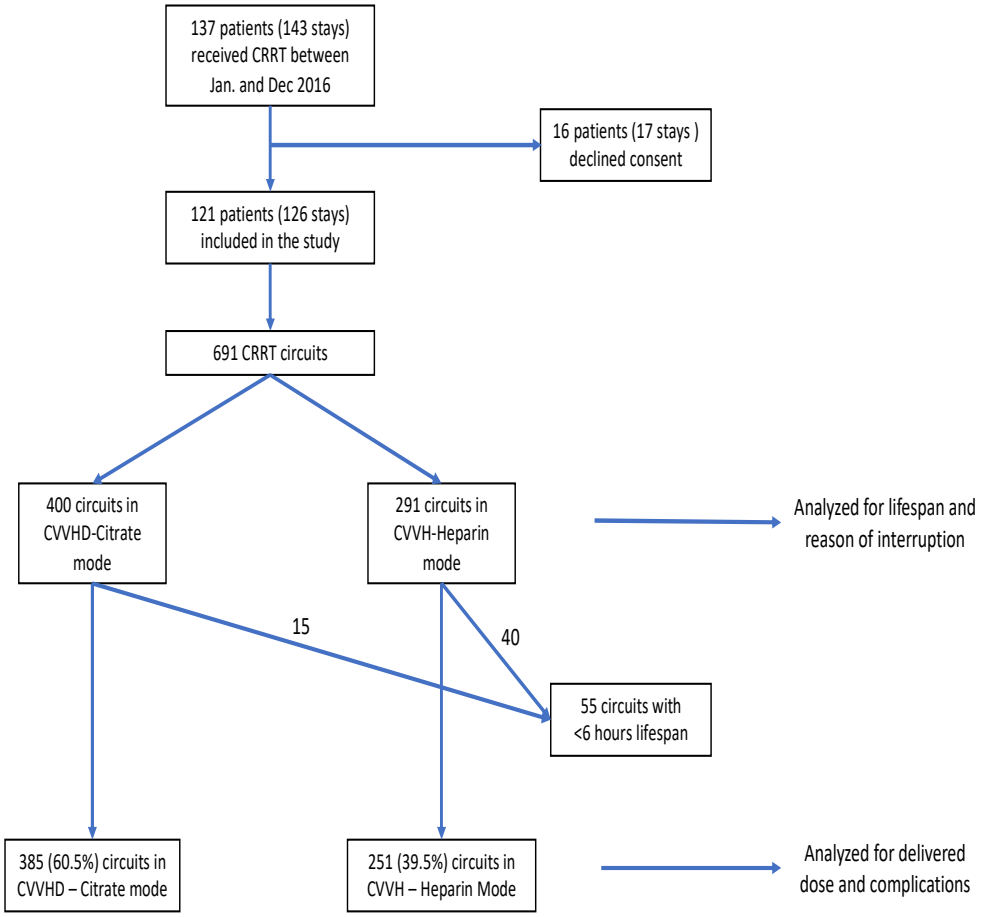

Figure 1: Patients and circuits flow chart.

All CRRT circuits were analyzed for lifespan and reason of interruption, however only CRRT sessions lasting more than 6 hours were analyzed for complications and dose delivered.

CVVHD-citrate =Continuous Veno-Venous HemoDialysis with regional citrate anticoagulation; CVVH-Heparin = Continuous Veno-venous Hemofiltration with systemic heparin anticoagulation.

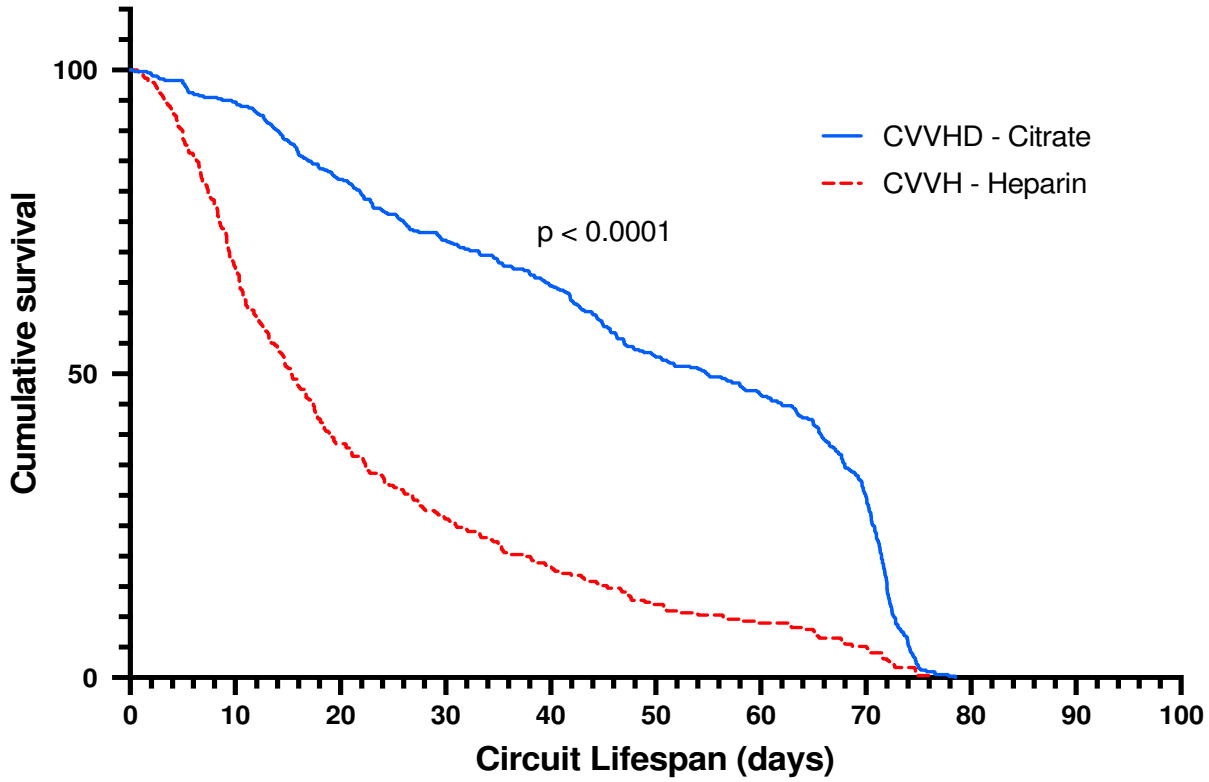

Figure 2: Kaplan-Meier plot for circuit lifespan in CVVHD-Citrate versus CVVH-Heparin methods. Median lifespan was 54.9 hours (IQR 44.6) for CVVHD-RCA vs. 15.3 hours (IQR 22.4) for CVVH-Heparin. P value for log-rank test.

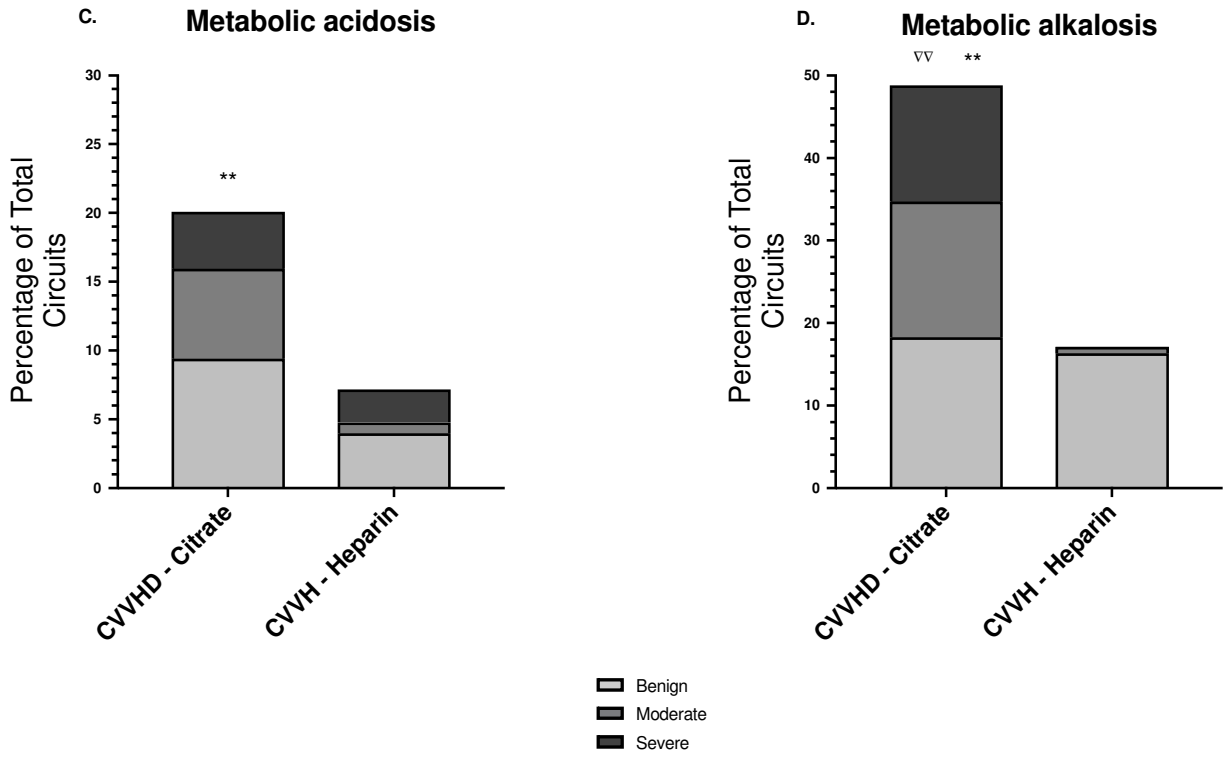

Figure 3: Therapy associated acid-base alterations

Complications recorded for CRRT session with a lifespan > 6 hours (385 CVVHD-RCA sessions and 251 CVVH-Heparin sessions). Panel A: Metabolic acidosis: pH<7.35 &/or BE=-2:-4 (benign), pH<7.25 &/or BE=-4:-6 (moderate), or pH<7.20 &/or BE<-6 (severe)

Panel B: Metabolic alkalosis pH>7.5 &/or BE=2:4 (benign), pH>7.55 &/or BE=4:6 (moderate), pH>7.6 &/or BE>6 (severe)

* $p<0.05$ for overall comparison; ** $p<0.01$ for overall comparison; ∇ $p<0.05$ for comparison between severe events; ∇∇ $p<0.01$ for comparison between severe events.

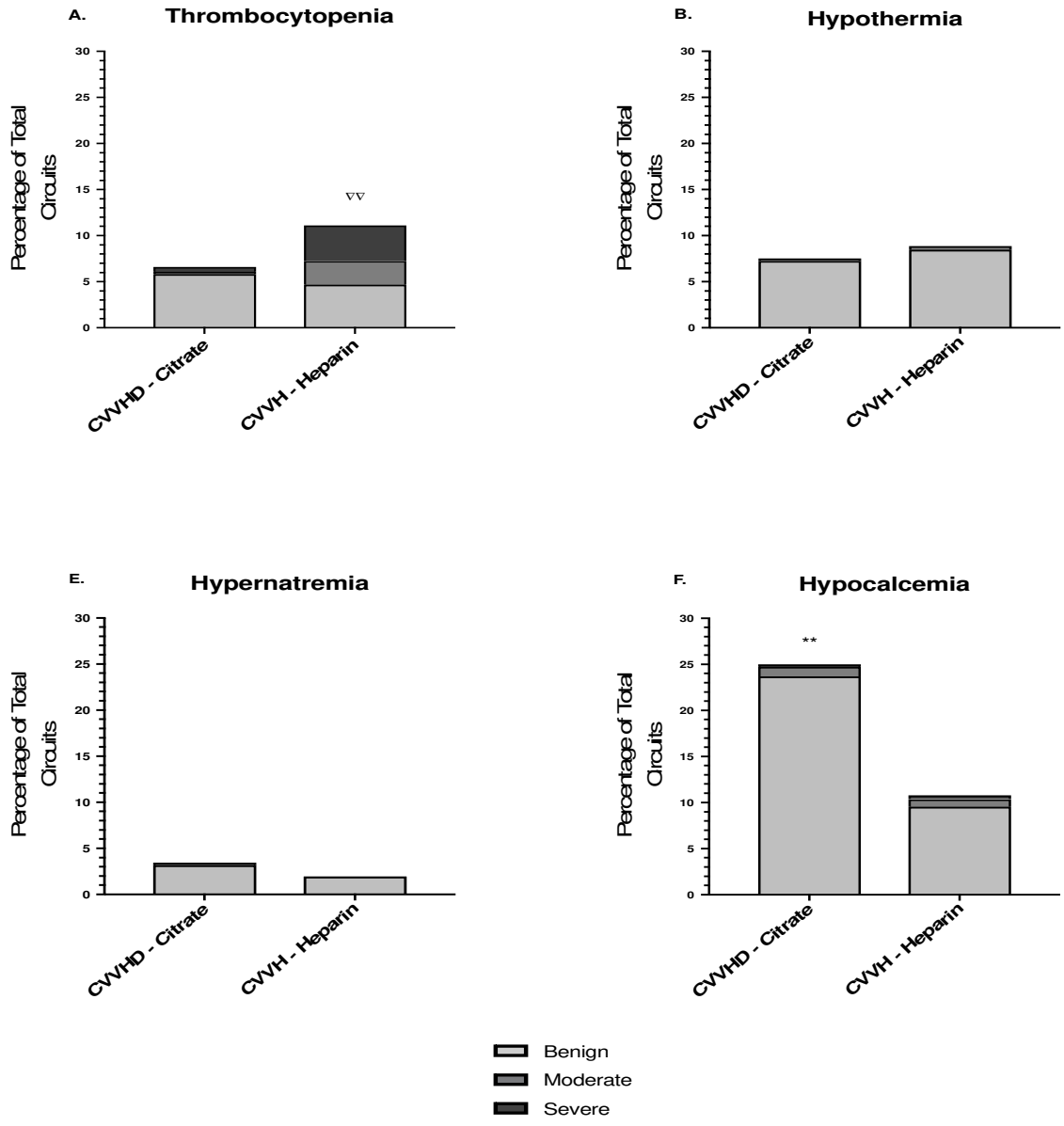

Figure 4: Other therapy associated complications

Complications recorded for CRRT session with a lifespan > 6 hours (385 CVVHD-RCA sessions and 251 CVVH-Heparin sessions).

Definitions:

A. Thrombopenia: thrombocyte level <150G/L (benign), <100 G/L (moderate) or <50 G/L (severe);

B. Hypothermia: body temperature 32-35°C (benign), 32-28°C (moderate)

E. Hypernatremia: Sodium plasma level >145mmol/L (benign), >152mmol/L (moderate)

F. Hypocalcemia: systemic ionized calcium <1.05mmol/L (benign), <0.95mmol/L (moderate) or <0.85mmol/L (severe).

* $p<0.05$ for overall comparison; ** $p<0.01$ for overall comparison; ∇ $p<0.05$ for comparison between severe events; $\nabla\nabla$ $p<0.01$ for comparison between severe events.