GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

Volume 3 - Issue 25

FPIN
Family Physicians Inquiries Network

What's in this week's issue?

Week of June 19 - 23, 2023

SPOTLIGHT: Intravenous Iron - Does It Pose an Infection Risk?

Intravenous Iron: Does It Pose an Infection Risk?

Risk of Infection Associated with Administration of Intravenous Iron: A Systematic Review and Meta-Analysis

Shah AA, Donovan K, Seeley C, et al. Risk of Infection Associated With Administration of Intravenous Iron: A Systematic Review and Meta-analysis [published correction appears in *JAMA Netw Open*. 2022 Jan 4;5(1):e2146637]. *JAMA Netw Open*. 2021;4(11):e2133935. Published 2021 Nov 1. doi:10.1001/jamanetworkopen.2021.33935

KEY TAKEAWAY: Patients treated with intravenous (IV) iron have a higher risk of developing an infection but show no difference in mortality or length of hospital stay compared to those treated with oral or no iron.

STUDY DESIGN: Systematic review and meta-analysis of 154 randomized controlled trials and eight nonrandomized studies (N=39,908)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: The efficacy of IV iron in reducing anemia is already supported and recommended by many guidelines. Iron is required for host immunity and pathogen replication and is stored away by the hormone hepcidin during infection. Intravenous iron increases levels of circulating unbound iron, therefore there is biological plausibility for increased risk of infection in patients receiving intravenous iron but the data on the risk of infection is conflicting.

PATIENTS: All patient populations

INTERVENTION: IV iron

CONTROL: Oral or no iron

PRIMARY OUTCOME: Risk of infection

Secondary Outcome: Mortality, hospital length of stay, changes in hemoglobin, red blood cell transfusion requirements

METHODS (BRIEF DESCRIPTION):

- Cochrane Collaboration, PRISMA, and GRADE were utilized to identify studies published between 1966 to January 31, 2021, comparing IV iron to oral iron or no iron.
- Study characteristics:
  - Included all patient populations of all ages, excluding healthy volunteers.
  - Wide range of clinical settings including inpatient and outpatient, across all continents
  - Sixty-four RCTs included sufficient data for analysis of the risk of infection.
- Intervention and control preparations:
  - The most common IV iron preparations evaluated were iron sucrose and ferric carboxymaltose 200–1,000 mg in one-time or divided doses.
  - The most common oral iron comparators were ferrous sulfate and ferrous fumarate at unspecified doses defined as the standard of care.

INTERVENTION (# IN THE GROUP): 10,010

COMPARISON (# IN THE GROUP):

- Oral Iron: 3,024
- No Iron: 6,108

FOLLOW-UP PERIOD: Unavailable

RESULTS:

Primary Outcome –

- IV iron increased infection risk compared to patients in the control groups (64 trials, N=19,322; relative risk [RR] 1.2; 95% CI, 1.01–1.3).

Secondary Outcome –

- IV iron significantly increased hemoglobin compared to control groups (111 trials, N=20,776; mean difference [MD] 0.57 g/dL; 95% CI, 0.50–0.64 g/dL).
- IV iron significantly reduced red blood cell (RBC) transfusions compared to control groups (54 trials, N=12,116; RR 0.93; 95% CI, 0.76–0.89).
- IV iron significantly reduced mean RBCs transfused compared to control groups (11 trials, N=1,690; MD –0.20; 95% CI, –0.32 to –0.08).
- There was no difference in short-term or long-term mortality between patients treated with IV iron compared to control groups.
- There was no difference in hospital length of stay between patients treated with IV iron compared to control groups.

LIMITATIONS:

- There were differences and variations in infection reporting between studies, therefore true understanding of the nature of infection risk may be limited.

- There was no analysis of health-related quality of life.
- There was variable quality of included studies; however, sensitivity analysis had minimal effect on pooled estimate.

Eric Rice, DO
Samaritan FMR Rural Training Program
Newport, OR

Calcium Supplementation for Pre-Eclampsia Prevention

Calcium for Pre-Eclampsia Prevention: A Systematic Review and Network Meta-Analysis to Guide Personalized Antenatal Care

Woo Kinshella, M-L, Sarr, C, Sandhu, A, Bone, JN, Vidler, M, Moore, SE, et al. Calcium for pre-eclampsia prevention: A systematic review and network meta-analysis to guide personalized antenatal care. *BJOG*. 2022; 129: 1833– 1843. doi:10.1111/1471-0528.17222

KEY TAKEAWAY: High-dose and low-dose calcium supplementation decrease the risk of pre-eclampsia in pregnant patients with baseline low calcium intake.

STUDY DESIGN: Systematic review and network meta-analysis of 30 studies (N= 20,445)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Pre-eclampsia affects 2–5% of pregnancies worldwide and negatively impacts maternal and neonatal morbidity and mortality. The World Health Organization recommends calcium supplementation at >20 weeks gestation and there is evidence supporting reduced risk of pre-eclampsia with calcium supplementation. It is unclear who should receive calcium for pre-eclampsia prevention and how calcium should be supplemented.

PATIENTS: Pregnant women without pre-eclampsia

INTERVENTION: High or low dose calcium supplementation

CONTROL: Placebo or no treatment

PRIMARY OUTCOME: Pre-eclampsia

Secondary Outcome: HELLP syndrome, severe maternal morbidity, birth at <37 weeks gestation, low birth weight

METHODS (BRIEF DESCRIPTION):

- Randomized controlled trials of calcium supplementation for pre-eclampsia prevention were sought out via a comprehensive online search of database platforms, hand searches, and expert input.
  - Two independent reviewers screened studies for eligibility and extracted data.
- Outcomes from the selected studies were pooled and a network meta-analysis was performed for each of the primary and secondary outcomes listed above.
- The trials mostly took place in high-income countries.
- Large inter-trial heterogeneity with overall outcome heterogeneity I^2=59%.

INTERVENTION (# IN THE GROUP): 9,963

COMPARISON (# IN THE GROUP): 10,482

FOLLOW-UP PERIOD: Through duration of pregnancy

RESULTS:

Primary Outcome –

- Overall, calcium supplementation reduced the risk of pre-eclampsia by 51% (RR 0.49; 95% CI, 0.39–0.61).
  - Risk reductions with high-dose supplementation and low-dose supplementation were similar.
  - In the NMA there was no benefit in patients with baseline adequate calcium (RR 0.62; 95% CI, 0.37–1.1).
  - In patients with low baseline calcium intake the risk reduction was 55% (RR 0.45; 95% CI, 0.29–0.57).

Secondary Outcome –

- The risk of HELLP syndrome was higher with calcium supplementation (RR 2.1; 95% CI, 1.1–4.0; risk difference 0.2%; the number needed to harm = 500).
- Calcium supplementation was associated with a lower risk of:
  - Composite severe maternal morbidity (RR 0.84; 95% CI, 0.71–0.99)
  - Birth <37 weeks gestational age (RR 0.82; 95% CI, 0.69–0.98)
  - Low birthweight (RR 0.85; 95% CI, 0.74–0.99)

LIMITATIONS:

- The study does not discuss the possible confounding use of aspirin for pre-eclampsia prevention.
- Many trials were greater than 20 years old.
- Significant inter-trial heterogeneity on the timing of the initiation of calcium supplementation. Some trials didn't include a baseline calcium intake.
- Although many trials took place outside of the United States, it does appear that there are similar baseline characteristics and incidences of diseases of pregnancy to generalize the findings.

Kristi Wegener, MD
UPHS Marquette FMR
Marquette, MI

Does Thrombectomy Improve Outcomes in Patients with Large Ischemic Strokes?

Trial of Endovascular Thrombectomy for Large Ischemic Strokes

Sarraj A, Hassan AE, Abraham MG, et al. Trial of Endovascular Thrombectomy for Large Ischemic Strokes. *N Engl J Med*. 2023;10.1056/NEJMoa2214403. doi:10.1056/NEJMoa2214403

KEY TAKEAWAY: Patients with large ischemic strokes treated with endovascular thrombectomy have better functional outcomes than those treated with medical care alone.

STUDY DESIGN: Prospective, randomized, open-label trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Endovascular thrombectomy in patients with small- and moderate-sized acute ischemic strokes due to large cerebral vessel occlusion results in significantly improved functional outcomes compared to medical therapy. However, studies evaluating thrombectomy in similar large strokes are limited. This study evaluated if thrombectomy in patients with a large acute ischemic stroke improved functional outcomes.

PATIENTS: Adults with ischemic stroke

INTERVENTION: Endovascular thrombectomy

CONTROL: Standard medical care

PRIMARY OUTCOME: Functional status at 90 days

Secondary Outcome: Functional independence, independent ambulation, safety, and procedural complications

METHODS (BRIEF DESCRIPTION):

- This was a prospective, randomized nonblinded trial that included patients with internal carotid artery or proximal middle cerebral artery strokes.
  - Ischemia on CT was quantified with the Alberta Stroke Program Early Computed Tomography Score (ASPECTS), whereas the volume of ischemia was determined by MRI.
- Patients with ASPECTS value of 3 to 5, or those with ischemic core volume ≥50 ml were included, while those with stroke onset more than 24 hours prior, additional imaging abnormalities, or clots outside of large arteries were excluded.
- Participants had a median age of 66.5 years with a median NIH stroke scale (NIHSS) score of 19, median ASPECTS value of 4, and median ischemic core volume of 80 ml.
- Patients were randomly assigned to receive endovascular thrombectomy and medical care, or standard medical care alone.
- Thrombectomy started within 24 hours after stroke onset.
- The functional status, ambulation ability, safety issues, and procedural complications among participants were evaluated at the time of randomization, 24 hours, 5–7 days, 30 days, and 90 days.
- Functional status was assessed using the modified Rankin scale (scores 0–6, with lower values indicative of better functional status).
- Assessments completed at 30 and 90 days were blinded.
- The trial was stopped for significant efficacy of thrombectomy after 300 patients completed follow-up.

INTERVENTION (# IN THE GROUP): 178

COMPARISON (# IN THE GROUP): 174

FOLLOW-UP PERIOD: 90 days post-stroke

RESULTS:

Primary Outcome –

- At 90 days, thrombectomy resulted in greater functional status compared to standard medical care (odds ratio [OR] 1.5; 95% CI, 1.2–1.9).

Secondary Outcome –

- More patients in the thrombectomy group had improved 90-day functional independence as compared to the medical care group (20.3% vs. 7.0%, respectively; relative risk [RR] 3.0; 95% CI, 1.6–5.5).
- More patients in the thrombectomy group could ambulate independently at 90 days as compared to the medical care group (37.9% vs. 18.7%, respectively; RR 2.1; 95% CI, 1.4–3.0).
- Symptomatic intracranial hemorrhage was similar between the thrombectomy and medical care groups (0.6% and 1.1%, respectively; RR 0.49; 95% CI 0.04–5.4).
- 33 patients (18.5%) in the thrombectomy group had procedural complications.

LIMITATIONS:

- As the intervention was surgical, treatment was open-label.
- Early termination may have overestimated the effect of the intervention, underestimated adverse events, and resulted in a smaller sample size.
- Some patients with ischemic core volumes < 50 ml were included due to low ASPECTS values, requiring additional analysis with these patients excluded.

Zafarullah M. Chaudhary, MD
St. Joseph's Health, Department of Family Medicine
Paterson, NJ

Fluid Resuscitation in Acute Pancreatitis: Is More Fluid Better?

Aggressive or Moderate Fluid Resuscitation in Acute Pancreatitis

de-Madaria E, Buxbaum JL, Maisonneuve P, et al. Aggressive or Moderate Fluid Resuscitation in Acute Pancreatitis. *New England Journal of Medicine*. 2022;387(11):989-1000. doi:10.1056/nejmoa2202884

KEY TAKEAWAY: Aggressive fluid resuscitation for the treatment of acute pancreatitis leads to a higher risk of volume overload without improvement in clinical outcomes as compared to moderate fluid resuscitation.

STUDY DESIGN: Multicenter, open-label, randomized controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to the study being underpowered)

BRIEF BACKGROUND INFORMATION: Previous RCTs comparing the volume of intravenous fluid were limited by small size and inclusion criteria and have provided conflicting results. The purpose of this study was to compare outcomes of aggressive fluid resuscitation versus fluid resuscitation with moderate fluid resuscitation in adult patients with acute pancreatitis.

PATIENTS: Adult patients with a diagnosis of acute pancreatitis

INTERVENTION: Moderate fluid resuscitation

CONTROL: Aggressive fluid resuscitation

PRIMARY OUTCOME: Development of moderately severe or severe acute pancreatitis

METHODS (BRIEF DESCRIPTION):

- 249 adult patients at 18 centers across four countries (India, Italy, Mexico, and Spain) with the diagnosis of acute pancreatitis according to the Revised Atlanta Classification
- Revised Atlanta Classification: meeting two of the following three criteria: typical abdominal pain, serum amylase or lipase level higher than 3 times the upper limit of the normal range, or signs of acute pancreatitis on imaging) presenting to the emergency department.
- Inclusion criteria: no more than 24 hours after onset of pain and receiving a diagnosis of acute pancreatitis no more than eight hours before enrollment.
- Patients were excluded if they met criteria for moderately severe or severe disease at baseline, had baseline heart failure, or had uncontrolled arterial hypertension, hypernatremia, hyponatremia, hyperkalemia, hypercalcemia, had an estimated life expectancy of less than one year or had chronic pancreatitis, chronic renal failure, or decompensated cirrhosis.
- Patients were randomly assigned in a 1:1 ratio into 2 groups:
  - Aggressive fluid resuscitation group:
    - Initial bolus - LR dosed at 20 ml/kg body weight administered over 2 hours.
    - Subsequent infusion – LR dosed at 3 ml/kg/hour.
  - Moderate fluid resuscitation group:
    - Patients with hypovolemia: initial bolus - LR dosed at 10 ml/kg body weight over a period of two hours.
    - Patients without hypovolemia: initial bolus - none.
    - Subsequent infusion (both) – LR dosed at 1.5 ml/kg/hour.

INTERVENTION (# IN THE GROUP): 127

COMPARISON (# IN THE GROUP): 122

FOLLOW-UP PERIOD: 72 hours

RESULTS:

Primary Outcome –

- There was no significant difference in the development of moderately severe or severe acute pancreatitis between aggressive fluid resuscitation vs moderate (22.1% vs 17.3%, respectively; adjusted relative risk 1.3; 95% CI, 0.78–2.2).

Secondary Outcome –

- Aggressive fluid resuscitation was associated with a significantly higher incidence of fluid overload than moderate fluid resuscitation (20.5% vs 6.3%, respectively; adjusted relative risk 2.9; 95% CI, 1.4–5.9).

LIMITATIONS:

- The trial was underpowered to evaluate efficacy outcomes definitively after being terminated at the first interim analysis due to the higher risk of

volume overload in the aggressive fluid resuscitation group.
- This trial was open-label, which may have involved bias.

Aaron Surbaugh, DO
David Grant Medical Center FMRP
Travis AFB, CA

The opinions and assertions contained herein are those of the author and are not to be construed as official or as reflecting the views of the U.S. Air Force Medical Department, the Air Force at Large, or the Department of Defense.