Management of Citrate Toxicity in Pediatric Patients

by
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Relevant Disclosures

- None
Learning Objectives

At the end of the session participants should be able to:

• Understand the known pathophysiologic factors that contribute to citrate toxicity in children
• Understand the range of management approaches by pediatric apheresis centers on the management of citrate toxicity.
• Construct potential approaches in dealing with this complication.
What is Citrate?

- **Definition**: salt or ester of citric acid
  - Chemical formula: $\text{C}_6\text{H}_5\text{O}_7^{3-}$ or $\text{C}_3\text{H}_5\text{O}^{\text{-}}\text{(COO)}_3^{3-}$
- **Intermediate in the Krebs cycle**
- **Capable of binding many cations**
  - Postulated by Sabbatani (1901) to bind calcium and to inhibit blood coagulation by lowering calcium levels in blood (Sabbatani, 1902)
- **NMR/X-ray diffraction studies (Glusker, 1980)**
  - 3 dimensional analysis of citrate binding to $\text{Ca}^{2+}$ (tridentate binding)
Sources of Citrate

- ACD-A solution used for anticoagulation
- Citrate in blood products
  - FFP (if used for plasma exchange)
  - RBC units (for erythrocytapheresis)
### Citrate Content of Various Anticoagulant-Preservative Formulations

<table>
<thead>
<tr>
<th></th>
<th>ACD</th>
<th>CPD/CPDA-1</th>
<th>AS-1</th>
<th>AS-3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Citrate Concentration (mg/dL)</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole Blood</td>
<td>280</td>
<td>246</td>
<td>206</td>
<td>274</td>
</tr>
<tr>
<td>Packed RBC</td>
<td>87</td>
<td>76</td>
<td>54</td>
<td>181</td>
</tr>
<tr>
<td>FFP</td>
<td>436</td>
<td>384</td>
<td>384</td>
<td>384</td>
</tr>
<tr>
<td><strong>Total Citrate (mg)</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole Blood</td>
<td>1451</td>
<td>1261</td>
<td>1261</td>
<td>1681</td>
</tr>
<tr>
<td>Packed RBC</td>
<td>200</td>
<td>176</td>
<td>176</td>
<td>596</td>
</tr>
<tr>
<td>FFP</td>
<td>976</td>
<td>843</td>
<td>843</td>
<td>843</td>
</tr>
</tbody>
</table>

*assumes 450 mL donation, Hct 41%, and no movement of citrate into cells. For ACD, CPD and CPDA-1 assumes the production of packed RBC with Hct 80%; FFP 230 mL; and platelet concentrates, 55 mL. For AS-1 and AS-3 assumes production of RBCs with final Hct 56%, FFP 230 mL and platelet concentrate 55 mL. (Modified from Table 2, Dzik and Kirkley, 1988)
Amount of Citrate in Replacement Fluids

- FFP: 17.4 mmol/L
- Albumin: 4.4 mmol/L
- Saline: 0 mmol/L
## Normal Adult Concentrations of Citrate and Ionized Calcium

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Citrate*</th>
<th>Ionized Calcium</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg/dL</td>
<td>0.9-2.5</td>
<td>4.5-5.4</td>
</tr>
<tr>
<td>mEq/L</td>
<td>0.14-0.39</td>
<td>2.3-2.7</td>
</tr>
<tr>
<td>mmol/L</td>
<td>0.047-0.130</td>
<td>1.1-1.4</td>
</tr>
</tbody>
</table>

*slightly higher in children and patients with renal/liver disease*
Control of Calcium Homeostasis

Citrate Clamp Experiments

Fig. 1. Blood ionized calcium (B-Ca\(^{2+}\)) concentrations (\(\bullet\); mean ± total SD, technical and biological) and serum parathyroid hormone-(1-84) [S-PTH-(1–84)] concentrations (\(\square\); mean ± SE) obtained during citrate clamp in 12 volunteers.

Fig. 2. B-Ca\(^{2+}\) concentrations (\(\triangle\); mean ± total SD, technical and biological) and S-PTH-(1–84) concentrations (\(\times\); mean ± SE) obtained during calcium + citrate clamp in 12 volunteers.

Control of Calcium Homeostasis

PTH response is related to the rate of decrease/increase of ionized calcium and the ionized Ca\(^{2+}\) concentration (Grant et al, 1990)
PTH Response to Hypocalcemia

• **Mobilization of calcium from bone:**

• **Enhancing absorption of calcium from the small intestine:**
  – Indirectly by via increased production of the active form of vitamin D in the kidney.
    • Induces synthesis of a calcium-binding protein in intestinal epithelial cells that facilitates efficient absorption of calcium into blood.

• **Suppression of calcium loss in urine:**
  – Via stimulation of tubular reabsorption of calcium.
  – PTH also stimulates loss of phosphate ions in urine.
Therapeutic Apheresis Citrate Related Complications in Children

• Published experience in children is limited
• Most publications relate to hematopoietic stem cell collection
• Limited information on the risk of complications in children, including normal physiologic response to electrolyte disturbances
Factors Affecting The Development of Citrate Toxicity

• **Type of Replacement Fluid**
  – Duration of procedure
  – Rate of infusion

• **Type of Anticoagulation**

• **Individual Variation**
  – Metabolism by liver and other tissues
  – Elimination by the kidney

• **Underlying Medical Conditions**

• **Age**
  – Especially newborns within the first 3 days of life, (Nincsoy et al., 1982)
Dincsoy et al.
J Pediatr 1982;100:277-283
RCT of IV magnesium supplementation in LVL adult PBSC donors (Haddad et al, Transfusion 2005;45:934-944)
Therapeutic Hemapheresis, “Protein and Biochemical Changes During Plasma Exchange”, pp 13-52, 1980
Citrate Infusion During PBSC Collection

Note: Inter-individual variability but consistency of procedures
Note: These are adult patients!

Bolan et al. Transfusion 2002;42:835-46
Major Electrolyte Effect of Citrate Infusion: Hypocalcemia

- **Symptoms:**
  - Most common: perioral/peripheral paresthesias
  - Less common: dysgeusia, nausea, light-headedness
  - Rare: shivering, twitching, tremors

- **Severe hypocalcemia:**
  - Continuous muscle contraction- involuntary carpopedal spasms, progressing to tetany (including laryngospasm/Grand mal seizures).
  - PE: Chvostek’s sign & Trousseau’s sign.

- **EKG:**
  - Prolongation of QT interval, widening QRS, new arrhythmias

**Exacerbated By:** hypothermia, liver disease/transplantation, renal disease, hyperventilation
Citrate Toxicity in Children Vs. Adults

- **Children are at higher risk:**
  - Lower TBV
    - Need for the inlet rate to be faster (in order to establish interface, especially for small children undergoing PBSC harvest)
    - Higher degree of error in calculation of TBV
      - Which may lead to higher inlet rates if TBV is over estimated
      - Inability to express early “classic” symptoms
  - In PBSC collections, need to potentially process more blood volumes because of higher CD34/kg dose requirements compared to adult protocols
Hypocalcemia: Major Potential Citrate Complication in Pediatric Procedures

- Quebec retrospective study: 1994 – 2002
  - 186 patients (<18 years old), 1632 procedures (COBE Spectra)
  - Anticoagulation: ACD-A : WB 1:15 -1:20 with heparin 20 U/kg/hr
  - Tums (10 mg/kg, before then hourly) or calcium gluconate infusion 1 mL/kg/hr (10 percent calcium gluconate, 10 mL in 50 mL NS)
  - RBC prime for patient <15 kg

<table>
<thead>
<tr>
<th>Complication</th>
<th>TPE Apher.</th>
<th>TPE Patients</th>
<th>HPC-A Apher.</th>
<th>HPC-A Patients</th>
<th>RBCX Apher.</th>
<th>RBCX Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension requiring fluid infusion</td>
<td>3.2</td>
<td>48</td>
<td>9.5</td>
<td>20.5</td>
<td>5.3</td>
<td>20</td>
</tr>
<tr>
<td>Probable hypocalcemia</td>
<td>10.3</td>
<td>72</td>
<td>9.5</td>
<td>18.8</td>
<td>5.3</td>
<td>20</td>
</tr>
<tr>
<td>Documented hypocalcemia</td>
<td>6.6</td>
<td>64</td>
<td>2.3</td>
<td>5.1</td>
<td>5.3</td>
<td>24</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>6.0</td>
<td>24</td>
<td>0</td>
<td>0</td>
<td>2.7</td>
<td>8</td>
</tr>
<tr>
<td>Severe anemia</td>
<td>1.7</td>
<td>48</td>
<td>6.2</td>
<td>14.5</td>
<td>0.9</td>
<td>4</td>
</tr>
</tbody>
</table>

Michon et al. Transfusion 2007;47:1837-42
Hypocalcemic Symptoms in Pediatric Apheresis

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Rate (%)</th>
<th>Per apheresis procedure</th>
<th>Per patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paresthesias</td>
<td>4.2</td>
<td></td>
<td>14.0</td>
</tr>
<tr>
<td>Nausea and/or vomiting</td>
<td>5.3</td>
<td></td>
<td>21.0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>6.6</td>
<td></td>
<td>16.1</td>
</tr>
<tr>
<td>Pallor</td>
<td>1.8</td>
<td></td>
<td>12.4</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>0.4</td>
<td></td>
<td>3.2</td>
</tr>
<tr>
<td>Headaches</td>
<td>1.9</td>
<td></td>
<td>9.1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0.7</td>
<td></td>
<td>4.3</td>
</tr>
</tbody>
</table>

Michon et al. Transfusion 2007;47:1837-42
Other Electrolyte Effects of Citrate Infusion:

- **Hypomagnesemia**
  - 2º chelation by citrate
  - May exacerbate symptoms related to hypocalcemia
- **Hypokalemia**
  - 2º metabolic alkalosis
- **Metabolic alkalosis**
  - 2º metabolism of citrate by mitochondrial rich tissue
Hypokalemia

- **Symptoms**: Musculoskeletal = weakness, cramps, paresthesias, paralysis; GI = nausea, anorexia, vomiting, diarrhea; CNS = lethargy, confusion.
- **Physical findings**: hyporeflexia
- **Lab findings**: low urine specific gravity; low serum K+ (<3.5 mEq/L requires therapy).
- **EKG findings**: flat or inverted T waves; ST depression. Less commonly: QT Long, wide QRS, U wave.
Hypokalemia

- May be due to rapid changes in pH:
  Remember:
  “Alkalosis drives K into cells” “Acidosis pulls K out of cells.”

In general, a 0.1 unit change in pH yields a 0.6 mEq/L change in serum [K+]. If pH rapidly rises from 7.2 to 7.4, serum [K+] will decrease ≈ 1.2 mEq/L.
Hypokalemia: how much K+ to give?

- **Under normal circumstances:** ~ 2 meq K/100 mL
- Thus, under ordinary conditions where a patient has a normal cardiovascular status, and normal renal function, adequate electrolytes will be provided using an intravenous fluid containing ¼ normal saline (Na = approx. 35 mEq/l), with 20 mEq of potassium per liter.
- At CNMC, if hypokalemia is present, we will ask primary service to add K to the maintenance fluids during the procedure or add 10-20 meq K/L in our calcium gluconate solution, patient weight/hr.
  - Max: 0.5 meq/Kg/hr
    ex. 20 kg patient, at 20 mL/hr with 10-20 meq K+/L will receive only 2-4 meq/20 kg/hr = 0.1-0.2 meq/kg/hr

*Caveat: Need to monitor*
ASFA International Survey of Pediatric Apheresis

<table>
<thead>
<tr>
<th>Type of Procedure</th>
<th>% of Responders (Anticoagulation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPE and RCE</td>
<td>78.3% (Citrate)</td>
</tr>
<tr>
<td></td>
<td>14.2% (Citrate/Heparin)</td>
</tr>
<tr>
<td>PBSC collection</td>
<td>65.7% (Citrate)</td>
</tr>
<tr>
<td></td>
<td>28.6% (Citrate/Heparin)</td>
</tr>
<tr>
<td>ECP</td>
<td>19.4% (Citrate)</td>
</tr>
<tr>
<td></td>
<td>11.1% (Heparin/Citrate)</td>
</tr>
<tr>
<td></td>
<td>63.8% (Heparin)</td>
</tr>
</tbody>
</table>
ASFA International Survey: Calcium Supplementation Depends on Procedure

- **TPE**: 90% No, 0% Only if symptomatic or laboratory evidence, 10% Yes
- **RCE**: 70% No, 20% Only if symptomatic or laboratory evidence, 10% Yes
- **Leukocyte reduction**: 60% No, 30% Only if symptomatic or laboratory evidence, 10% Yes
- **Platelet reduction**: 40% No, 50% Only if symptomatic or laboratory evidence, 10% Yes
- **HPC**: 80% No, 20% Only if symptomatic or laboratory evidence, 0% Yes
- **Therapeutic cells**: 70% No, 30% Only if symptomatic or laboratory evidence, 0% Yes
- **Photopheresis**: 50% No, 40% Only if symptomatic or laboratory evidence, 10% Yes
- **LDL Apheresis**: 30% No, 50% Only if symptomatic or laboratory evidence, 20% Yes
### ASFA International Survey: Only a Minority of Centers Do Not Monitor

<table>
<thead>
<tr>
<th>Type of monitoring</th>
<th>No. of responses (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Point-of-care testing, e.g., i-STAT</td>
<td>15 (16)</td>
</tr>
<tr>
<td>Laboratory testing</td>
<td>18 (20)</td>
</tr>
<tr>
<td>Mixture of point of care and laboratory testing</td>
<td>13 (14)</td>
</tr>
<tr>
<td>No regular laboratory monitoring, but may check iCa if concerned clinically</td>
<td>34 (37)</td>
</tr>
<tr>
<td>No laboratory testing</td>
<td>12 (13)</td>
</tr>
</tbody>
</table>
ASFA International Survey of Pediatric Apheresis: Of Those That Routinely Use Calcium Supplementation

- **Calcium gluconate**
  - TPE, albumin replacement: n=98
  - TPE, plasma replacement: n=101
  - RCE: n=81
  - HPC: n=85

- **Calcium chloride**
  - TPE, albumin replacement: n=98
  - TPE, plasma replacement: n=101
  - RCE: n=81
  - HPC: n=85

- **Calcium carbonate**
  - TPE, albumin replacement: n=98
  - TPE, plasma replacement: n=101
  - RCE: n=81
  - HPC: n=85
Magnesium Supplementation (ASFA Survey)

- 17/92 centers (19%) indicated that they used magnesium supplementation routinely.
- Routine use of magnesium supplementation was most frequent for:
  - HPC collections in 5/13 centers (38%)
  - TPE in 5/15 centers (33%)
- For plasma exchange procedures, if a patient was symptomatic or if there was laboratory evidence of hypomagnesemia, 9/15 centers (60%) would use magnesium supplementation.
- Approximately, two-thirds of centers also used magnesium supplementation when indicated for all types of apheresis procedures.
Potassium Supplementation
(ASFA Survey)

- Potassium supplementation was used for TPE by 19/91 (21%) centers.
- Potassium supplementation was used approximately 6 times more frequently with albumin replacement than with FFP replacement.
- However, once a patient became symptomatic, approximately 40% of respondents (n=19) used potassium supplementation, regardless of the type of replacement solution.
Maneuvers to Minimize Hypocalcemia

- **PO Calcium carbonate**
  - **Pros:**
    - IV not needed (Especially with current electrolyte shortages)
  - **Cons:**
    - Potentially not well tolerated
    - Cannot, if NPO, especially in the younger children
Maneuvers to Minimize Hypocalcemia

• **Calcium carbonate regimens (selected):**
  – 10 mg/kg initially, then every hr (Michon et al, 2007)
  – For children >11 years, 2 extra strength Tums (300 mg calcium carbonate) pre procedure, then 2 every 30 min to 1 hr (max 10, CNMC unpublished)
    • Tums smoothies may be used (CNMC)

• **Other**
  – Oral calcium gluconate 10%, 100 – 200 mg/kg/hr (Urban et al 1997, pts <20 kg, 2 BVs processed)
  – Isotonic sports drink (adults, Kishimoto et al, 2002)
Maneuvers to Minimize Hypocalcemia

- **Continuous IV infusion**
  - Procedures using only ACD-A (or ACD-A/heparin)
  - **Calcium gluconate**
    - 1 mL/kg/hr (10 mL of 10% calcium gluconate in 50 mL NS) (Michon et al, 2007),
    - 20 mg/mL calcium gluconate in NS, run at patient weight (kg)/hr (CNMC)
  - **Calcium chloride**
    - Administer 0.6 mg elemental calcium ion per every mL of ACD-A (1.2 mmol calcium/10 mmol citrate, Bolan et al, 2004)

- **Intermittent IV**: calcium gluconate bolus (100 mg/10 mL ampule, adults) over several minutes with development of symptoms only (rare reports in children with little details on concentration of calcium gluconate used)
**Maneuvers to Minimize Hypocalcemia**

- **IV Calcium Chloride (5 mg/Kg/hr) for therapeutic plasma exchange (ECMO, only) CNMC (unpublished)**
  - (CaCl₂ 8000 mg in 1000 mL of 0.9% NS [8mg/mL])
  - Initiate infusion rate at (___mg/hr) ___mL/hr to be infused

Titrare CaCl₂ drip rate to maintain the patient’s iCa²⁺ between 1.1-1.3 mmol/L as follows:

<table>
<thead>
<tr>
<th>Patient Ca²⁺ (mmol/L)</th>
<th>Weight ≥ 20 Kg</th>
<th>Weight &lt; 20Kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Action</td>
<td>Action</td>
</tr>
<tr>
<td>&gt; 1.3</td>
<td>↓ rate by 10 mL/hr</td>
<td>↓ rate by 5 mL/hr</td>
</tr>
<tr>
<td>1.1-1.3</td>
<td>No Change</td>
<td>No Change</td>
</tr>
<tr>
<td>0.9-1.1</td>
<td>↑ rate by 10 mL/hr</td>
<td>↑ rate by 5 mL/hr</td>
</tr>
<tr>
<td>&lt;0.9</td>
<td>↑ rate by 20 mL/hr</td>
<td>↑ rate by 10 mL/hr</td>
</tr>
</tbody>
</table>
Maneuvers to Minimize Hypocalcemia

- Electrolyte Supplementation in Albumin Replacement Solution During Plasma exchange
  - Kim (2010)
    - Especially with > 0.8 mL ACD-A /min/L TBV
    - Albumin replacement, 2-3 mL 10% calcium gluconate can be added to each 250 mL bottle.
    - FFP replacement, 2-3 mL 10% calcium gluconate bolus (over 10 minutes/continuous infusion can be given with each 100 mL FFP)
  - Krishnan RG & Coulthard MG (2007)
    - Supplemented albumin replacement by adding 2 mmol/l calcium chloride and 0.8 mmol/l magnesium sulphate
Effect of Calcium and Magnesium Supplementation

Fig. 2 Total calcium (a), ionised calcium (b), and magnesium (c) concentrations during plasmapheresis using 80 ml/kg exchanges. Concentrations are shown before the start, after the first 85% of the plasma replacement using human albumin solution (HAS), and after 15 min of exchange with fresh frozen plasma (FFP). Blue symbols and lines indicate the use of standard HAS, and red indicates the use of calcium and magnesium supplemented HAS.

Recommendation if Severe Hypocalcemia Occurs

- If severe reactions occur (i.e. tetany)
  - Option 1: 0.5 to 1.0 mL of 10% calcium gluconate/kg over 10 min. (Kim 2010)
    - Avoid scalp veins and small or foot veins to avoid possibility of skin necrosis and sloughing due to extrasvasation
  - Option 2: 20 mg/kg (0.2 mL/kg) of 10% calcium chloride over 10 minutes via central line (Kim 2010)
  - In the case of cardiac symptoms (e.g. EKG changes, arrhythmias, hypertension) correct hypomagnesememia if cardiac symptoms do not improve with calcium replacement
- Note: Plasma ionized calcium < 0.75 mmol/L requires immediate correction
Maneuvers to Minimize Hypocalcemia

- Another caveat: Cardiac Patients:
  - The heart denervated by either transplantation or pharmacological blockade is extremely sensitive to lowered ionized calcium (Corbascio and Smith, 1967; Smith and Hurley, 1969).
Pediatric large-volume leukapheresis: 
a single institution experience with heparin versus 
citrate-based anticoagulant regimens

Charles D. Bolan, Yu Ying Yau, Herbert C. Cullis, Mitchell E. Horwitz, Crystal L. Mackall, 
A. John Barrett, Harry L. Malech, Nadja N. Rehak, Alan S. Wayne, and Susan F. Leitman

Transfusion 2004;44:229-238

**Table 1. Donor demographics according to anticoagulant group**

<table>
<thead>
<tr>
<th>Group</th>
<th>Subjects (number)</th>
<th>Procedures (number)</th>
<th>Weight (kg)</th>
<th>Age (year)</th>
<th>RBC prime (number)</th>
<th>Autologous/Allogeneic (number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>5</td>
<td>11</td>
<td>14 (11-20)</td>
<td>8 (3-11)</td>
<td>8</td>
<td>8/3</td>
</tr>
<tr>
<td>II</td>
<td>5</td>
<td>10</td>
<td>27 (20-30)</td>
<td>8 (6-10)</td>
<td>2</td>
<td>2/8</td>
</tr>
<tr>
<td>III</td>
<td>6</td>
<td>11</td>
<td>23 (18-29)</td>
<td>8 (5-11)</td>
<td>1</td>
<td>9/2</td>
</tr>
<tr>
<td>IV</td>
<td>22</td>
<td>42</td>
<td>23 (12-30)</td>
<td>8 (1-13)</td>
<td>5</td>
<td>29/13</td>
</tr>
</tbody>
</table>

**Table 2. Apheresis variables according to anticoagulant group**

<table>
<thead>
<tr>
<th>Group</th>
<th>WBFR* (mL/min)</th>
<th>WBFR/ donor weight (mL/kg/min)</th>
<th>Net volume processed (L)</th>
<th>BVs processed (number)</th>
<th>Run time (min)</th>
<th>Fluid balance (mL/kg/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>27 (25-40)</td>
<td>1.9 (1.5-2.5)</td>
<td>5.7 (3.6-9.8)</td>
<td>5.4 (3.1-10.8)</td>
<td>242 (146-458)</td>
<td>-0.6 (-4.5-0.8)</td>
</tr>
<tr>
<td>II</td>
<td>46 (25-60)</td>
<td>1.7 (1.2-2.1)</td>
<td>7.7 (4.8-9.7)</td>
<td>3.8 (3.0-4.8)</td>
<td>208 (145-262)</td>
<td>2.3 (1.1-3.4)</td>
</tr>
<tr>
<td>III</td>
<td>32 (23-45)</td>
<td>1.4 (1.1-1.6)</td>
<td>5.1 (1.9-9.3)</td>
<td>3.1 (0.9-5.0)</td>
<td>201 (55-358)</td>
<td>6.3 (4.0-12.2)</td>
</tr>
<tr>
<td>IV</td>
<td>42 (15-60)</td>
<td>1.8 (1.1-2.1)</td>
<td>7.7 (2.8-13.0)</td>
<td>4.4 (2.1-6.5)</td>
<td>219 (108-350)</td>
<td>8.5 (2.1-15.4)</td>
</tr>
</tbody>
</table>

* WBFR = whole-blood flow rate (CS-3000) or inlet flow rate (Spectra).

Group 1: Heparin sole anticoagulant
Group 2: Heparin with reduced dose citrate
Group 3: Full dose citrate + IV calcium infusion
Group 4: Full dose citrate + IV calcium/magnesium infusion
Magnesium sulfate infusion: (Bolan et al, 2004)
  - Created by pharmacy
  - Magnesium solution: 6 mL (24 meq) of 50 percent magnesium sulfate (American Pharmaceutical Partners) to a final volume of 98.6 mL of half normal saline, providing **3 mg of magnesium ion per mL**
  - Administered at 0.18 mg of magnesium ion per mL of ACD-A (0.6 mmol magnesium/10 mmol citrate).

Calcium solution: were prepared from 10-percent vials of calcium chloride to a final concentration of **2 mg calcium ion per mL** (two 10-mL CaCl₂ vials added to 250 mL of half normal saline).
  - Administered at 0.6 mg of calcium ion per mL of ACD-A (1.2 mmol calcium/10 mmol citrate)
Maneuvers to Minimize Hypomagnesemia

• **Example:**
  - ACD-A inlet flow rate of 2 mL/min on the Spectra,
    A) Want: 0.6 mg Ca\(^{2+}\) ion per 1 mL ACD-A
      Have: Ca\(^{2+}\) solution at 2 mg/mL

    **Know:** 2 mL/min (ACD-A) x 60 min/hr = 120 mL/hr (ACD-A)
    120 mL/hr (ACD-A) x 0.6 mg Ca\(^{2+}\) ion/mL ACD-A = 72 mg Ca\(^{2+}\) needed/hr
    You have Ca\(^{2+}\) solution at 2 mg/mL

    **Therefore you need 72/2 or 36 mL/hr Ca\(^{2+}\) solution/hr!**

•  


Maneuvers to Minimize Hypomagnesemia

- **Example:**
  - ACD-A inlet flow rate of 2 mL/min on the Spectra,
  - B) Want: 0.18 mg Mg ion per 1 mL ACD-A
    Have: Mg ion solution at 3 mg/L

**Know:**

2 mL/min (ACD-A) x 60 min/hr = 120 mL/hr (ACD-A)
120 mL/hr (ACD-A) x 0.18 mg Mg 2+ ion/mL ACD-A = 21.6 mg magnesium ion needed/hr
You have Mg ion solution at 3 mg/mL

Therefore you need 21.6/3 or 7.2 mL Mg2+ solution/hr!

- No differences between Group III and IV in iCa, total Ca, iMg, total Mg or K initially
- Group III vs. IV
  - iCa decreased 4.6 ± 9% vs. 4.0 ± 8% (NS)
  - iMg decreased 33 ± 6% vs. 8.5 ± 12% (p <0.01)
  - K decreased <10% (NS)

**TABLE 6. Clinical and laboratory data in donors experiencing adverse effects**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Anticoagulant group</th>
<th>Age (year)</th>
<th>Weight (kg)</th>
<th>Type</th>
<th>BVs (number)</th>
<th>WBFR* (mL/kg/min)</th>
<th>CIR† (mL-AC/L-BV/min)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematoma</td>
<td>I</td>
<td>7</td>
<td>12</td>
<td>Autologous</td>
<td>6.4</td>
<td>2.1</td>
<td>NA</td>
<td>Direct pressure. PLT transfusion. Decrease WBFR 20%, increase calcium infusion by 20%.</td>
</tr>
<tr>
<td>Lip tingling</td>
<td>III</td>
<td>11</td>
<td>18</td>
<td>Autologous</td>
<td>5.0</td>
<td>1.3</td>
<td>1.95 (1.26)</td>
<td>Decrease WBFR 20%, increase calcium infusion by 20%.</td>
</tr>
<tr>
<td>Lip tingling</td>
<td>IV</td>
<td>11</td>
<td>27</td>
<td>Allogeneic</td>
<td>4.5</td>
<td>1.5</td>
<td>2.23 (1.34)</td>
<td>Interrupt procedure. Verify laboratory data. Administer antiemetic.</td>
</tr>
<tr>
<td>Nausea</td>
<td>IV</td>
<td>10</td>
<td>21</td>
<td>Autologous</td>
<td>3.8</td>
<td>1.2</td>
<td>1.91 (1.17)</td>
<td></td>
</tr>
</tbody>
</table>

* WBFR = whole-blood flow rate.
† CIR = citrate infusion rate.
Maneuvers to Minimize Hypomagnesemia

- RCT of IV magnesium supplementation in large volume leukapheresis adult PBSC donors (Haddad et al, 2005)
  - Significant impact on serum magnesium levels
  - No reduction in the frequency or severity of the relatively mild citrate-related effects observed in LVL performed with continuous IV calcium prophylaxis
  - Concluded:
    - Magnesium infusions may be considered in pediatric patients who receive higher citrate administration rates during LVL than adults, in patients with prior hypomagnesemia, and in subjects undergoing repetitive LVL procedures.
Conclusions

- Citrate toxicity is a common and potential severe complication in pediatric patients undergoing apheresis procedures.
- The primary side effect of citrate toxicity is hypocalcemia which may be easily managed by careful monitoring and/or use of oral calcium carbonate, continuous calcium gluconate/chloride infusion.
- Magnesium supplementation does not appear to be necessary in healthy allogeneic donors; however, hypomagnesemia has the potential to blunt PTH response to hypocalcemia and may be needed in symptomatic or susceptible patients.
- Based on a recent ASFA survey, the majority of centers perform calcium gluconate infusions for hypocalcemia prophylaxis, with a minority performing magnesium and potassium infusions (TPE), especially if symptomatic or if there is laboratory evidence.
References


References

14. Sabbatani L. Arch Ital Biol 1901; 36 :397