

Green Nephrology: Citrate, the Green Alternative to Heparin in Hemodialysis

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INTRODUCTION

The International Society of Nephrology wants environmentally sustainable kidney care and according to the Lancet, heparin is a threat to planetary health.^{1,2} One of the steps to achieve sustainable care is to find a green alternative to heparin. The literature was searched for alternatives to heparin regarding the external environment. In addition, the effects of heparin and its alternatives on the internal environment of the patient on hemodialysis (HD) were investigated.

DISCUSSION

Heparin and the External Environment

The raw material for heparin is the intestinal mucosa of pigs (Figure 1). The waste, nearly equal to the weight of the raw material, is the greatest source of pollution. The solvents used during the production cause air and water pollution. The detergents and disinfectants used for cleaning also cause water pollution.³ One pig yields approximately 650 mg of crude heparin

containing about 65,000 IU of both antifactor IIa and antifactor Xa activity.⁴ Therefore, based on the usual heparin dose of 5000 IU of unfractionated heparin or 5000 IU of dalteparin, a low molecular weight heparin, 1 pig has to be slaughtered per 13 dialysis sessions. The carbon footprint of raising 1 pig is about 670 kg CO₂ equivalent, which poses a serious threat to the external environment.⁵

Heparin and the Internal Environment

Heparin does not prevent the activation of platelets, neutrophils, monocytes, and complement during HD. Activated platelets release platelet factor 4 and RANTES. Platelet factor 4 promotes neutrophil adhesion to endothelial cells and RANTES promotes monocyte adhesion to the same cells. Both mediators are involved in the pathogenesis of arteriosclerosis. Membrane-activated neutrophils release myeloperoxidase and nitric oxide. Myeloperoxidase triggers the generation of oxidized low-density lipoproteins, the key components of arteriosclerosis, and nitric oxide damages the vascular endothelium.⁶ Activated monocytes release proinflammatory cytokines associated with arteriosclerosis.⁷

Complement activation increases FGF23-induced cardiac hypertrophy and produces acute changes in the lipid spectrum, which are associated with arteriosclerosis. Therefore, heparin enables HD at the expense of arteriosclerosis, resulting in a mortality rate due to cardiovascular disease that is 20 times higher than in the general population.⁸

An alternative to heparin could be a membrane that does not activate platelets. Asymmetric triacetate membranes and heparin-free HD have been tested. Unfortunately, preterm clotting occurred in more than 10% of the sessions.⁹ Fluorinated polyurethane surface-modifying macromolecules membranes and heparin-free HD were more successful. No preterm clotting occurred.¹⁰ Although it is not yet known whether fluorinated polyurethane surface-modifying macromolecule membranes are harmful to the patient, it is certainly harmful to the external environment. Denmark, Germany, Norway, Sweden, and the Netherlands plan to phase out almost all fluorinated polyurethane surface-modifying macromolecules by 2030.

Other alternatives to heparin could be thrombin inhibitors such as hirudin and recombinant-hirudin which have a lower carbon footprint than heparin, but they have a similar effect on arteriosclerosis. Thrombin inhibitor argatroban, a 4-methylpiperidine derivative, is isolated from coal tar which has a high carbon footprint.¹¹ Danaparoid, a low molecular weight heparinoid devoid of heparin, has similar effects on the external environment and arteriosclerosis as heparin. Epoprostenol, a platelet aggregation inhibitor, has already been used in patients with increased bleeding risk. However, premature termination

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Figure 1. First step of producing heparin, separating mucosa from the pig intestines. Reprinted with permission from Chemical and Engineering News. Copyright ©2016 by the American Chemical Society. This image file first appeared in volume 94, issue 40 on October 10, 2016.

of HD is not uncommon. Citrate enabled heparin-free HD because it chelates ionized Calcium (Ca), which is essential in the activation

of factor II, factor VII, factor IX, and factor X. Citrate has to be used with a Ca-free dialysis fluid and Ca suppletion after the dialyzer. With

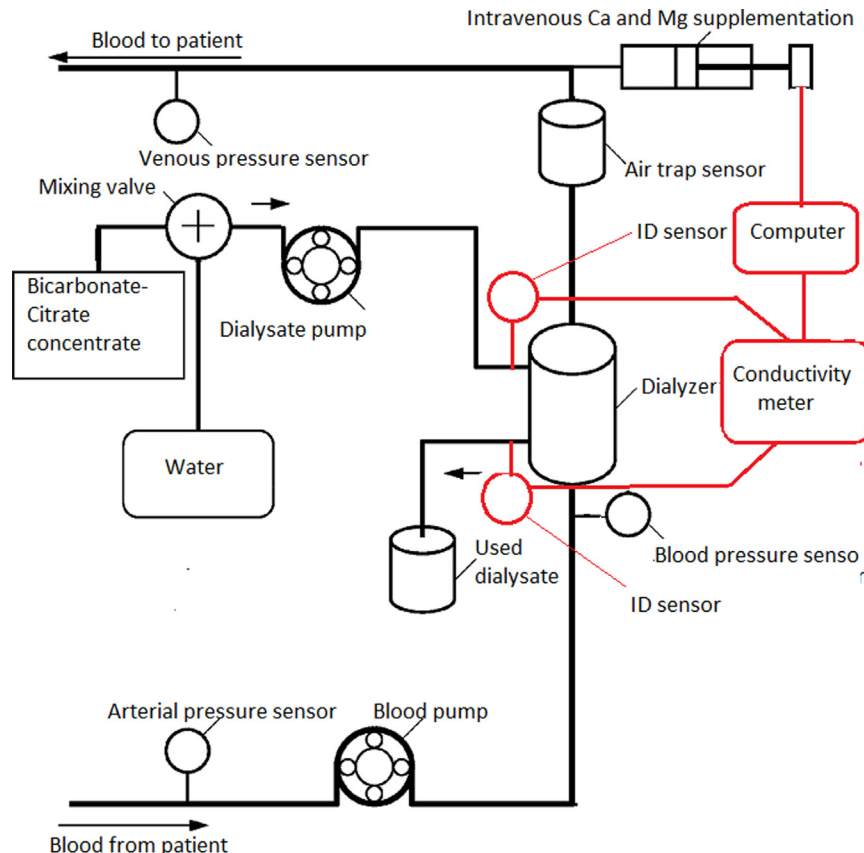


Figure 2. Intravenous calcium and magnesium supplementation controlled by conductivity meter and computer.

a Ca- and Magnesium (Mg)-free dialysis fluid, the citrate dose can be lower.^{S3} Citrate has a low carbon footprint. Beet molasses are the raw material for citric acid. The carbon footprint of 1 kg (5.2 mol) citric acid is 20 kg CO₂ equivalent.^{S4} Therefore, the carbon footprint of 13 dialysis sessions of 4-hour with 1.02 mmol/min citrate is 0.94 kg CO₂ equivalent. This is less than 1.5% of the carbon footprint of heparin. Regarding arteriosclerosis, chelating ionized Ca reduces the activation of platelets, neutrophils, monocytes, and complement.⁶

One of the side effects of citrate is metabolic alkalosis. One mmol of citrate is converted into 3 mmol of bicarbonate. Therefore, the buffer content of the dialysis fluid should be reduced to prevent alkalosis.^{S5} A Ca-free and Mg-free dialysis fluid makes intravenous Ca and Mg suppletion necessary. In the past, repeated serum samples of ionized Ca and Mg had to be taken because the suppletion rate depends on the effective urea clearance. Fortunately, in the past 20 years the effective urea clearance can be measured online with ultraviolet absorbance or ionic dialysance. Ultraviolet-absorbance uses a spectrophotometer, which measures all dialysate passing through a flow cuvette. Ionic dialysance uses conductivity sensors at the dialyzer inlet and outlet. At the inlet, the dialysis fluid conductivity is transiently increased, and the conductivity sensors measure the drop in the dialysate conductivity. To calculate the rate of intravenous suppletion of Ca and Mg, the following formula is used: infusion rate suppletion fluid * Ca/Mg concentration in suppletion fluid = ionic dialysance * conventional Ca/Mg concentration dialysis fluid.^{S6} The conductivity meter sends the ionic dialysance to a computer, which calculates the infusion rate

and controls the infusion pump (Figure 2).

CONCLUSION

Citrate is mostly administered intravenously in the arterial line before the blood pump. An accepted dosage is 0.34 mmol of citrate per 100 ml of blood and the citrate pump should be coupled to the blood pump.^{S7} Another way to administer citrate is to add it to the dialysis fluid.^{S8} A 1.0 mmol/l citrate-containing dialysis fluid results in a lower citrate load. Assuming a 4-hour HD session (blood flow 300 ml/min, hematocrit 35%, and citrate extraction coefficient 70%), the citrate load is 48 mmol when it is administered in the dialysis fluid and 75 mmol when it is given intravenously. The lower load is effective because due to priming, citrate is already present when the blood enters the dialyzer.^{S9} With such a lower citrate load, even patients with severe liver dysfunction can be dialyzed.^{S10} Disadvantages of citrate in the dialysis fluid are that single-needle HD and slow continuous ultrafiltration are not possible.^{S11,S12}

Citrate with a Ca-free and Mg-free dialysis fluid and intravenous suppletion of Ca and Mg is the green

alternative to heparin in HD. It is not only better for the external, but most likely also be better for the internal environment. Online measurement of the ionic dialysance controls the necessary supplementation of Ca and Mg and obviates monitoring these divalent cations.

DISCLOSURE

JvdM owns European patent EP2826476A1 on a calcium-free dialysis fluid.

SUPPLEMENTARY MATERIAL

[Supplementary File \(PDF\)](#)

Supplementary References.

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