International symposium at the occasion of
20 YEARS
OF CITRATE USE IN HEMODIALYSIS
IN SLOVENIA

December 5, 2013
Grand Hotel Union, Ljubljana, Slovenia

Programme and lectures
Dear colleagues,

We invite you in Ljubljana, on December 5th, 2013, to the international symposium on citrate anticoagulation in hemodialysis, at the occasion of 20 years of citrate use in hemodialysis in Slovenia. Symposium is organized by Gambro and Slovenian Dialysis and Transplant Association.

Citrate is increasingly used in hemodialysis, both for regional anticoagulation as well as locking solution for hemodialysis catheters. In the last years dialysate with citrate instead of acetate is increasingly used in chronic hemodialysis patients.

The aim of symposium is to present development and state-of-the-art of citrate use in hemodialysis.

We are honoured to have the opportunity to host international experts and learn from them. We will also have the opportunity to present achievements of Slovenian nephrologists to our colleagues from other countries.

We hope that you will have great time in Ljubljana that is especially beautiful and exciting in December.

Best wishes,

Local organizers

Rafael Ponikvar and Jadranka Buturović-Ponikvar
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PROGRAMME
Thursday, December 5, 2013
8.00
Registration
8.50
Welcome address

9.00-10.30
Citrate use in hemodialysis
_Moderators:_ Aljoša Kandus, Andrej Bren

9.00-9.30
20 years of citrate use at University Medical Center Ljubljana
_Jadranka Buturović Ponikvar_

9.30-10.00
Hemodialysis anticoagulation - citrate in dialysis
_Gunilla Grundstrom_

10.00-10.30
Clinical evaluation of citrate in chronic hemodialysis patients
_Giuseppe Rombola_

10.30-11.00
Coffee break

11.00-13.00
Citrate in special dialysis procedures
_Moderators:_ Miha Benedik, Bojan Knap

11.00-11.30
The role of long-term citrate anticoagulation in chronic hemodialysis – our experiences and future challenges
_Jakob Gubenšek_

11.30-12.00
Light chain nephropathy and Theralite citrate hemodiafiltration
_Andreja Marn Pernat_

12.00-12.30
Use of high cut-off membranes for extracorporeal blood purification in the treatment of rhabdomyolysis-associated acute kidney injury
_Vladimir Premru_

12.30-13.00
Intermittent high-volume predilution on-line citrate haemofiltration in critically ill patients with acute kidney injury
_Nataša Škofič_

13.00-14.30
Lunch

14.30-15.00
Citrate lock for hemodialysis catheters
_Jadranka Buturović Ponikvar_

15.00-15.30
4% vs. 15% citrate as anticoagulant during therapeutic plasma exchange: a prospective randomized trial
_Manja Antonič_

15.30-16.00
Low and high-concentrated citrate solutions
_Kai Harenski_

16.00-16.30
Coffee break

16.30-18.45
Citrate anticoagulation in critically ill adults and children
_Moderators:_ Rina Rus, Nina Battelino

16.30-17.00
Dilemmas in renal replacement therapy in critically ill patients
_Rafael Ponikvar_

17.00-17.30
Regional citrate anticoagulation in pediatric renal replacement therapy
_Jacek Zachwieja_

17.30-18.00
CRRT for the treatment of acute kidney injury in critically ill newborns and small children
_Rafael Ponikvar_

18.00-18.15
Prolonged citrate CVVHD in a newborn with acute kidney injury due to hemorrhagic shock during labour
_Barbara Vajoči Trampuž_

18.15-18.30
The use of SelectBag® Citrate in our dialysis center: preliminary experience
_Karmen Romozi_

18.30-18.45
Closing remarks:
The future of citrate use in hemodialysis
_Jadranka Buturović Ponikvar_

19.30
Dinner
INVITED LECTURES AND ORAL PRESENTATIONS
Jadranka Buturovic-Ponikvar graduated from the University of Belgrade Medical School as valedictorian, awarded by the Serbian Medical Association (GPA 9.93/10). She received her Master's Degree in urology at the Medical School in Belgrade (thesis: Xanthogranulomatous pyleonephritis, mentor prof. dr. Vladimir Petronić) in 1983. In 1988 she became a specialist of internal medicine. In 1993 she received her PhD at the Medical Faculty of the University of Ljubljana; thesis: The influence of various factors on hemostasis activation during hemodialysis, mentor prof. dr. Andrej Bren. In 1994 she became Assistant Professor, in 1999 Associate Professor, and in 2004 Professor of Medicine at the Medical Faculty of the University of Ljubljana. During this period she was employed, first from 1982-1988 at the Center for Dialysis and Transplantation, Institute of Urology and Nephrology, University Medical Center Belgrade. From 1988 up to the present she has been employed at the Department of Nephrology, University Medical Center Ljubljana. She was Chief of the Center for Pediatric Dialysis and Transplantation from 1995-1999 (until the center was moved to the Department of Pediatrics), and since 1999 she has been Chief of the Ultrasound Unit. She has been a chairman of the Slovenian Renal Replacement Therapy Registry from 2004. From 2011 she is a vice-head of the Department of Nephrology, head of the Research Group of the Department of Nephrology and a national coordinator for nephrology fellowship at the Medical Chamber in Slovenia. She is a member of the Council for medicine at the Slovenian Research Agency, responsible for cardiovascular disease. Major interests are: anticoagulation, citrate, hemodialysis, kidney transplantation, vascular access, Doppler ultrasonography, renovascular disease, acute and chronic kidney disease.

She is a member of ERA-EDTA (European Renal Association – European Dialysis and Transplant Association), ESOT (European Society for Organ Transplantation), AST (American Society for Transplantation), IPTA (International Pediatric Transplant Association), ASDIN (American Society for Diagnostic and Interventional Nephrology), NKF (National Kidney Foundation), ISN (International Society of Nephrology), VAS (Vascular Access Society), Slovenian Society of Nephrology, Slovenian Society for Ultrasonics and a president of SDTA (Slovenian Dialysis and Transplant Association).

Her bibliography is accessible on the pubmed and web of science under the following names: buturovic j; buturovic-ponikvar j; ponikvar jb; buturovicponikvar j, and on COBISS and SICRIS, code number 10649.

20 YEARS OF CITRATE USE AT UNIVERSITY MEDICAL CENTER LJUBLJANA

Jadranka Buturovic-Ponikvar

Department of Nephrology, University Medical Center Ljubljana, Ljubljana, Slovenia

Introduction. Citrate has many characteristics of the ideal anticoagulant for hemodialysis. Its anticoagulant effect is excellent and is limited to the dialysis circuit, without causing systemic anticoagulation. In addition to inhibiting coagulation, it reduces platelet deposition on the dialyzer membrane. By decreased activation of platelets and coagulation, citrate anticoagulation might increase delivered dialysis dose. By chelating calcium and magnesium, citrate reduces some of the effects of blood interaction with the dialyzer membrane, which are calcium and magnesium-dependent, thus improving biocompatibility of dialysis circuit. Using citrate, we avoid heparin-induced thrombocytopenia, the condition that is increasingly recognized, especially in intensive care units. Citrate is easily dialyzable (molecular weight of trisodium citrate is 294 Da), its removal during high-flux dialysis is 83%. The cost of citrate is low and many hospital pharmacies are able to produce citrate solutions of various concentrations. Low cost and accessibility of citrate may be seen in some way as citrate’s misfortune in the past, because of the lack of industry promoting its important advantages. However, in the last years it seems that the interest in citrate from the industry is growing, so we may expect expansion of citrate use in the future.

History of citrate use. The first hemodialysis using regional citrate anticoagulation was reported by Morita et al in 1961 (Am J Med Sci). Citrate gained wider attention after Pinnick et al published report in citrate anticoagulation during 15 hemodialysis procedure in 4 patients in NEJM 1983. The idea of introducing citrate anticoagulation in our dialysis center occurred in the early nineties of the 20th century, during work on PhD thesis “The influence of various factors on hemostasis activation during hemodialysis”. At that time citrate anticoagulation was believed to be extremely complicated and dangerous. We decided to use protocol from Mehta et al (KI 1990) designed for CVVHD and modified it for intermittent hemodialysis. As in Mehta protocol, 4% trisodium citrate* was used, with the dose of citrate targeted to the lowest possible for clotting prevention (approximately 2.5% of the blood flow, with obligatory use of calcium-free dialysate). 4% trisodium citrate and 1M CaCl2 solution were prepared by hospital pharmacy of the University Medical Center Ljubljana, who was our indispensable partner in citrate use for 20 years. With the support of our dialysis center head nurse Ljiljana Gaber and dialysis staff, we started with introduction of regional citrate anticoagulation for hemodialysis in 1993.

Citrate hemodialysis in early nineties was different than today in several important issues. Low flux membranes were used in majority of patients, with lower citrate clearance and consequently more metabolic complications. Bedside ionometers were not available at that time, so we relied on regular laboratory values of total calcium with significant delay in calcium dose adjustment. Hemodialysis monitors did not have such easy possibility of adjusting and profiling of sodium and bicarbonate concentration in dialysate as today. Close clinical and ECG monitoring of the patients were necessary, adding to procedure complexity.
Infusion pumps were not as widely available as today. Because of the fear of metabolic alkalosis, the use of 1M hydrochloric acid was anticipated and included in the first protocols, however, we have never used it.

Despite all technical complexities, it turned out that dialysis nurses accepted citrate anticoagulation willingly and preferred it to heparin-free dialysis (the only option in the patients at risk of bleeding before introducing citrate). This was the critical factor for further citrate anticoagulation expansion in our center. The major issue in nurses’ acceptance of citrate was perfectly “clean” dialysis circuit and diaalyzer after dialysis, usually without any clot. This was achieved in parallel with patients’ safety (both general and related to bleeding risk) and acceptable procedure complexity.

During subsequent years different adjustments occurred. For some period no calcium-free dialysate was available at Slovenian market. In this period we have used dialysate concentrate for tap water with final calcium concentration of 0.15 mmol/l instead of calcium free dialysate. Concentrated potassium chloride solution prepared by our hospital pharmacy was added into dialysate to adjust dialysate potassium level to the need of individual patient.

Besides standard bicarbonate hemodialysis we have successfully used citrate for CRRT, single-needle hemodialysis (Buturović-Ponikvar et al, Ther Apher Dial 2005, Gubenšek et al, Blood Purif 2007), predilutional on-line hemofiltration (Gubenšek et al, Ther Apher Dial 2009), and plasma exchange (Buturović-Ponikvar et al, Ther Apher Dial 2005, Antonič et al, Ther Apher Dial 2009). The use of calcium-containing dialysate (1.25 mmol/l) was associated with significant clotting in venous bubble trap, both during hemodialysis (Buturović-Ponikvar et al, Int J Artif Organs 2008) as well as hemodiafiltration, despite higher citrate dose (Buturović-Ponikvar et al, Int J Artif Organs 2008). Predilutional on-line hemofiltration was the only procedure with standard, calcium-containing infusate (1.25 mmol/l) and successful regional citrate anticoagulation.

Recently, we have successfully used citrate anticoagulation during high cut-off (Theralite™, Gambro, Lund, Sweden) hemodialysis and hemodiafiltration, both using calcium-free dialysate/infusate and a short heparin-free dialysis at the end of the procedure, to remove citrate load (Kovač et al, Ther Apher Dial 2011), as it was described in our study of sequential citrate/heparin-free anticoagulation (Buturović et al, Artif Organs 2008).

Current status of citrate use in our dialysis center. In 2012 we have performed 6246 citrate procedures (17.7% of % of a total of 35.328 hemodialysis and apheresis procedures in 2012). More than a half of acute hemodialysis procedures in 2012 (2.932/5286, 55.5%) were performed with citrate anticoagulation. We perform between 15 to 20 citrate procedures per day (average ~18 procedures per day) and serve as a training center for citrate anticoagulation for physicians and nurses from Slovenia and other countries.

A number of our chronic hemodialysis patients are treated by long-term citrate anticoagulation, some of them for years (Gubenšek et al, Ther Apher Dial 2011). In 2013 we have introduced SelectBag® Citrate dialysate in all our chronic hemodialysis patients dialyzed with Gambro hemodialysis monitors (99 patients).

Citrate research in our dialysis center. From the introduction of citrate into clinical practice we were active in citrate related research. Twelve original studies focused on citrate use in hemodialysis were published by our group in SCI journals. USA patent on sequential citrate anticoagulation was approved in 1998 (Patent Number 5,709,993: Process of anticoagulation during extracorporeal blood circulation sequentially using citrate or nafamostat and heparin). The cost for the procedure of patent approval was funded by a special grant from the Slovenian Research Agency. Assist. prof. Jakob Gubenšek has completed his PhD thesis with a title “Regional citrate anticoagulation for hemodialysis procedures” in 2006. Currently he is a mentor for just approved PhD Thesis proposal focused on citrate with a title “Some improvements in regional citrate anticoagulation in hemodialysis”.

New citrate protocol. During all these years we were reluctant to significantly change our original protocol with 4% citrate in 500 ml polypropylene bottles, mainly for safety issue. We were concerned that if another citrate solution would be introduced, it might cause confusion with nurses or the use of wrong solution or wrong citrate infusion rate, especially in intensive care units or during nights, when supervision from other staff may be relaxed. However, 4% citrate in 500 ml bottles had some logistic problems. Usually 3 bottles had to be used for one hemodialysis procedure. Exchanging citrate bottles during hemodialysis increased procedure complexity and could interrupt continuity of anticoagulation. We have discussed these issues with our hospital pharmacy and their own limitations in solution production and finally decided to replace 4% citrate in 500 ml polypropylene bottles for 8% citrate in 1000 ml bottles. Main arguments in favor of this solutions were: 1) we wanted more concentrated citrate than 4%, to decrease the volume, however at the same time we did not want highly concentrated citrate solutions; 2) we wanted one bottle of citrate solution to be sufficient for the whole duration of hemodialysis procedure; 3) 8% trisodium citrate was chosen for easy switch from the old protocol (300 ml of 4% citrate equals 150 ml of 8% citrate, all other parts of the “old” protocol remaining the same) 4) lower cost of 8% citrate anticoagulation per dialysis compared to 4%. The new protocol was recently tested clinically without adverse events.

In conclusion, from introduction of regional citrate anticoagulation in our center in 1993, citrate is increasingly used, reaching more than 6000 citrate hemodialysis and apheresis procedures in the year 2012 (approximately 18 citrate procedures per day). Citrate containing dialysate (SelectBag® Citrate) is currently used in approximately half of our chronic hemodialysis patients. In parallel with research activity focused on reducing dialysis induced inflammation and citrate effects beyond anticoagulation we believe that this fascinating molecule will play significant role in hemodialysis of the next decade.

*citrate is used for trisodium citrate in the text
Heparin in various concentrations has traditionally been (and still is) the gold standard as the catheter locking solution in interdialysis period. However, it is far from ideal. Heparin as catheter lock induces systemic anticoagulation, lacks antimicrobial activity and may induce biofilm formation, as demonstrated by Shanks et al, NDT 2006. Alternatives to heparin as a locking solution were intensively studied in the last two decades. Citrate has the important place among them. It safely prevents thrombosis and infection, reduces biofilm formation, does not induce systemic systemic anticoagulation, all that at low cost.

**Citrate lock in our center.** According to our best knowledge, we were among the first who reported the use of citrate instead of heparin as a locking solution for hemodialysis catheters (Buturović et al, Blood Purif 1994, abstract, Buturović et al, Artif Organs 1998). The main reason for replacing heparin with citrate was avoidance of systemic anticoagulation. The trigger for this idea was the patient in the intensive care unit who experienced severe gastrointestinal bleeding after heparin-free hemodialysis. After analyzing what could cause bleeding immediately after hemodialysis procedure, we came to the conclusion that locking of two femoral catheters with concentrated heparin caused systemic heparinization. We checked this hypothesis in a few stable patients measuring activated thromboplastin time from the peripheral vein 15 minutes after catheter was locked in a standard way, with concentrated heparin. Significant prolongation of partial thromboplastin time (more than 3 times from the upper normal limit) was demonstrated, indicating intensive systemic heparinization after catheter locking with heparin. At that time we were just introducing regional citrate anticoagulation into clinical practice using 4% citrate, so we decided to use 4% citrate solution also for catheter lock. Soon after that we have completely abandoned the use of heparin for catheter lock for noncuffed catheters. We have used 4% citrate lock for almost 10,000 catheters in the years after. The majority of catheters were noncuffed catheters, both femoral and jugular, used both as temporary as well as long-term vascular access. In the minority of patients we have used 4% citrate for locking of silastic, cuffed single-lumen catheters. In 2002 Weijmer et al (NDT) reported on antimicrobial effect of citrate in the in vitro study, another significant advantage in addition to avoidance of systemic anticoagulation. After randomized clinical study of Weijmer et al in JASN 2005 was published (comparing 30% citrate with heparin), we have switched to 30% citrate for all hemodialysis catheters (from 4%). The main reason was better antimicrobial activity of more concentrated citrate.

**Spillage of locking solution** from the catheter is highly important. During injection, hydraulic effects inevitably cause lock solution to spill into the systemic circulation, approximately 20-25% if locking volume is equal to catheter priming volume (and more if locking volume exceeds catheter priming volume, Polaschegg, Blood Purif 2007). Nevertheless, in European Union catheter lock solutions are regarded as medical device rather than a systemic drug. Spillage during instillation is a consequence of a laminar flow distribution within the catheter and cannot be avoided. Further spillage of lock solutions due to gravity occurs if high concentrated citrate is used (30% or 46.7%) with a density higher than blood (Polaschegg, ASAIO Journal 2005). Reverse flow of whole blood into the catheter is frequently observed clinically. The amount of spillage may be related also to catheter design and the presence of side holes (Sung et al, NDT 2007).

**Which citrate concentration?** The question of optimal citrate concentration for catheter locking still remains unanswered. Higher concentrations have better antimicrobial activity including prevention of Candida growth. The potential disadvantages of high concentrated citrate could be local hypocalcemia, that could possibly cause arrhythmia, if jugular catheter and increased locking volume were used. Such complication was reported even with femoral catheter (Punt et al, Clin Nephrol 2008). The other disadvantage is returning the blood into the catheter. This might be the cause of catheter thrombosis with embolization, if catheters with side holes are used, as it was reported by Williscombe et al, AJKD 2010, using Ash-Split catheter and 43% citrate locking. Recently, protein precipitation was demonstrated inside hemodialysis catheters in an in vitro study with various citrate concentrations (Schilcher et al, NDT 2012). The authors’ conclusion was that maximum citrate concentration should not exceed 10%. We have not experienced clinically significant embolization with the use of concentrated (30%) citrate, neither significant arrhythmia. However, patients sometimes experience metallic taste when 30% citrate is instilled into the catheter. According to data from literature and our experience of close to 1,000 catheters inserted annually for years, the majority of them noncuffed and all locked with 30% citrate from 2006, including all catheters for critically ill patients, and with our past experience of up to 10,000 of catheters locked with 4% citrate, we believe that concentrations of > 30% are not necessary or advisable. It is also possible that locking solution should be chosen depending on the type of the catheter. The definition of optimal citrate concentration requires further study. We believe that citrate locking, in addition to catheter design and nursing care, enabled the use of non-cuffed (»temporary«) catheters for long-term use, as we do in our center for years (Ponikvar et al, Ther Apher Dial 2005).

**Citrate in composite locking solutions.** Citrate was used as a component of several composite locking solutions like TauroLock™ (4% citrate with taurulinidin, Solomon et al AJKD 2010), citrate in combination with ethanol (4% citrate with 30% ethanol, in vitro study, Takla et al, J Vasc Access 2007), with gentamycin (3.13% citrate and 40 mg/ml gentamycin, ratio 1:2, Dogra et al, JASN 2002, with the systemic gentamycin exposure demonstrated by predialysis concentration). Recently a large randomized trial AZEPTIC was published comparing heparin and composite lock solution ZurAsept™ (7% citrate, 0.15% methylparaben and 0.015% propylparaben) (Maki et al, Crit Care Med 2011). All composite solutions that included citrate were compared to heparin and not to citrate alone. TauroLock™ was demonstrated to have problem with catheter thrombosis, so low dose heparin or urokinase was added to the mixture of citrate and taurulinidin in different variants of taurulinidin-containing locking solutions.

**In conclusion,** citrate has many characteristics of the ideal locking solution for hemodialysis catheters in interdialysis period: both anticoagulant as well as antimicrobial activity, prevention of biofilm formation and low cost. The optimal citrate concentration is not defined and will probably be focus of further studies. Higher concentration have better...
antimicrobial activity, however, there are concerns on protein precipitation, more intense spillage from the catheters and some reports on arrhythmia and embolization. 4% citrate was demonstrated to be safe and efficient and could probably replace heparin for the vast majority of patients.

Jakob Gubenšek was born in Ljubljana in 1976 and graduated from Faculty of Medicine, University of Ljubljana in 2002. He was accepted in the “young researchers” programme at the Department of Nephrology, University Medical Centre Ljubljana, Slovenia and received his PhD in Biomedicine in 2006 with thesis “Regional citrate anticoagulation for hemodialysis procedures” (mentor prof. dr. Jadranka Buturović Ponikvar). He completed his residency in internal medicine in 2010 and works mainly in the field of acute and chronic hemodialysis and interventional nephrology. With co-workers he has published over 20 articles in SCI journals. In 2012 he became assistant professor at the Medical Faculty, University of Ljubljana. In addition to continued interest in the field of citrate anticoagulation in different extracorporeal procedures his research topics also include acute kidney injury, plasmapheresis, renal registries and kidney transplantation.

assist. prof. Jakob Gubenšek, MD, PhD
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In chronic hemodialysis regional citrate anticoagulation is the preferred mode of anticoagulation in patients with increased bleeding risk. Citrate provides efficient anticoagulation, which is entirely limited to the extracorporeal circuit. It is invaluable especially in the setting of single-needle hemodialysis. In the majority of patients the causes of increased bleeding risk are transient (e.g. post-operative state, trauma, gastro-intestinal bleeding, etc.) and citrate anticoagulation is therefore only used for short periods of up to a few weeks.

In some cases, long-term citrate anticoagulation is needed due to a persistent bleeding risk. We analyzed 16 patients from our center on long-term (>3 months) citrate anticoagulation. Their mean age was 67 ± 15 years at the start of citrate anticoagulation, 13 (81%) were male, their dialysis vintage was 2.6 (range 0.4 – 9.0) years. Citrate anticoagulation was performed for 4 months and up to 6.3 years (median of 12 months). The indications for long-term citrate anticoagulation were: recurrent gastrointestinal bleeding in nine patients, heparin-induced thrombocytopenia, retroperitoneal hematoma, chronic subdural hematoma, proliferative diabetic retinopathy, vascular malformations in the brain in one patient, and others in two patients. The citrate anticoagulation protocol was simplified, the number of blood samples reduced and calcium supplementation was mainly modified by the attending nurse to maintain ionized calcium within target range. Patients tolerated citrate anticoagulation well and there were no serious complications. Ionized calcium was stable during the procedures; significant hypocalcemia (<0.9 mmol/L) was rare (2.1% of procedures). There were no clinically significant acid-base disturbances and no clotting problems during the procedures. In the short term (1 – 3 months after starting citrate), the iPTH increased in 73% of patients (from 325 ± 310 to 591 ± 793 pg/L, p = 0.11). In the long term (1 – 2 years), an increase in iPTH was observed in 3/6 patients. The time period (before/after starting citrate) was a significant predictor of iPTH using main-effects ANOVA (p < 0.001).

When regional citrate anticoagulation is used for short periods the main objective is to achieve efficient anticoagulation and to prevent complications, mainly hypocalcemia, during the procedure. On the other hand, when citrate anticoagulation is used for longer periods, additional concerns arise. Firstly, the reduction of work-load for the personnel and reduction of laboratory controls to a safe minimum is needed. Secondly, effect of interfering with calcium homeostasis and the consequent effects on mineral and bone disease (CKD-MBD) should be considered. In light of that, the optimum target range for ionized calcium, which should be maintained during citrate anticoagulation, is not clear, in order to prevent positive calcium balance on one hand and over-stimulation of the parathyroid glands on the other. Further research is needed to clarify this issue. Thirdly, the issue of increasing the biocompatibility of hemodialysis procedure is also important when citrate is used for prolonged periods. It is well known that hypocalcemia, achieved during citrate anticoagulation, reduces many of the blood-surface interactions. It not only inhibits coagulation cascade but also the complement system and reduces activation of leucocytes and thrombocytes. Since these effects are mainly related to the level of hypocalcemia, increasing the dose of citrate may provide increased biocompatibility. While there are many different protocols published for citrate anticoagulation in various dialysis procedures, there are no comparisons on the dose of citrate.

In conclusion, citrate anticoagulation can be performed safely and efficiently and its long-term use is needed in rare cases to reduce persistent bleeding risk. The main indications would include heparin-induced thrombocytopenia, severe anemia due to persistent blood loss (e.g. from gastro-intestinal tract) or other persistent inclination to bleeding. Mild hypocalcemia during dialysis with citrate anticoagulation may contribute to a short- and long-term increase in iPTH in these patients. Some of the questions deserving further attention in citrate anticoagulation are: the optimal target values for arterial ionized calcium with regard to calcium balance and stimulation of iPTH secretion and optimal dose of citrate, especially in regard to increased biocompatibility of the circuit.
Andreja Marn Pernat, MD, PhD, is internal medicine specialist and nephrologist at the Department of Nephrology University Medical Center Ljubljana, Slovenia, and Associate Professor of Medicine at Medical School of the University of Ljubljana. She graduated at University Medical School of Ljubljana in 1992 and completed her residency in Department of Internal Medicine. She gained her masters in essential hypertension. In year 1998-99 she did a research fellowship at the Institute of Critical Care Medicine, Palm Springs, USA, where she learned basics of laboratory research. She completed a project on optimizing timing of ventricular defibrillation during heart arrest by developing a new parameter which helps to identify the best time for delivering electrical shock. This work also served her as PhD theses in Slovenia. Last 10 years she is active in pre- and postgraduation teaching, she habilitated as Associate Professor of Medicine in 2008. In 2000 she started her training in nephrology, dialysis and transplantation. Since 2003 Andreja Marn Pernat has been clinical nephrologist, followed as a consultant-nephrologist and she is also head of Nephrology Outpatient Clinic in Ljubljana. Her areas of clinical work and research include acute kidney injury, chronic kidney disease and its complications, end stage renal disease, dialysis, apheresis, renal transplantation and general nephrology. In summer 2010 she held postdoctoral fellowship at Renal Research Institute, New York City, USA. Her work was dedicated to improving the outcomes of patients with chronic kidney disease requiring dialysis. She’s been elected as the secretary of the Slovenian Society of Nephrology between 2004-2012. Her bibliography is accessible on the Web of Science under the following names: marn pernat a, marn a, pernat am.

Light Chain Nephropathy and Theralite™ Citrate Hemodiafiltration

Andreja Marn Pernat

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Background.

Acute renal failure occurs in 12-20% of all multiple myeloma patients. Up to 80% of these patients remains dialysis dependent. The principal renal pathology is the tubule-interstitial lesion cast nephropathy called myeloma kidney, which is a direct consequence of the high serum levels of immunoglobulin free light chains (FLCs). Monoclonal FLCs may be toxic to the tubules and form obstructing tubular casts. Myeloma cast nephropathy occurs most often in patients with high rates of production and excretion of immunoglobulin FLCs. Rapid reduction of FLC levels in the blood is necessary to recover renal function. Unless the FLCs serum levels are rapidly decreased, acute kidney injury will become irreversible. One novel measure in treating light chain nephropathy is reducing light chain levels with extended haemodialysis sessions using high cut-off dialysers (HCO) as an adjuvant treatment to chemotherapy for patients with acute kidney injury complicating multiple myeloma. The analysis of 67 patients with dialysis-dependent renal failure secondary to multiple myeloma who were treated with high cut-off hemodialysis and chemotherapy showed that 76 % of the population had a sustained reduction in serum FLC concentrations by Day 12 and 63% subsequently became independent of dialysis. Factors, which predicted independence of dialysis were the degree of FLC reduction and the time to initiating high cut-off hemodialysis. To increase the efficacy of immunoglobulin FLC removal by high cut-off haemodialysis, we proposed a combination of convective and diffusive transport mechanism as hemodiafiltration dialysis technique. On the other hand, we successfully introduced regional citrate anticoagulation during hemodiafiltration to reduce the bleeding risk due to thrombocytopenia and to decrease the adherence of blood constituents to the membrane, which may result in potentially better performance of dialyzer. Recently, our group has described citrate anticoagulation for hemodiafiltration with high cut-off membrane.

The aim of this report is to present our experience with citrate extended high cut-off hemodiafiltration in treatment of acute renal failure secondary to myeloma kidney between 2010 and 2013.

Methods.

Twenty-two light chain nephropathy patients with serum FLC levels above 500 mg/L were treated with 8-hour hemodiafiltration procedures using the high cut-off hemodialysis membrane with 2.1 m² and cut-off level of 45 kD (Theralite™ 2100; Gambro, Lund, Sweden). The extended treatment was performed daily or every other day. At the same time, patients underwent chemotherapy according to protocols. Vascular access was obtained through two 8 Fr, single-lumen, two pre-curved catheters inserted into the same jugular vein in 18 patients but femoral catheters were placed in the rest of 4 patients. The blood flow rate was set at 300–330 mL/min, the dialysate flow rate at 500 mL/min, and the infusate flow rate (in post-dilution mode) at 3 L/h. Regional
anticoagulation was performed with 4% sodium citrate for the first 7 h of hemodiafiltration, and anticoagulant-free hemodiafiltration was performed for the last hour in order to avoid citrate accumulation. Calcium-free, magnesium 0.5 mmol/L dialysate and infusate were used for the citrate part of hemodiafiltration procedure, while dialysate and infusate with calcium of 1.5 mmol/L were used for the anticoagulant-free part of the procedure. 40 g of albumin in 20% solution was infused per each TheraliteTM hemodiafiltration procedure during the last 2 h to prevent excess albumin loss.

Results.
The population was predominately male (59%) with new presentation of multiple myeloma (91%) and did not have a history of chronic kidney disease (77%). Eleven patients were diagnosed with λ FLC multiple myeloma and 11 patients with κ type. In 22 myeloma patients 132 extended high cut-off hemodiafiltration procedures were performed (2–24 per patient). No serious side-effects occurred during TheraliteTM treatment. Trisodium citrate 4% was infused into the arterial line at a fixed rate of 300 mL/h. Calcium was supplemented as 1 mmol/L calcium chloride. Serum ionized calcium was stable throughout the treatment. Anticoagulation was excellent, and no significant clotting was noted in the extracorporeal circuit. There was no metabolic alkalosis or hypernatremia after the procedures.

With intensive TheraliteTM therapy the average concentration of λ FLC was reduced from 14,709 mg/L (range 830-53000 mg/L) to 2,367 mg/L (range 36-8530) and the average concentration of κ FLC was reduced from 14,986 mg/L (range 1500-52000 mg/L) to 2,545 mg/L (range 682-3150 mg/L). At the beginning of TheraliteTM therapy, renal impairment with serum creatinine concentrations between 272 μmol/L and 1060 μmol/L were detected. During follow up period, seven patients died, but deaths were not TheraliteTM procedure-related. Among survivals, 67 % of patients became independent of dialysis.

Conclusions.
Our three-years experience with TheraliteTM treatment of acute renal failure secondary to light chain nephropathy supports citrate extended high cut-off hemodiafiltration as a mandatory up-to-date therapy. The combination of TheraliteTM hemodiafiltration and chemotherapy resulted in sustained reductions in serum FLC concentrations in all patients and a high rate of independence of dialysis. We feel that hemodiafiltration with a high cut-off membrane may be at least as effective in removing serum FLCs as hemodialysis. Regional citrate anticoagulation was effective and safe. Close monitoring during all 132 citrate TheraliteTM procedures showed no serious side effects. We believe that regional citrate anticoagulation could be superior to systemic heparin anticoagulation in complicated patients, especially in patients with bleeding diathesis and profound deficiencies in hemostasis.

References:
Vladimir Premru graduated at the Medical School of the University Ljubljana in 1980. After few months of his service as general practitioner, he spent four years at Department for Out-of-Hospital Emergency Medicine. Afterwards he worked at the Department for vascular disease at the University Medical Center Ljubljana for one year, and thereafter returned to practice in GP office for another three years. Finally, he joined the Nephrology Department at the University Medical Center Ljubljana in 1990. He became a specialist of internal medicine in 1996, and later on also a specialist of nephrology. In 2004 he earned his Master’s Degree in nephrology at the Medical School of the University Ljubljana by his research on characteristic patterns of ambulatory blood pressure in peritoneal dialysis population in comparison to hemodialysis patients.

Other areas of his research interest mirror several fields of his practical work and include acute kidney injury and chronic renal failure, and various aspects of renal replacement therapy. His expertise extended to interventional nephrology and vascular access, especially concerning dialysis catheters, notably in the acute setting. In the last several years, his research focused on rhabdomyolysis and myoglobinuric AKI. Recently, he and his coworkers published some novel observations on myoglobin kinetics in rhabdomyolysis, and some of the first reports on the use of high permeability membranes for removal of myoglobin by hemodiafiltration.

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USE OF HIGH CUT-OFF MEMBRANES FOR EXTRACORPOREAL BLOOD PURIFICATION IN THE TREATMENT OF RHABDOMYOLYSIS-ASSOCIATED ACUTE KIDNEY INJURY

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Rhabdomyolysis is (mostly acute) pathological destruction of muscle cells with leakage of intracellular contents into body fluids resulting in a clinical syndrome characterized by muscular weakness and pain, tea-coloured urine, and acute kidney injury (AKI) with or without anuria, hyperkalemia, and less frequently also DIC, or pulmonary enema. It can be induced by various physical, chemical, or metabolic factors, such as heat, exertion, drugs, toxins, hypoxia, ischemia-reperfusion, or inherited disorders of mitochondrial oxidative metabolism. Myoglobin plays a key role in the pathogenesis of kidney injury through its heme-mediated direct toxicity, exaggerated vasoconstriction, and obstruction of tubules. Serum myoglobin concentrations can rise up to 10,000-times physiological levels. Rhabdomyolysis-induced AKI was reported to occur in about 10% of patients, with generally benign course. Its incidence and associated mortality rate were significantly increased in intensive care setting, and especially when renal replacement therapy (RRT) was required. We used myoglobin as a marker to analyze the incidence of dialysis-dependent myoglobinuric AKI in a cohort of 484 patients with peak serum myoglobin higher than 1 mg/l. The need for hemodialysis (HD) increased considerably (to 28%, and 37%, respectively) in patients with myoglobin levels higher than 15 mg/l and 20 mg/l, respectively.

Attempts of myoglobin elimination by HD or hemofiltration (HF) with conventional high-flux filters, or plasmapheresis had very limited success. Recently, implementation of large pore size (high cut-off; HCO) hemofilters combined with sufficient exchange volumes in HD, CVVH, or HDF mode allowed a considerably higher removal of myoglobin into dialysate/filtrate, with clearance values several-folds higher than achieved before, and cumulative mass removal exceeding 5-7 grams. Different HCO membranes and treatment modalities vary with regard to their capacity for myoglobin removal in experimental and clinical conditions. Superiority of HCO-based treatments was confirmed by mathematically derived kinetic modelling. However, the proposed models are approximates at best as in clinical practice, the course of rhabdomyolysis is individual and unpredictable. Precise contribution of myoglobin release on one side, and its metabolic elimination on the other side, to the observed myoglobin dynamics is at present unknown. We observed net acquisition of myoglobin into the circulation continuing for more than 3 days, indicating that initially muscle destruction by far outweighed endogenous myoglobin clearance mechanisms. We measured the rebound of serum myoglobin after the HCO-HDF procedure in patients with severe myoglobinuric AKI (myoglobin >20 mg/L), and demonstrated the increase to 2.4 times the post-procedural levels within 8-12 hours. In a recent report from China, a mean myoglobin rebound was 19.4% in a less than 1 hour dialysis-free interval during filter exchange in HCO-CVVHD/CVVH. Following the conclusion of HCO treatments, a slow exponential fall in serum myoglobin was observed, with a t½ of 35 hours, presumably not influenced to an appreciable extent by conventional HD. The decay in serum myoglobin...
in the course of therapy observed with CRRT using conventional or HCO filters thus should not be over-interpreted to be a result of the extracorporeal removal alone, and the opposing processes mentioned above should be taken into consideration.

Depending on the unique disease pattern in individual patient, each modality could have specific advantages or disadvantages. From the practical standpoint, we find extended 8-12-hour HCO-HDF the most efficient initial modality allowing most rapid and substantial myoglobin removal. Additionally, we observed that sieving potential of the membrane was well preserved even during long-lasting procedures, possibly due to regional citrate anticoagulation which by inhibition of platelet aggregation and concentration polarization could prevent occlusion of the pores. Electrolyte and acid-base equilibrium was well maintained with the balanced use of citrate. The major draw-back of such intense combined diffusive and convective depuration was extraordinarily high albumin loss into dialysate requiring up to 100 g supplementation within a single procedure. In comparison, the amount of albumin lost in HF mode was 5-10 times lower, along with approximately 4 times lower removal rate of myoglobin. The albumin loss was estimated in the Chinese study to reach 65g daily in CVVHD mode, mostly confined to the first few hours of the procedure and reduced by 75% by the 4th hour due to considerably decreased albumin permeability. The pathogenic actions of myoglobin and other constituents spilled from disintegrated cellular structures might extend beyond kidneys, with potential consequences to other organs such as lungs, and tissues such as vascular endothelium. The most intense release of those substances into blood might precede the development of clinical AKI by days. It is within this time window that expedite substantial reduction of myoglobin burden by HCO-based HD/HF therapies might prove to be most valuable to prevent rather than cure the damage. However, the potential clinical benefits of HCO treatments remain to be proven. In our limited experience, mortality was 33% in septic ICU patients with rhabdomyolysis and associated AKI, and even 100% in patients who developed myoglobinuric AKI after heart/great vessel surgery. To elucidate whether HCO treatments contribute to recovery of renal function or even improve other patient’s outcomes mandates more extensive studies such as the ongoing randomized HicoRhabdo (Myoglobin Removal by High Cut-off CVVHD) trial inquiring clinical outcomes of treatment with SepteX membrane. Moreover, the many potential advantages of citrate anticoagulation for blood purification especially in the ICU population warrant further exploration also in the setting of rhabdomyolysis.

References:
Nataša Škofic graduated at the Faculty of Medicine of the University of Ljubljana, Slovenia in 1999. She completed specialization in internal medicine in 2008 and achieved the PhD degree in Biomedicine at the Faculty of Medicine of the University of Ljubljana with her doctoral dissertation ‘Intermittent high-volume predilution online haemofiltration versus standard intermittent haemodialysis in critically ill patients with acute kidney injury: a prospective randomized study’ in 2010. She has been working at the Department of Nephrology, University Medical Centre Ljubljana, Slovenia, since 2002. Her major interests in clinical work and research include acute kidney injury in critically ill patients, haemodialysis in intensive care units, critical care nephrology, haemodialysis catheters, citrate anticoagulation, chronic haemodialysis, plasmapheresis, chronic/end-stage kidney disease, cardiovascular complications.

INTERMITTENT HIGH-VOLUME PREDILUTION CITRATE HAEMOFILTRATION IN CRITICALLY ILL PATIENTS WITH ACUTE KIDNEY INJURY

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Background. Development of acute kidney injury (AKI) as part of multiple organ failure (MOF) in critically ill patients treated in intensive care units (ICUs) is associated with high in-hospital mortality rates of 50–80%. Many fundamental issues concerning the optimal approach to dialysis management of AKI in critically ill patients with MOF, including the selection of the optimal dialysis modality, remain undefined. There is currently no consistent evidence that particular dialysis modality is superior to the others owing to better clinical outcomes. Standard and most commonly prescribed dialysis modality is intermittent haemodialysis (HD). Haemofiltration (HF) has been established mainly as continuous modality, while intermittent high-volume predilution on-line HF is relatively new and rarely applied in everyday clinical practice. Intermittent HF is presently well-established in chronic dialysis patients, in whom various studies proved important advantages of chronic HF compared to HD. In AKI as part of MOF, high-volume HF is supposed to confer beneficial effects particularly in critically ill patients due to higher convective clearances for middle/high-molecular-weight humoural mediators involved in the development of MOF. We performed the first prospective, randomized, controlled clinical study in critically ill ICU patients with AKI as part of MOF that compared clinical outcomes (i.e. mortality, recovery of kidney function and the need for dialysis support) between intermittent high-volume predilution on-line HF and standard intermittent HD (Škofic N, Arnol M, Buturović-Ponikvar J, Ponikvar R. Intermittent high-volume predilution online haemofiltration versus standard intermittent haemodialysis in critically ill patients with acute kidney injury: a prospective randomized study. Nephrol Dial Transplant. 2012; 27(12): 4348-56).

Methods. This prospective, randomized single-centre clinical study was undertaken at the Centre for acute and complicated dialysis, Department of Nephrology, University Medical Centre Ljubljana, Slovenia. Patients were recruited from different ICUs of the University Medical Centre Ljubljana. Patients were eligible for enrolment if they were at least 18 years old, in ICU-treated critically ill patients, who had AKI due to acute tubular necrosis (ATN) requiring acute dialysis support and a failure of at least one additional (non-renal) organ as well. Patients were excluded from the study if they had AKI due to other aetiology (not solely due to ATN), chronic kidney disease (baseline serum creatinine concentration ≥150 μmol/L), prior kidney or other organ transplantation, acute haematological or terminal stage malignancy, if they had received more than one intermittent or >24 h of continuous dialysis procedure prior to enrolment or if less than one study dialysis procedure was performed after enrolment (i.e. <50% of the first procedure due to patient death). Eligible patients were randomly assigned to either the HF study group (treated with intermittent high-volume predilution on-line HF) or the HD study group (treated with intermittent HD) in 1:1 ratio.
Several parameters of HF were dictated by the study protocol, i.e. dialysis monitor: Gambro AK-200 ULTRA S (Gambro, Lund, Sweden) with individual water treatment system WRO 300 (Gambro), haemofilter: biocompatible synthetic highly permeable hollow-fibre membrane, with an area of 2.4 m² (Polyflux 24S; Gambro) or 2.2 m² (FX 100; Fresenius Medical Care, Bad Homburg, Germany), blood flow rate: 250–400 mL/min, volume of infusate: ~1.3 times the dry body weight (i.e. 60-100 L), degree of predilution (infusate flow rate/blood flow rate ratio): 1–1.5. Other parameters of HF were prescribed individually, i.e. composition and temperature of infusate, netto ultrafiltration, frequency of procedures, anticoagulation: standard heparin or regional citrate anticoagulation in patients with increased bleeding risk. Temporary untunnelled HD catheters were used as vascular access (Škofic N, Buturović-Ponikvar J, Kovač J, et al. Hemodialysis catheters with citrate locking in critically ill patients with acute kidney injury treated with intermittent online hemofiltration or hemodialysis. Ther Apher Dial. 2009;13:327–33).

Original protocol for regional citrate anticoagulation for intermittent predilution on-line HF was designed and applied in patients in the HF study group with increased bleeding risk. Temporary untunnelled HD catheters were used as vascular access (Škofic N, Buturović-Ponikvar J, Kovač J, et al. Hemodialysis catheters with citrate locking in critically ill patients with acute kidney injury treated with intermittent online hemofiltration or hemodialysis. Ther Apher Dial. 2009;13:327–33).

Regional citrate anticoagulation in HF procedures was performed using 4% trisodium citrate infused at the arterial line (starting at 400 mL/h) and 1 M calcium chloride infused at the venous line (starting at 7 mL/h and changed as necessary to maintain serum concentration of ionized calcium between 1.0 and 1.1 mmol/L). Standard on-line prepared infusate containing calcium and lowered concentration of bicarbonate was used (1.25 mmol/L calcium, 28 mmol/L bicarbonate).

The primary study outcome was mortality from any cause by day 60 after randomization. Secondary outcomes included 30-day and in-hospital all-cause mortality along with 30-day and in-hospital recovery of kidney function. Time to kidney function recovery and the number of required dialysis procedures were analysed in the subgroup of patients with in-hospital recovery of kidney function.

**Results.** Altogether 290 critically ill adult patients with AKI as part of MOF treated in different ICUs were enrolled in the study. 146 patients were randomly assigned to the HD and 144 patients to the HD study group. A total of 17 (5.9%) patients were withdrawn after randomization because they were subsequently found to be ineligible for the study. Finally, 273 patients (138 patients in the HF and 135 patients in the HD study group) continued the study and were included in the final analyses. Only one patient in the HD group was lost to follow-up, all other patients were followed up until the end of hospitalization.

Baseline patient characteristics at dialysis initiation (age, gender, weight, diuresis, serum concentration of creatinine, urea, potassium, bicarbonate and pH, presence of oliguria (diuresis < 400 mL/day), serum concentration of creatinine >300 μmol/L, urea >30 mmol/L, potassium >5.5 mmol/L, pH <7.2, fluid overload, mechanical ventilation, aetiological factors of AKI, number of failed non-renal organs and values of three different scoring systems, i.e. Acute Physiology and Chronic Health Evaluation II score (APACHE II), Cleveland Clinic Foundation–Acute Renal Failure score and Modified Organ System Failure score) were similar between the two study groups. The mean (±SD) age was 68.7 ± 12.5 years, 66.3% of patients were male, 42.1% had oliguria and 75.1% required mechanical ventilation. AKI was most frequently attributed to sepsis (80.6%), ischaemia (69.2%) and major operation (39.2%). Other common aetiological factors were nephrotoxic antibiotics, myoglobinuria and radiocontrast agents. Multiple potential causes of AKI were present in 84.6% of patients.

Regional citrate anticoagulation was used in 33.7% of all study patients, more frequently in patients treated with HF than with HD (41.3 vs. 25.9 %). Citrate anticoagulation in HF procedures was effective at all points of the circuit, there was no total occlusion of the circuit requiring termination of procedure and no line replacement necessary. The expected metabolic side effects of trisodium citrate, i.e. metabolic alkalosis and hypernatraemia, were rare and mild, requiring no therapy. Serum concentration of ionized calcium was stable during the procedures.

Total all-cause mortality by day 60 was 65.3% and was similar between the HF and the HD study group (65.0 vs. 65.5%, P = 0.94). Multivariate analysis adjusted for the pre-specified variables (i.e. patient age, gender, APACHE II score, presence of oliguria, sepsis and major surgery) confirmed that dialysis treatment with HF was not significantly associated with 60-day mortality (hazard ratio, 0.98; 95% confidence interval, 0.71–1.33; P = 0.87). Mortality by day 60 was also not significantly different between the two study groups relating to all prespecified subgroups (defined by the presence or absence of patient age >65 years, APACHE II score >25, oliguria and sepsis).

Total 30-day and in-hospital all-cause mortality was 51.2 and 70.7%, respectively. Total 30-day and in-hospital recovery of kidney function was 60.6 and 45.4%, respectively. Multivariate analyses showed no significant differences in any of the secondary outcomes between both modality groups.

Kidney function has recovered during hospitalization in 124 (45.4%) patients, which is in all hospital survivors as well as in 44 (22.8%) hospital non-survivors. There was a trend towards fewer required dialysis procedures and faster recovery of kidney function in the HF subgroup compared to the HD subgroup of patients with in-hospital recovery of kidney function, but the differences were not significant.

Hypotension was detected in lower proportion, but hypokalaemia and hypophosphataemia in higher proportion of patients treated with HF than with HD (40.6 vs. 50.4%, 42.8 vs. 35.6% and 10.1 vs. 7.4%, respectively); however, the differences were not significant. The proportions of patients who underwent at least one episode of any serious adverse event requiring discontinuation of dialysis procedure were very low and not significantly different between the two modality groups.

**Conclusions.** In this randomized, controlled single-centre clinical study in critically ill ICU patients with AKI as part of MOF, intermittent high-volume predilution on-line HF did not significantly decrease mortality, improve recovery of kidney function or reduce the need for dialysis support compared to standard intermittent HD. Complications associated with dialysis treatment were reported in similar proportions of patients in both modality groups.

In our dialysis centre, we have long-term clinical experiences with intermittent high-volume predilution on-line HF in chronic dialysis patients, in addition to even longer, wide-ranging and well-established clinical practice along with significant research achievements in the field of regional citrate anticoagulation for different extracorporeal procedures, which altogether was a valuable advantage as regards the design and performance of the study. First of all, there were no reports on citrate anticoagulation for intermittent on-line HF prior to this study. Owing to the advantages of our big and busy dialysis centre, we were able to design
and test our own original protocol for regional citrate anticoagulation for intermittent predilution on-line HF. The newly designed protocol was initially successfully applied in chronic dialysis patients and consequently also in critically ill patients with AKI treated in the ICUs. The study results indicate, that regional citrate anticoagulation for predilution on-line HF, performed according to our protocol using standard calcium-containing infusate and additional calcium substitution, is feasible, effective and safe (with very good anticoagulant effect in the circuit and rare metabolic side effects), which represents an additional scientific contribution of the study. Regarding the financial issue, in a recent study by Kron et al. (Kron J, Kron S, Wenkel R, et al. Extended daily on-line high-volume haemodiafiltration in septic multiple organ failure: a well-tolerated and feasible procedure. Nephrol Dial Transplant. 2012;27:146–52), in which the conventional on-line dialysis equipment already available in daily routine of dialysis facility was used (like in our study as well), the material costs per one intermittent high-volume on-line convective procedure were comparable to the costs per one standard HD procedure and thus much more cost-effective compared to conventional continuous modalities requiring expensive solution bags.

Although our study did not show improved clinical outcomes with novel convective dialysis modality compared to standard intermittent HD, it demonstrated that high-volume predilution on-line HF with individual reverse osmosis and regional citrate anticoagulation can be performed easily, safely and effectively also in the most severely ill ICU patients, which promises favourable options for further exploration of high-volume on-line convective modalities as well as of regional citrate anticoagulation in the ICUs.

We believe that individual dialysis care, including individual selection of dialysis modality and of all other dialysis parameters, is the optimal approach to dialysis management of AKI in critically ill ICU patients. Therefore the availability of larger choice of different dialysis modalities (diffusive and convective as well as intermittent and continuous) together with regional citrate anticoagulation for different modalities is utmost important.

Manja Antonič received her medical degree from Medical school at University of Ljubljana in 2005. She worked as a medical fellow from 2006 to 2007 in General Hospital Celje, where she started residency in nephrology in 2007. As nephrology resident she spent four years training at Department for Nephrology at University Medical Centre Ljubljana, mostly at the Department for dialysis. At that time she became interested in plasma exchange treatment and in 2010 started her postgraduate study at the field of citrate anticoagulation in plasma exchange treatment. She also attended fellowships at Nephrology departments at Ospedale Maggiore Policlinico in Milano, Italy in 2011 and at Medizinische Hochschule Hannover, Germany in 2012.

In October 2012 she became specialist of nephrology. Since then she has been working as clinical nephrologist at the Department for nephrology and dialysis in General Hospital Celje. Her research interests are related to clinical work in hemodialysis and plasma exchange treatment.
COMPARISON OF PLASMA EXCHANGE EFFICACY AND SIDE-EFFECTS USING 4% OR 15% CITRATE ANTICOAGULATION - INTERIM RESULTS OF A PROSPECTIVE RANDOMIZED STUDY

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Citrate anticoagulation in membrane plasma exchange (PE) often raises concerns about citrate accumulation, side effects and volume overload. Diluting plasma in the system with citrate volume could also influence the efficacy of treatment. In patients at high risk of bleeding who need plasma exchange 4% citrate anticoagulation is performed. With citrate additional fluid is infused into the patient. To reduce the volume of infused citrate used for anticoagulation during PE we introduced more concentrated 15% citrate solution. The aim of our prospective randomized study was to compare the efficacy of PE, citrate accumulation, and (micro)anticoagulation effect in 4% vs. 15% citrate anticoagulation protocol.

In a single centre study 70 PE procedures performed in 19 patients (aged 51±14 years, 6 females, 13 males) were included in this interim analysis. Before treatment PE procedures were randomly assigned in a 1:1 ratio to 4% or 15% citrate group. Standard PE treatments using human albumin and bicarbonate-based electrolyte solution as a replacement solution were performed. Trisodium citrate (4% or 15%) was infused into arterial line and calcium chloride (1M CaCl2) into the venous line at starting infusion rates according to the protocol. Serum concentrations of immunoglobulins, electrolytes (sodium, calcium, magnesium), pH and bicarbonate were measured before and after the procedures. Serum ionized calcium was targeted and regarded as safe above 0.9 mmol/l. Post-filter ionized calcium (target range 0.2-0.4 mmol/l) was used to evaluate the anticoagulation effect. Visual assessment of anticoagulation after PE was performed at plasmafilter, arterial and venous bubble trap using the score of 5 (excellent anticoagulation) to 1 (total clotting). Sieving coefficient (SC) for immunoglobulin G was calculated at the start and at the end of the procedure with the fall of SC at the end predicting microanticoagulation failure at plasmafilter. Accumulation of citrate was determined indirectly by calculating total-to-ionized calcium ratio after PE (>2.5 indicating citrate accumulation) and directly by measuring serum citrate concentration after PE. Treatment efficacy was evaluated by the reduction rate of immunoglobulins (1-IgG pre/IgGpost).

There were 38 PE procedures performed with 4% citrate and 32 procedures with 15% citrate. Citrate infusion rate was 201±60 ml/h in 4% and 60±3 ml/h in 15% citrate group. Calcium chloride infusion rate was similar in both groups (4.7±1.7 ml/h vs 4.5±1.9 ml/h). The reduction rate of IgG was 0.57±0.06 in 4% citrate and 0.55±0.11 in 15% citrate group (p=0.47), showing no significant difference in the efficacy of treatment. Concerning safety, serum iCa was stable during the procedures, without hypocalcemia in both groups. There were no significant differences in post-PE pH, bicarbonate or magnesium between the two groups and no hypernatremia was observed in either group. Post-filter ionized calcium was 0.37±0.09 mmol/l in 4% citrate and 0.35±0.11 mmol/l in 15% citrate (p=0.39) with visual assessment showing mostly excellent anticoagulation of a system after procedures. SC was calculated in 24 procedures with no significant decrease in SC in either group (p=0.46). This concludes that similar good microanticoagulation effect at plasmafilter was achieved. The total-to-ionized Ca ratio after the procedure increased to 2.37±0.3 in 4% citrate and to 2.36±0.3 in 15% citrate (p=0.94). Serum citrate concentrations after PE with 15% citrate (2046±2243 μmol/l, N=18) were also not significantly higher than in 4% citrate group (1747±1230 μmol/l, N=15, p=0.64). The 15% citrate anticoagulation protocol was associated with a significantly reduced citrate infusion volume compared to a 4% citrate protocol (174±60 ml vs. 498±71 ml, p<0.001).

We can conclude that 15% trisodium citrate anticoagulation protocol provides similar PE efficacy, anticoagulation and safety as 4% citrate, while significantly reducing infused volume of anticoagulant. This strategy may be of special importance in patients who need citrate anticoagulation in PE and are at high risk for hypervolemia.
DILEMMAS IN RENAL REPLACEMENT THERAPY OF CRITICALLY ILL PATIENTS

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Intermittent vs continuous renal replacement therapy. Tonelli et al published a systematic review in AJKD 2002, on the impact of dialytic modality on mortality and recovery of renal function. There was no difference between intermittent hemodialysis (IHD) and continuous therapies (CRRT) in mortality or recovery of renal function. One of the most elegant randomized controled studies comparing IHD and CRRT was published by Vinsonneau et al in Lancet 2006. He compared 184 patients on IHD and 175 on CVVHDF. They used the same membrane for both procedures, bicarbonate buffer as dialysate and infusate. There was no difference in mortality rate between IHD and CVVHDF. They even concluded that almost all patients were able to be treated with IHD.

Dialysis dose. In the Lancet 2000, Ronco et al published a randomized controled trial in which he evaluated the impact of the ultrafiltration rate on outcome of critically ill patients with AKI. He enrolled totally 425 patients which were devided into 3 groups and he found that survival of the patients with ultrafiltration rate of 20 ml/kg BW/hour was significantly lower compared to the patients with ultrafiltration of 35 ml/kg/hour or 45ml/kg BW/hour. He recommended ultrafiltration rate at least 35ml/kgBW/hour. However, in a multicenter prospective randomized study, conducted by the VA/NIH Acute Renal Failure Trial Network, published in the NEJM July 2008, investigators enrolled totally 1,124 patients. 563 in intensive RRT (IHD/SLED – 6 x /week or CVVHDF with ultrafiltration ≥35ml/kg BW/hour) and 561 patients in less intensive group (IHD/SLED – 3 x /week or CVVHDF with ultrafiltration 20 ml/kgBW/hour). They did not find any difference in patients’ survival between intensive and less intensive RRT. Another prospective randomized controled trial published in NEJMJ in October 2009, compared the impact of high (40 ml/kg BW/hour) and low (25 ml/kgBW/ hour) effluent flow on totally 1,508 patients with AKI in ICU. Again there was no difference in mortality between the two groups.

When to start RRT in AKI. Currently there is no accepted consensus on the optimal indications and timing for the RRT. According to the data of 2 randomized trials, 2 retrospective studies and 13 retrospective trials, Ostermann et al concluded that presence of oliguria, fluid overload and association of non-renal organ failure should lead the decision for the beginning of RRT, rather than serum concentrations of urea and creatinine (NDT 2012).

Citrate anticoagulation for RRT is not only anticoagulant of choice in patients at risk of bleeding but can also improve extracorporeal therapy because of blockade of complement activation. Heleen M. Oudemans- van Straaten inadvertently revealed that citrate anticoagulation significantly improved cumulative survival of the ICU patients with AKI, especially in surgically, septic and high SOFA score patients.
**Vascular access** is one of the most important parts of RRT. Among several side events, malfunction and catheter related infections are the most relevant. Our experience with 534 acute, temporary catheters in 290 ICU patients which were inserted into femoral (92.3%), jugular (5.4%) or subclavian vein (2.3%) revealed very low incidence of catheter related exit site infections and bacteremias, probably due to the use of precurved jugular catheters, mupirocin or gentamycin ointment at exit site and dressing with dry gauze. We did not notice the difference between femoral and jugular or subclavian catheters in terms of catheter related infections. There was less thrombotic complications with jugular and subclavian than with femoral catheters (7.7/1000 vs 21.8/1000 catheter days) and less with single lumen than with double lumen (11.4/1000 vs 32.2/1000 catheter days) (Škofic and Ponikvar, TAD 2009).

**Could dialysis therapy be harmfull, »primum non nocere«.** Highly efficient RRT modalities are usually not harmfull by itself but can provoke so called »dial-trauma« by intradialytic hypotension, electrolyte disturbances, hypophosphatemia, too low doses of antibiotics in septic patients. There are also complications related to central catheters. In this respect it is not surprising that higher doses of RRT had equal or worse survival outcome compared lower doses of RRT.

From the late 1980s the number of AKI patients steadily increases while mortality declines (Waikar SS et al JASN 2006). Increasing age of the AKI patients with preexiting CKD led to developing or worsening of CKD. Some patients never recovered their renal function after AKI and remained dialysis dependent.

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**CRRT FOR THE TREATMENT OF ACUTE KIDNEY INJURY IN CRITICALLY ILL NEWBORNS AND SMALL CHILDREN**

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Since the first report of successful treatment of 4 newborn children with CAVH by Ronco and colleagues in 1984, CRRT of newborns became routine therapy and even became the therapy of choice and lifesaving procedure in newborns and small children after abdominal, thoracic or cardiovascular surgery. Peritoneal dialysis which is very useful therapy of AKI in newborns and small children unfortunately couldn’t be used in such cases. In Ljubljana the first infant, 2 months old, with body weight of 4,280 g, was treated with membrane plasma-exchange because of hemolytic –uremic syndrome in March 1986.

In newborns acute kidney injury (AKI) occurs more frequently than at any other time during childhood. GFR is 20 ml/min/1.73 m² at birth, 48 ml/min/1.73 m² at first month and 80 ml/min/1.73 m² at 6 months. GFR of 20 ml/min/1.73 m² is CKD 4 and means very vulnerable renal function in terms of developing of AKI.

From 1986 until 2013, 30 newborns (age up to 30 days) and infants (age of 1 month to 1 year) with AKI and multiple organ failure (MOF) have been treated with CRRT or plasmaexchange in ICU of the Department of Pediatric Surgery and carried out by the Center for Acute and Complicated Dialysis of the Department of Nephrology, University Medical Center Ljubljana. Eighteen were newborns, 11 boys and 7 girls, aged 1-37 days, with body weight 2,470-5,800 g and 12 were infants, 7 boys and 5 girls, aged50.279 days with body weight 2,200- 10,700 g. Underlying diagnoses were abdominal surgery in 14, cardiovascular surgery in 4, thoraco-abdominal surgery in 1, ECMO therapy in 3, hemolytic uremic syndrome in 3, fulminant hepatic failure in 1, congenital hyperammonemia in 3, low output syndrome in 1 and hemorrhagic shock during labour in 1 patient.

At first beginnings there were no dedicated CRRT monitors for small children. Having been very familiar with therapeutic membrane plasma-exchange monitors at that time, we began to use them as CRRT monitors: they had very precise blood pump with actual blood flow from 0- 200 ml/min. We used to use Organon Teknika, Travenol and Bellco BL 791 plasmapheresis monitors and after March 1999 Prisma – Hospal and since January 2012 Prismaflex – Gambo, both CRRT dedicated monitors. CRRT hemofilters were Amicon Minifilter, Amicon 10, 20 and 30 and Hospal Preset M 60 and 100 and recently Prismaflex HF 20 Set.

Plasmafilters were Curesis plasmfilter and Gambo 1000 plasmfilter. Before 1999 blood lines were shortened to minimize priming volume. Extracorporeal system was always primed with mixture of packed red cells and saline solution and anticoagulated with 0.2- 0.6 IU of heparin/1ml of blood. All CRRT procedures were predilutional CVVH and CVVHDF procedures. Replacement solutions were lactate buffered at the beginning, bicarbonate was introduced in 1995. Anticoagulation during the procedure were heparin in 17/18 newborns and 11/12 infants, Prostacyclin in 2/18 newborns and 1/12 infants and citrate regional anticoagulation in 1/18 newborns.
Vascular access were double lumen 5F, 5 cm long and 7F, 7 cm long hemodialysis catheters inserted either surgically or percutaneously into femoral, subclavian and jugular vein. CRRT duration (days) was 1-27 (6.8±6.0) in newborns and 0.5-11 (3.1±3.6) in infants, blood flow was 10-50 ml/min (25±12) in newborns and 15-60 (32±14) in infants, ultrafiltration rate was 10-40 ml/h in newborns and 10-60 ml/h in infants.

The main adverse events in the first years were clottings of the hemofilters immediately after initiation of the procedure. Ever lasting problem were hemodialysis catheters, especially 5F catheters, with malfunction and need for replacement several times. Severe circulatory instability, as well as electrolyte disbalance were less pronounced.

Overall mortality rate was 56.7%, 55.5% in newborns and 58.3% in infants. Number of failing organs in survivors was 3.6±0.5 and in nonsurvivors 4.7±0.9.

Conclusions. In Ljubljana the first, 2 months old infant, was treated with membrane plasma-exchange in 1986, 2 years after the first newborn child in the world was treated with CAVH in Vicenza. Since then 30 newborns and infants have been treated with CRRT and membrane plasma-exchange. The therapy was feasible and safe. Mortality rate was lower than in adults with comparable severity of the disease.

In our children with AKI and MOF CRRT was the only possible and lifesaving renal replacement therapy without which surviving would not be possible.

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Curriculum vitae
I was born on 21st of July 1981 in Maribor, Slovenia. In our family, thorough education and dedicated work has always been a fundamental principle and the highest goal. Ever since I can remember I wanted to be a medical doctor and since I had become one I know this was the right choice.

After high school I attended the Medical Faculty, University of Ljubljana, where I successfully graduated in April 2007. I spent a part of my internship in the Dialysis center of the University clinical center Ljubljana, where I found great interest for nephrology, especially acute and chronic dialysis. I started my nephrology residency in May 2009 and have since worked as a resident in the Department of Nephrology, University Medical Centre Ljubljana. I have gained clinical experience in the field of chronic and acute hemodialysis, interventional nephrology and kidney transplantation, as well as clinical nephrology. I am also a postgraduate student (my mentor prof. dr. Jadranka Buturović-Ponikvar) and my main research topic is Vascular access in dialysis patients and kidney graft recipients.
Prolonged Citrate CVVHDF in a Newborn Child with AKI and MOF Due to Haemorrhagic Shock during Labour*

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Introduction.
Continuous renal replacement therapy (CRRT) is the therapy of choice in newborns with acute kidney injury (AKI), severe fluid overload or multiple organ failure (MOF) after thoracic or abdominal surgery. CRRT mimics the effects of glomerular function, regarding continuous ultrafiltration and solute clearance even in hemodynamically unstable patients. Due to the continuous fluid removal, fluid restrictions can be minimized, resulting in improved antibiotic and nutrient delivery. The extracorporeal circuits must operate continuously for CRRT to be effective, therefore anticoagulation is necessary. Since critically ill newborns and surgical patients are at increased risk for bleeding, regional citrate anticoagulation (RCA) is a valid treatment option. We present a case of a newborn with AKI and MOF due to haemorrhagic shock during labour, treated successfully with citrate continuous venovenous hemodiafiltration (CVVHDF).

Patient and methods.
A newborn baby boy, born at term, BW 3000 g, suffered AKI and MOF after haemorrhagic shock during labour. He was successfully resuscitated and referred to pediatric ICU. On the second day abdominal surgery was required due to necrosis of the small bowel. On the third day he presented with anuric AKI with anasarca and BW 3900 g. He was mechanically ventilated and needed norepinephrine support to maintain blood pressure around 70/40 mmHg. Serum creatinine was 293 μmol/L, urea 18.9 mmol/L, potassium 4.7 mmol/L, sodium 123 mmol/l and haemoglobin 123 g/L, pH 7.20, bicarbonate 14 mmol/L. On the fourth day citrate CVVHDF was started using Prismaflex CRRT monitor (Gambro, Lund, Sweden) with hemofilter HF 20 (surface area 0.2 m² and circuit volume 60 ml). Priming of the extracorporeal circuit was performed with packed red blood cells diluted with 0.9% saline. A 7F dual lumen catheter (Medcomp Inc., Harleysville, Pa) was inserted by surgeons into the right femoral vein for the vascular access. Citrate CVVHDF was started using Prismaflex CRRT monitor (Gambro, Lund, Sweden) with hemofilter HF 20 (surface area 0.2 m² and circuit volume 60 ml). Priming of the extracorporeal circuit was performed with packed red blood cells diluted with 0.9% saline. A 7F dual lumen catheter (Medcomp Inc., Harleysville, Pa) was inserted by surgeons into the right femoral vein for the vascular access. PrisomOcal dialysate (in mmol/L: Ca 0, Mg 0.5, Na 140, Cl 106, potassium 0, lactate 3, bicarbonate 32) and Prisomcrotair 10/2 citrate anticoagulant solution (in mmol/L: citrat 10, citric acid 2, sodium 136, chloride 106) were used. Potassium chloride and phosphate were added to the dialysis solution to maintain normal or near normal potassium and phosphate concentration. Operational settings using Prismaflex were as follows: blood flow 50 ml/min, dialysate PrisomOcal flow 700 ml/h, anticoagulant Prisomcrotair flow 700 ml/h. Patient was initiated with intravenous 1 molar CaCl2 at 2 ml/h (2 mmol/L/h), the dose was manually adjusted to around 1.3 ml/h, to maintain post-filter ionized calcium concentration at around 0.4 mmol/l and the serum ionised calcium concentration at around 1.1 mmol/L.

Results.
CVVHDF was uneventfully carried out for 27 days. Good circuit lifespan was observed. There was no adverse reaction with the polyarylethersulfone (PAES) membrane. Average ultrafiltration rate was 5 ml/h (0 - 25 ml/h) and was, when needed, adjusted to patient’s blood pressure and urine flow. During the first four days of CVVHDF total net ultra-filtration was 709 ml. Later on it was adjusted to maintain zero fluid balance. There were no serious side effects, i.e. haemorrhages or hypotension. A catheter malfunction (diminished blood flow) and a right leg swelling occurred due to the compromised venous drainage, but without deep vein thrombosis. They were one of the few adverse events during the CRRT therapy. Some minor electrolyte disturbances were observed, such as hyponatraemia (sodium <130 mmol/L), hypokalemia (potassium < 3 mmol/L) and hypophosphatemia (phosphate < 0.8 mmol/L), which were easily corrected with intravenous electrolyte replacement. The patient was completely anuric for the first 10 days of CVVHDF. In the next fourteen days urine output slowly increased and reached 210 ml/day (2.5 ml/kg/h) on the 24th day. On the 27th day CVVHDF was stopped. Serum creatinine was 18 μmol/L, urea 0.7 mmol/L, urin output was around 10 ml/h with furosemid. During the next 18 days the body weight remained stable, but serum creatinine and urea increased to 414 μmol/L and 26.1 mmol/L respectively, so peritoneal dialysis was initiated. Because of a high suspicion of malfunction, an acute peritoneal catheter was first inserted (due to easier insertion and removal). The acute catheter functioned well, so it was replaced with chronic peritoneal dialysis catheter which unfortunately did not function. In an attempt to continue with peritoneal dialysis, a chronic catheter was replaced with an acute one and extensive adhesiolysis was performed, but neither improved the catheter function. After three months of attempting PD, the peritoneal catheter was removed. After ceasing PD creatinine and urea were 268 μmol/L and 3.4 mmol/L, respectively, and during the next 12 months both remained stable. Unfortunately, during the past few months, the boy’s renal function has been slowly deteriorating. At 23 months of age, his current serum creatinine and urea levels are 314 μmol/L and 18.6 mmol/L respectively. His estimated GFR is 13 ml/min/1.73m² (Schwartz formula) indicating stage 5 chronic kidney disease. The ultrasound scan shows small hyperechogenic kidneys. The boy needs treatment with erythropoietin, iron supplementation, furosemid, calcitriol and calcium polystyrene sulphonate. His motor development is delayed and he is regularly seen by a physiotherapist. He is gaining weight, but his growth is stunted. However, he is at the present time still free of dialysis.

Conclusion.
Citrate CVVHDF was a feasible, effective and safe therapy in a newborn baby with AKI and MOF. At the time of presentation, our patient is 23 months old, he weighs 11 kg and measures 85 cm in height. He has stage 5 chronic kidney disease, but is still free of dialysis.

*This case was presented in part during Slovenian Congress of Nephrology in October 2012.
**THE USE OF SELECTBAG® CITRATE IN OUR DIALYSIS CENTER: PRELIMINARY EXPERIENCE**

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**Background.** Clotting of the dialyzer fibers and membrane pores is a common, but often unnoticed complication of dialysis, even with the use of systemic heparin anticoagulation. This subtle clotting does not interfere with the completion of the treatment but it reduces the efficiency of dialytic solute movements, thus lowering the efficiency of the treatment. Moreover, the stimulation of the clotting cascade also stimulates inflammatory proteins and may be partly responsible for dialysis-induced inflammatory response. Thus, reducing coagulation during dialysis is important to improve efficiency of dialysis and reduce the other negative consequences of clotting.

Citrasate® (Advanced Renal Technologies, Bellevue, WA), citric acid dialysate (CD), cleared for clinical use by FDA, is a dialysis acid concentrate containing citric acid (citrate) instead of acetic acid (acetate) as in standard bicarbonate dialysate. Citrate is a short-acting regional anticoagulant due to its binding with calcium and is rapidly metabolized in the liver and muscles (half-life of 49 min).

SelectBag® Citrate (Gambro, Lund, Sweden) is an acetate free concentrate used in combination Bicart Select Bag citrate system, allowing easy variation of potassium, calcium and glucose.

Unlike regional citrate anticoagulation, whose threshold concentration of citric acid is 7-15 mEq/L, citrate containing dialysate contains a much lower concentration of citrate, only 2.4 mEq/L. Such small amount of citrate used protects against intradialyser clotting while minimally affecting the calcium concentration, so no supplemental calcium replacement measures are needed. The absence of significant systemic repercussions is related not only to the low amount of citrate used but also to the before-mentioned rapid conversion of citrate into bicarbonate and results in a higher post-dialysis bicarbonataemia. Citric acid dialysates have been in use, principally in acute dialysis, for over 10 years and has demonstrated to be safe and effective. Published reports suggest that, presumably due to nonsystemic anticoagulant effects in the dialyzer, citrate containing dialysate may improve dialysis adequacy and, decrease hemodialysis heparin requirements. Acetate has been connected with several intradialytic symptoms, such as malaise and hemodynamic instability and some studies showed improved tolerance to dialysis treatment, when regular dialysis fluid was replaced with acetate-free, citrate-containing solutions. Citrate also has antioxidative properties and may reduce cellular injury and inflammatory response.

The aim of our retrospective, single-center study was to compare the impact of citrate- and acetate-based dialysates on acid-base status, rate of inflammation, calcium balance and dialysis efficiency, measured as predialysis concentrations of BUN, creatinine and phosphate, in a group of chronic dialysis patients treated in our center.
Patients and Methods. The study population consisted of 99 patients treated by chronic hemodialysis during the months of December 2012 and September 2013 in the Center for acute and complicated dialysis in University Medical Center Ljubljana. Before the switch to citric acid dialysate (Select Bag® Citrate, Gambro Lundia AB, Lund, Sweden), which occurred during the two-month period between March and May 2013, all of the clinic used regular bicarbonate dialysate acidified with acetic acid. All screened patient treatments used regular bicarbonate dialysate on either AK 200™ Ultra 5 or Artis™ hemodialysis monitors (Gambro Lundia AB, Lund, Sweden) for minimally 3 months of before switching to CD. During the observed period, routine medical and clinical practices remained unchanged. The patients’ blood urea nitrogen (BUN), creatinine, serum calcium, phosphate, carbon dioxide (CO2) and C-reactive protein (CRP) levels were monitored on a monthly basis, prior to the first-in-the-week hemodialysis session of the second half-month. Findings from February 2013 (pre-CD group) and September 2013 (CD group) were then compared. All the data for this study was obtained from the hospital’s laboratory database and the patient’s dialysis charts.

Results. 99 adult chronic hemodialysis patients participated in this study. Their median age was 62 ± 14.6 (range 26-92) years, 63% were male. Average laboratory results prior to changing to dialysis with citric acid dialysate (pre-CD group) were: creatinine 816.86 ± 242.63 μmol/l, BUN 27.22 ± 7.22 mmol/l, potassium 5.44 ± 0.89 mmol/l, calcium 2.13 ± 0.20 mmol/l and phosphate 1.56 ± 0.43 mmol/l. After switching to citric acid dialysate, there was a noticeable decline in serum creatinine and urea levels (793.04 ± 236.22 μmol/l and 26.73 ± 6.95 mmol/l, respectively), while serum potassium and phosphate levels increased (see Table 1). Predialysis calcium levels are comparable in both groups and are within normal parameters. There was a significant reduction of inflammation in the CD group, with only 18.2% of the patients having elevated C-reactive protein levels (defined as ≥ 10 mg/l), which is much lower compared to the pre-CD group, where 34.3% had elevated CRP levels. The total CO2 values were also higher in the CD group.

Table 1: Predialysis concentrations (N = 99)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Regular bicarbonate dialysate</th>
<th>Citric acid dialysate (CD)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium [mmol/l]</td>
<td>5.44 ± 0.89</td>
<td>5.65 ± 0.95</td>
<td>0.119</td>
</tr>
<tr>
<td>Calcium [mmol/l]</td>
<td>2.13 ± 0.20</td>
<td>2.14 ± 0.23</td>
<td>0.741</td>
</tr>
<tr>
<td>Phosphate [mmol/l]</td>
<td>1.56 ± 0.43</td>
<td>1.60 ± 0.47</td>
<td>0.544</td>
</tr>
<tr>
<td>Creatinine [μmol/l]</td>
<td>816.86 ± 242.63</td>
<td>793.04 ± 236.22</td>
<td>0.485</td>
</tr>
<tr>
<td>Urea [mmol/l]</td>
<td>27.22 ± 7.22</td>
<td>26.73 ± 6.95</td>
<td>0.625</td>
</tr>
<tr>
<td>C-reactive protein [mg/l]</td>
<td>27.62 ± 35.29</td>
<td>16.33 ± 10.55</td>
<td>0.079</td>
</tr>
<tr>
<td>Total CO2 [μg/l]</td>
<td>22.94 ± 2.99</td>
<td>24.76 ± 3.70</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation

a N = 34  
b N = 18

Conclusions. The switch from regular bicarbonate dialysate to citric acid dialysate was safe, effective and was made without any adjustments or modification to the machines. No dialysate-related problems occurred throughout the study period. While phosphate and potassium levels were slightly higher in the CD group, there was a slight decline in predialysis urea and creatinine, which confirms the assumption that switching to citric acid dialysate may improve dialysis adequacy, however, further studies are necessary. As expected, citrate dialysis was associated with an increase in predialysis total CO2 levels and can be explained by the conversion of citrate into bicarbonate during the dialysis session. There were no significant changes in predialysis serum calcium, however, there was a significant reduction of CRP values in the CD group. The positive impact of the citrate dialysate on dialyser efficiency, on acid-base status and the rate of inflammation together suggest that the substitution of citrate for acetate in dialysis fluids may improve haemodialysis in selected patients.