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Opinion

The Story of Dialysis Fluid

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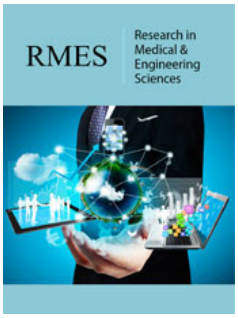

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Introduction

In the long-run of CKD-5 patients, treated with Hemodialysis, the problem of Calcification is well known. The causes of the patient's internal Calcification will not be handled here. Unfortunately, the classical prescription of Bicarbonate Dialysis Fluid does contribute to the patient's Calcification.

In 1953 Homer W. Smith (Physiologist in New York) had described the development from the unicellular over the amphibians to the mammalians (the book "From Fish to Philosopher"). In the unicellular, the supply with oxygen and the disposal of CO_2 will takes place by Diffusion. When animals became bigger, there was the development of a Heart-Circulation System, at first in coldblooded animals. Even in these, the form of transport of CO_2 will be Bicarbonate. In mammalians (with 37 °C temperature following to the high turn-over metabolism) the concentration of Bicarbonate will reach 24mmol/l and CO_2 1,2 mmol/l resp. 40mm Hg. So, there is the relation of 20:1. These 4 percents (of total CO_2) will work as the acidification in order to prevent the calcification between Bicarbonate and Ca^{++} and Mg^{++}. The conversion of CO_2 into Bicarbonate and the back-conversion in the lungs (from Bicarbonate into CO_2 will be done by the ubiquitous enzyme Carbonic Anhydrase. There will be no calcification at all.

With the beginning of Chronic Hemodialysis in March 1960 B. Scribner established the Bicarbonate concentration of Dialysis Fluid to 32mmol/l. This followed the short treatment time of Dialysis in comparison to the time of one week living (168 hours) in order to treat the metabolic acidosis, due to the fixed acids of nutrition. W. Kolff used experimentally acid Sodium Phosphate for Acidification. Scribner had taken over the way of acidification of N. Alwall (> Carbogen gas, 5% CO_2 mixed with 95% Oxygen). As there does exist Calcification, a paddle had added to the 120 Liter batch system of Travenol in order to stir the Dialysis batch. Next to Calcification, there was the problem of Pyrogenic Reaction, due to the prefabricated alkaline Bicarbonate solution (> for Exchange of the Dialysis batch fluid).

In 1960, S. Shaldon had deal with Dialysis. He was specialist in Hepatology(!). His CEO, S Sherlock, had ordered him for this. All parts of the way of Dialysis in 1960 appeared terrible to Shaldon (> Scribner-Shunt, Travenol batch dialysis system, the calcification, and the pyrogenic reactions)! In 1963, there was a meeting in Evian (at the lake of Geneve). Few doctors who worked with Dialysis, had taken part. There the EDTA was founded. In 1964/65, Shaldon had developed a completely new Dialysis Single-Pass System in Montpellier together with F. Mion. As Sholdon was Hepatologist in his first medical profession, he had set Acetate 32mmol/l as the qualified Buffer Precursor. Due to the pK=4,75, there was only the alkaline part of Acetate present in the Dialysis Fluid. This Acetate amount was metabolized by the liver to Bicarbonate and CO_2 for buffering. Acetate has a perfect solubility, with other words no calcification of the Dialysis Fluid! Shaldon treated Dialysis patients at first in the Royal Free Hospital (London). Later, he trained these patients for home-dialysis in his own center (NKC, London, Fairholme Gardens No. 3). His Dialysis Regime: 3x8 hours per week Hemodialysis, Kiil Dialyzer with

$1m^2$ surface, blood-flow middle fast). - Additional one detail to the Acetate Dialysis: At the beginning of the Dialysis (> in the first 30 minutes), there was a loss of the patient's own Bicarbonate, as the liver needed time for the metabolism of Acetate. So, the patients treated with Acetate Dialysis, became in the beginning a little more acidotic, due to the loss of Bicarbonate.

In 1971 Scribner published the "Square-Meter Hours Hypothesis". Whenever the Kt/V had not appeared, he used Dialyzers with a bigger surface and high blood flows, in order to compensate for the shortening of the Dialysis treatment time. With this new Regime of Scribner, there appeared a bigger pool of Acetate in the patients, as the metabolic capacity of the liver had over-runed. So, these important side-effects (nausea, vomiting and blood-pressure drop) were introduced by Scribner, as he was no Hepatologist! But most of the doctors and the majority of the patients agreed to the shortening of the Dialysis treatment time.

In 1978, the Bicarbonate Dialysis with 3mmol/l Acetate as Acidification was introduced, in order to prevent the side-effects of the Acetate Dialyse with shortened time. In other words: So, the Calcification had introduced again! When the Dialysis had finished, a disinfection and decalcification of the monitor is necessary. But the patient receives no Decalcification! Pyrogenic reactions appeared very seldom (small Bicarbonate containers). In 1990, the BiCart Cartridge appeared (dry powder sterile) as an important improvement of the quality of treatment. In France, 4 or 5mmol/l Acetate as Acidification will used until today. Without any reduction of the calcification! Even with Acidification with 3mmol/l Acetate (> this means a CO_2 partial pressure of 60mm HG) may be a bigger obstacle for patients with an obstructive ventilation disease, in order to eliminate this additional CO_2 load of the Dialysis Fluid.

In 1985, Bené (Lyon, Hospal Company) introduced the AFB Treatment (> Acetate Free Bio-Filtration). This was a Low-Volume HDF(Post-Dilution) with a kind of NaCl Fluid for Dialysis, only added with K^+, Ca^{++} and Mg++. So, there was no buffer (Bicarbonate) in the Dialysis Fluid! The Acidification was done by elimination of the patient's own Bicarbonate by the Dialyzer, a kind of Bicarbonate robbery. A little more of the eliminated Bicarbonate was given to the patient by the Substitution Infusion bag. An intelligent System, only for smaller patient, expensive treatment with special monitor, seldom used. But NO Calcification.

In 1997, B. Charra and G. Laurent from Tassin (South France, published in NDT) published their Dialysis results ("What is the secret of Tassin?"). A big group of patients in the age of 80 with 30 years of Dialysis and a little smaller group in the age of 90 year with 40 years of Dialysis. Treatment time most of all 3x8 hours per week, Dialyzers with $1m^2$ surface and blood-flow not too fast. Nutrition with only 2g NaCl per day with fresh cooking and reduced Sodium of Dialysis Fluid (Na^+ 135 mmol/l). They did NOT mention that the therapeutic mode was the classical Acetate Dialysis according Shaldon! In Tassin, the patients had no Acetate side-effects, as the Metabolic Capacity of the Liver had not exceeded! And NO calcification problem at all! - Five never studies with longer treatment time during the night did not show an improved survival: ➔ the calcifying Bicarbonate Dialysis with Acetate Acidification.

In 11/1999, the ART patent had accepted the first time in the US (US886469B2, Advanced Renal Technologies, Seattle, R. Callan and J. Cole, product "Citrasate"). The context and target of this patent was to replace Heparin as anticoagulant with equimolar Citrate as Acidification. As an anticoagulant, the Citrate based A-Component was not particularly successful to replace Heparin (> often clottings). This is easy to check, as the Classical RCA (Citrate Dialysis, CiCa System) will reach concentrations of Citrate in the range between 6-10mmol/l in the treated patient. With Citrasate, there are only 0.85mmol/l Citrate inside. Later-on, a reduction of Heparin up to 50 % with Citrate based A concentrates had been reached in several studies. Chemical trained man had recognized the Chelate Binding of Ca^{++} and Mg^{++} by Citrate as a second principle of working in order to prevent the Calcification.

In 2018, A. Pasch (Nephrologist), G Schmaderer and G. Lorenz (both Chemists) developed the T50-Test (patent in Switzerland) for measurement the patient's Total Calcification in the serum. Together with U. Heemann (Munich, published in NDT) they investigated 78 CKD-5 patients. In the first three months, the patients were treated with Citrate Acidification, then switching to regular Acetate Acidification. The results had a clear reduction of Total Calcification when these patients were treated with Citrate Acidification. This study shows a trend in a short treatment time. A statement concerning mortality is with this short study not possible.

A little explanation. The Chelate-Binding between Citrate and Ca^{++}/Mg^{++} will be stronger than the classical covalent binding and concerning energy favorable. Citrate will give two Electrons for the Chelate-Binding to Ca^{++} and Mg^{++}. So, the Ca^{++} and Mg^{++} Ions were present in the Dialysis Fluid, but the Calcification will be hindered! This context remains not well understood by Medical Doctors(!). Also, in the Medical Authorities (> FDA Dep. Medical Products and BfArM Institute in Germany) are Medical Doctors. They have the same problems, understanding the Chelate-Binding of Citrate(!). Additionally, the Medical Authorities have NO VIGILANCE for problems with Medical Products!

In conclusion, the Acidification with only one step never can prevent the Calcification in the Dialysis Fluid. The Bicarbonate concentration with 32mmol/l is simply too high. That's why Acidification with Citrate is the best option.

A last advice. The concentration of Ca^{++} should be elevated a little in order to prevent a state of lowered Ca^{++} in the patient, as Citrate will run into the patient's blood and binds a small amount of Ca^{++}.

How will it run? Probably most of the CKD-5 patients will further treat with Acetate Acidification (> with Calcification). In the US, several years ago, one big provider of Dialysis (40% of the US Dialysis patients) switched to Citrate Acidification (by management decision!). In the following entire year, in the USRDS Registry there was better survival in the US CKD-5 patients, whenever the Kt/V and the time of treatment had not changed!

When the theme of Citrate Acidification appears as a Congress-Theme, there will be only spoken concerning the dosage reduction of the anticoagulant Heparin. But the main effect of Citrate remains the prevention of Calcification in the prescription! - Naturally it may happen that a politician for health may hear from this context when he has one Dialysis patient in his own family. In this case, the problem of the Calcification of the Dialysis Fluid may be solved perhaps in a shorter time.

It' just time for Bicarbonate Dialysis without Calcification!