Acquired Hemolysis Related to Common IV Nutrient Therapies

Clinical Practice Guidelines

Background:

Acquired hemolytic crisis is a known entity in clinical and emergency medicine. The causes of this phenomenon however are quite varied and include many etiologies not common to the general practice of IV nutrient therapy (IVNT). There are however two instances particular to IVNT that every practitioner should be aware of and able to diagnose and manage should they arise. The author has managed, on behalf of many clinics around North America multiple instances of IVNT triggered acquired hemolysis. Below is a standard operating procedure developed using the available peer-reviewed data and clinical practice.

Most Common Causes:

As mentioned above there are multiple cause areas for acquired hemolysis in medicine ranging from immunologic to pharmacological and other areas. In IVNT however the two most likely and common are accidental infusion of Sterile Water for Infusion (SWI) without additives (hypotonic hemolysis) [1] and infusion of oxidative therapies in people with Red Blood Cell (RBC) fragility syndromes such as G6PD deficiency [2] (and less common but potentially Sickle Cell Disease and, Alpha or Beta Thalassemia Major).

Pathogenesis:

Hypotonic Hemolysis:

While most hypotonic hemolysis is caused by accidental use of SWI with few or no additives (yielding an osmolarity of 0 mOsm/L or similar) it has also happened in IV Albumen infusions with SWI as diluent. Every case the author has managed has been caused by drug error (normally the person compounding the infusion choosing a bag of SWI instead of the isotonic solution ordered, e.g., Normal Saline (NS) or similar product).

In the case of an ultra-low osmolarity infusion (especially via a peripheral line) the RBC's encounter the infusate and will hemolyze in its presence. Underlying conditions such as plasma osmolarity, speed of

infusion and volume of infusion all factor into the potential for hemolysis. For example, in one case after a hyperosmolar infusion of Vitamin C (IVC) with an osmolarity of 1007 mOsm/L, given over three hours via peripheral IV a Resident incorrectly infused 250 mL of SWI before realizing the error and there was no hemolysis triggered. This lack of hemolysis was judged to be due to the hyperosmolality of the plasma post IVC. While this instance was a positive outcome to a medication error, it is still not one which should be repeated. In other cases, such as the SWI diluted albumen infusions, have led to hemolysis and death.

A CLINICAL NOTE: This does bring up the obvious question "what osmolarity is safe to infuse?" Many IVNT trainings INCORRECTLY teach that hypotonic solutions cannot be safely infused. This is not correct because some tonicities in the "hypotonic" range can be infused and some cannot since hypotonic osmolarity is a range of 0 mOsm/L to 280 mOsm/L. [3] The common base solution "Half-normal Saline" (0.45 NS) has an osmolarity of 154 mOsm/L and can be safely infused without additives in most people (especially when the patient is dehydrated). So clearly some hypotonic solutions can be infused. It is generally accepted NOT to infuse below an osmolarity of 150 mOsm/L. [4]

RBC Fragility Hemolysis:

As opposed to Hypotonic Hemolysis (which can happen to any human) RBC Fragility Hemolysis (RFH) occurs when the RBC and its membrane cannot withstand a chemical insult, normally an oxidative stress. The RBC under oxidative stress then lyses and the hemolytic event follows. In IVNT this typically happens when a person with G6PD deficiency (or other fragility such as Sickle Cell Disease, Beta Thalassemia Major or Alpha Thalassemia 3 gene / major form – Note that this does not include "trait" or "minor" forms of these disorders) has an infusion of an oxidative infusate such as High Dose Intravenous Vitamin C (HDIVC), Ozone and potentially Hydrogen Peroxide or Artesunate. Other drugs can cause this but are not commonly used in IVNT.

The only cases of this type of hemolysis managed by the author have been either due to the physician not checking the G6PD and CBC status of the patient prior to infusion of an oxidative IV or a medication error where an oxidative IV was inappropriately given.

Signs and Symptoms:

Because this paper is limited to IVNT triggered hemolysis the signs and symptoms will be limited to those common to such triggers and should not be taken as an exhaustive list.

Specific symptoms such as back, flank or abdominal pain and in the case of peripheral IV pain at the infusion site or regional phlebalgia are common. Nonspecific symptoms include fatigue, dyspnea, hypotension, and tachycardia are common but typically present later and only if large scale hemolysis exists.

The hallmark sign is often a mixed hematuria / bilirubinuria which can be pink to black in color. This can happen during or after the IV. It is of note that this is different from a condition seen during IVNT in persons with prostate diseases, renal cysts, bladder disorders, or obstructive uropathies which is a frank hematuria often presenting with clots. If this frank hematuria is present and the patient has one of the above conditions (and no ultra-hypotonic solution or G6PD defect is present) then those disorders should be worked up before a presumption of hemolysis is made.

Laboratory Studies:

“The initial workup of hemolytic anemia begins with a complete blood count illustrating normocytic or macrocytic anemia.” “Testing should (also) include measurement of lactate dehydrogenase, haptoglobin, reticulocyte, and unconjugated bilirubin levels, as well as urinalysis.”

“Lactate dehydrogenase is intracellular, and levels increase when RBCs rupture. Haptoglobin binds to free hemoglobin, and levels decrease in hemolysis. Unconjugated bilirubin levels rise as its production exceeds elimination capability. Hemolysis usually induces a reticulocytosis causing macrocytosis, unless significant iron deficiency or marrow suppression is present. Urinalysis may be positive for hemoglobinuria in hemolytic anemia despite no visible RBCs on microscopy. The constellation of reticulocytosis, increased lactate dehydrogenase levels, increased unconjugated bilirubin levels, and decreased haptoglobin levels confirms hemolysis. The absence of these findings should prompt a search for other causes.” [5]

In most acute instances the presence of the signs and symptoms above plus the likelihood of a triggering IV should cause a STAT urinalysis which normally will show increased urobilinogen and or bilirubin as well as positive for blood.

Clinical Management:

Obviously, the best treatment for anything is prevention. Constant attention to detail such as pre IVNT laboratory studies and patient history as well as strict pharmacy procedures to avoid medication errors are paramount to such prevention methods. As with all things in clinical medicine there are times where the efforts at prevention fail for various reasons.

Acute hemolytic crisis triggered by IVNT is a limited entity and because of this there is normally prompt identification of the problem (whether osmotic or RBC fragility) coupled with removal of the triggering IV. This combination generally limits the damage created.

If the clinician does not feel competent to manage the case as outlined below in office, then appropriate referral to an emergency department should be made. The STAT urinalysis and IV fluids should be initiated IMMEDIATELY IN the clinician office REGARDLESS OF the decision to treat in office or refer for hospital evaluation.

Supportive care is generally all that is warranted and is much less involved than most types of acquired hemolysis.[6] Supportive care is the use of isotonic IV infusion such as 0.9% normal saline which should be hung and infused at a rate of 250 mL / hour immediately upon discontinuing the triggering IV. This infusion should be progressing while the initial STAT urinalysis is performed. If managing as an outpatient then a total of 1000 to 1500 mL 0.9% normal saline should be infused in any patient not at risk for fluid overload. After the initial 500 mL is infused at 250 mL / hour the rate can be slowed to 125 mL / hour.

After starting the above IV fluids and obtaining the STAT urinalysis blood should be drawn for a CBC with a differential and platelet count with reticulocytes as well as chemistries including a comprehensive metabolic panel with eGFR, lactate dehydrogenase, haptoglobin, and unconjugated bilirubin levels.

Follow up studies to assure normal renal function are necessary in every case of acute acquired hemolysis. And although in IVNT caused hemolysis is generally self-limited and completely resolves patients with prior renal disorders may have long term effects:

“Episodes of acute kidney injury, especially those that fail to completely resolve, predispose to CKD. Interestingly, after exposure to heme proteins, the kidney shows markedly increased expression of MCP-1 (monocyte chemoattractant protein 1) and transforming growth factor β1 isoform 1 (TGF-β1), cytokines that potently recruit monocytes/ macrophages and provoke fibrosis, respectively.” [7]

Serial blood chemistries (Taken with the CBC, PLT, Diff and Reticulocyte count etc. mentioned above) with an eGFR at 4- and 12-weeks post event are normally sufficient to document renal function.

In all the cases managed by the author those triggered by IVNT with appropriate management as outlined above have never resulted in a fatality or any long-term damage.

References:

1. Pierce LR, Gaines A, Varricchio F, Epstein J and Lawrence A. Trissel LA. Hemolysis and renal failure associated with use of sterile water for injection to dilute 25% human albumin solution. American Journal of Health-System Pharmacy, Volume 55, Issue 10, 15 May 1998, Page 1057, https://doi.org/10.1093/ajhp/55.10.1057

2. Bubp J, Jen M; and Matuszewski K, Caring for Glucose-6-Phosphate Dehydrogenase (G6PD)–Deficient Patients: Implications for Pharmacy. Pharmacy and Therapeutics September 2015. Vol. 40 No. 9

3. Rosenthal K. IV Rounds: Intravenous Fluids. July 2006, Volume :36 Number 7, page 26 - 27

4. D. Roethlisberger et al. Journal of Pharmaceutical Sciences 106 (2017) 446-456

5. Phillips J and Henderson AC. Hemolytic Anemia: Evaluation and Differential Diagnosis. Am Fam Physician. 2018;98(6):354-361

6. Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 8th. edition. Chapter 237: Acquired Hemolytic Anemia, Laurie Ann Dixon; Robin R. Hemphill

7. Qian Q, et. Al. Hemolysis and Acute Kidney Failure. Am J Kidney Dis. 2010 October ; 56(4): 780–784. doi:10.1053/j.ajkd.2010.03.025.