ANTICOAGULACIÓN REGIONAL CON CITRATOS

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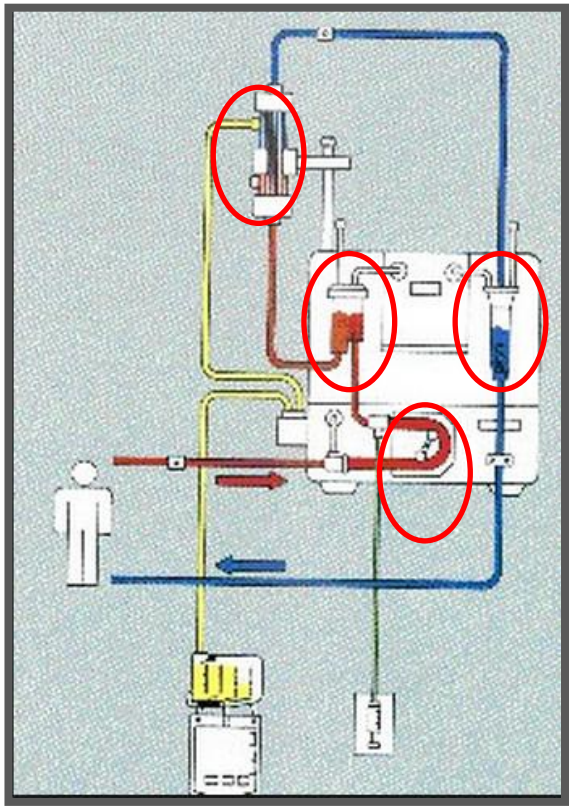
Hospital Germans Trias i Pujol

INTRODUCCIÓN

COAGULACIÓN DEL CIRCUITO

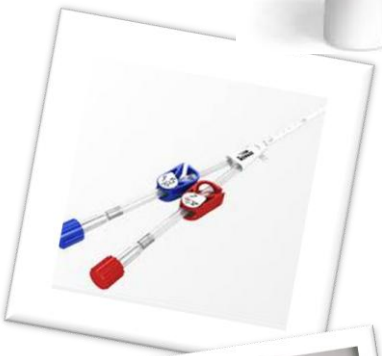
- Infradosificación de hemodiálisis/ hemofiltración al reducir el tiempo de terapia
- Pérdida hemática cuando existe imposibilidad de retorno sanguíneo
- Aumento cargas enfermería
- Incremento costos

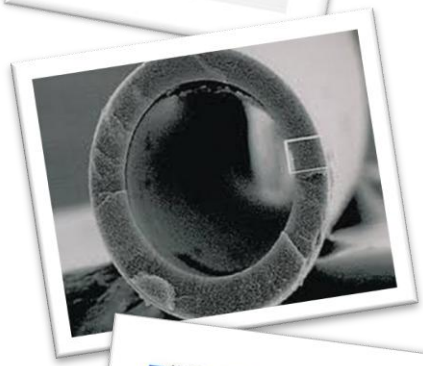
COAGULACIÓN DEL CIRCUITO

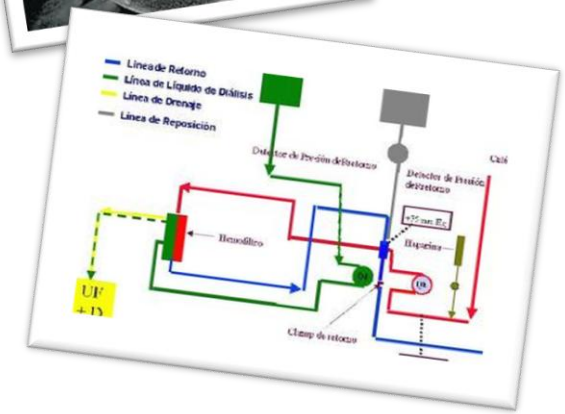


CAUSAS
Contacto sangre con material extraño
Contacto sangre con aire
“Turbulencias” de sangre
Hemoconcentración
Hipotermia

COAGULACIÓN DEL CIRCUITO



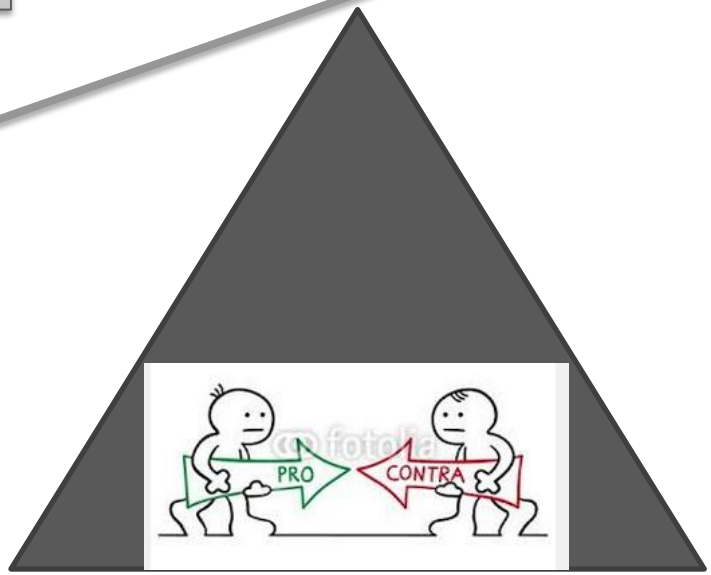




ESTRATEGIAS PARA PROLONGAR EL FILTRO
Acceso Vascular y Catéter apropiado
Membranas biocompatibles
Reposición en prefiltro
Ajuste de flujos
Reducción contacto de la sangre con el aire
Reacción rápida a las alarmas

ANTICOAGULACIÓN

SANGRADO

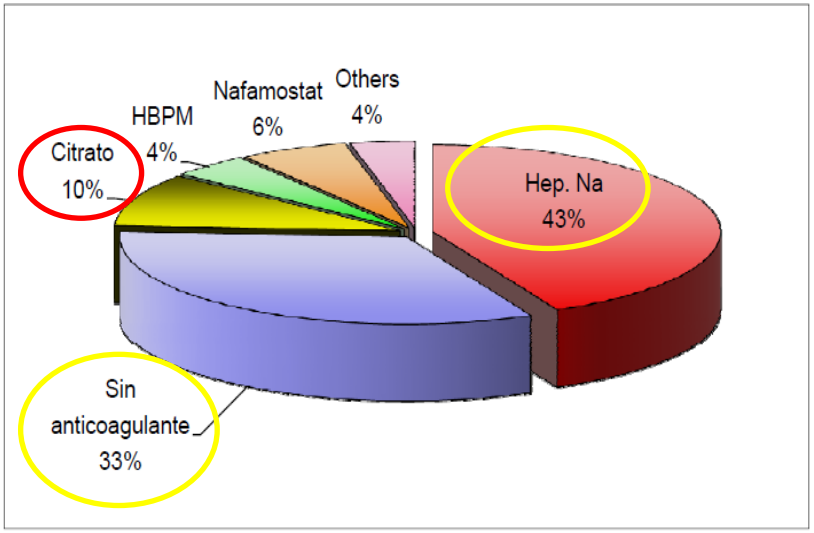


COAGULACIÓN DEL CIRCUITO

Pauta	Sustancia	Dosis	Control
Sin anticoagulación	NaCl al 0,9%	100-150 mL/h	Visualizar el filtro
Dextrano de bajo p. molecular	Rheomacrodex^{R}	25 mL/h	Visualizar el filtro
Citratos	Citrato trisódico 4% Calcio i.v.	100-180 mL/h 4 mEq/h	Monitorizar Calcio Visualizar tras bolos de 100 mL de salino
Prostaglandinas y derivados	PGI_2 Epoprostenol PE1 Taprostene	4-8 ng· Kg^{-1}· min^{-1} 5 ng. Kg^{-1}· min^{-1} 20 ng· Kg^{-1}· min^{-1} 25-35 ng. Kg^{-1}· min^{-1}	Visualizar el filtro
Inhibidor de proteasas	Mesilato de Nafamostat	0,1 mg· Kg^{-1}· h^{-1}	TCA
Heparina no fraccionada uso de protamina	Heparina sódica Heparina-Protamina	5-10 UI· Kg^{-1} 1 mg de protamina por cada 100 UI de heparina Na	APTT, TCA APTT, Heparinemia
Heparinas de bajo peso molecular Membranas con heparina	Enoxaparina Dalteparina sódica Duraflo	10-40 mg/6h 2500-5000 UI/12h	anti-Factor Xa anti-Factor Xa

Mehta RL. Anticoagulatiopn during continuous renal replacement therapy. ASAIO J 1994; 40: 931-935
Mehta RL. Anticoagulation strategies for continuous renal replacement therapies: What works?. Am J Kidney Dis 1996; 28 (5S3): S8-S14

B.E.S.T. Kidney (The Beginning and Ending Supportive Therapy for the kidney).
23 paises, 54 UCIs, 1006 pacientes en TCRR

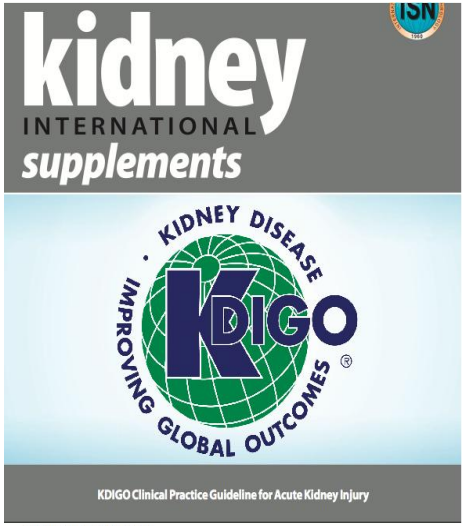


Intensive Care Med. 2007;33(9):1563-70

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JULY 3, 2008 VOL. 359 NO. 1

Intensity of Renal Support in Critically Ill Patients with Acute Kidney Injury

Anticoagulant — no. of treatments (%)	
None	1736 (54.6)
Heparin	645 (20.3)
Citrate	649 (20.4)
Other	148 (4.7)
Percent of prescribed dose of therapy delivered	89±39



VOLUME 2 | ISSUE 1 | MARCH 2012
http://www.kidney-international.org

KIDNEY DISEASE | IMPROVING GLOBAL OUTCOMES

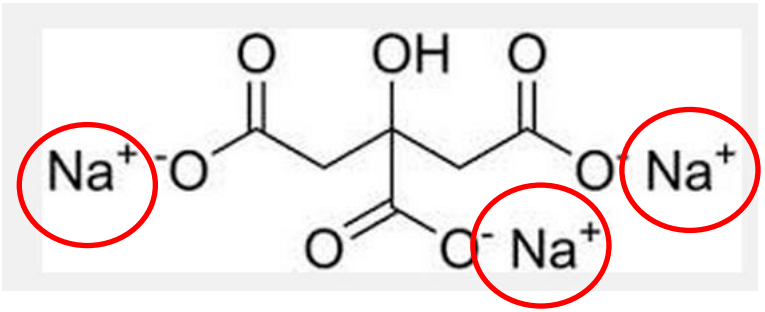
KDIGO Clinical Practice Guideline for Acute Kidney Injury

http://kdigo.org/home/guidelines/acute-kidney-injury/

1. Pacientes **sin riesgo** aumentado de sangrado o un deterioro de la coagulación y sin recibir coagulación sistémica efectiva, recomiendan:
   - El uso de citratos más que la heparina en pacientes que no tienen contraindicaciones para el uso de citratos (2B)
   - En pacientes con contraindicaciones para el uso de citratos, sugieren el uso de heparina no fraccionada o heparina de bajo peso molecular antes que otro tipo de anticoagulación (2C)

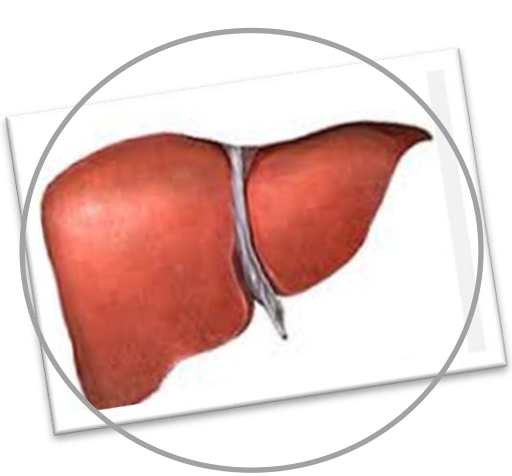
2. Para pacientes **con riesgo** aumentado de sangrado que no están recibiendo anticoagulación, durante las TCRR recomiendan:
   - Usar citratos antes que no anticoagular el sistema, siempre que no existan contraindicaciones para el uso de citrato (2C)
   - Evitar heparinización regional en pacientes con riesgo aumentado de sangrado (2C)

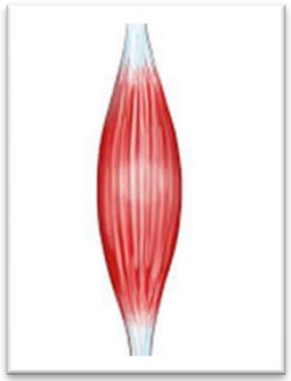
QUÉ ES EL CITRATO

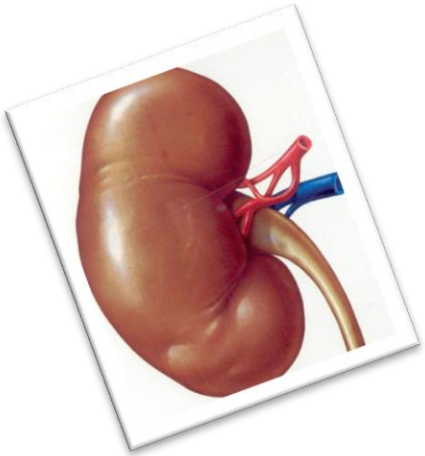


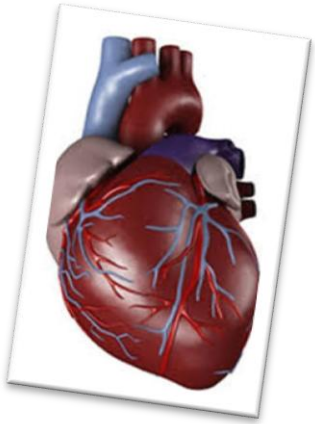
= $Na_3C_6H_5O_7$ = CITRATO TRISÓDICO

Se metaboliza a **HCO_3** en



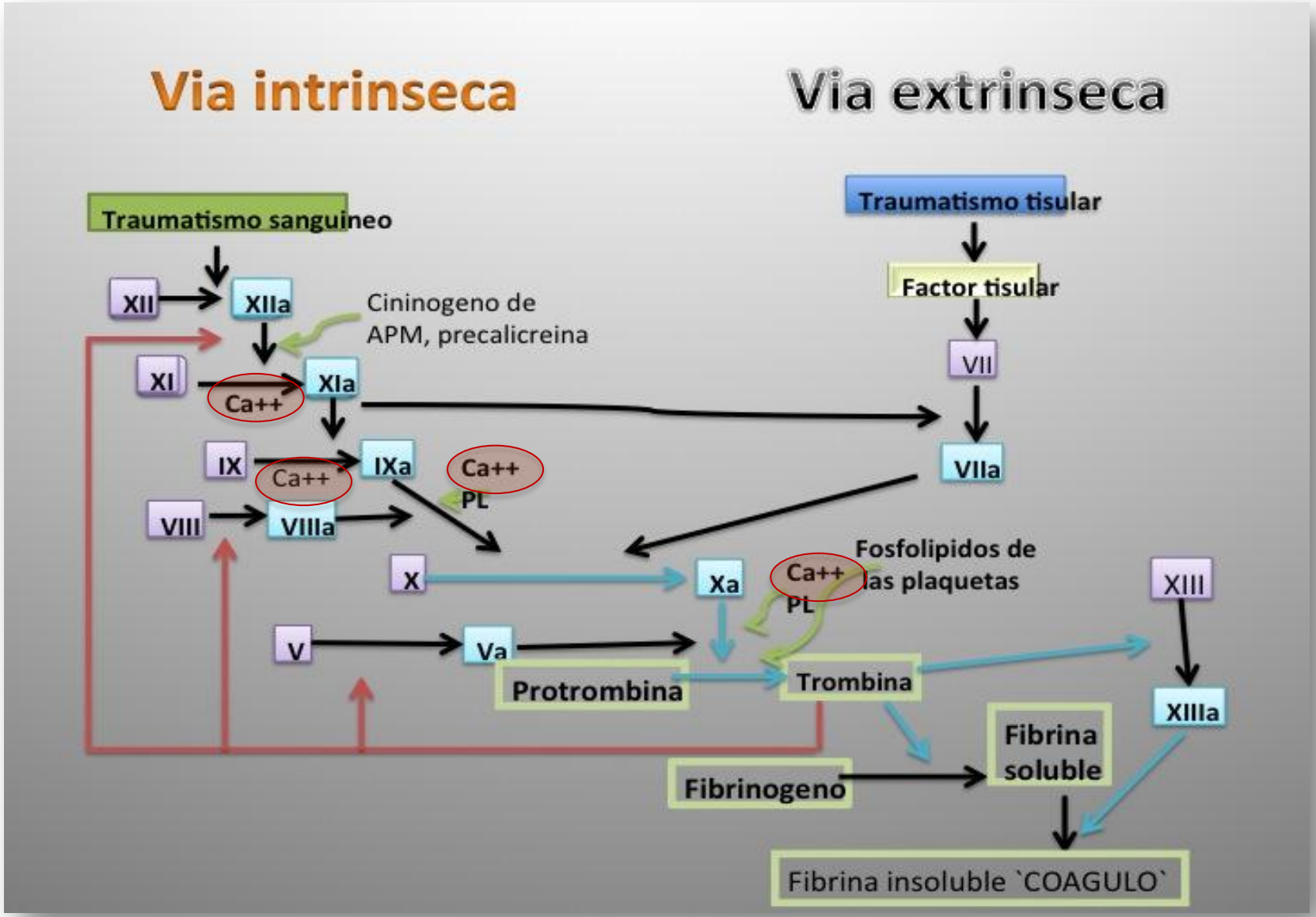


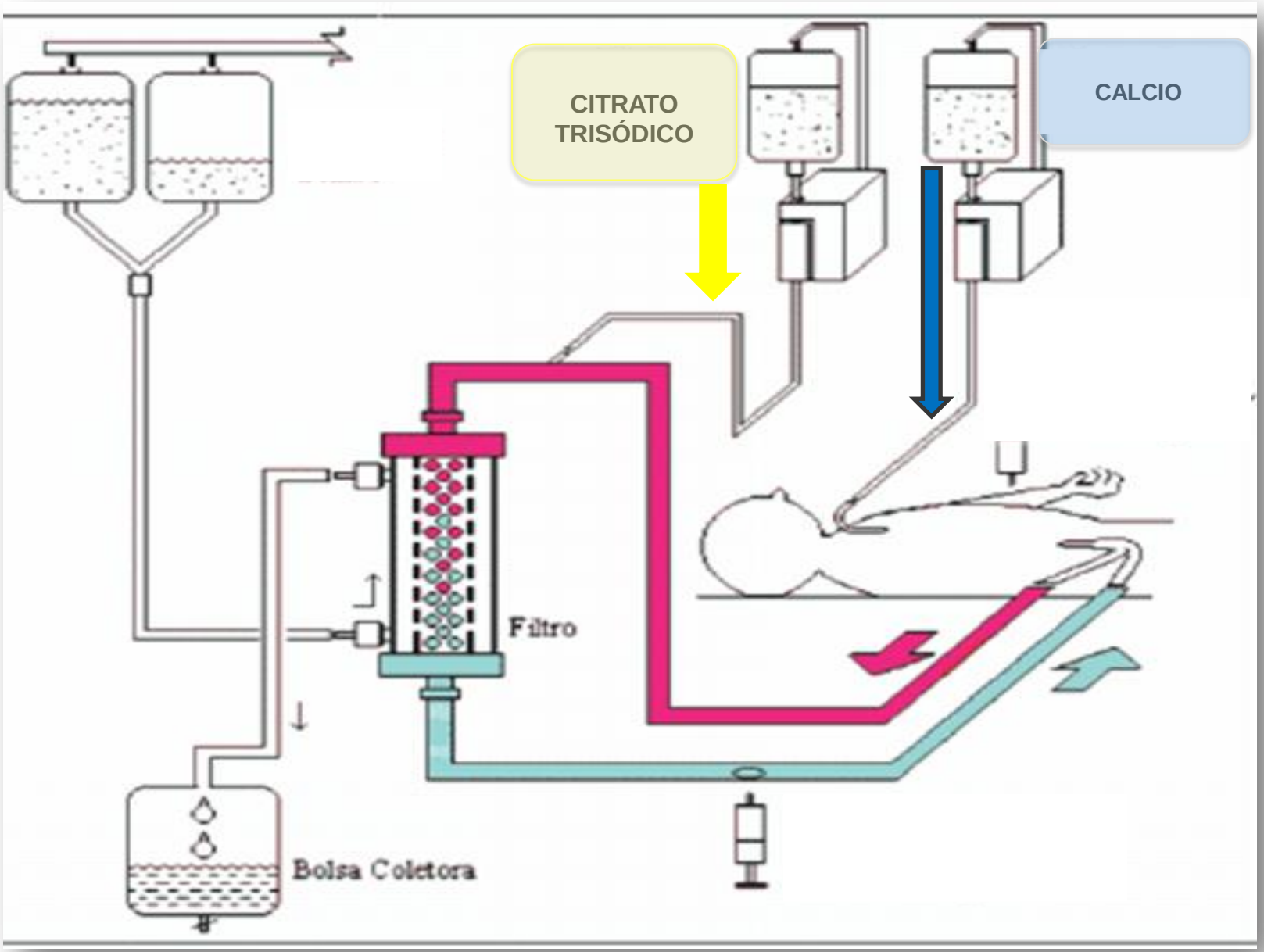




1 mol $Na_3C_6H_5O_7$ =
3 moles HCO_3 + liberación Ca iónico

CÓMO FUNCIONA




CITRATO TRISÓDICO
CALCIO
Filtro
Bolsa Colectora

COMPLEJO Ci-Ca

- **Objetivo: HIPOCALCEMIA DEL CIRCUITO: 0,25-0,35 (postfiltro)**

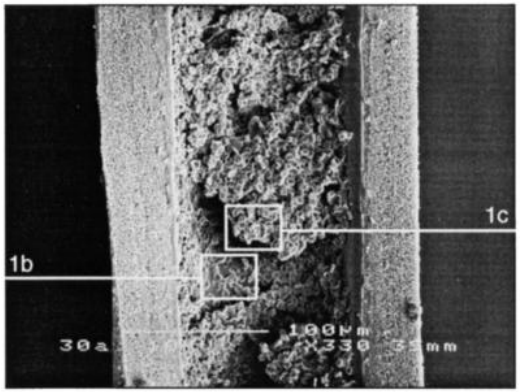
- **A tener en cuenta:**
  - Tanto el complejo Ci-Ca, como el calcio iónico y el unido a proteínas se pierden en el ultrafiltrado
  - El complejo Ci-Ca que pasa a la circulación sanguínea se diluye en el flujo venoso
  - El citrato que pasa a la circulación se metaboliza en el hígado, músculo esquelético y riñón (1 mol citrato: 3 moles de HCO3+ Ca + Na)
  - La vida media del citrato es de 5 min (no se produce anticoagulación sistémica)

EFICACIA

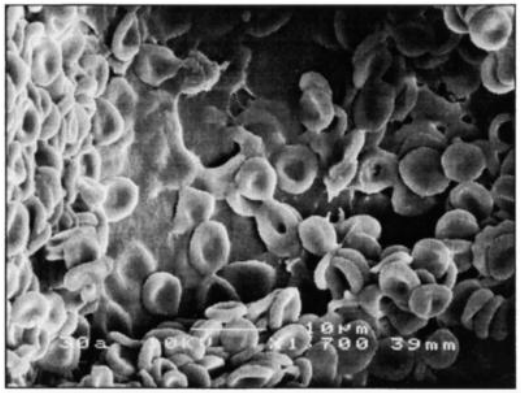
Autor	Año	Citrato %	[Citrato] mmol/L	Qs ml/min	QRpre ml/h	QD ml/h	[Citrato] S. mmol/L
Mehta	1993	4%	140	AV	170 + Rpre	1000	4,2-11,2
Palsson	1999	0,38%	13,3	180	1400	0	2
Tolwani	2001	2%	70	150	250	1000	2
Kutsogiannis	2005	4%	145	125	190 + 1000	1000	3,1

- Mehta: 24 -172 h
- Palsson: 29, 5h ± 17,9 h
- Tolwani: 61% a las 48 h
- Kutsogiannis: mediana 5,1 días / 70% a las 48 h

HEPARINA NO FRACCIONADA

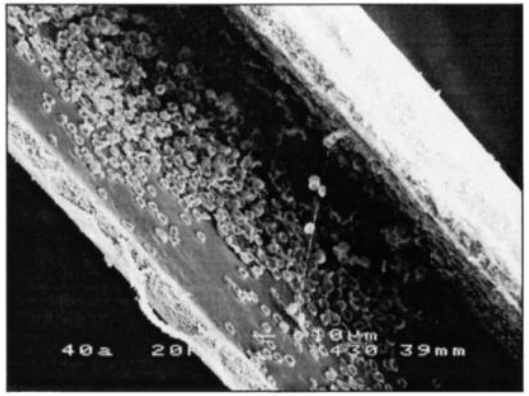


1a

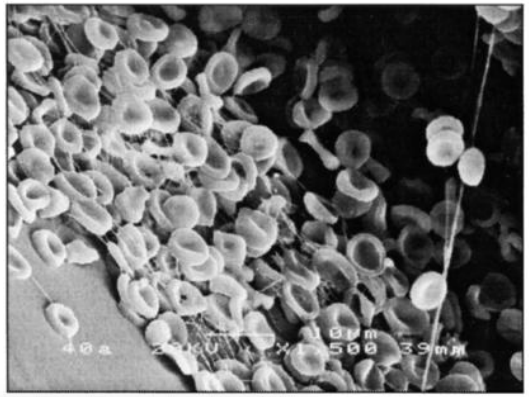


1b

HBPM

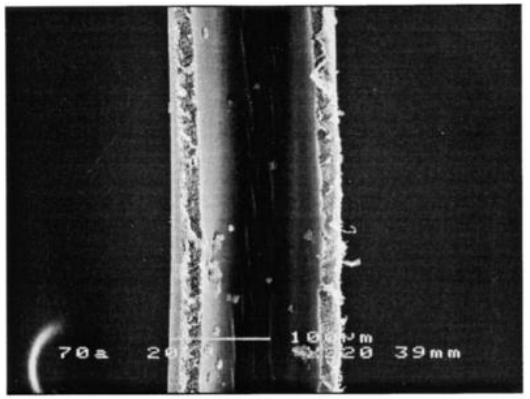


2a

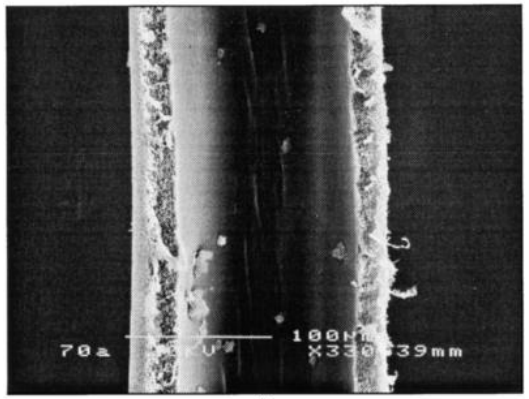


2c

CITRATO



3a



3b

Kidney International, Vol. 56 (1999), pp. 1578–1583

Effect of anticoagulation on blood membrane interactions during hemodialysis

ROLAND HOFBAUER, DORIS MOSER, MICHAEL FRASS, RAINER OBERBAUER, ALAN D. KAYE, O. WAGNER, STYLIANOS KAPIOTIS, and WILFRED DRUML

SOFTWARE INTEGRADO

Oudemans-van Straaten *et al. Critical Care* 2011, **15**:202
http://ccforum.com/content/15/1/202

CRITICAL CARE

REVIEW

Clinical review: Anticoagulation for continuous renal replacement therapy - heparin or citrate?

Table 1. Randomized clinical studies comparing citrate with heparin anticoagulation for CRRT

		Circuit life (hours)[a]		Bleeding		Transfusion (RBC/day[b])		Survival	
Reference	**Design**	**Citrate**	**Heparin**	**Citrate**	**Heparin**	**Citrate**	**Heparin**	**Citrate**	**Heparin**
Monchi and colleagues [63]	RCOT, $n = 20$	70 (44 to 140), $P < 0.001$	40 (17 to 48)	$n = 0$	$n = 1$	0.2 (0 to 0.4), $P < 0.001$	1.0 (0 to 2.0)		
Kutsogiannis and colleagues [64]	RCT, $n = 30$	125 (95 to 157), $P < 0.001$	38 (25 to 62)	RR 0.17 (0.03 to 1.04), $P = 0.06$		0.53 (0.24 to 1.20), $P = 0.13$			
Betjes and colleagues [65]	RCT, $n = 48$			0%, $P < 0.01$	33%	0.43, $P = 0.01$	0.88		
Oudemans-Van Straaten and colleagues [35]	RCT[c], $n = 200$	27 (13 to 47), NS	26 (15 to 43)	6%, $P = 0.08$	16%	0.27 (0 to 0.63), $P = 0.31$	0.36 (0 to 0.83)	52%[d], $P = 0.03$	37%[d]
Hetzel and colleagues [66]	RCT, $n = 170$	37.5 ± 23, $P < 0.001$	26.1 ± 19.2	14.5%, $P = 0.06$	5.7%			±30%[e], NS	±43%[e]

CRRT, continuous renal replacement therapy; RCOT, randomized cross-over trial; RCT, randomized controlled trial; NS, not significant; RR, relative risk. [a]Median (interquartile range). [b]Number of red cell units per day of continuous venovenous hemofiltration. [c]Comparing citrate with the low molecular weight heparin nadroparin. [d]Three-month survival on an intention-to-treat analysis. [e]Thirty-day mortality, estimated from the Kaplan–Meier curve.

Schilder *et al. Critical Care* 2014, **18**:472
http://ccforum.com/content/18/4/472

CRITICAL CARE

RESEARCH Open Access

Citrate anticoagulation versus systemic heparinisation in continuous venovenous hemofiltration in critically ill patients with acute kidney injury: a multi-center randomized clinical trial

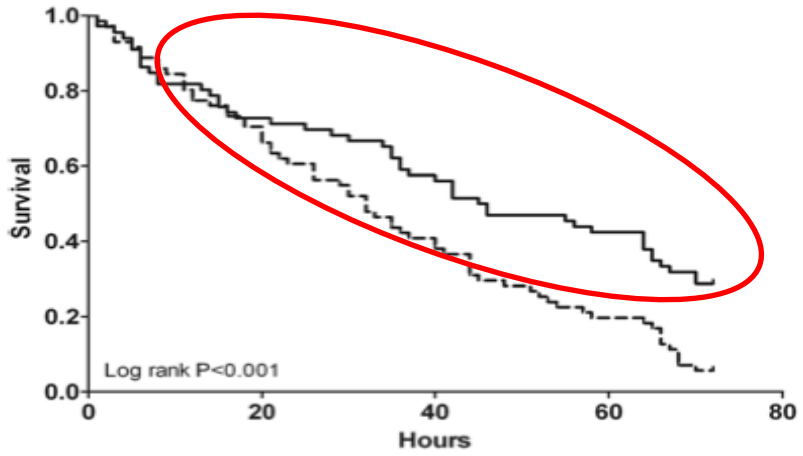


Figure 2 Survival times for the first filter. Continuous line represents citrate, dotted line represents heparin.

	Citrate (n = 66)	Heparin (n = 73)	*P*-value
Efficacy, per protocol	n = 61	n = 49	
Number of filters used within 72 h	1 (1 to 5)	2 (1 to 9)	0.04
Off-time within 72 h, h	2 (0 to 12)	0 (0 to 31)	0.01
Total duration of CWH, h	117 (4 to 999)	70 (5 to 672)	0.04

Critical Care Medicine

A Randomized Controlled Trial of Regional Citrate Versus Regional Heparin Anticoagulation for Continuous Renal Replacement Therapy in Critically Ill Adults*

David J. Gattas, MD, MMed (ClinEpi), FCICM, FRACP[1,2];
Dorrilyn Rajbhandari, RN Post Grad Dip (Clinical Nursing)[1,2]; Celia Bradford, MD, FCICM[3];
Heidi Buhr, RN, MClinTPrac[1]; Serigne Lo, PhD, AStat[2];
Rinaldo Bellomo, MBBS, MD (Hons), FRACP, FCICM, PG Dip Echo[4,5]

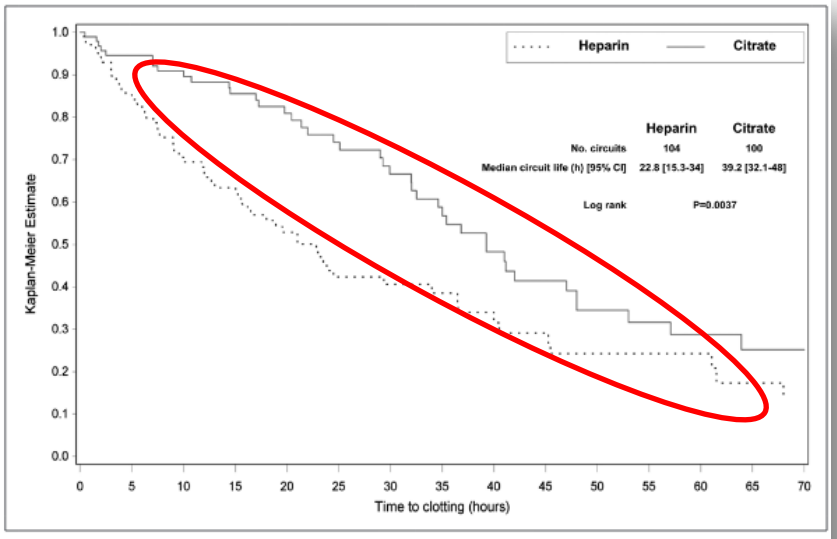


Figure 2. Kaplan-Meier estimate of the probability of continuous renal replacement therapy circuit survival for the first circuit.

Variable	Citrate ($n = 105$)	Heparin ($n = 107$)	Total	p
Clinical				
ICU mortality, *n*/total (%)	28/105 (26.7)	25/107 (23.4)		0.58
ICU length of stay, median (IQR), d	9.0 (12)	9.0 (13)		0.79
Hospital mortality, *n*/total (%)	33/105 (31.4)	31/107 (29.0)		0.7
Red cells transfused				
Patients transfused, *n*/total (%)	52/101 (52)	48/103 (47)		0.58
Volume of red cells, mean (SD)	908 (770)	872 (917)		0.83
CRRT process				
Filter outcome				
Clotted	226	310	536	
Did not clot	127	112	239	
Unclear	37	45	82	
TOTAL	390	467	857	
Duration of CRRT				
Total patient time on circuit (hr)	8,281	8,015	16,296	
Per patient on circuit (hr), median (IQR)	55.7 (86.6)	50.6 (73.4)		0.6

Crit Care Med. 2015 Aug;43(8):1622-9

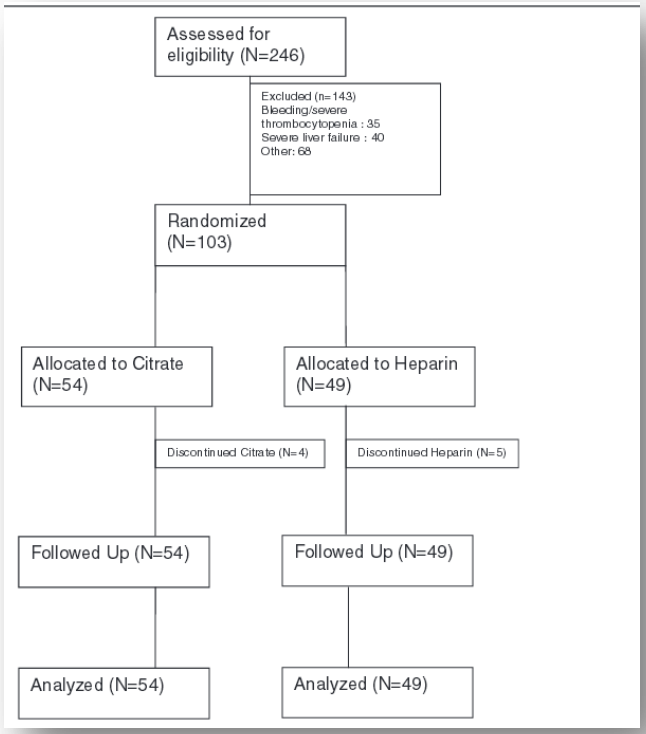
Stucker *et al. Critical Care* (2015) 19:91
DOI 10.1186/s13054-015-0822-z

CRITICAL CARE

RESEARCH Open Access

Efficacy and safety of citrate-based anticoagulation compared to heparin in patients with acute kidney injury requiring continuous renal replacement therapy: a randomized controlled trial

Fabien Stucker[1†], Belen Ponte[1†], James Tataw[1], Pierre-Yves Martin[1], Hannah Wozniak[2], Jérome Pugin[2] and Patrick Saudan[1*]



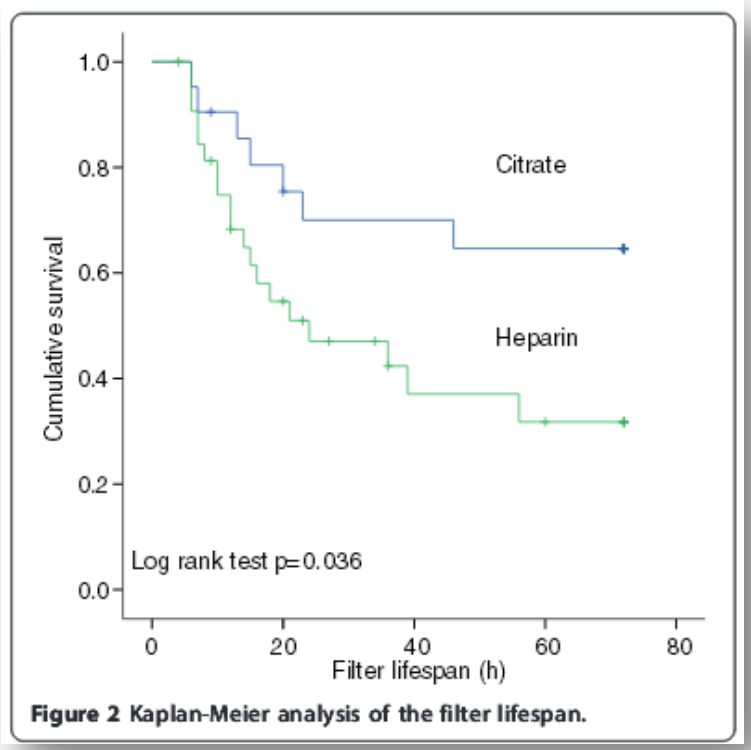


Figure 2 Kaplan-Meier analysis of the filter lifespan.

1 Fallo hepático
1 problema técnico en la infusión de Ca
2 Hipocalcemia relevante

2 Sangrado mayor
3 coagulación repetida del filtro

Variables	Citrate (n = 54)	Heparin (n = 49)	*p*
Delivered RRT dose, ml/kg/h	29 (3)	27 (5)	**0.005**
Effective delivered RRT dose*, ml/kg/h	28 (5)	26 (4)	0.15
Filter lifespan, h	49 (29)	28 (23)	**0.004**
Mean heparin, IU/ml dose	6,757 (5,455)	10,567 (7,760)	0.005
pH, day 1	7.32 (0.10)	7.31 (0.11)	0.62
Bicarbonate, mmol/L, day 1	18 (4.6)	19 (7.2)	0.96
Na, mmol/L, day 1	136 (15)	138 (7)	0.42
Chloride, mmol/L, day 1	104 (15)	108 (7)	0.15
Potassium, mmol/L, day 1	6 (14)	5.3 (5.6)	0.61
Lactate, mmol/L, day 1	1.3 (0.9 to 2.9)	1.3 (0.8 to 1.8)	0.67
Total calcium, mmol/L, day 3	2.52 (0.19)	2.41 (0.22)	0.02
Ionized calcium, mmol/L, day 3	1.14 (0.10)	1.20 (0.11)	0.01
pH, day 3	7.40 (0,06)	7.41 (0.06)	0. 39
Bicarbonate, mmol/L, day 3	23.71 (1.81)	25.17 (4.31)	0.43
Na, mmol/L, day 3	138 (3.37)	138 (4)	0.71
Chloride, mmol/L, day 3	104 (3.4)	107 (4)	0.00
Potassium, mmol/L, day 3	4 (0.52)	4.3 (0.6)	0.03
Lactate, mmol/L, day 3	1.4 (0.9 to 2.2)	1.1 (0.9 to 1.4)	0.50
Side effects	32	27	0.17
Bleeding	0	4 (8)	
HIT	1 (2)	2 (4)	
Filter clotting	3 (6)	18 (37)	
Metabolic disorders:	14	3	
Metabolic alcalosis	3	0	
Respiratory alkalosis	0	1	
Metabolic acidosis	3	1	
Severe hypocalcemia	6	1	
Ca total/calcium ion ratio >2.5	1	0	
CRRT, days	3 (2 to 6)	3 (2 to 5)	0.30
ICU, days	7 (4 to 15)	7 (4 to 12)	0.79
Hospital, days	22 (6 to 35)	16 (9 to 30)	0.45
Survival at 28 days	43 (80)	36 (74)	0.46
Survival at 90 days	40 (74)	35 (73)	0.90

Morabito *et al. Critical Care* 2012, **16**:R111
http://ccforum.com/content/16/3/R111

CRITICAL CARE

RESEARCH Open Access

Regional citrate anticoagulation in cardiac surgery patients at high risk of bleeding: a continuous veno-venous hemofiltration protocol with a low concentration citrate solution

	RCA (*n* = 152)	Heparin (*n* = 73)	No AC (*n* = 77)
CIRCUIT LIFETIME			
Mean ± SD (hours)	**49.8 ± 35.4*** **	30.6 ± 24.3	25.7 ± 21.2
Median (hours)	41	22	20
> 24 hours	74%	45%	40%
> 48 hours	41%	25%	14%
> 72 hours	27%	12%	5%
CRRT STOPPING CAUSES			
CVC malfunction	34.9%	17.8%	15.6%
Alarm handling/technical issues	23.7%	12.3%	2.6%
Scheduled	19.7%	0%	1.3%
Medical procedures	13.8%	2.8%	3.9%
Clotting	0%	61.6%	68.8%
Unidentified	7.9%	5.5%	7.8%
DIALYSIS DOSE[a]			
Prescribed dose (ml/kg/hour)	26.8 ± 3.8	27.3 ± 4.7	26.6 ± 7.1
Delivered dose (ml/kg/hour)	**25.6 ± 4.9****	23.7 ± 7.2	23.1 ± 8
Delta dose (%)	**4.7 ± 12.1*****	13 ± 20.5	12.7 ± 19.1

Oudemans-van Straaten *et al. Critical Care* 2011, **15**:202
http://ccforum.com/content/15/1/202

CRITICAL CARE

REVIEW

Clinical review: Anticoagulation for continuous renal replacement therapy - heparin or citrate?

MORTALIDAD

Table 1. Randomized clinical studies comparing citrate with heparin anticoagulation for CRRT

		Circuit life (hours)[a]		Bleeding		Transfusion (RBC/day[b])		Survival	
Reference	**Design**	**Citrate**	**Heparin**	**Citrate**	**Heparin**	**Citrate**	**Heparin**	**Citrate**	**Heparin**
Monchi and colleagues [63]	RCOT, $n = 20$	70 (44 to 140), $P < 0.001$	40 (17 to 48)	$n = 0$	$n = 1$	0.2 (0 to 0.4), $P < 0.001$	1.0 (0 to 2.0)		
Kutsogiannis and colleagues [64]	RCT, $n = 30$	125 (95 to 157), $P < 0.001$	38 (25 to 62)	RR 0.17 (0.03 to 1.04), $P = 0.06$		0.53 (0.24 to 1.20), $P = 0.13$			
Betjes and colleagues [65]	RCT, $n = 48$			0%, $P < 0.01$	33%	0.43, $P = 0.01$	0.88		
Oudemans-Van Straaten and colleagues [35]	RCT[c], $n = 200$	27 (13 to 47), NS	26 (15 to 43)	6%, $P = 0.08$	16%	0.27 (0 to 0.63), $P = 0.31$	0.36 (0 to 0.83)	52%[d], $P = 0.03$	37%[d]
Hetzel and colleagues [66]	RCT, $n = 170$	37.5 ± 23, $P < 0.001$	26.1 ± 19.2	14.5%, $P = 0.06$	5.7%			±30%[e], NS	±43%[e]

Citrate anticoagulation for continuous venovenous hemofiltration*

Oudemans-van Straaten, Heleen M. MD, PhD; Bosman, Rob J. MD; Koopmans, Matty RN; van der Voort, Peter H. J. MD, PhD, MSc; Wester, Jos P. J. MD, PhD; van der Spoel, Johan I. MD; Dijksman, Lea M. MSc; Zandstra, Durk F. MD, PhD

Critical Care Medicine:
February 2009 - Volume 37 - Issue 2 - pp 545-552

0.03), per protocol 45% and 62% ($p = 0.02$). Citrate reduced mortality in surgical patients ($p = 0.007$), sepsis ($p = 0.01$), higher Sepsis-Related Organ Failure Assessment score ($p = 0.006$), and lower age ($p = 0.009$).

Conclusions: The efficacy of citrate and nadroparin anticoagulation for CVVH was similar, however, citrate was safer. Unexpectedly, citrate reduced mortality. Less bleeding could only partly explain this benefit, less clotting could not. *Post hoc* citrate appeared particularly beneficial after surgery, in sepsis and severe multiple organ failure, suggesting interference with inflammation.

REVIEW

Clinical review: Anticoagulation for continuous renal replacement therapy - heparin or citrate?

Oudemans-van Straaten *et al. Critical Care* 2011, **15**:202
http://ccforum.com/content/15/1/202

Table 2. Advantages and disadvantages of heparin or citrate anticoagulation during continuous renal replacement therapy

	Heparins	Citrate
Biochemical		
Anticoagulation	Critically ill patients exhibit heparin resistance due to: • Low antithrombin (high consumption and degradation) • Acute phase proteins and apoptotic/necrotic cells bind heparin (UFH >LMWH)	
Proinflammatory effects	Inhibit the anti-inflammatory properties of antithrombin (UFH >LMWH) Trigger antithrombin degradation by elastase Release myeloperoxidase, elastase, platelet factor 4, superoxide dismutase into the circulation (UFH, LMWH) Increase in lipopolysaccharide-induced, LPB-dependent IL-8 and IL-1β secretion from monocytes (LMWH, UFH)	
Anti-inflammatory effects	Inhibit thrombin generation (UFH, LMWH) Block P-selectin and L selectin-mediated cell adhesion (UFH, LMWH) Decrease cytokine generation *in vitro*, not *in vivo*	Its use prevents the release of granular products from neutrophils and platelets
Phagocytosis	Bind to apoptotic and necrotic cells and may delay phagocytic clearance (UFH >LMWH)	
Bio-energetic properties		Provides energy without needing insulin for entrance into the cell May protect against mitochondrial dysfunction

Critical Care Medicine

A Randomized Controlled Trial of Regional Citrate Versus Regional Heparin Anticoagulation for Continuous Renal Replacement Therapy in Critically Ill Adults*

David J. Gattas, MD, MMed (ClinEpi), FCICM, FRACP[1,2];
Dorrilyn Rajbhandari, RN Post Grad Dip (Clinical Nursing)[1,2]; Celia Bradford, MD, FCICM[3];
Heidi Buhr, RN, MClinTPrac[1]; Serigne Lo, PhD, AStat[2];
Rinaldo Bellomo, MBBS, MD (Hons), FRACP, FCICM, PG Dip Echo[4,5]

Variable	Citrate[a]			Heparin[b]			p[c]
	t = 0 Hr	t = 48–72 Hr	Change Score	t = 0 Hr	t = 48–72 Hr	Change Score	
IL-6, median, pg/mL (IQR)	102.7 (214.0)	48.3 (58.1)	−29.3 (171.5)	141.7 (285.6)	53.8 (99.0)	−66.5 (262.1)	0.4
IL-8, median, pg/mL (IQR)	108.0 (114.0)	54.7 (42.6)	−26.2 (127.4)	115.8 (132.4)	53.8 (48.8)	−25.8 (131.0)	0.86
IL-10, median, pg/mL (IQR)	40.3 (63.3)	36.7 (44.9)	−0.7 (39.6)	37.7 (143.0)	36.2 (53.2)	−6.9 (111.1)	0.76

Variable	Citrate (*n* = 105)	Heparin (*n* = 107)	Total	p
Clinical				
ICU mortality, *n*/total (%)	28/105 (26.7)	25/107 (23.4)		0.58
ICU length of stay, median (IQR), d	9.0 (12)	9.0 (13)		0.79
Hospital mortality, *n*/total (%)	33/105 (31.4)	31/107 (29.0)		0.7

Crit Care Med. 2015 Aug;43(8):1622-9

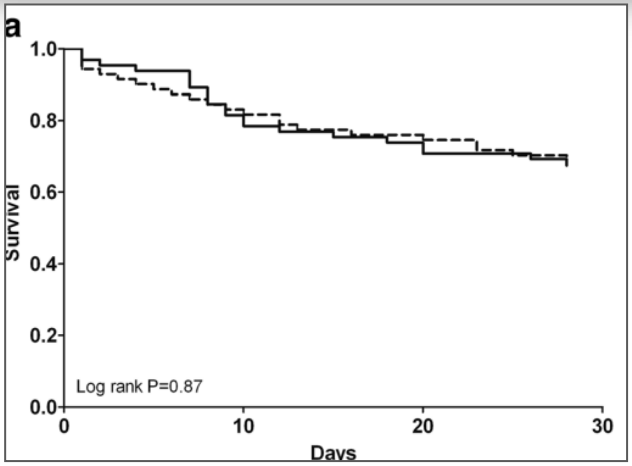
MORTALIDAD

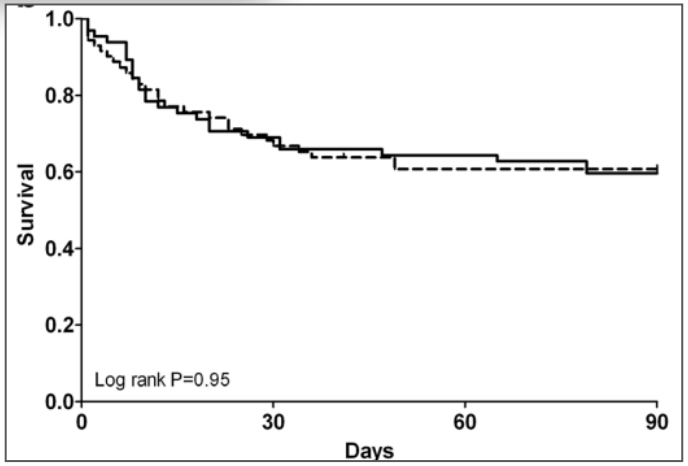
Schilder *et al. Critical Care* 2014, **18**:472
http://ccforum.com/content/18/4/472

CRITICAL CARE

RESEARCH Open Access

Citrate anticoagulation versus systemic heparinisation in continuous venovenous hemofiltration in critically ill patients with acute kidney injury: a multi-center randomized clinical trial





RESEARCH Open Access

Efficacy and safety of citrate-based anticoagulation compared to heparin in patients with acute kidney injury requiring continuous renal replacement therapy: a randomized controlled trial

Fabien Stucker[1†], Belen Ponte[1†], James Tataw[1], Pierre-Yves Martin[1], Hannah Wozniak[2], Jérome Pugin[2] and Patrick Saudan[1*]

Stucker *et al. Critical Care* (2015) 19:91
DOI 10.1186/s13054-015-0822-z

ICU, days	7 (4 to 15)	7 (4 to 12)	0.79
Hospital, days	22 (6 to 35)	16 (9 to 30)	0.45
Survival at 28 days	43 (80)	36 (74)	0.46
Survival at 90 days	40 (74)	35 (73)	0.90

COSTES

Schilder et al. Critical Care 2014, 18:472
http://ccforum.com/content/18/4/472

CRITICAL CARE

RESEARCH Open Access

Citrate anticoagulation versus systemic heparinisation in continuous venovenous hemofiltration in critically ill patients with acute kidney injury: a multi-center randomized clinical trial

Efficacy, per protocol	n = 61	n = 49	
Number of filters used within 72 h	1 (1 to 5)	2 (1 to 9)	0.04
Off-time within 72 h, h	2 (0 to 12)	0 (0 to 31)	0.01
Total duration of CWH, h	117 (4 to 999)	70 (5 to 672)	0.04
Costs			
Total cost of first 72 h of CWH, €	553 (436 to 872)	663 (320 to 1,319)	<0.001
Replacement fluid, €	316 (225 to 366)	429 (119 to 736)	<0.001
Wage nursing staff for filter change, €	19 (19 to 95)	38 (19 to 171)	0.02

Therapeutic Apheresis and Dialysis

Therapeutic Apheresis and Dialysis 2016; ••(••):••–••
doi: 10.1111/1744-9987.12331

Transition From Heparin to Citrate Anticoagulation for Continuous Renal Replacement Therapy: Safety, Efficiency, and Cost

TABLE 5. *Outcomes by before and after transition (per CRRT day)*

	Before ($N = 155$)	After ($N = 711$)	P-value
Characteristics			
Time on filter (h/day)	18.3	21.5	0.01
Days achieved prescribed dialysis dose (%)	61.9%	68.2%	0.01
Costs AU$/day			
Total cost (AU$)	433 (195)	483 (230)	0.02
Corrected cost (AU$)	506	483	–
Safety – Bleeding risks			
Transfusion	83 (54%)	187 (26%)	0.02

Data are presented as mean (SD). ABG, arterial blood gas; APTT, activated partial thromboplastin time; HF, hemofiltration; SBE, standard base excess.

ANTICOAGULACIÓN REGIONAL CON CITRATOS

INDICACIONES

ANTES

Riesgo de hemorragia

Trombopenia inducida por heparina

Anticoagulación repetida filtro…

AHORA

KIDNEY DISEASE | IMPROVING GLOBAL OUTCOMES

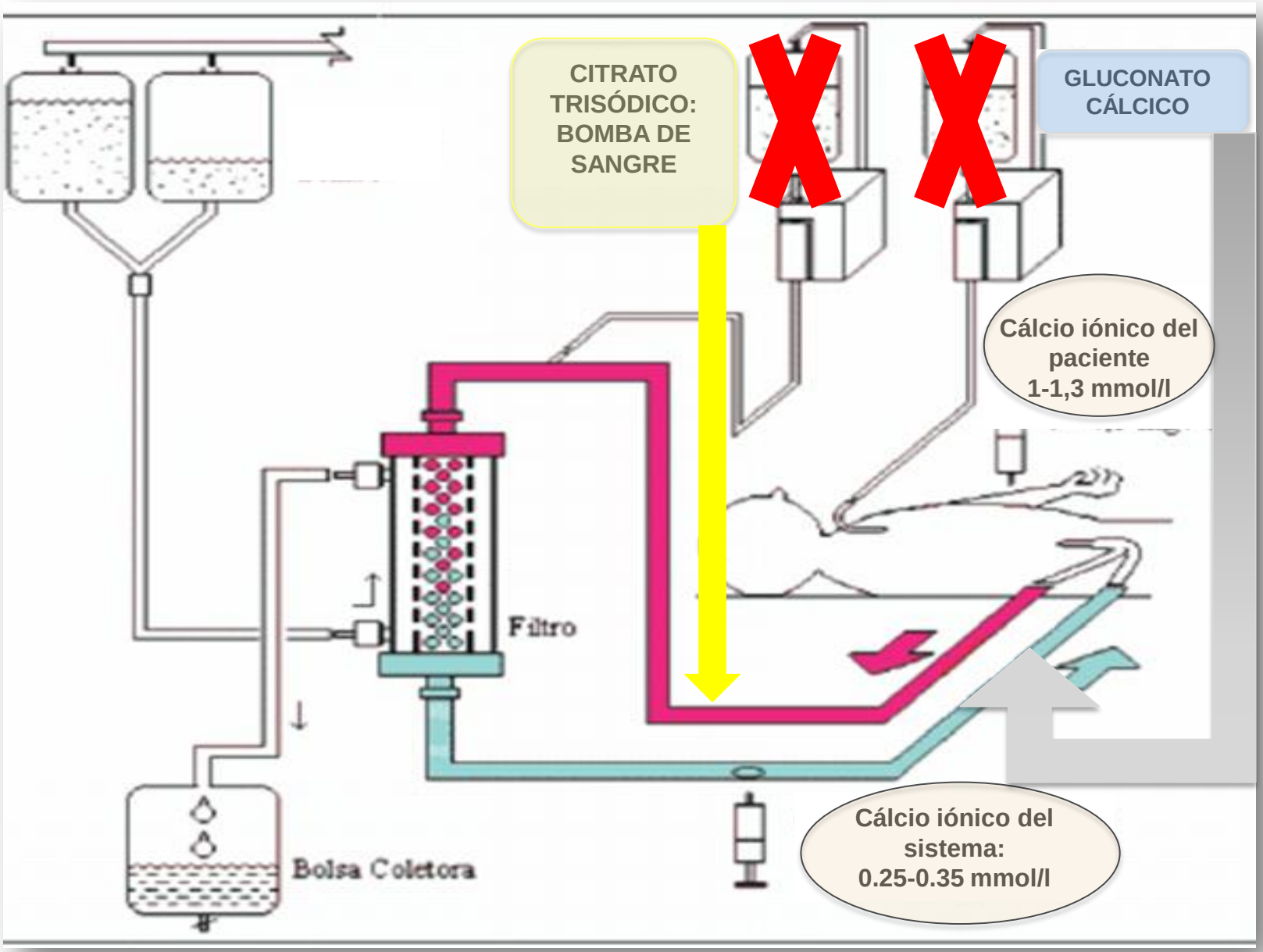
KDIGO Clinical Practice Guideline for Acute Kidney Injury

http://kdigo.org/home/guidelines/acute-kidney-injury/

1. Pacientes **sin riesgo** aumentado de sangrado o un deterioro de la coagulación y sin recibir coagulación sistémica efectiva, recomiendan:
   - El uso de citratos más que la heparina en pacientes que no tienen contraindicaciones para el uso de citratos (2B)
   - En pacientes con contraindicaciones para el uso de citratos, sugieren el uso de heparina no fraccionada o heparina de bajo peso molecular antes que otro tipo de anticoagulación (2C)

2. Para pacientes **con riesgo** aumentado de sangrado que no están recibiendo anticoagulación, durante las TCRR recomiendan:
   - Usar citratos antes que no anticoagular el sistema, siempre que no existan contraindicaciones para el uso de citrato (2C)
   - Evitar heparinización regional en pacientes con riesgo aumentado de sangrado (2C)

ESCOGER UN MONITOR

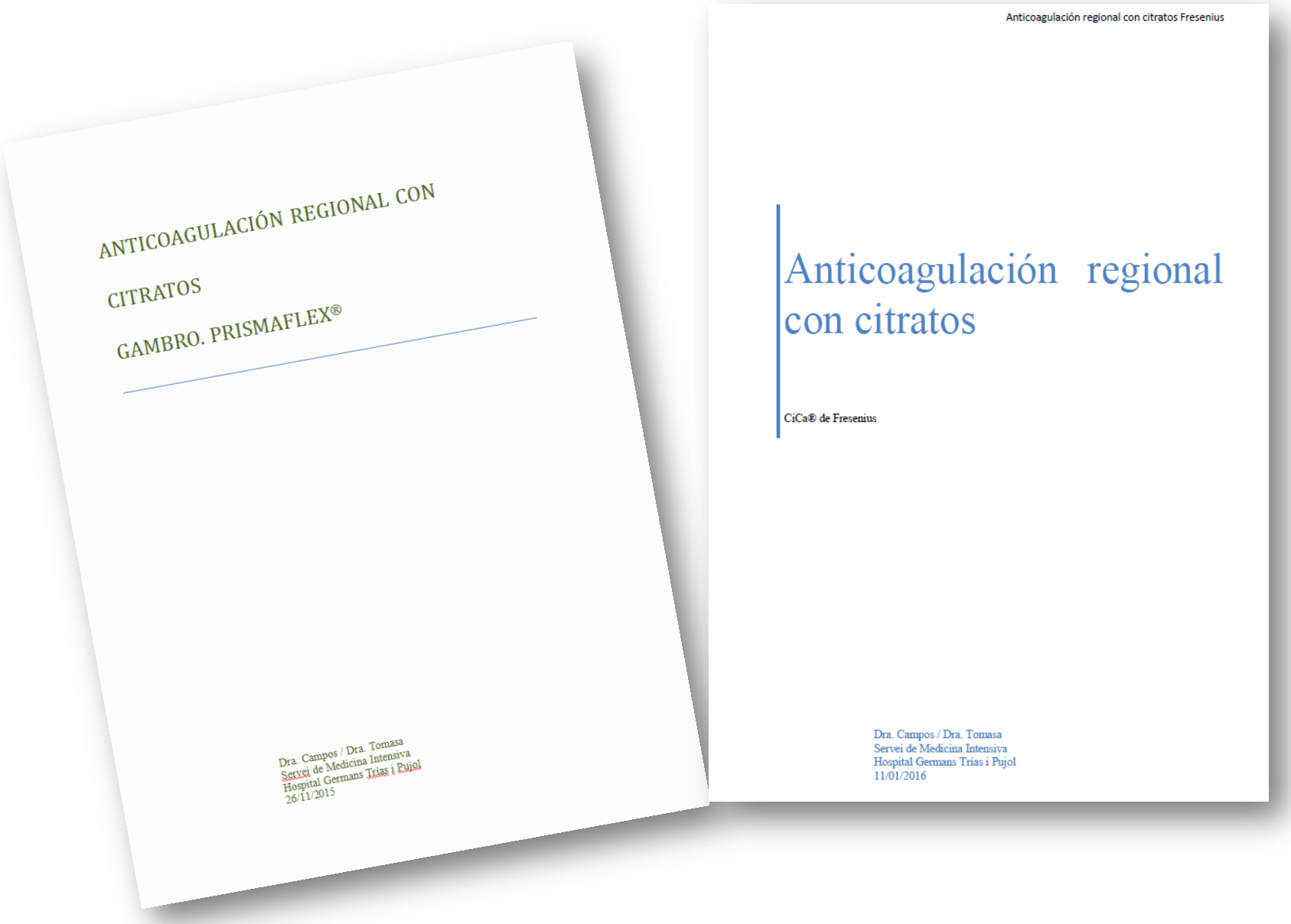

CITRATO TRISÓDICO: BOMBA DE SANGRE
GLUCONATO CÁLCICO
Cálcio iónico del paciente 1-1,3 mmol/l
Filtro
Bolsa Colectora
Cálcio iónico del sistema: 0.25-0.35 mmol/l

SOLUCIONES PARA LA ANTICOAGULACIÓN CON CITRATO

COMPOSICIÓN ESTANDAR LÍQUIDO DE DIÁLISIS	
Sodio	136-146
Potasio	0-4
Calcio	2,5-3,5
Magnesio	1-1,5
Cloro	96-115
Bicarbonato	35-45
Lactato	
Glucosa g/L	200-250

	Ci-Ca Dialysate k2	Ci-Ca Dialysate k4	Ci-Ca Dialysate K2 Plus	Ci-Ca Dialysate K4 Plus	PrismoOcal
Sodio	133	133	133	133	140
Potasio	2	4	2	4	0
Calcio	0	0	0	0	0
Magnesio	0,75	0,75	1	1	0,5
Cloro	116,5	118,5	115,75	117,75	106
Bicarbonato	20	20	20	20	32
Lactato					3
Glucosa g/L	100	100	100	100	0
Fosfato mmol/l			1,25	1,25	

PROTOCOLOS



ANTICOAGULACIÓN REGIONAL CON CITRATOS

GAMBRO. PRISMAFLEX®

Dra. Campos / Dra. Tomasa
Servei de Medicina Intensiva
Hospital Germans Trias i Pujol
26/11/2015

Anticoagulación regional con citratos Fresenius

Anticoagulación regional con citratos

CiCa® de Fresenius

Dra. Campos / Dra. Tomasa
Servei de Medicina Intensiva
Hospital Germans Trias i Pujol
11/01/2016

PAUTAR LA TERAPIA

- En función del monitor: HDVVC, HDFVVC
- Flujos: dependerán únicamente del peso del paciente

CON FRESENIUS: HDVVC

Dosis de citrato 4mmol/l (CVVHD EMIC2)

Peso Kg	Flujo sangre ml/min	Flujo Diálisis ml/h
<60	80	1600
60-90	100	2000
>90	120	2400

CON HOSPAL GAMBRO: HDFVVC

Peso	Qs	Qd	Qr-post	Dosis de UF
50	100	1000	200	37 ml/Kg/h
60	110	1100	400	37 ml/Kg/h
70	120	1200	500	35 ml/Kg/h
80	130	1300	500	33 ml/Kg/h
90	140	1400	500	31 ml/Kg/h
100	150	1500	600	31 ml/Kg/h
110	160	1600	700	30 ml/Kg/h
120	170	1700	800	30 ml/Kg/h
130	180	1800	1000	30 ml/Kg/h

PAUTAR LA TERAPIA

¿Que dosis de calcio necesito?

- Ca postfiltro 0,25-0,35 mmol/l
- Ca iónico del pacientes 1-1,3 mmol/l

CONTROLES

Calcio iónico (paciente y postfiltro)	**Antes, 1 hora tras iniciar terapia, cada 4/6 horas**
Calcio total	A diario
pH y HCO3	Cada 6 horas
Na, K, Cl	Cada 6 horas
Magnesio y Fosfato	A diario

Schwarzer *et al. Critical Care* (2015) 19:321
DOI 10.1186/s13054-015-1027-1

CRITICAL CARE

RESEARCH Open Access

Discrepant post filter ionized calcium concentrations by common blood gas analyzers in CRRT using regional citrate anticoagulation

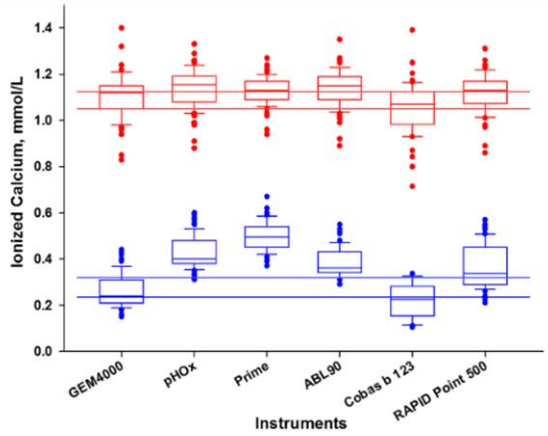
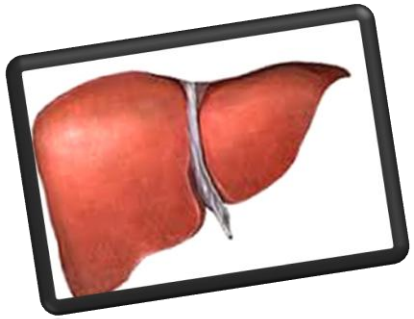
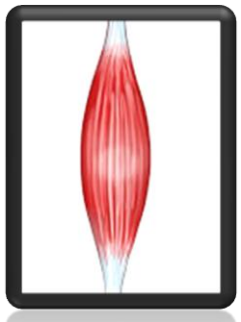


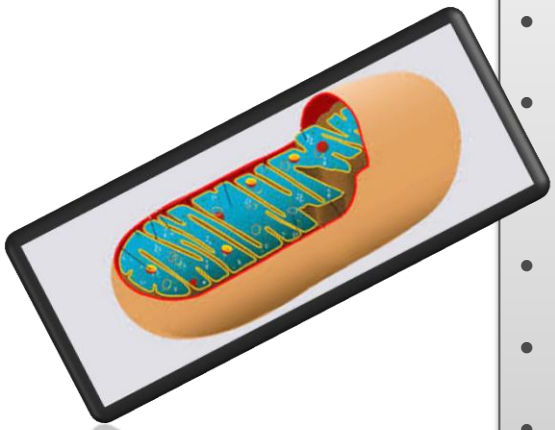
Fig. 2 Measurements of ionized calcium illustrated as box plots for systemic and post filter samples by instrument. *Lower row* (*blue boxplots*), post filter samples; *upper row* (*red boxplots*), systemic samples. *Horizontal lines*, respective upper and lower limits of target intervals according to previous publications [7, 8]

From a clinical point of view RCA in CRRT can be controlled by using the systemic iCa and disregarding the post filter iCa. The post filter iCa should only be used to prove that the blood is anticoagulated but not to control citrate dose. Lowering citrate flow because of false low post filter iCa concentrations would increase the risk of coagulation in the extracorporeal circuit. Increasing citrate flow because of false high post iCa concentrations might provoke citrate intoxication. Both are potentially life-threatening complications in critically ill patients.

CONTRAINDICACIONES







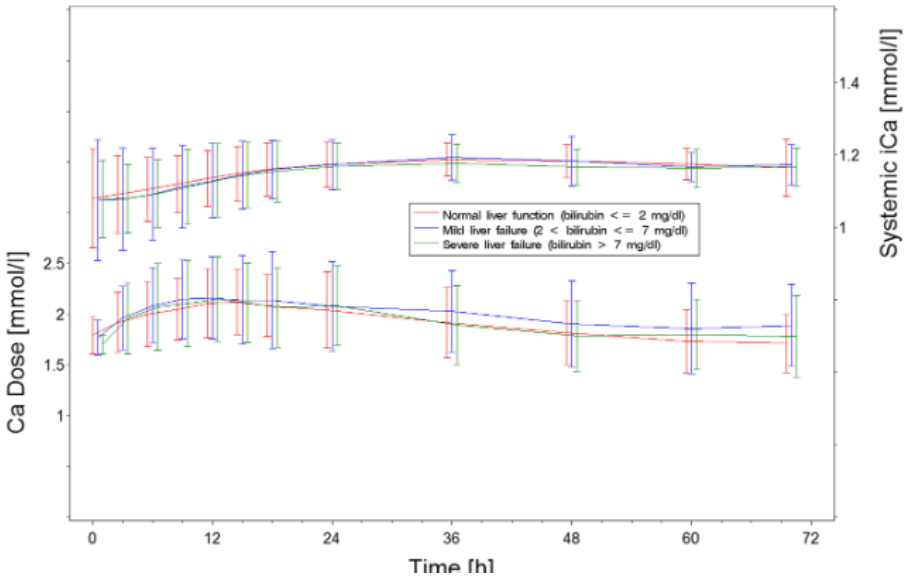
- **Alergia al citrato**
- Disfunción hepática moderada-severa
- Transfusión de hemoderivados (>2500ml)
- Hemofiltración con volumen >50 ml/kg
- Elevados flujos de sangre > 200 ml/min
- Shock séptico + acidosis láctica (hipoperfusión tisular severa)
- Alteraciones en “la mitocondria”: intoxicación por tóxicos mitocondriales (etilenglicol…), enfermedades mitocondriales (MELAS, MERRF…)

Slowinski et al. Critical Care (2015) 19:349
DOI 10.1186/s13054-015-1066-7

CRITICAL CARE

RESEARCH Open Access

Safety and efficacy of regional citrate anticoagulation in continuous venovenous hemodialysis in the presence of liver failure: the Liver Citrate Anticoagulation Threshold (L-CAT) observational study



	Normal liver function (bilirubin ≤2 mg/dl)		Mild liver failure (bilirubin 2–7 mg/dl)		Severe liver failure (bilirubin ≥7 mg/dl)	
	Start	End	Start	End	Start	End
Number of patients	48		43		42	
Total bilirubin (mg/dl)	0.8 ± 0.4	1.1 ± 0.8	3.6 ± 1.3	4.5 ± 3.2	18.4 ± 13.0	17.0 ± 11.2
Aspartate aminotransferase (U/L)	193 ± 454	196 ± 414	716 ± 1864	636 ± 2021	391 ± 1206	391 ± 1336
Alanine aminotransferase (U/L)	154 ± 602	104 ± 161	344 ± 766	361 ± 961	210 ± 476	199 ± 505
Creatinine (mg/dl)	3.5 ± 1.5	1.4 ± 0.7	2.7 ± 1.4	1.4 ± 0.6	2.3 ± 1.1	1.6 ± 1.9
Urea (mg/dl)	123 ± 75	53 ± 24	102 ± 59	49 ± 25	135 ± 69	74 ± 40
Sodium (mmol/L)	141 ± 5	142 ± 4	140 ± 6	142 ± 4	140 ± 7	140 ± 4
Potassium (mmol/L)	4.7 ± 0.7	4.3 ± 0.5	4.6 ± 0.8	4.4 ± 0.6	4.5 ± 0.7	4.3 ± 0.6
Phosphorus (mmol/L)	1.8 ± 0.9	0.8 ± 0.3	1.7 ± 0.8	0.8 ± 0.4	1.5 ± 0.7	1.0 ± 0.5
Magnesium (mmol/L)	1.1 ± 0.4	0.9 ± 0.1	1.0 ± 0.4	0.9 ± 0.2	1.0 ± 0.3	1.0 ± 0.2
Hematocrit (%)	30 ± 4	31. ±4	29 ± 5	30 ± 6	28 ± 5	29 ± 4
Platelet count (count/nl)	195 ± 170	159 ± 164	109 ± 85	92 ± 87	103 ± 91	98 ± 85
INR	1.7 ± 1.0	1.4 ± 0.7	1.5 ± 0.3	1.4 ± 0.4	1.8 ± 0.7	1.7 ± 0.6
aPTT (s)	52 ± 20	46 ± 10	50 ± 12	49 ± 17	59 ± 25	54 ± 16
Serum protein (g/dl)	4.9 ± 1.1	5.2 ± 1.0	4.8 ± 1.1	5.0 ± 1.0	5.2 ± 1.1	5.3 ± 1.2
Serum albumin (g/dl)	2.2 ± 0.6	2.2 ± 0.6	2.1 ± 0.6	2.3 ± 0.9	2.3 ± 0.6	2.3 ± 0.6
Total calcium (mmol/L)	2.0 ± 0.3	2.1 ± 0.2	2.0 ± 0.4	2.3 ± 0.3	2.1 ± 0.3	2.3 ± 0.3
Ratio total/ionized Ca^{2+}	1.8 ± 0.1	1.9 ± 0.1	1.8 ± 0.1	1.9 ± 0.2	1.8 ± 0.2	2.0 ± 0.3
Postfilter iCa (mmol/L)	0.27 ± 0.05	0.28 ± 0.03	0.27 ± 0.06	0.29 ± 0.03	0.30 ± 0.03	0.30 ± 0.02

aPTT activated partial thromboplastin time, *iCa* ionized calcium, *INR* international normalized ratio
Mean ± SD

Key messages

- This citrate anticoagulation protocol for CVVHD can be used safely in patients with LF.
- It yields excellent filter patency and thus can be recommended as first-line anticoagulation.
- Citrate accumulation in patients with LF is rare, but caution is needed, particularly in patients with impaired cellular respiration.

Schwarzer *et al. Critical Care* (2015) 19:321
DOI 10.1186/s13054-015-1027-1

CRITICAL CARE

RESEARCH Open Access

Discrepant post filter ionized calcium concentrations by common blood gas analyzers in CRRT using regional citrate anticoagulation

Patrik Schwarzer[1], Sven-Olaf Kuhn[2], Sylvia Stracke[3], Matthias Gründling[2], Stephan Knigge[2], Sixten Selleng[2], Maximilian Helm[1], Sigrun Friesecke[4], Peter Abel[4], Anders Kallner[5], Matthias Nauck[1] and Astrid Petersmann[1*]

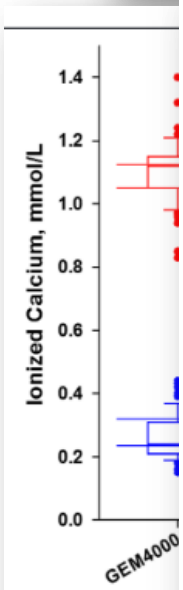
Honore *et al. Critical Care* (2015) 19:386
DOI 10.1186/s13054-015-1103-6

CRITICAL CARE

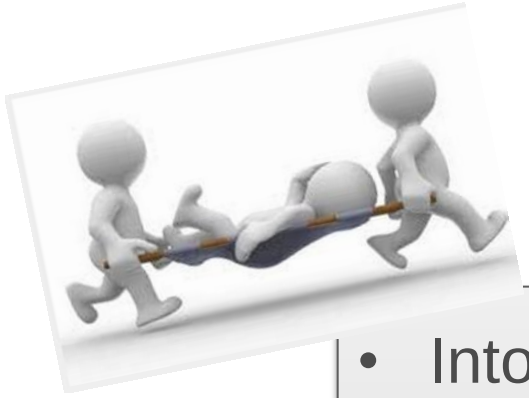
LETTER Open Access

Optimizing citrate dose for regional anticoagulation in continuous renal replacement therapy: measuring citrate concentrations instead of ionized calcium?

Patrick M. Honore*, Rita Jacobs, Inne Hendrickx, Elisabeth De Waele, Viola Van Gorp and Herbert D. Spapen



COMPLICACIONES



- Intoxicación por citratos **LA MAS GRAVE**
- Alteración equilibrio Ácido-Base **LA MAS FRECUENTE**
- Diselectrolitemias:
  - Hiper/hipocalcemia
  - Sodio
  - Potasio
  - Fósforo
  - Magnesio

COMPLICACIONES

INTOXICACIÓN POR CITRATO

- **Elevación del ratio CaT/Cai > 2,5**
- Fallo hepático agudo
- Alcalosis metabólica
- Aumento de anión gap

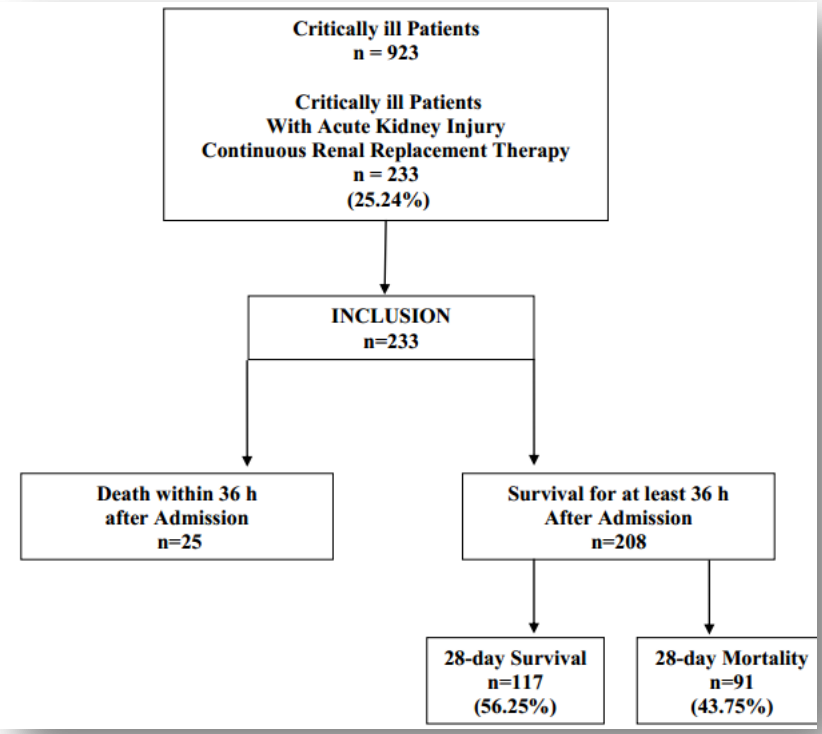
❑ Implicación pronóstica

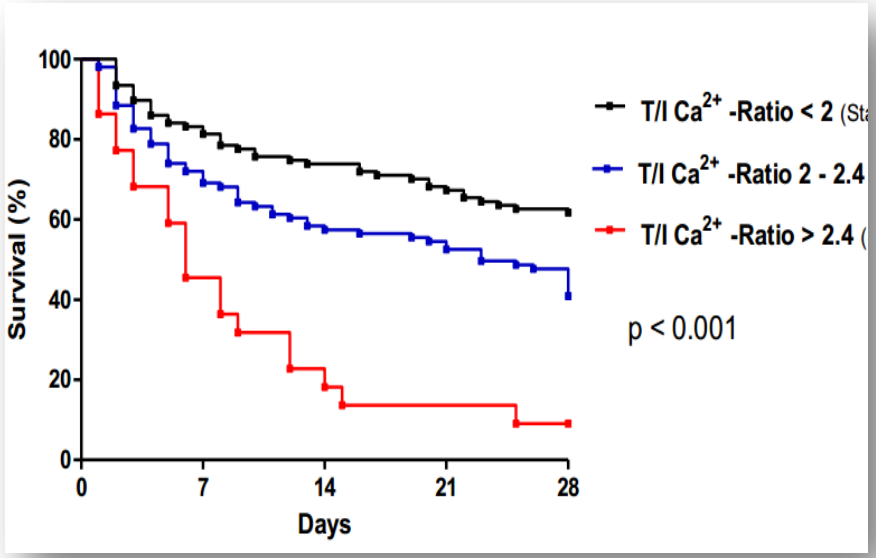
Link *et al. Critical Care* 2012, **16**:R97
http://ccforum.com/content/16/3/R97

CRITICAL CARE

RESEARCH Open Access

Total-to-ionized calcium ratio predicts mortality in continuous renal replacement therapy with citrate anticoagulation in critically ill patients





Nurmohamed et al. BMC Nephrology 2013, 14:89
http://www.biomedcentral.com/1471-2369/14/89

BMC Nephrology

RESEARCH ARTICLE Open Access

Continuous venovenous haemofiltration with citrate-buffered replacement solution is safe and efficacious in patients with a bleeding tendency: a prospective observational study

Table 3 Clinical and biochemical characteristics of patients with and without citrate accumulation

	Citrate accumulation n = 9	No citrate accumulation n = 88	P
Prescribed dose (ml/kg/h)	30 ± 4	24 ± 5	0.001
At start CVVH			
pH	7.31 ± 0.08	7.32 ± 0.10	0.77
Lactate (mmol/l)	6.2 ± 3.6	3.5 ± 3.4	0.17
Anion gap (mmol/l)	22 ± 6	19 ± 6	0.13
Alanine aminotransaminase (U/l)	652 ± 1031	227 ± 424	0.03
Aspartate aminotransaminase (U/l)	1861 ± 3305	409 ± 942	0.01
Gamma-glutamyl transferase (U/l)	86 ± 97	86 ± 113	0.99
Alkaline phosphatase (U/l)	123 ± 74	132 ± 154	0.80
Bilirubin (μmol/l)	133 ± 133	53 ± 106	0.21
Lactate dehydrogenase (U/l)	1396 ± 1088	1626 ± 3336	0.73

Table 3 Clinical and biochemical characteristics of patients with and without citrate accumulation

	Citrate accumulation n = 9	No citrate accumulation n = 88	P
Anion gap (mmol/l)			
t = 0 h	22 ± 6	19 ± 6	0.34
t = 6 h	22 ± 5	21 ± 5	0.35
t = 12 h	20 ± 7	20 ± 6	0.96
Hospital mortality	6 (86)	50 (59)	0.02

COMPLICACIONES

ALTERACIONES EN EL EQUILIBRIO ÁCIDO-BASE

Alcalosis metabólica:

- Por la metabolización de citrato a bicarbonato

Disminuir el flujo de sangre o incrementar aclaramiento de citrato (aumentando flujo de diálisis)

Acidosis metabólica

- Sospechar acumulación de citrato si el ratio CaT/Cai >2.5
- Valorar interrumpir la técnica si disfunción hepáptica grave

Schilder et al. Critical Care 2014, 18:472
http://ccforum.com/content/18/4/472

CRITICAL CARE

RESEARCH Open Access

Citrate anticoagulation versus systemic heparinisation in continuous venovenous hemofiltration in critically ill patients with acute kidney injury: a multi-center randomized clinical trial

	Citrate (n = 66)	Heparin (n = 73)	*P*-value
Safety, discontinuation of study anticoagulant			
Within 72 h	2 (3)	9 (12)	0.06
Bleeding episode	0	2 (22)	
HIT	0	2 (22)	
Frequent filter failure	0	3 (33)	
Citrate accumulation	2 (100)	0	
Miscellaneous	0	2 (22)	
Within 28 days	5 (8)	24 (33)	<0.001
Bleeding episode	0	8 (33)	
HIT	0	6 (25)	
Frequent filter failure	0	7 (29)	
Citrate accumulation	4 (80)	0	
Miscellaneous	1 (20)	3 (13)	
Bleeding episode within 28 days	3 (5)	10 (14)	0.08
Requirement of >2 packed cells	2 (3)	4 (6)	0.68
Metabolic derangements, during first 72 hours of therapy			
pH >7.50	1 (2)	0	1.00
Sodium >150 mmol/L	4 (7)	3 (5)	0.71
Magnesium <0.7 mmol/L	8 (15)	6 (9)	0.40

RESEARCH Open Access

Regional citrate anticoagulation in cardiac surgery patients at high risk of bleeding: a continuous veno-venous hemofiltration protocol with a low concentration citrate solution

Santo Morabito[1*], Valentina Pistolesi[1], Luigi Tritapepe[2], Laura Zeppilli[1], Francesca Polistena[1], Emanuela Strampelli[1] and Alessandro Pierucci[1]

Morabito *et al. Critical Care* 2012, **16**:R111
http://ccforum.com/content/16/3/R111

Table 3 Main metabolic and electrolyte parameters throughout RCA-CVVH days.

	Days on RCA				
	1	2	3	4	Last day
Systemic Ca^{++} (mmol/l)	1.2 (1.09-1.36)	1.2 (1.14-1.25)	1.19 (1.15-1.24)	1.16 (1.12-1.26)	1.19 (1.13-1.24)
Circuit Ca^{++} (mmol/l)	0.39 (0.33-0.43)	0.37 (0.31-0.4)	0.32 (0.28-0.37)**	0.35 (0.31-0.39)	0.34 (0.32-0.39)
Systemic sodium (mmol/l)	136 (134-139.2)	135 (133-138)	134 (132-138)*	134 (131.7-136)*	135 (134-136)
Estimated citrate load (mmol/hour)	11.3 (10.1-12.4)	11.3 (10.2-12.3)	11.3 (10.1-12.5)	11.3 (10.2-12.5)	10.7 (10.1-11.9)
Calcium Ratio	1.88 (1.78-2.04)	1.96 (1.87-2.04)	1.96 (1.84-2.1)	1.92 (1.82-2.1)	2 (1.89-2.08)
pH (units)	7.4 (7.35-7.43)	7.4 (7.36-7.42)	7.4 (7.34-7.43)	7.4 (7.35-7.43)	7.41 (7.37-7.43)
Systemic bicarbonates (mmol/l)	22.9 (20.6-23.9)	22 (20.9-22.8)	22 (20.7-23.2)	21.4 (20.2-23.3)	22 (20.4-23.2)
Base excess	-3 (-4.7 to -1.1)	-3.2 (-3.8 to -2)	-3.1 (-4.1 to -2)	-3 (-3.5 to -1.6)	-2.5 (-4 to -1)
Systemic lactate (mmol/l)	1.3 (1-1.8)	1.2 (0.9-1.5)	1.05 (0.8-1.25)	1 (0.9-1.3)	1.1 (0.7-1.65)

Data are expressed as median (interquartile range). All points of considered parameters were not significant, except for time day 3 versus day 1 of circuit Ca^{++} (** $P < 0.02$) and for time day 3 and 4 versus day 1 of systemic sodium (* $P < 0.05$). RCA-CVVH, regional citrate anticoagulation-continuous veno-venous hemofiltration.

Stucker *et al. Critical Care* (2015) 19:91
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CRITICAL CARE

RESEARCH Open Access

Efficacy and safety of citrate-based anticoagulation compared to heparin in patients with acute kidney injury requiring continuous renal replacement therapy: a randomized controlled trial

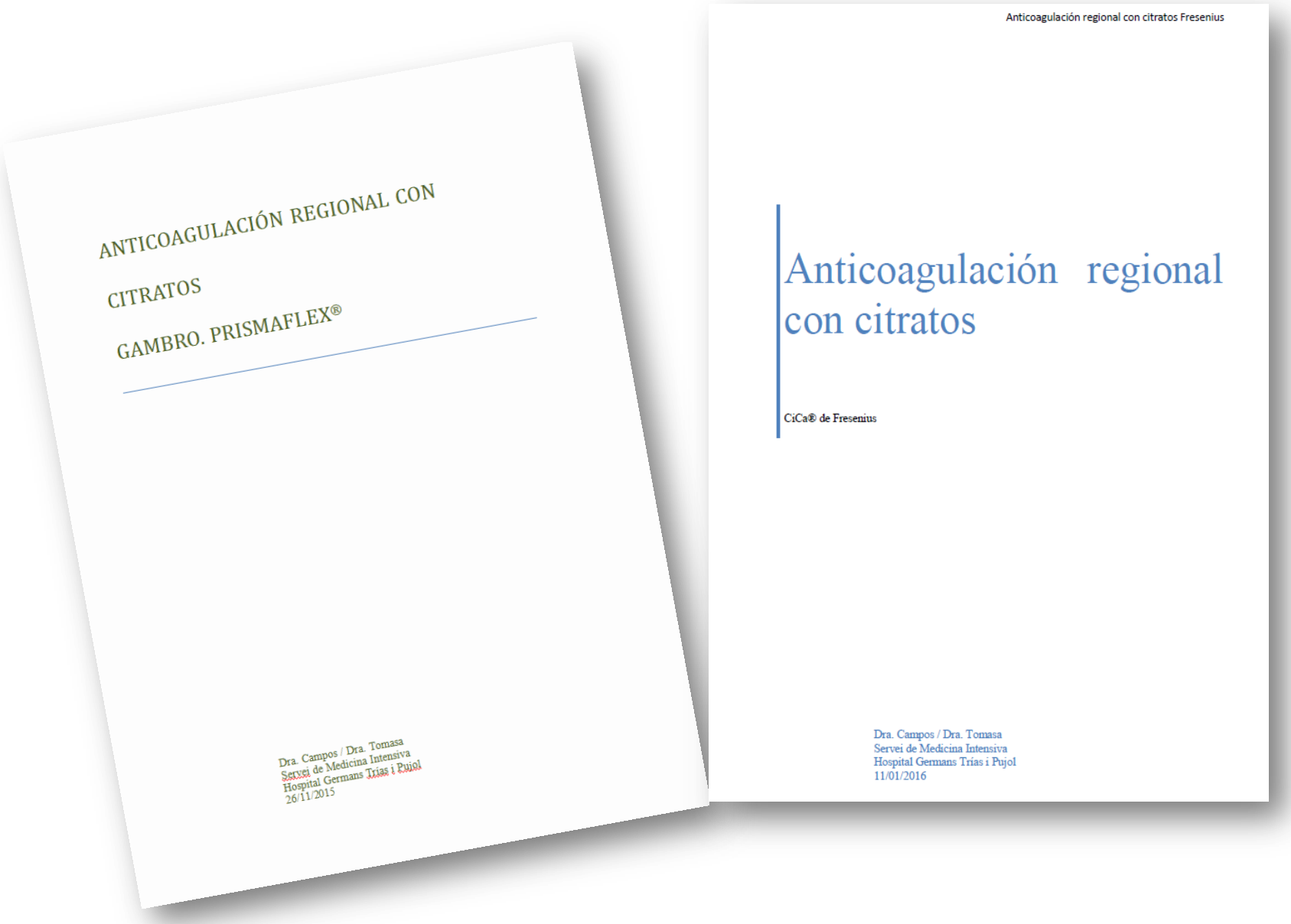
Fabien Stucker[1†], Belen Ponte[1†], James Tataw[1], Pierre-Yves Martin[1], Hannah Wozniak[2], Jérome Pugin[2] and Patrick Saudan[1*]

pH, day 1	7.32 (0.10)	7.31 (0.11)
Bicarbonate, mmol/L, day 1	18 (4.6)	19 (7.2)
Na, mmol/L, day 1	136 (15)	138 (7)
Chloride, mmol/L, day 1	104 (15)	108 (7)
Potassium, mmol/L, day 1	6 (14)	5.3 (5.6)
Lactate, mmol/L, day 1	1.3 (0.9 to 2.9)	1.3 (0.8 to 1.8)
Total calcium, mmol/L, day 3	2.52 (0.19)	2.41 (0.22)
Ionized calcium, mmol/L, day 3	1.14 (0.10)	1.20 (0.11)
pH, day 3	7.40 (0,06)	7.41 (0.06)
Bicarbonate, mmol/L, day 3	23.71 (1.81)	25.17 (4.31)
Na, mmol/L, day 3	138 (3.37)	138 (4)
Chloride, mmol/L, day 3	104 (3.4)	107 (4)
Potassium, mmol/L, day 3	4 (0.52)	4.3 (0.6)
Lactate, mmol/L, day 3	1.4 (0.9 to 2.2)	1.1 (0.9 to 1.4)
Side effects	32	27
Bleeding	0	4 (8)
HIT	1 (2)	2 (4)
Filter clotting	3 (6)	18 (37)
Metabolic disorders:	14	3
Metabolic alcalosis	3	0
Respiratory alkalosis	0	1
Metabolic acidosis	3	1
Severe hypocalcemia	6	1
Ca total/calcium ion ratio >2.5	1	0
CRRT, days	3 (2 to 6)	3 (2 to 5)
ICU, days	7 (4 to 15)	7 (4 to 12)
Hospital, days	22 (6 to 35)	16 (9 to 30)
Survival at 28 days	43 (80)	36 (74)
Survival at 90 days	40 (74)	35 (73)

PUNTOS CLAVE

- ❑ Mayor duración
- ❑ Mayor dosis administrada
- ❑ Menos eventos hemorrágicos
- ❑ Coste-efectivo
- ❑ Adaptable a distintos objetivos de tratamiento

PROTOCOLOS



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That's all Folks!