Best practice in CRRT anticoagulation

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No conflict to disclose

Acknowledge to A. Deep, King’s College Hospital, London
• Why do we change filters? Is everything related to clotted filters?
• Why do filters/circuits clot?
• Various Anticoagulants available – Actions, advantages, disadvantages
• Is there a single best anticoagulant?
• Available evidence
• In practice
Circuit lifespan: “Host-circuit” determinants

“circuit” factors
- flow rate
- Filtration fraction
- pre-dilution
- catheter size
- **anticoagulation**

“patient” factors
- primary condition !!
- PT/INR
- platelet count and F1
- haemoglobin
- venous access issues
- blood products use.
Reason for circuit change

- Clotting
- Manufacturer recommendation (72 hours)
- Access malfunction - kinking, bending, leakage, inappropriately small size
- Machine malfunction
- Unrelated patient indication (e.g., needs CT scan)
- CRRT discontinued
Effects of circuit/filter clotting

• Decreased efficacy of treatment -
  (important in circumstances like in ALF)
• Increased blood loss especially in newborns
• Increased costs
• Propensity to increased haemodynamic instability during re-connection
• Staff dissatisfaction
Anticoagulation « cascade »

INTRINSIC PATHWAY

- Damaged Surface
  - Kininogen
  - Kallikrein
  - Factor XII
  - Factor XI
  - Factor IX
  - Factor VIIIa
  - Factor V
  - Factor X
  - Factor Xa
  - Prothrombin (II)
  - Thrombin (IIa)

EXTRINSIC PATHWAY

- Trauma
  - Tissue factor
  - Factor VIIa
  - Factor VII
  - Factor X
  - Factor Xa
  - Factor V

FINAL COMMON PATHWAY

- Fibrinogen (I)
  - Fibrin (Ia)
  - Factor XIIIa
  - Cross-linked fibrin clot
A “newer model” of the coagulation pathway: importance of the balance between pro/anti coag factors

Key:
- Inhibits
+ Activates

Acknowledges A. Deep
1- Factors related to premature Clotting:

Patient related
Access related
Circuit related
Treatment related

2- Where does thrombus form?

- Any blood-artificial surface interface
  - Hemofilter
  - Bubble trap
  - Vascath

- Areas of turbulence /Resistance
  - Luer lock connections
  - 3 way stopcocks

Small vascath sizes and lower blood flows add to already existing challenges in paediatric population
Ideal Anticoagulation

- Readily available
- **Safe** - Selectively active in the circuit – minimal effects on patient hemostasis
- Prolonged filter life ideally > 48 hours
- Monitoring – Rapid and Simple
- Rapidly reversible in case of complications
- Uncomplicated, easy to follow consistently delivered protocols-Staff training
- Cost Effective
Anticoagulation for renal replacement therapy for patients with acute kidney injury.

Saline Flushes
• **Heparin (UFH)**
• Low molecular weight heparin
• Citrate regional anticoagulation
• **Prostacyclin**
• Nafamostat mesilate
• Danaparoid
• Dermatan sulfate
• Fondaparinux
• Hirudin/Lepirudin
• Argatroban (thrombin inhibitor).
**Heparin**

- Most commonly used anticoagulant
- Large experience
- Short biological half-life
- Availability of an efficient inhibitor
- Possibility to monitor its effect with routine laboratory tests – ACT.

Heparin enhances binding of antithrombin III to factor II & X

Large fragments – Anti IIa Activity
Small fragments : Anti Xa activity

Acts directly and Metabolised by the liver

Metabolites are eliminated by the kidneys

Plasma half-life is approximately 90 minutes
Heparin Use in Continuous Renal Replacement Procedures: The Struggle Between Filter Coagulation and Patient Hemorrhage

J. van de Wetering, R.G.J. Westendorp, J.G. van der Hoeven, B. Stolk, J.D.M. Feuth, and P.C. Chang

![Graph showing the relationship between APTT and incidence of coagulation and hemorrhage.

<table>
<thead>
<tr>
<th>APTT&lt;sup&gt;a&lt;/sup&gt; (s)</th>
<th>CAVH/DF-Time (h)</th>
<th>Filter Coagulation</th>
<th>Patient Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Number (per 1000 h)</td>
<td>Incidence</td>
</tr>
<tr>
<td>Treatment with Heparin Only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-35</td>
<td>2718</td>
<td>48</td>
<td>17.7</td>
</tr>
<tr>
<td>35-45</td>
<td>3150</td>
<td>38</td>
<td>12.1</td>
</tr>
<tr>
<td>45-55</td>
<td>1632</td>
<td>21</td>
<td>12.9</td>
</tr>
<tr>
<td>&gt;55</td>
<td>1224</td>
<td>11</td>
<td>9.0&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>All (mean, 42)</td>
<td>8724</td>
<td>118</td>
<td>13.5</td>
</tr>
</tbody>
</table>
Heparin – Side Effects

• Bleeding -10-50% (Dose ACT adjusted)

• Heparin Resistance +++ (AT reduced in sick patients + increased AT degradation)

• Heparin Induced Thrombocytopenia (HIT)? In children?

(<1 to 5%) The antibody–platelet factor 4–heparin complex subsequently binds to platelets, inducing platelet activation, aggregation and activation of the coagulation pathways.

• Unpredictable and complex pharmacokinetics of UFH
Heparine interfere with inflammation!
LMWH

Daltaparin, enoxaprin, and nadroparin

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher anti Xa activity</td>
<td>No quick antidote</td>
</tr>
<tr>
<td>More predictable pharmacokinetics-hence more reliable anticoagulant</td>
<td>Effect more prolonged in renal failure</td>
</tr>
<tr>
<td>response</td>
<td>Special assays to monitor anti-Xa activity</td>
</tr>
<tr>
<td>Reduced risk of bleeding</td>
<td>Increased cost</td>
</tr>
<tr>
<td>Less risk of HIT</td>
<td>No difference in filter life</td>
</tr>
</tbody>
</table>
Enoxaparin vs. unfractionated heparin for anticoagulation during continuous veno-venous hemofiltration: a randomized controlled crossover study

Fig. 1 Study design. The study was designed as a randomized controlled trial using a crossover design. Every patient was treated with both forms of anticoagulation. Randomization to either arm A or B decided the order of anticoagulation. A wash-out time of 12 h was applied between each anticoagulation cycle.

Fig. 2 Kaplan–Meier plot of filter survival during heparin and enoxaparin anticoagulation in CVVH (p = 0.035, ANOVA for repeated measurements)
Heparin- Summary

• Most commonly used
• Easy to use, monitor
• No evidence on dose
• Systemic side-effects
• Contraindicated in bleeding patients
Citrate anticoagulation

- How does it work?
- Is there an advantage over heparin?
- What are the side effects?
- How easy is it to use?
- What are the protocols?
- What is needed to make it work?
How does citrate work

- Clotting is a calcium dependent mechanism, removal of calcium from the blood will inhibit clotting
- Adding citrate to blood will bind the free calcium (ionized) calcium in the blood thus inhibiting clotting
- Common example of this is banked blood
CONTACT PHASE
XII activation
XI IX

Tissue Factor
TF:VIIa

monocytes / platelets / macrophages

Phospholipid surface

Ca^{++}

Fibrinogen

CITRATE

Natural Anticoagulants (APC, ATIII)

fibrinogen

CLOT

Thrombin

Ca^{++}

Xa

prothrombin

Ca^{++}

Ca^{++}

Ca^{++}

Ca^{++}

CITRATE

Fibrinolysis Activation
Fibrinolysis Inhibition
How is citrate used?

• In most protocols citrate is infused post patient but prefilter often at the “arterial” access of the dual (or triple) lumen access that is used for hemofiltration (HF) ...

• Calcium is returned to the patient independent of the dual lumen HF access or can be infused via the 3rd lumen of the triple lumen access
What happens to Ca-citrate?

- Ca-citrate gets filtered/dialysed
- More than 50% gets removed in dialysate
- Remaining enters circulation – TCA cycle – citric acid (liver, muscle, renal cortex)
- 1mmol citrate – 3mmol NaHCO3 (risk of metabolic alkalosis and hypernatremia)
- Citrate/Ca mismatch → hypocalcemia
Citrate: Technical Considerations

- Measure patient and system iCa in 2 hours then at 6 hr increments
- Pre-filter infusion of Citrate
  - Aim for system iCa of 0.3-0.4 mmol/l
    - Adjust for levels
- Systemic calcium infusion
  - Aim for patient iCa of 1.1-1.3 mmol/l
    - Adjust for levels
Complications of Citrate: “Citrate Lock”

• Seen with rising total calcium with dropping patient ionized calcium
  • Essentially delivery of citrate exceeds hepatic metabolism and CRRT clearance
  • Metabolic acidosis with an enlarged anion gap
  • A serum total to ionic calcium ratio of $\geq 2.5$ is assumed to be a critical threshold for the prediction of citrate accumulation

• Rx of “citrate lock”
  • Decrease or stop citrate for 3-4 hrs then restart at 70% of prior rate or Increase D or FRF rate to enhance clearance
Citrate in ALF and cardiac failure?

- Metabolic alkalosis
  - Metabolized in liver / other tissues
- Electrolyte disorders
  - Hypernatremia
  - Hypocalcemia
  - Hypomagnesemia
- “Cardiac toxicity” - dysrhythmia
  - Neonatal hearts
Total-to-ionized calcium ratio predicts mortality in continuous renal replacement therapy with citrate anticoagulation in critically ill patients

Andreas Link, Matthias Klingele, Timo Speer, Ranja Rbah, Janine Röss, Anne Lerner-Gräber, Danilo Fliser and Michael Böhm

B:

- T/I Ca\(^{2+}\) - Ratio < 2 (Day 3)
- T/I Ca\(^{2+}\) - Ratio = 2.4 (Day 3)
- T/I Ca\(^{2+}\) - Ratio > 2.4 (Day 3)

p < 0.001
Citrate Anticoagulation

• Well-designed and flexible protocol
• Adjusted to the local preferences of modality and dose
• Results of ionized calcium measurement should be available 24 hours a day (Keep circuit [Ca$^{++}$] levels around .30 for best results)
• Training of staff – understand monitoring and side effect profile
# Citrate versus Heparin

## Table 1. Randomized clinical studies comparing citrate with heparin anticoagulation for CRRT

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Circuit life (hours)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Bleeding</th>
<th>Transfusion (RBC/day)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Citrate</td>
<td>Heparin</td>
<td>Citrate</td>
<td>Heparin</td>
</tr>
<tr>
<td>Monchi and colleagues [63]</td>
<td>RCOT, n = 20</td>
<td>70</td>
<td>40</td>
<td>n = 0</td>
<td>n = 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(44 to 140), P &lt; 0.001</td>
<td>(17 to 48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kutsogiannis and colleagues [64]</td>
<td>RCT, n = 30</td>
<td>125</td>
<td>38</td>
<td>RR 0.17</td>
<td>RR 0.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(95 to 157), P &lt; 0.001</td>
<td>(25 to 62)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betjes and colleagues [65]</td>
<td>RCT, n = 48</td>
<td>27</td>
<td>26</td>
<td>0%</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(13 to 47), NS</td>
<td>(15 to 43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oudemans-Van Straaten and colleagues [35]</td>
<td>RCT, n = 200</td>
<td>27</td>
<td>26</td>
<td>6%</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(13 to 47), P = 0.08</td>
<td>(15 to 43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hetzel and colleagues [66]</td>
<td>RCT, n = 170</td>
<td>37.5 ± 23, P &lt; 0.001</td>
<td>26.1 ± 19.2</td>
<td>14.5%</td>
<td>5.7%</td>
</tr>
</tbody>
</table>
Citrate anticoagulation for continuous renal replacement therapy in small children

Jolanta Soltysiak · Alfred Warzywoda · Bartłomiej Kociński · Danuta Ostalska-Nowicka · Anna Benedyk · Magdalena Siśka-Dittmar · Jacek Zachwieja

Table 4 Adverse events among the pediatric patient cohort on RCA-CRRT and HA-CRRT

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RCA-CRRT</td>
</tr>
<tr>
<td>Hypernatremia (&gt;143.0 mmol/l)</td>
<td>3 (18.75)</td>
</tr>
<tr>
<td>Hyponatremia (&lt;129.0 mmol/l)</td>
<td>3 (18.75)</td>
</tr>
<tr>
<td>Hyperkalemia (&gt;5.8 mmol/l)</td>
<td>2 (12.5)</td>
</tr>
<tr>
<td>Hypokalemia (&lt;3.6 mmol/l)</td>
<td>10 (62.5)</td>
</tr>
<tr>
<td>Hypercalcemia (&gt;1.2 mmol/l)</td>
<td>7 (43.75)</td>
</tr>
<tr>
<td>Hypocalcemia (&lt;0.9 mmol/l)</td>
<td>7 (43.75)</td>
</tr>
<tr>
<td>Metabolic acidosis (pH &lt; 7.35 and HCO₃&lt;sub&gt;-2&lt;/sub&gt; &lt; 22 mmol/l)</td>
<td>7 (43.75)</td>
</tr>
<tr>
<td>Metabolic alkalosis (pH &gt; 7.45 and HCO₃&lt;sub&gt;-2&lt;/sub&gt; &gt; 26 mmol/l)</td>
<td>4 (25)</td>
</tr>
</tbody>
</table>

RCA, regional citrate anticoagulation; CRRT, continuous renal replacement therapy; HA, heparin anticoagulation

P = 0.03
**Regional citrate anticoagulation was superior to heparin for the filter lifetime and transfusion requirements in ICU patients treated with CRRT**
Final Decision – Citrate vs Heparin

• Local familiarity with protocol, patient population
• Heparin common as vast experience, easy to monitor, good circuit life
• Problems – Systemic anticoagulation, bleeding
  (sometimes life-threatening), HIT, resistance
• Citrate – comparable filter life, no risk of bleeding

Why is citrate not the standard of care?

- Physician’s perception- use of citrate complex,
- Citrate module not in every machine
- Metabolic complications with regular monitoring, metabolism in liver disease complex
- Huge training resource
- Cost

• In UK – Heparin is the most commonly used ACG for ease of use.
Renal replacement therapy in adult and pediatric intensive care

Recommendations by an expert panel from the French Intensive Care Society (SRLF) with the French Society of Anesthesia Intensive Care (SFAR) French Group for Pediatric Intensive Care Emergencies (GFRUP) the French Dialysis Society (SFD)

2.3.2 In patients at low risk of hemorrhage not requiring systemic anticoagulation:
2.3.2.1 In intermittent RRT, unfractionated heparin or low-molecular-weight heparin should probably be preferred to other systemic anticoagulants. (Expert opinion) Strong agreement
2.3.2.2 In continuous RRT, in adults, regional citrate anticoagulation should probably be preferred, unless there is a contraindication, so as to prolong circuit lifetime. Poor agreement

2.3.2.3 In continuous RRT, if there is a contraindication to citrate, unfractionated heparin anticoagulation should probably be preferred. (Expert opinion) Strong agreement

2.3.2.4 In children, in continuous RRT, citrate or unfractionated heparin should be used for anticoagulation, the choice being guided by the experience of the team. Strong agreement
**Prostacyclin PGI\textsubscript{2}**

- A lipid molecule-eicosanoid
- **Epoprostenol** – synthetic derivative (Flolan)
- **Platelet aggregation and adhesion inhibitor (PGI\textsubscript{2})**
- Heparin sparing effect
- Reversibly inhibits platelet function by diminishing the expression of platelet fibrinogen receptors and P-selectin
- Reduces heterotypic platelet-leukocyte aggregation.

Fig. 1 - Production and action of prostaglandins. Adapted from FlizGerald GA, Patrano CP. The coxibs, selective inhibitors of cyclooxygenase-2. *N Engl J Med* 2001; 345: 433-442.
Prostacyclin (PGI$_2$): more than anti-thrombotic!

<table>
<thead>
<tr>
<th>Kinetics</th>
<th>Dynamics</th>
</tr>
</thead>
</table>
| • Half life – 42 seconds | • Anti-thrombotic  
  o Inhibits platelet aggregation and adherence to vessel wall |
| • Vasodilator effect at 20 ng/kg/minute | • Vessel tone  
  o Reduces SMC proliferation and increased vasodilatation |
| • Platelet effect at 2-8 ng/kg/minute -½ life 2 hours | • Anti-proliferative  
  o Reduces fibroblasts, increases apoptosis |
| • Limited clinical experience | • Anti-inflammatory  
  o Reduces pro-inflammatory cytokines and increased anti-inflammatory cytokines |
| • Flolan – epoprostenol sodium | • Anti-mitogenic |
Side effects

• Limited clinical experience
• Scant data on efficacy and safety
• **Hypotension, raised ICP, Hyperthermia**
• Facial flushing, headache
• **Ventilation-perfusion mismatching**
• Cost is the use-limiting factor
Evidence for use of Prostacyclin

• None out there especially in Paediatrics
• Dose ???
• Route -?
• Indications -?
• Most work carried out in patients where there is contraindication to heparin/citrate


**Factors affecting circuit life during continuous renal replacement therapy in children with liver failure.**

*Goonasekera CD1, Wang J, Bunchman TE, Deep A.*
Continuous haemofiltration in acute renal failure with prostacyclin as the sole anti-haemostatic agent

Plattlets sparing effect!
46 patients on CVVH

- Group -1 Heparin (6.0 +/- 0.3 IU/kg/hr for group 1),
- Group -2 PGI2 (7.7 +/- 0.7 ng/kg/min )
- Group-3 PGI2 and heparin (6.4 +/- 0.3 ng/kg/min, 5.0 +/- 0.4 IU/kg/hr)
- Filter life, haemostatic variables and haemodynamic variables at various times
- Mean hemofilter duration :
  ✓ PGI2 + heparin 22 hours
  ✓ Only heparin -14.3 hours
  ✓ Only PGI2 – 17.8 hours

Heparin +PGI2:
Better hemodynamic profiles
Enhanced hemofilter duration
Regional anticoagulation and antiaggregation for CVVH in critically ill patients: a prospective, randomized, controlled pilot study

L. P. Fabris, M. Nucera, M. Al Malyan and C. Bicchi

Department of Medical and Surgical Critical Care, Section of Anaesthesia and Intensive Care, Florence University, Florence, Italy

Patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>G1 (n = 46)</th>
<th>G2 (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71 ± 1.3</td>
<td>70.3 ± 7.6</td>
</tr>
<tr>
<td>SAPS II</td>
<td>51 ± 11</td>
<td>61 ± 4</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>22/24</td>
<td>21/23</td>
</tr>
<tr>
<td>Kidney transplantation/post-surgery (abdominal, thoracic/sepsis/cardiac failure)</td>
<td>6/12/18/10</td>
<td>4/12/20/8</td>
</tr>
<tr>
<td>Indication for CVVH: oliguria/hyperkalaemia/volumetric overfilling</td>
<td>40/33</td>
<td>39/23</td>
</tr>
<tr>
<td>CVVH flow rate (ml/min)</td>
<td>120 ± 10</td>
<td>110 ± 15</td>
</tr>
<tr>
<td>Baseline coagulation status PT (%)/PTT (s)</td>
<td>90 ± 10/36 ± 4</td>
<td>88 ± 7/38 ± 5</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD or ratio.

n, number of patients; SAPS II, Simplified Acute Physiology Score II; PT, prothrombin time; PTT, partial thromboplastin time; CVVH, veno-venous haemofiltration; G1, Group 1; G2, Group 2.

Fig. 3. Kaplan-Meier curve of filter runtime. P = 0.0001 between Group 1 (G1) and Group 2 (G2).
GUIDELINES FOR THE USE OF EPOPROSTENOL IN PATIENTS ON CRRT

Epoprostenol is a prostaglandin that is a potent inhibitor of platelet aggregation and is a powerful smooth muscle relaxant producing profound vasodilation. It has a very short half-life and is given by continuous infusion. Epoprostenol is indicated for use in continuous renal replacement therapy when the use of heparin carries a high risk of causing or exacerbating bleeding or when heparin is otherwise contraindicated. (Maintain ACT within 180-220 secs, if contraindication to Heparin exists start Epoprostenol)

**Paediatric Dose:** Start at 4 nanograms / kg / min (Range 2-8 ng/kg/min), Monitor circuit life. If less than 48hrs increase sequentially by 2ng/kg/min to max of 8ng/kg/min. Closely observe for side effects

**Infusion:** Each ml of reconstituted drug = 10 mcg
Dilute 12mcg/kg (1.2 mls /kg) of reconstituted Epoprostenol in 0.9% NaCl to make a total of 50 mls

**Infusion Rates:**
- 0.5 ml/hr = 2ng/kg/min
- 1.0 ml/hr = 4ng/kg/min
- 1.5 ml/hr = 6ng/kg/min
- 2.0 ml/hr = 8ng/kg/min

Acknowledge to A. Deep, KCH, London
Summary

- Heparin and citrate anticoagulation most commonly used methods
- Heparin: bleeding risk
- Citrate: alkalosis, citrate lock !!!
- Evidence favors the use of citrate (not universally used)
- Prostacyclin: platelets sparing effect, a good alternative in patients with liver disease / bleeding diathesis, but cost implications
Anticoagulation in Special Circumstances

• In a child with advanced liver disease?
• In a child with post arrest / cardiac failure?
• In a child on ECMO?
• In a child in septic shock?
• In a child heparin induced thrombocytopenia?
• In a neonates / premies?
Anticoagulation in Special Circumstances

• In a child with advanced liver disease: **No (or PGI2 ?)**
• In a child with post arrest / cardiac failure: **Heparin**
• In a child on ECMO: **Heparin, Citrate (PGI2?)**
• In a child in septic shock: **No, heparin**
• In a child heparin induced thrombocytopenia: **Irudin**
• In a neonates / premies: **Heparin (PGI2?)**
Best practice - conclusion

• No perfect choice for anticoagulation exists
• Choice of anticoagulation is best decided locally
• Think of patient’s disease process, access issues, blood product use
Thank you

And see you in Lisbon for ESPNIC 2017