The Children's Hospital

University of Colorado
Denver | Anschutz Medical Campus

Magnesium Supplementation During Pediatric Apheresis Procedures

F. Bernadette West, MD

Assistant Professor of Pathology, University of Colorado Denver, Anschutz Medical Campus

Associate Medical Director, Transfusion Medicine, The Children's Hospital in Aurora

The Children's Hospital

Outline

- Citrate
- Anticoagulant Options: TPE
- Citrate: Primary and Side Effects
- Cases
- Conclusions

Citrate

- A ubiquitous acid
  - Naturally occurring
  - Food/beverage/other industry
  - Metabolism
  - Laboratory and blood banking
    - 1914 Albert Hustin: first use of citrate to anticoagulate blood
    - Continuous Renal Replacement Therapy and Apheresis

Anticoagulant Options:TPE

Citrate

- Salt or ester of citric acid
- Half-life 5.5 minutes
- Local anticoagulation
- Largely metabolized by mitochondria in liver, kidneys, skeletal muscle → bicarbonate.
- Use of blood products → additional citrate exposure

Heparin

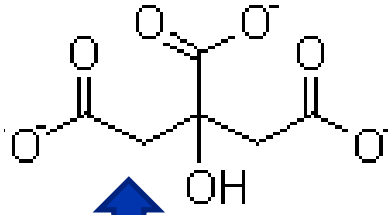
- Glycosaminoglycan with anticoagulant properties
- Half-life 90 minutes
- Systemic anticoagulation
- Partially metabolized in liver → uroheparin; much is excreted unchanged
- Possible increased risk of hemorrhage, Heparin-Induced Thrombocytopenia and Thrombosis (HIT, HITT)

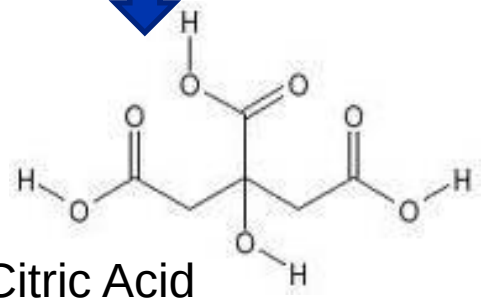
Citrate and Heparin

Anticoagulant Options: TPE

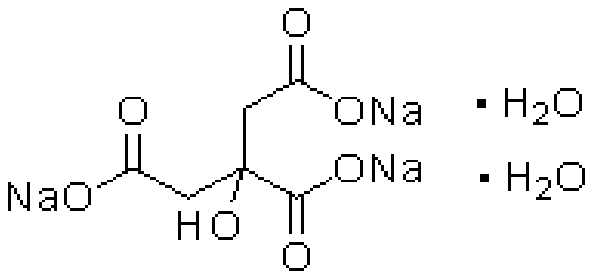
Citrated Solutions

Citrate ion





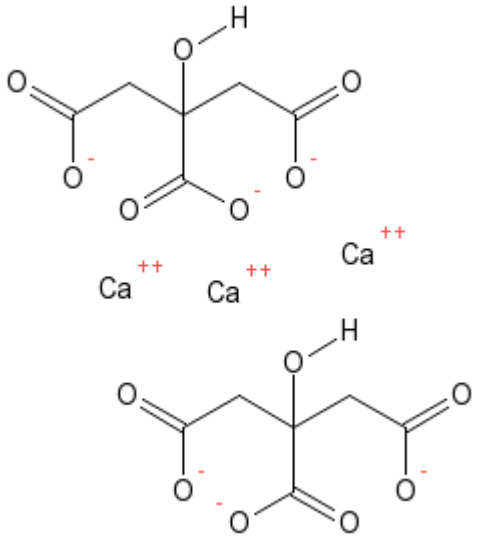
Citric Acid



Sodium citrate dihydrate

- ACD-A
  - 3% citrate solution
  - Ratio of WB to AC of 9:1 to 14:1
- ACD-B
  - 2% citrate solution
  - Ratio of 6:1 or 9:1
- TCA
  - 4% trisodium citrate anticoagulant
  - Leukapheresis procedures, CRRT

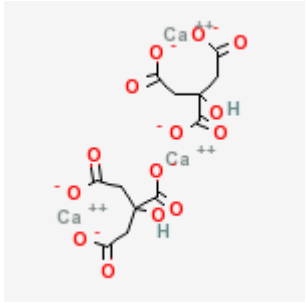
Citrate: Primary Effects



- Major effect: suspension of coagulation cascade by binding ionized calcium in 2: 3 ratio
  - Metabolized quickly by liver → bicarbonate
    - 1 citrate → 3 bicarb

- Binds ionized magnesium which is also important in the coagulation cascade

- Thought to reduce leukocyte and monocyte activation as they pass through the extracorporeal circuit (Davenport et.al.)



Citrate: Side Effects

- "Citrate toxicity": similar to hypovolemic and vasovagal reactions:
  - shivering, lightheadedness, fainting, flatus, nausea, vomiting, diarrhea

- Citrate chelates metal divalent cations: Ca^{2+}, Mg^{2+} ,Zn^{2+}
  - Hypocalcemia
  - Hypomagnesemia
  - Metabolic alkalosis (hepatic dysfunction and large citrate infusions) and hypernatremia (more of a problem with TCA)

(Symptomatic) Electrolyte Deficiencies

Hypomagnesemia

Common symptoms (mild): Muscular weakness, Tremors, Seizure, Paresthesias,Tetany, Positive Chvostek sign and Trousseau sign, Vertical and horizontal nystagmus, Nonspecific T-wave changes - U waves, nonspecific ECG changes, including ST-segment depression. Severe magnesium deficiency may cause PR prolongation or widened QRS complexes. Tachycardia, premature beats. Prolonged QT and QU interval, Repolarization alternans, V.fib, PVCs. Clinically may see hypokalemia (up to 60% of the time) and hypocalcemia.

Hypocalcemia

Common symptoms (mild): tingling, oral and peripheral paresthesias, twitching, tremor. Moderate / severe: seizure, carpopedal spasm, tetany, cardiac arrhythmias,

Hypokalemia

Common symptoms (mild):Palpitations, Skeletal muscle weakness or cramping, Paralysis, paresthesias, Constipation, Nausea or vomiting, Abdominal cramping , Polyuria, nocturia, or polydipsia, Psychosis, delirium, or hallucinations, Depression. Severe hypokalemia may include the following:Signs of ileus, Hypotension, Ventricular arrhythmias, Cardiac arrest, Bradycardia or tachycardia, Premature atrial or ventricular beats, etc. Clinically may see hypomagnesemia.

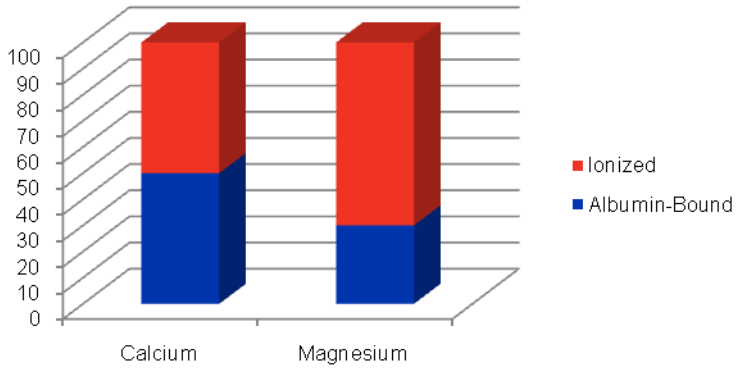
Calcium and Magnesium

Total Calcium = bound + ionized

- 40% bound (albumin) + 10% complexed (bicarb, phosphate, citrate)+ 50% free

Normal range values (serum)

- total calcium: 9-10.5 mg/dL
- ionized calcium: 1.1-1.4 mmol/L



Total Magnesium = bound + ionized

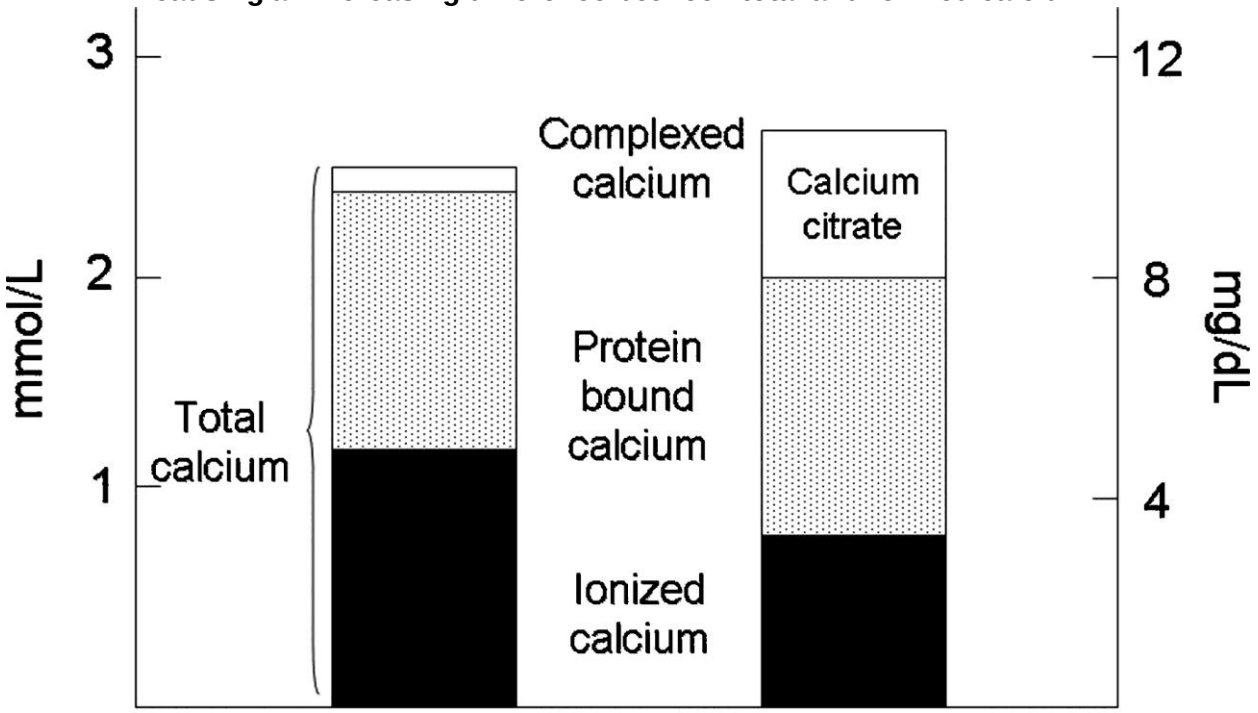
- 29% bound + 71% free

Normal Value ranges (serum)

- total magnesium: 1.5-2.3mg/dL
- ionized magnesium: 0.45-.60 mmol/L (Nova analyzer)

Ionized fractions represent the biologically active and available component

If citrate cannot be metabolized, then the total serum calcium concentration appears to increase, with a corresponding fall in ionized calcium due to the increase in calcium complexed with citrate, as the calcium–citrate complex is not directly measured it is termed the 'calcium gap' as causing an increasing difference between total and ionized calcium.



Davenport A , Tolwani A NDT Plus 2009;2:439-447

© The Author 2009. Published by Oxford University Press [on behalf of ERA -EDTA]. All rights reserved. For Permissions, please e-mail: journals.permissions@oxfordjournals.org

NDT PLUS Nephrology Dialysis Transplantation

Was It Just Bad Luck?

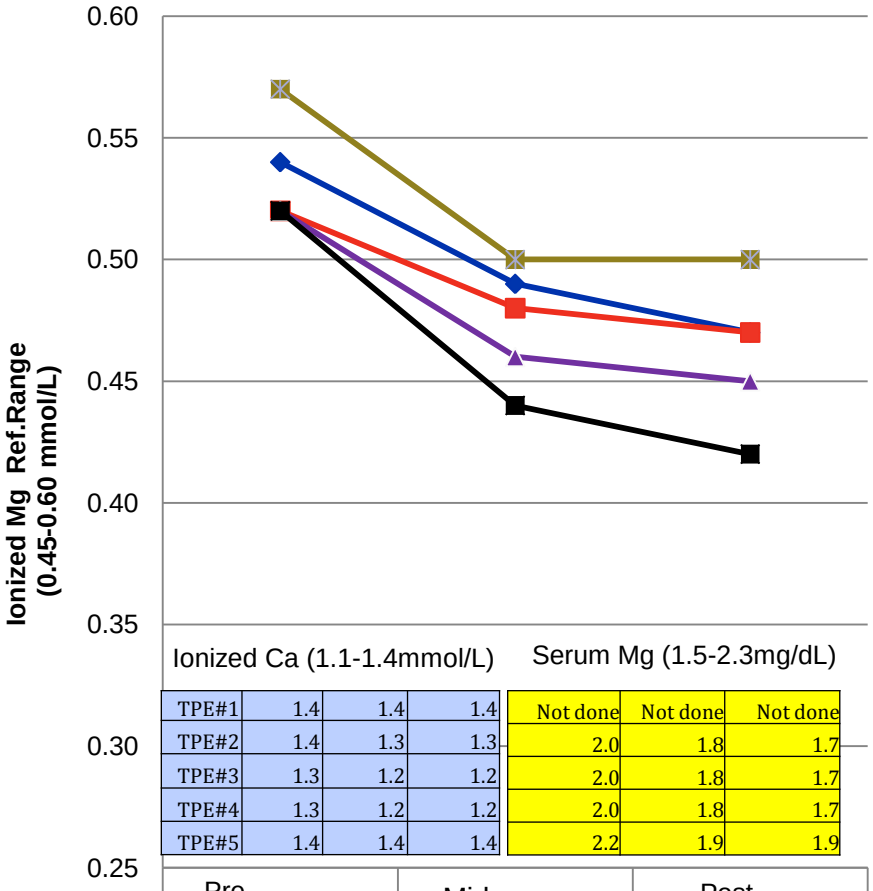
- Overall, TPE is a pretty safe procedure
- Several prior adverse events concerned us
  - 28 procedures on 7 patients
    - Dx: Transverse Myelitis, atypical Hemolytic Uremic Syndrome, two were status-post cardiac transplant, Chronic Inflammatory Demyelinating Polyradiculopathy (CIDP) and Warm AutoImmune Hemolytic Anemia
  - New-onset cardiac arrhythmias (2) and severe hypotension occurring during or just after plasma exchange (6)
  - Routine monitoring of ionized calcium with continuous calcium replacement
  - Absence of another clinical explanation…
  - What about magnesium levels?

We began measuring Mg but did not yet replenish…

- 24 procedures on 7 patients
  - 4 autoimmune, 3 s/p cardiac transplant

Patient 1 Female, 5y/o , 18kg, Indication for TPE: myasthenia gravis; replacement fluid: 5% human albumin; No Mg replacement

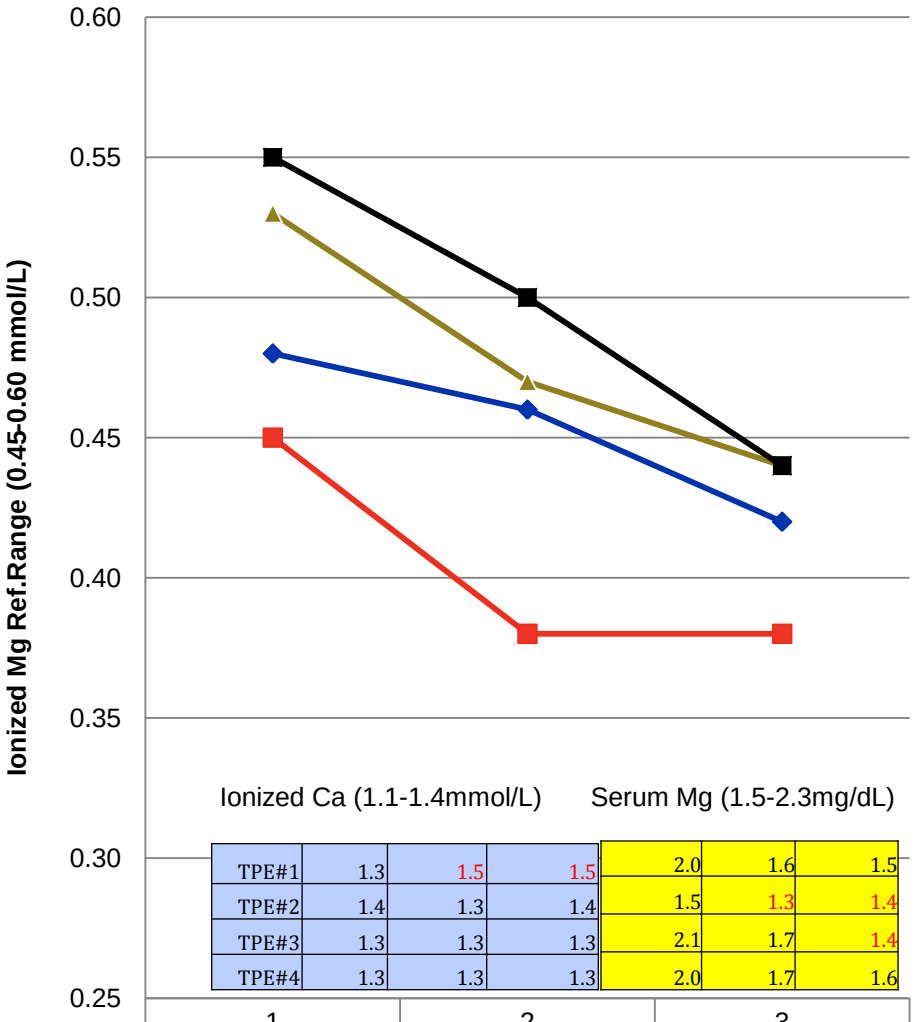
Comps: TPE 3 Hypotension; TPE 5 tachycardia to 130's bpm (baseline: 110s)



	Ionized Ca (1.1-1.4mmol/L)			Serum Mg (1.5-2.3mg/dL)		
TPE#1	1.4	1.4	1.4	Not done	Not done	Not done
TPE#2	1.4	1.3	1.3	2.0	1.8	1.7
TPE#3	1.3	1.2	1.2	2.0	1.8	1.7
TPE#4	1.3	1.2	1.2	2.0	1.8	1.7
TPE#5	1.4	1.4	1.4	2.2	1.9	1.9

	Pre	Mid	Post
TPE#1	0.54	0.49	0.47
TPE#2	0.52	0.48	0.47
TPE#3	0.52	0.46	0.45
TPE#4	0.52	0.44	0.42
TPE#5	0.57	0.50	0.50

Patient 2 Female, 26 y/o, 73.5kg, Indication for TPE; anti-HLA Abs; replacement fluid: 5% human albumin; No Mg replacement

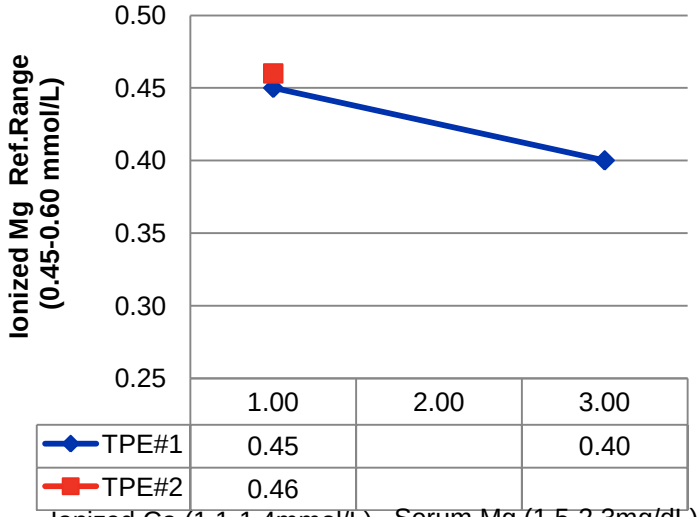


	Ionized Ca (1.1-1.4mmol/L)			Serum Mg (1.5-2.3mg/dL)		
TPE#1	1.3	1.5	1.5	2.0	1.6	1.5
TPE#2	1.4	1.3	1.4	1.5	1.3	1.4
TPE#3	1.3	1.3	1.3	2.1	1.7	1.4
TPE#4	1.3	1.3	1.3	2.0	1.7	1.6

	1	2	3
TPE#1	0.48	0.46	0.42
TPE#2	0.45	0.38	0.38
TPE#3	0.53	0.47	0.44
TPE#4	0.55	0.50	0.44

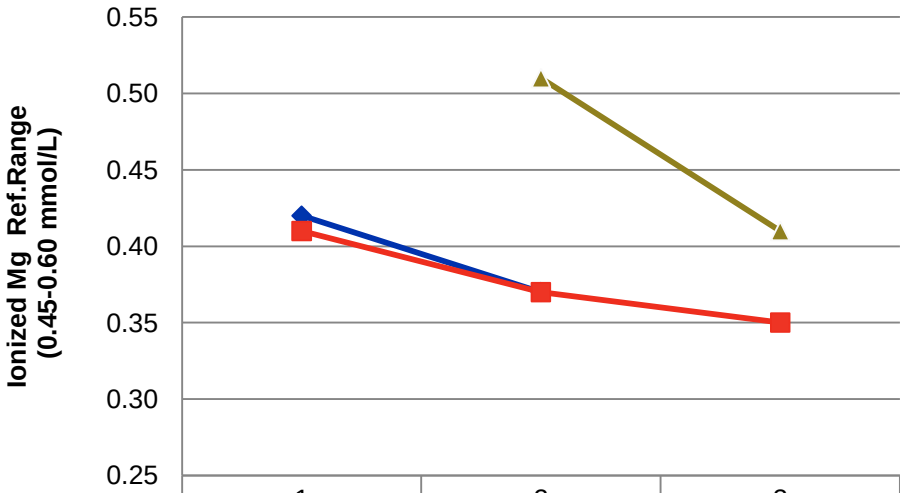
Patient 3 Female, 24y/o, 51kg,

Indication for TPE: anti-HLA Abs;
replacement fluid: 5% human albumin;
No Mg replacement



	1.00	2.00	3.00
TPE#1	0.45		0.40
TPE#2	0.46		

	Ionized Ca (1.1-1.4mmol/L)			Serum Mg (1.5-2.3mg/dL)		
TPE#1	1.3	1.2	1.3	Not done	Not done	Not done
TPE#2	1.3	1.3	1.3	1.3	1.2	
TPE#3	1.3	1.2	1.2	1.7	1.4	1.3
TPE#4	1.2	1.2	1.2	1.7	1.5	1.3



	1	2	3
TPE#1	0.42	0.37	
TPE#2	0.41	0.37	0.35
TPE#3		0.51	0.41

Patient 4 Female, 14y/o, 45kg, Indication for TPE: anti-HLA Abs; replacement fluid: 5% human albumin; No Mg replacement

	Ionized Ca (1.1-1.4mmol/L)			Serum Mg (1.5-2.3mg/dL)		
TPE#1	1.3	1.3	Not done	Not done	Not done	Not done
TPE#2	1.3	1.3	1.3	1.6	1.4	1.3
TPE#3	1.2	1.3	1.4	2.6	1.8	1.6

Ionized and Serum Mg and percentage change without supplementation:

Demonstrating lack of correlation between ionized and serum Mg measurements

PRE-I-MG 0.45-0.60 MMOL/L	MID-I-MG	% diff, from pre to mid iMg	POST-I-MG	% diff, pre to post iMg	PRE-S-MG 1.5-2.3 mg/dL	MID-S-MG	POST-S-MG	% diff, pre to post SMg
0.54	0.49	9.26	0.47	12.96				---
0.52	0.48	7.69	0.47	9.62	2.0	1.8	1.7	15
0.52	0.46	11.54	0.45	13.46	2.0	1.8	1.7	15
0.52	0.44	15.38	0.42	19.23	2.0	1.8	1.7	15
0.57	0.50	12.28	0.50	12.28	2.2	1.9	1.9	13.63
0.48	0.46	**4.17**	0.42	12.50	2.0	1.6	1.5	25
0.45	0.38	15.56	0.38	15.56	1.5	1.3	1.4	6.66
0.53	0.47	11.32	0.44	16.98	2.1	1.7	1.4	33.33
0.55	0.50	9.09	0.44	20.00	2.0	1.7	1.6	20
0.45	ND	---	0.40	11.11	ND	ND	ND	---
0.46	ND	---	ND	---	1.3	1.2	ND	---
ND	ND	---	ND	---	1.7	1.4	1.3	23.52
ND	ND	---	ND	---	1.7	1.5	1.3	23.59
0.42	0.37	11.90	clotted	---	ND	ND	ND	---
0.41	0.37	9.76	0.35	14.63	1.6	1.4	1.3	18.75
lab not rec'd	0.51	---	0.41	---	2.6	1.8	1.6	38.46
ND	ND	---	0.43	---	ND	ND	ND	
ND	ND	---	0.39	---	ND	ND	ND	---
		---		---	1.0	1.8	1.8	-80
		---		---	1.5	ND	ND	100
0.53	0.42	20.00	0.41	21.90	1.7	1.5	1.5	11.76
0.44	0.40	9.09	0.41	6.82	1.7	1.5	1.5	11.76
0.44	0.30	**31.82**	0.39	11.36	1.6	1.4	1.3	18.75
0.44	0.41	6.82	0.40	9.09	1.6	1.5	1.4	12.5

Legend: ND = not done; --- = unable to be calculated

Electrolyte Supplementation

- Serum magnesium levels may be low in patients with hypocalcemia.
- Hypocalcemia may not respond to calcium therapy if hypomagnesemia is not corrected.
- Severe hypomagnesemia causes hypocalcemia by impairing the secretion and action of parathormone (PTH).
- Measurement of ionized magnesium can prevent over or under dosing of magnesium supplements
- Consider oral supplementation for patients who are asymptomatic but have low levels.
- The use of cardiac monitors may reveal previously undetected arrhythmias due to apheresis procedures.

After supplementation

- Total of 68 procedures had magnesium levels monitored, *with* magnesium supplementation.
- Twelve patients (age 5 to 17 years; 9 with autoimmune disorder, 1 status-post cardiac transplant, 1 with atypical hemolytic uremic syndrome)
- Side effects were experienced by five patients (7 procedures): peripheral paresthesias, diarrhea, and transient (but severe) hypotension.
- No arrhythmias or other cardiac changes not explainable by underlying medical issues were encountered

Conclusions

- Incapacitated and very young patients may not be able to adequately voice their symptoms.
- Significant citrate-induced reduction of ionized magnesium has been observed in adult and pediatric populations during large-volume leukapheresis leading to the support of intra-procedural replenishment of magnesium (and calcium),
- Perhaps this standard of care should be extended to plasma exchange procedures.
- Plasma exchange procedures are much shorter in duration than leukaphereses but significant ion chelation still occurs.
- Prophylactic intravenous replacement of magnesium and calcium may be given to help avoid the side effects associated with the depletion of these ions during plasma exchanges.

References

Bolan CD, Yau YY, Cullis HC et al. Pediatric large-volume leukapheresis: a single institution experience with heparin versus citrate-based anticoagulant regimens. Transfusion 2004; 44;229-238.

Davenport A, Tolwani A. Citrate anticoagulation for continuous renal replacement therapy (CRRT) in patients with acute kidney injury admitted to the intensive care unit. Nephr Dial Transpl Plus 2009; 2:439-447.

Haddad S, Leitman SF, Wesley RA et.al. Placebo-controlled study of intravenous magnesium supplementation during large volume leukapheresis in healthy allogeneic donors. Transfusion 2005; 45:934-944.

- http://emedicine.medscape.com/article/921844-diagnosis (Pediatric Hypocalcemia)
- http://www.sigmaaldrich.com/catalog/ProductDetail.do?D7=0&N5=SEARCH_CONCAT_PNO%7CBRAND_KEY&N4=82581%7CFLUKA&N25=0&QS=ON&F=SPEC (chemical structure images)
- http://www.chemicalland21.com/lifescience/foco/CALCIUM%20CITRATE.htm (chemical structure images)
- http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=13136 (chemical structure images)