Strategies for Optimizing the CRRT Circuit
Citrate Anticoagulation

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Anticoagulation During Acute Renal Replacement Therapy

• Contact of blood with artificial surfaces leads to activation of the Hageman or surface factor XII which initiates and triggers a series of enzymatic reactions culminating in the generation of thrombin and the formation of fibrin.

• All elements of the blood, including platelets, erythrocytes, and leukocytes, may enter into the formation of a thrombus.

• The goal of anticoagulation during ARRT is to reduce clotting in the hemofilter to avoid
  – Patients’ blood loss
  – Interruptions in the therapy (that may substantially reduce total treatment time and efficacy)
Delivered dose of renal replacement therapy and mortality in critically ill patients with acute kidney injury

Prospective multicentre observational study in 30 ICUs from 8 countries

553 AKI patients with RRT, including 338 who received CRRT only and 87 who received IRRT only

No beneficial effect of more-intensive RRT dose on ICU survival, but shorter ICU stay and duration of mechanical ventilation

Median prescribed CRRT dose: 34.3 ml/kg/hour (IQR = 27.3 to 42.9)

Median delivered CRRT dose: 27.1 ml/kg/hour (IQR = 22.1 to 33.9).

>20% difference prescribed vs. delivered dose!

Clotting most common cause for CRRT interruption (74% of episodes)
Options for Anticoagulation

• Systemic anticoagulation
  – Unfractionated heparin
  – Low-molecular weight heparin
  – Direct thrombin inhibitors
  – Prostaglandins
  – Nafamostat mesylate

• Regional anticoagulation
  – Heparin/Protamin
  – Citrate

• Bleeding risk ↑
• Specific side effects (e.g., HIT-2)
Regional Anticoagulation with Heparin/Protamin

- Combining a prefilter dose of heparin to prolong extracorporeal aPTT, with postfilter neutralization with protamine to normalize systemic aPTT.

- Difficult to titrate because heparin has a much longer half-life than protamine, inducing a risk of rebound.

- Exposes patients to the side-effects of both heparin (mainly the risk of HIT) and protamine:
  - anaphylaxis
  - platelet dysfunction
  - hypotension
  - pulmonary vasoconstriction with right ventricular failure
Regional Anticoagulation with Heparin/Protamin

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  – anaphylaxis
  – platelet dysfunction
  – hypotension
  – pulmonary vasoconstriction with right ventricular failure

*Not recommended by current AKI guidelines!*
Regional Citrate Anticoagulation

- Citrate binds calcium ions
- Ionized Ca$^{++}$ is required at several steps of plasmatic coagulation cascade
- Plasmatic coagulation is blocked at iCa$^{++}$ $\sim$0.3 mval/L

Intrinsic pathway

Extrinsic pathway
Regional Citrate Anticoagulation During ARRT

Citrate infusion

iCa++ ~1.1 mval/l

Blood Circuit

iCa++ ~0.3 mval/l

Calcium infusion

Dialysate

Waste

Dialysate Circuit
Pre-connected Lines for Citrate and Calcium Infusion

Double-lumen tubings to the patient

Citrate and calcium line connected with the blood lines
Regional Citrate Anticoagulation During ARRT

- One mol citrate converted to 3 moles bicarbonate
- One mol trisodium citrate converted to 3 moles sodium

Must use adapted dialysate:
  - Calcium-free
  - Reduced sodium
  - Reduced bicarbonate

<table>
<thead>
<tr>
<th>Na⁺</th>
<th>133 mmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>K⁺</td>
<td>2 mmol/l</td>
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<tr>
<td>Mg²⁺</td>
<td>0.75 mmol/l</td>
</tr>
<tr>
<td>Ca⁴⁺</td>
<td>0 mmol/l</td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>20 mmol/l</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>116.5 mmol/l</td>
</tr>
<tr>
<td>Glucose</td>
<td>1 g/l</td>
</tr>
</tbody>
</table>
Automated Regional Citrate Anticoagulation (Multifiltrate, FMC)

- Drip chamber
- Roller pump
- Citrate
- Calcium
Citrate and calcium flow rates adjusted through CRRT user interface

Blood and dialysate flow
⇒ Adjustment of the acid-base status

Citrate dose
⇒ Adjustment of the regional anticoagulation

Calcium dose
⇒ Adjustment of the calcium balance
Citrate anticoagulation during CVVHDF
Prescription of Citrate and Calcium Dose

**Initial citrate dose:**
4.0 mmol/l

- Check the post-filter ionised calcium concentration every ≈ 6 h
- Change the citrate dose in steps of 0.1 mmol/l if needed
- Continue during the treatment

**Initial calcium dose:**
1.7 mmol/l

- Check the systemic ionised calcium concentration every ≈ 6 h
- Change the calcium dose in steps of 0.2 mmol/l if needed
- Continue during the treatment
Management of the Acid-Base-Status

Higher blood flow ⇒ higher citrate infusion

Citrate is partly systemically infused and metabolised to bicarbonate

Higher blood flow shifts the effect on the patient's acid-base status to alkalosis

Dialysis against the 20 mmol/l bicarbonate dialysate removes buffer bases from the blood

Higher dialysate flow shifts the effect on the patient's acid-base status to acidosis

Normal acid-base status can be achieved by changing the ratio of dialysate to blood flow
Management of acid-base status

20% change of blood or dialysate flow
=>
approx. 4 mmol/l change of the acid-base status
Citrate Regional Anticoagulation
Clinical Results
• Randomized, nonblinded, controlled single-center trial (Amsterdam, The Netherlands).

• Patients: 215 adult critically ill patients needing CVVH for acute renal failure and without an increased bleeding risk.

• Interventions: Regional anticoagulation with citrate or systemic anticoagulation with the low-molecular weight heparin nadroparin (2,850 IU bolus, 380 IU continuously)
The efficacy of citrate and nadroparin anticoagulation for CVVH was similar, however, citrate was safer.

Citrate reduced mortality. Less bleeding could only partly explain this benefit, less clotting could not.

Post hoc citrate appeared particularly beneficial after surgery, in sepsis and severe multiple organ failure, suggesting interference with inflammation.

**Citrate anticoagulation for continuous venovenous hemofiltration**

Heleen M. Oudemans-van Straaten, MD, PhD; Rob J. Bosman, MD; Matty Koopmans, RN; Peter H. J. van der Voort, MD, PhD, MSc; Jos P. J. Wester, MD, PhD; Johan I. van der Spoel, MD; Lea M. Dijksman, MSc; Durk F. Zandstra, MD, PhD

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Regional citrate versus systemic heparin for anticoagulation in critically ill patients on continuous venovenous haemofiltration: a prospective randomized multicentre trial

- Prospective, randomized, nonblinded, multicentre trial (Germany).

- **Patients**: 174 adult critically ill patients on mechanical ventilation needing CVVH for acute renal failure

- **Interventions**: Regional anticoagulation with citrate or systemic anticoagulation with unfractionated heparin.

- Primary outcome: acid-base status on Day 3 and on each consecutive day.

- No difference in standard bicarbonate from Day 3 to Day 11

- Use of citrate resulted in less systemic anticoagulation, a lower risk of bleeding and a longer haemofilter patency

Regional citrate versus systemic heparin for anticoagulation in critically ill patients on continuous venovenous haemofiltration: a prospective randomized multicentre trial

No difference in survival
Prospective, randomized, nonblinded, multicentre trial.

Patients: 139 adult critically ill patients treated with CVVH for acute renal failure, 10 ICUs in The Netherlands.

Interventions: Regional anticoagulation with citrate or systemic anticoagulation with unfractionated heparin.

Primary outcome: mortality at day 28 and day 90; renal outcome

Results: No difference survival or renal recovery 28 days after start of CVVH

Use of citrate resulted in longer filter patency (median 46 versus 32 hours, $P=0.02$), lower number of filters used ($P=0.002$) and less the off time within 72 hours ($P=0.002$).
Citrate anticoagulation versus systemic heparinisation in continuous venovenous hemofiltration in critically ill patients with acute kidney injury: a multi-center randomized clinical trial

Louise Schilder, S Azam Nurmohamed, Frank H Bosch, Ilse M Purmer, Sylvia S den Boer, Cynthia G Kleppe, Marc G Vervloet, Albertus Beishuizen, Armand RJ Girbes, Pieter M ter Wee, AB Johan Groeneveld and for the CASH study group

<table>
<thead>
<tr>
<th></th>
<th>Citrate</th>
<th>Heparin</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Survival time first filter, h</td>
<td>46 (1 to 138)</td>
<td>32 (1 to 72)</td>
<td>0.02</td>
</tr>
<tr>
<td>Number of filters used within 72 h</td>
<td>1 (1 to 5)</td>
<td>2 (1 to 9)</td>
<td>0.002</td>
</tr>
<tr>
<td>Off-time within 72 h, h</td>
<td>1 (0 to 12)</td>
<td>3 (0 to 31)</td>
<td>0.002</td>
</tr>
<tr>
<td>Reason for circuit disconnection</td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Circuit clotting</td>
<td>16 (24)</td>
<td>35 (51)</td>
<td></td>
</tr>
<tr>
<td>Elective filter change (72 h)</td>
<td>20 (30)</td>
<td>6 (9)</td>
<td></td>
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<tr>
<td>Catheter dysfunction</td>
<td>4 (6)</td>
<td>8 (12)</td>
<td></td>
</tr>
<tr>
<td>Termination of CVH¹</td>
<td>10 (15)</td>
<td>10 (12)</td>
<td></td>
</tr>
<tr>
<td>Transport</td>
<td>4 (6)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Technical problems</td>
<td>8 (12)</td>
<td>5 (7)</td>
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<tr>
<td>Therapy change²</td>
<td>2 (3)</td>
<td>3 (4)</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>2 (3)</td>
<td>1 (1)</td>
<td></td>
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Schilder L et al, *Crit Care* 2014; 18: 472
• 116 patients with AKI, 807 SLED sessions based on the use of anticoagulant citrate dextrose solution formulation A (ACD-A) and standard dialysis equipment.

• Median treatment time 8 hours, AK200S Ultra machine (Gambro) and polysulfone filters (F8HPS, 1.8 m², $K_{UF}$ 18 ml/mm Hg per hour (Fresenius), blood flow 200 ml/min.

• Patients’ blood recalcification was obtained from calcium backtransport from dialysis fluid.

→ Efficacious and safe anticoagulation protocol
Intravenous calcium for ionized hypocalcemia (<3.6 mg/dl or <0.9 mmol/L) was needed in only 28 sessions (3.4%).
Citrate accumulation never occurred, even in patients with liver dysfunction.
Systematic review and meta-analysis of RCTs comparing regional citrate vs heparin anticoagulation in CRRT; 6 RCTs with 488 patients were identified.

Similar efficacy for CRRT anticoagulation, however citrate was associated with a significant decrease in bleeding (RR, 0.34; 95% CI, 0.17-0.65)
Efficacy and safety of regional citrate anticoagulation in critically ill patients undergoing continuous renal replacement therapy

- Systematic review and meta-analysis, 6 RCTs with regional citrate anticoagulation in CRRT
- Longer filter life and less bleeding complications with citrate

**Filter life**

**Bleeding complications**

Citrate Regional Anticoagulation

KDIGO AKI Guidelines

http://www.kdigo.org/clinical_practice_guidelines/AKI.php
2. For patients **without an increased bleeding risk or impaired coagulation** and not already receiving effective systemic anticoagulation, we suggest the following:

1. For anticoagulation in intermittent RRT, we recommend using either unfractionated or low-molecular weight heparin, rather than other anticoagulants. (1C)

2. For anticoagulation in CRRT, we suggest using regional citrate anticoagulation rather than heparin in patients who do not have contraindications for citrate. (2B)

3. For anticoagulation during CRRT in patients who have contraindications for citrate, we suggest using either unfractionated or low-molecular-weight heparin, rather than other anticoagulants. (2C)
AKI Guideline 5.3.

3. For patients **with an increased bleeding risk** who are not receiving anticoagulation, we suggest the following for anticoagulation during RRT:

   3. We suggest using regional citrate anticoagulation, rather than no anticoagulation, during CRRT in a patient without contraindications for citrate. (2C)

   4. We suggest avoiding regional heparinization during CRRT in a patient with increased risk of bleeding. (2C)

4. In a patient with HIT who does not have severe liver failure, we suggest using argatroban rather than other thrombin or Factor Xa inhibitors during RRT. (2C)
Contraindications for using citrate?

• Citrate accumulation may occur in patients with impaired metabolism
  – Persistent shock with reduced muscle perfusion

Watch out for elevated serum lactate!
Contraindications for using citrate?

- Citrate accumulation may occur in patients with impaired metabolism
  - Persistent shock with malperfusion of muscles
  - Severe liver failure
Warning signs of reduced citrate metabolism in patients with liver failure

Accumulation of Calcium-Citrate Complexes

Anion Gap Acidosis

Calcium tot. [mmol/l]

<table>
<thead>
<tr>
<th>Calcium tot. [mmol/l]</th>
<th>Physiological</th>
<th>Hypercalcemia</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>iCa++</td>
<td>iCa++</td>
</tr>
<tr>
<td>0.4</td>
<td>Protein-Ca++</td>
<td></td>
</tr>
<tr>
<td>0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Anion gap: Na⁺ – (Cl⁻ + HCO₃⁻) = 8 - 12 mmol/L

H. Peters, in:ANV auf der Intensivstation
A Jörres (Hrsg.) Dt. Ärzteverlag 2009
• 133 consecutive adult ICU patients prospectively observed for 72 hours of citrate-CVVHD.

• Patients were stratified into 3 groups of liver function impairment according to their serum bilirubin (mg/dl)
  – normal: \( \leq 2, n = 47 \)
  – mild: \( > 2 \) to \( \leq 7, n = 44 \)
  – severe: \( > 7, n = 42 \)

• End-points for safety were: severe acidosis or alkalosis (pH \( \leq 7.2; \geq 7.55 \)) and severe hypocalcemia or hypercalcemia (\( \leq 0.9; \geq 1.5 \text{ mmol/l} \)) of any cause.

• End-point for efficacy was the filter lifetime.

_Critical Care 2011, 15(Suppl 1):P127_
The frequency of safety end-points of any cause did not differ between the three patient strata:
- severe alkalosis (normal: 2%, mild: 0%, severe: 5%; $P = 0.41$);
- severe acidosis (normal: 13%, mild: 16%, severe: 14%; $P = 0.95$);
- severe hypocalcemia (normal: 8%, mild: 16%, severe: 12%; $P = 0.57$);
- severe hypercalcemia (0% in all strata).

Only in 3/133 patients an increased ratio of total to ionized calcium ($\geq 2.5$) was detected (2%).

Overall filter lifetime was 49% after 72 hours; however, after censoring for discontinuation due to non-clotting causes (for example, renal recovery, death) 96% of all filters were running after 72 hours.

*Critical Care* 2011, 15(Suppl 1):P127
Summary
Citrate Anticoagulation During CRRT

- Safe and easy to use on modern CRRT platforms
- Requires adapted dialysis fluids (reduced bicarbonate and sodium, calcium-free)
- Leads to less bleeding complications compared to systemic anticoagulation
- Enables longer filter patency

- May accumulate in patients with impaired citrate metabolism (severe liver failure; persisting shock with impaired muscle perfusion)
- Can be monitored by comparing total and ionized Ca^{++}