Citrate anticoagulation for continuous renal replacement therapy

Clinical Problem
A 73 year old female patient presented to the Accident and Emergency Department (A&E) with a profound anaemia, acute kidney injury (AKI) and severe hyperkalaemia. She had a background of Chronic Obstructive Pulmonary Disease (COPD), osteoarthritis, hypertension, morbid obesity and a very poor functional status. She described a one week history of bleeding haemorrhoids. She was not actively bleeding at the time of presentation.

Management
Despite management of her serum potassium of 7.0mmol/l she suffered a cardiac arrest. Standard Advanced Life Support management including calcium chloride was instigated and she had a return of spontaneous circulation after approximately two minutes. She was not intubated as this had been set as a limit of care after earlier discussion with the patient and her family. She rapidly recovered haemodynamic stability and consciousness.

With transfusion ongoing she was moved to the Intensive Care Unit (ICU) for renal replacement therapy (RRT) to control the hyperkalaemia whilst she was transfused. There was a concern her potassium would not be manageable through conservative means whilst she received packed red cells. Her acute kidney injury itself did not mandate RRT as her urea was 20mmol/l and creatinine 190micromol/l.

A trialyse line was placed in her right internal jugular vein. As per standard unit practice she was commenced on continuous veno-venous haemodiafiltration (CVVHDF). Given concerns about a bleeding risk the filter was primed with saline and anticoagulation was not used. The unit standard anticoagulation is with heparin, epoprostenol is also available.

Over the following 12 hours the filter clotted off three times, leading to difficulties with potassium control. There were issues with access pressures despite seemingly optimal line position but the main issue is likely to have been the lack of anticoagulation.

The patient was ultimately successfully transfused and discharged from the ICU, she later deteriorated on the ward and a decision was made at this point that re-escalation to ICU would be inappropriate.

The ICU is currently planning a switch to citrate anticoagulation for RRT and this case highlighted some of the issues we currently face with achieving successful filtration. This patient presented an increased bleeding risk and had problems with access flow and poor filter survival. This expanded case summary has been chosen to explore the efficacy and safety of citrate in RRT and to assess whether it represents a better option for RRT on our ICU.
Discussion

Citrate functions as an anticoagulant by chelating calcium, which is essential at many points in the coagulation cascade. It has a number of proposed benefits:

- When administered pre filter it acts regionally and minimises systemic anticoagulation. As such it in theory reduces the risk of bleeding complications when compared to heparin.
- Heparin's effects are less predictable in critical illness due to altered protein binding and levels (as a consequence of the acute phase response). This means the anticoagulant effect is not entirely predictable or reliable. Citrate's anticoagulation effect is unaffected by acute illness.
- As a consequence of the more effective anticoagulation:
  - blood flows are typically lower in citrate protocols and thus sub-optimal lines may be more manageable.
  - Filter life should be longer.

Risks are related to the citrate itself:

- Metabolic derangement, both acidosis and alkalosis. This is due to the buffering ability of citrate and the high sodium content of some citrate preparations.
- Greater than 50% of the calcium-citrate complex is filtered and so calcium needs replacing. Systemic hypocalcaemia is a potential risk with resulting cardiovascular instability.
- The rest of the citrate-calcium complex is cleared by the liver, skeletal muscle and kidneys. Citrate accumulation can occur if its metabolism is inadequate, typically in liver failure. This can cause a severe metabolic acidosis if it is not managed. As such many trials avoid liver failure patients, but data is starting to emerge to support the safety of citrate RRT in liver patients.

Heparin anticoagulation is a cheap and simple process, most ICU's have extensive experience of its use. Filter life is a persistent issue, this is documented extensively in literature and in local audit, and bleeding complications are seen. Citrate costs more in raw materials but if it prolongs filter life sufficiently it may be able to reduce expenditure. Protocols and training are also a little more complex, largely due to citrate’s twin action of anticoagulant and buffer. Modern replacement fluids and protocols have hopefully simplified these issues for the end user.

There have been a number of randomised controlled trials and meta-analyses of citrate RRT in ICU. As is frequently the case with intensive care research the trials are small to medium sized and techniques and patient mix vary.

The most recent trial was a multi-center RCT using continuous veno-venous haemofiltration (CVVHF) on ICU patients with an AKI. They recruited 139 patients and randomised them to heparin or citrate, cross over for clinical reasons was allowed. This study was of fair quality. Problems include
randomisation by sealed envelopes rather than computer, lack of blinding to the
data analysers, prolonged recruitment and subsequent early termination. There
was also industry funding of some of the authors.

Their results show no difference in their primary endpoints of mortality and
renal outcome, but the early termination left the study underpowered for this.
However, their results showed more frequent problems necessitating
discontinuation in the heparin group (5 vs 28, p<0.001). It should be noted that
only by combining a number of poorly defined safety issues did this reach
significance. There were statistically significant differences in filter survival,
number of filters used and costs, with heparin being more expensive. Also time
off filter was higher in the heparin group.

Overall the results of this study must be interpreted with caution but they do
support the premise that citrate prolongs filter life without increasing costs or
causing a safety issue.

The older studies are all broadly similar. They all have flaws in their design and
methodology. As always, studies in intensive care are difficult to design and
control, allowances have to be made and judgement used. The other issue is the
continuous refinement of the relatively new technique of citrate, it is possible
that newer citrate formulations and protocols are safer and more effective.

Smaller trials include those by Monchi\textsuperscript{4}, Kutsogiannis\textsuperscript{5}, Betjes\textsuperscript{6} and Fealy\textsuperscript{7}.

Monchi\textsuperscript{4} and colleagues studied CVVHF in 20 patients in a crossover fashion.
They found significantly longer filter life and reduced transfusion rates in the
citrate arm. A small study, with no blinding and a number of exclusions that
make applicability to normal practice more difficult (high bleeding risk and liver
failure notably).

Kutsogiannis\textsuperscript{5} studied CVVHDF in 30 patients. This trial again showed longer
filter life. The paper claims a significant reduction in red cell transfusion but the
p value is 0.06, narrowly missing the accepted definition of statistical
significance. Again an unblinded trial with industry funding.

Betjes\textsuperscript{6} studied continuous vено-venous haemodialysis in 48 patients. Similar
filter life was shown but reduced bleeding and transfusion rates. No industry
involvement but similar problems to the preceding trials.

The trial by Fealy et al\textsuperscript{7}, on 10 patients, is too small to draw meaningful
conclusions from. It showed no difference in filter life and no bleeding incidents
in either arm.

Larger trials, looking at CVVHF, were undertaken by Hetzel\textsuperscript{8} and Oudemans-van
Straaten\textsuperscript{9}, 174 and 200 patients respectively. Both trials were randomized.
Hetzel compared citrate with heparin, Oudemans-van Straaten compared citrate
with low molecular weight heparin (LMWH).
The Hetzel trial showed a trend (but not reaching significance) to decreased bleeding in the citrate arm and a significantly longer filter life. Oudemans-van Straaten claimed improved safety with citrate by amalgamating all cause discontinuations and showing this happened more with LMWH, a dubious analysis. Filter life was not significantly different between groups. To the surprise of the authors however, a mortality and renal outcome benefit was shown in the citrate arm. It is postulated that this is due to the negative effect of heparin on anti-thrombin III and improved biocompatibility of the citrate. There is evidence in intermittent haemodialysis of citrate reducing cellular activation and oxidative effects. This is the only trial that has shown a mortality or renal outcome benefit, it is however the largest.

The Hetzel trial had industry involvement but Oudemans-van Straaten did not. Both trials appear to have been run to a reasonable standard. Blinding of analysers does not appear to have occurred. The trial comparing citrate with LMWH is not directly comparable to practice in this region.

Potential risks of citrate anticoagulation include metabolic derangement, hypocalcaemia and citrate accumulation. There is little evidence of worse metabolic derangement in the citrate arms of these trials. Hypocalcaemia is, unsurprisingly, more common but no evidence of a clinical problem is demonstrated. Citrate accumulation may be artificially low in these trials as liver failure was an exclusion criterion in most. The trial by Hetzel with 174 patients had only one case of citrate accumulation, in a patient with pre-existing liver cirrhosis. Oudemanns-van Straaten, with 200 patients, had two citrate arm discontinuations “because of accumulation and early clotting (protocol violation).”

Issues frequently occurring in these studies include detection bias, industry involvement, lack of clarity of protocols, over stating of results and pooling of outcomes to generate statistically significant results. Some also have very slow recruitment or high drop out rates.

There is such huge variation in inclusion criteria and protocols that pooled data analysis is of debatable value, especially when different RRT modalities have been used. However there is a detectable pattern of reduced bleeding and increased filter life with at least equivalent safety. This is supported by the meta-analyses by Zhang and Liao. Zhang found increased filter life and reduced bleeding. Liao felt filter life data could not be pooled but found reduced bleeding. Neither analysis found any safety concerns.

The international KDIGO guidelines agree, they state “For anticoagulation in CRRT, we suggest using regional citrate anticoagulation rather than heparin in patients who do not have contraindications for citrate”.

Lessons Learnt
The trial evidence is not unassailable. As always in ICU research it is difficult to design and execute clean trials. There is a clear need for a large, properly randomised, outcome assessor blinded trial. Follow up would need to be long
enough to assess progression to long term RRT and mortality. Inclusion should be broad enough to ensure applicability to a wide range of ICU’s. Cost data would be of interest. Avoidance of industry involvement would also aid legitimacy.

The evidence as it stands does however support a switch to citrate. There is reasonably strong evidence to show at least equivalent safety, reduced bleeding and longer filter life. There is some evidence of reduced cost. The possibility of reduced mortality and increased renal recovery is tantalising but would need to be validated in future studies.

References