Baxter

CITRATE DIALYSIS FLUID

CITRATE IN DIALYSIS

WHAT IS CITRATE?

Citrate is a natural metabolite, which is a source of cellular energy, providing buffering capacity to the patient. Citrate is an intermediate in the citric acid cycle and is widely used in the food and drug industry because of its buffering, anticoagulant and antioxidant capacities.

As a chelator, citrate is able to bind calcium and metals that catalyse the production of Reactive Oxygen Species.[1]

Under physiologic circumstances, citrate is metabolized in the liver, skeletal muscle and renal cortex.[2]

Citrate clearance is not impaired in patients with chronic renal failure.[3]

WHY CITRATE IN DIALYSIS?

An acid is required in bicarbonate dialysis to avoid insoluble calcium and magnesium precipitation. Acetic acid is commonly used at a concentration up to one hundred times higher than normal plasma acetate levels.[4] Body gain of acetate is particularly high in convective treatments.[5] This results in a substantial increase in plasma acetate which may promote hemodynamic instability, inflammation and acidosis.[4]

Citric acid has been proposed as an alternative dialysis buffer due to its anticoagulant, anti-inflammatory and anti-oxidant properties.[6]

WHAT IS THE INTENDED USE OF **SOFTPAC CITRATE** AND **SELECTBAG CITRATE** IN HEMODIALYSIS?

HD concentrate Citrate product is intended to be used as a citrate based acid concentrate in bicarbonate dialysis for on-line preparation of hemodialysis, hemodiafiltration and hemofiltration fluids on compatible dialysis machines.*

The Baxter **SoftPac Citrate** and **SelectBag Citrate** concentrate allows for acetate-free dialysis fluids which may help to promote patient well-being with all the beneficial properties of Citrate.[1]

* Baxter **SoftPac Citrate** and **SelectBag Citrate** Instruction for Use.

CITRATE IN DIALYSIS

ARE YOU AWARE OF THE BIOCOMPATIBLE PROPERTIES OF CITRATE?[4,7]

In vitro data show that:

- low concentration of citrate can reduce complement and granulocyte activation in human whole blood.[7]
- the dispensation of citrate per se reduces endothelial death and inflammation in a hyperglycemic environment.[1]
- at concentration commonly used in clinical practice, acetate dialysate increases oxidative stress and may act as an adjunct to the other proinflammatory stimuli to which HD patients are exposed. Citrate dialysate does not produce such a cell activation.[8]
- citrate dialysis reduces endothelial cell dysfunction and vascular smooth muscular cell osteoblastic differentiation.[6]
- citrate dialysate favorably affects calcification propensity.[9]

Ex-Vivo data show that:
Citrate-acidified bicarbonate dialysis protects against calcium accumulation in rat aortic walls cultured ex vivo.[10]

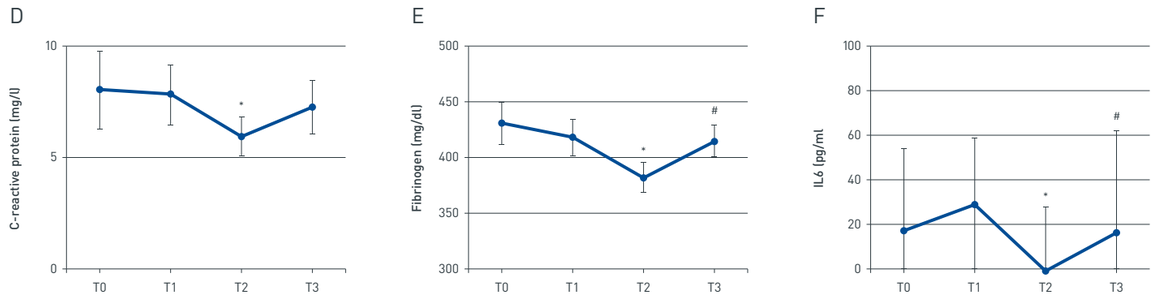
In clinical trials
Baxter citrate concentrate fluid has been shown:

- to reduce the intra-dialytic rise in pentraxin-3 (PTX3) compared to control in a short-term randomized controlled cross-over study. PTX3 is an inflammatory marker known to be induced by HD treatments.[4]
- to lower pre-dialysis levels of the inflammatory marker C-reactive protein (CRP) in a controlled cross-over study in patients in on-line haemodiafiltration.[11]
- to significantly reduce chronic inflammation parameters such as CRP, fibrinogen, IL6, and adipokine chemerin when switching from acetate to citrate in a cross-over study, patients being treated in sequence with acetate, citrate and again acetate buffered dialysis solutions.[6]

Chronic HD patients suffer from high cardiovascular morbidity and mortality mainly due to a chronic systemic inflammation coupled with an aberrant metabolic state[6]

In vitro studies show that citrate is a promising substitute for acetate for a more biocompatible dialysis, most likely resulting in less adverse effects for the patients[7]

In this randomized cross-over study the duration was 9 months; in the first 3 months patients were treated with a standard dialysis solution containing 3 mmol/l acetate, the following 3 months an acetate-free solution containing 1 mmol/L citrate (**Select Bag** Citrate) and the last 3 months again the acetate solution were used.



Patients' clinical data at the different study time points, (D) pre-dialysis values of plasma C-Reactive Protein (CRP), (E) pre-dialysis plasma fibrinogen, (F) pre-dialysis serum IL6.
T0: study start; T1: end of 1st acetate period (3 months from study start); T2 end of citrate (6 months); T3 end of 2nd acetate period (9 months).
*p < 0.05 when data were compared with T1; #p < 0.05 when data were compared with T2.
Adapted from Dellepiane[6] N=45

IMPROVED HEMODYNAMIC STABILITY

A recent randomized controlled study has shown that compared to acetate dialysates, citrate containing fluids may offer a greater hemodynamic stability with significantly fewer episodes of arterial hypotension.[12]

This is aligned with the results of previous studies:

- reduction in the frequency of hypotensive episodes, especially in the most symptomatic and severe episodes of hypotension.[13]
- the use of citrate rather than acetate as a dialysate decreases peripheral resistances and slightly reduces systolic and diastolic blood pressure. Nonetheless, both the analysis of maximum fluctuations in peripheral resistances during dialysis and data describing subjective tolerance suggest a trend towards improved haemodynamic stability for patients on the citrate schedule.[14]

WHY IS IT IMPORTANT TO REDUCE INTRADIALYTIC HYPOTENSION?
In addition to a reduced sense of well-being caused by the symptoms of intradialytic hypotension (IDH), patients who experience IDH have been shown to be at higher risk of mortality.[15,16]

In a prospective, multicenter, randomized and crossed study of 32 weeks duration, with 56 patients randomly assigned to receive 16 consecutive weeks of citrate concentrate followed or preceded by 16 weeks of acetate fluid, there were fewer episodes of hypotension during the sessions at the baseline visit with the citrate concentrate (1 versus 3, p=0.04). The 46 patients who completed the study performed 4416 HD sessions, 2208 with acetate and 2208 with citrate. **Hypotension occurred in 14.1% with acetate versus 10.8% with citrate (p<0.01).[12]**

IMPROVED CONTROL OF ACID-BASE BALANCE

Citrate is rapidly metabolized in the body into bicarbonate in a 1:3 molar ratio.[17] Patients with reduced kidney function are in positive acid balance. During each HD session, a large surge of HCO_3^- enters the circulation and typically overcorrects predialysis acidosis to alkalosis and alkalemia. The acid-base alterations may have an impact on cardiovascular system, central nervous system, pulmonary function, tissue oxygenation and metabolism, inflammation and defense against infection.[18]

Since 2000, KDOQI guidelines recommend maintaining predialysis serum bicarbonate at ≥ 22 mmol/L.[19]

As documented by the DOPPS, both high (>27 mEq/L) and low (≤17 mEq/L) serum bicarbonate levels are associated with increased risk for mortality and hospitalization.[21] A more recent publication showed an increase in mortality with low serum bicarbonate, but did not show the same increase in mortality with higher serum bicarbonate levels.[20]

ACIDOSIS & ALKALOSIS PREVENTION

CORRECTED BETWEEN-TREATMENT ACIDOSIS AND REDUCED POST-TREATMENT ALKALOSIS

	PRE-HEMODIALYSIS		POST-HEMODIALYSIS		SIGNIFICANCE	
	ADF	CDF	ADF	CDF	ADF-CDF	ADF-CDF
Bicarbonate, mmol/l	23.0 (1.87)	22.8 (2.20)	28.5 (3.0)	26.9 (1.5)	0.668	0.032

Adapted from de Sequera[12] N=56

In a prospective, multicenter, randomized and crossed study, of 32 weeks duration, in patients in three-week HD, 16 weeks with ADF (acetate dialysis fluid) and 16 weeks with CDF (citrate dialysis fluid) **SelectBag Citrate**.

Dialysis with citrate achieves a better control of post-dialysis acid-base balance by decreasing/avoiding post-dialysis alkalemia compared to acetate.[12]

Citrate dialysate helps to control acid base balance by correcting acidosis between sessions and avoiding/reducing post dialysis alkalosis. Acute alkalaemia induced by the addition of (missing) bicarbonate during dialysis is an issue which has considerable clinical significance. It has been related to important adverse effects, such as hemodynamic instability, cardiac arrhythmia, paraesthesia/cramps, reduced cerebral blood flow, respiratory distress, headache, and a procalcifying effect.[22]

DECREASED THROMBOGENICITY

By chelating ionized calcium in plasma, citrate containing dialysate concentrates have anticogulant properties in a concentration-dependent manner:

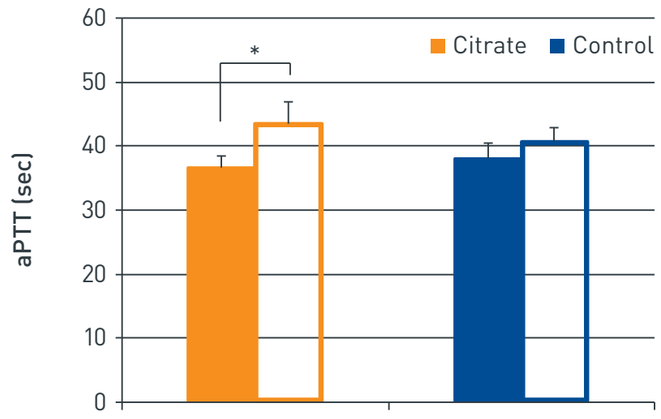
- Citrate fluid induces a significant intradialytic increase in aPTT (activated partial thromboplastin time).[4]
- Citrate has local anticoagulant effect inside the dialyzer, allowing reduced heparin dosing while maintaining extracorporeal patency[23] and optimizing dialyzer clearances [4,6,11]

SoftPac Citrate and **SelectBag Citrate** products are not intended to obviate the need for anticoagulation in all patients.[24]

ALTERNATIVE MODE OF LOW SYSTEMIC ANTICOAGULATION

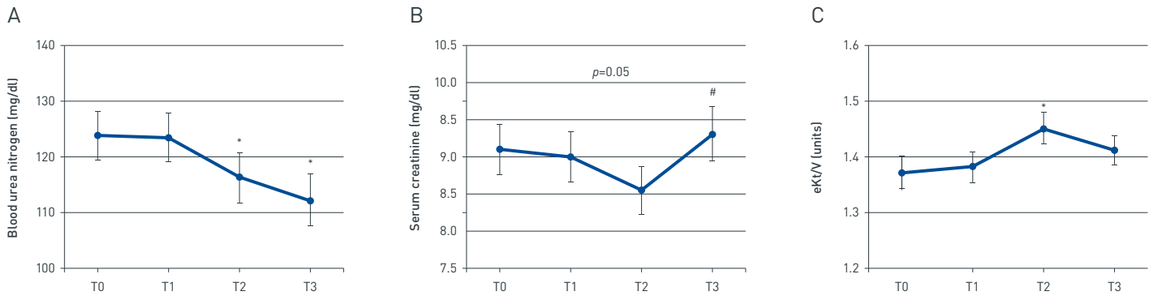
The combination of citrate dialysate with the heparin–grafted membrane Evodial has been shown to be a valid alternative to regional citrate anticoagulation.[23,25,26]

In an open-labeled cross-over trial (6+6) weeks with 8 treatments wash-out in between. Patients were randomly assigned to start with either citrate dialysis fluid rate or control acetate fluid.



Increased Activated Partial Thromboplastin Time (APTT) post dialysis when using **SelectBag Citrate** dialysis fluid.[1] Solid bars represent pre-dialysis values and shadowed bars post-dialysis values. Data are shown as means ±SEM, p*=0.003. Adapted from Grundstrom.[4] N=24

In this randomized cross-over study the duration was 9 months; in the first 3 months patients were treated with a standard dialysis solution containing 3 mmol/l acetate, the following 3 months an acetate-free solution containing 1 mmol/L citrate (**Select Bag Citrate**) and the last 3 months again the acetate solution were used.



Patients' clinical data at the different study time points, (A) Pre-dialysis blood urea nitrogen levels, (B) pre-dialysis serum creatinine values, (C) dialysis efficacy estimated with the eKt/V Daugirdas formula.
Period (3 months from study start);
T2 end of citrate (6 months);
T3 end of 2nd acetate period (9 months).
*p < 0.05 when data were compared with T1;
#p < 0.05 when data were compared with T2.
Adapted from Dellepiane[6] N=45

THE EFFECT OF CITRATE ON CALCIUM BALANCE

Calcium mass balance is easily maintained during treatment

Citrate binds ionized calcium and causes a change in the total calcium mass transfer compared to dialysis fluids without citrate, unless compensated for. A kinetic model developed by Baxter Research shows that with one mmol/l of citrate in the dialysis fluid an additional 0.15 mmol/l of calcium is required to achieve a mass balance within the dialyzer that is equivalent to dialysis fluid without any citrate.[27] Clinical data support these theoretical results.[4,28,29]

Baxter citrate concentrates offer augmented calcium concentration, making it easy to maintain the proper calcium mass balance.

Some patients may not benefit from the use of citrate dialysate and need to be closely monitored: patients with hypocalcemia, hypomagnesemia and uncontrolled secondary hyperparathyroidism.[12]

CITRATE DIALYSIS

Suitable for every patient

Citrate is a well-known antioxidant and anticoagulant buffer that is a well-tolerated and biocompatible alternative to regular acetate.

Citrate-containing acetate free dialysis is suitable for every patient.

CITRATE CLINICAL ADVANTAGES:

- Improved hemodynamic stability
- Improved control of acid-base balance
- Decreased thrombogenicity

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