Review Article

Intravenous Iron to Treat Anemia becomes an Essential Service to Conserve Blood during the COVID-19 Pandemic

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Abstract

With the outbreak of Coronavirus Disease 2019 (COVID-19), blood drives have been cancelled, resulting in significantly fewer donations. However, blood components are still being used to treat patients with acute and chronic hemorrhage, trauma, cancer, hematologic disorders and even COVID-19 with disseminated intravascular coagulation. Consequently, national and local blood supplies will dwindle and may become critically limited. The clinician's stewardship in anemia management and blood use has become ever more important during this pandemic. Clinicians are responsible for the timely diagnosis of anemia, its treatable causes and prompt therapy with alternatives to blood transfusions. However, there are challenges during this pandemic with restrictions on travel with many institutions and practitioners limiting patient visits to prevent community spread of COVID-19.

To conserve the supply of blood components during the COVID-19 pandemic, proactive and efficient measures to diagnose anemia and timely treat with intravenous iron when indicated, while minimizing clinic visits are imperative. We advocate and share our experience with an anemia management process. Randomized controlled trials, cohort studies, and our institution's case examples demonstrate robust hemoglobin increases within as little as two weeks of treatment. Unfortunately, unsubstantiated concerns about the safety, costs and logistical challenges of administering intravenous iron have limited its use despite a safety profile similar to that of oral iron and superior to allogeneic blood transfusions. We argue that intravenous iron is integral to institutions' and clinicians' stewardship of blood supplies during the current shortage triggered by the COVID-19 pandemic.

Glossary of Terms

ASA-PS: American Society of Anesthesiologists Physical Status; CBC: Complete blood count; COVID-19: Coronavirus Disease 2019; eGFR: Estimated glomerular filtration rate; F: Female; FDA: Food and Drug Administration; Hb: Hemoglobin; IDA: Iron-deficiency anemia; IRB: Institutional Review Board; PPAE: Pre-procedure anemia evaluation; TIBC: Total iron binding capacity; TSAT: Transferrin saturation; TSH: Thyroid stimulating hormone; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

Introduction

As a precautionary measure during the Coronavirus Disease 2019 (COVID-19) pandemic, thousands of community-based blood drives have been canceled due to restrictions on gatherings and stay-at-home directives [1,2]. These restrictions have led to reductions in blood donations and availability of blood components [2]. Packed red blood cells have a shelf-life of 35-42 days, depending on the preservative used [3], and the recommended time interval between whole blood donations is 8 weeks [4]. The American Red Cross estimates that someone in the United States receives

blood every two seconds [4]. Perhaps this demand can be mitigated by wider adoption of recommended transfusion triggers. The American Red Cross issued an open letter projecting severe constraints on their inventory of red blood cells [1] and has encouraged blood donation at local blood banks amidst blood drive cancellations. Blood donors are critical to our medical infrastructure and there is growing concern that as the COVID-19 pandemic persists, potential donors, blood bank staff and resources will be affected [2]. Furthermore, although there have been no reported incidences of blood

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transmission of the severe acute respiratory syndrome coronavirus 2, SARS-CoV-2, the donor pool will be further limited if SARS-CoV-2 is found to be transmissible through blood [5].

Blood banks are exploring ways to mitigate the need for blood components in the coming months. The Food and Drug Administration (FDA) issued an update loosening restrictions on individuals deemed at higher risk of transmitting human immunodeficiency virus, Creutzfeldt-Jakob Disease and malaria [2]. Nationwide, cancellations of elective surgeries is estimated to reduce the number of blood units transfused weekly by 25% [1]. This measure helps, but does not eliminate the ongoing demand for blood components. However, as the pandemic abates and previously deferred surgeries are once again being done, there may be a surge in demand. In addition, in an attempt to defer procedures and limit patient appointments, patients with ongoing or newly developed medical conditions with associated anemia may not be receiving treatments, such as endoscopy for ulcers, or hormonal or interventional therapies for dysfunctional uterine bleeding, that can eliminate blood loss. Therefore, they may present with more severe anemia. Patients with cancer, trauma, acute bleeds and hematologic disorders also continue to require blood transfusions.

In collaboration with the blood bank, our anemia clinic, embedded within the preoperative clinic and entirely managed by anesthesiologists, has expanded services to non-surgical patients and made concerted efforts to educate providers about our services. Efforts to identify patients with the potential need for blood components, the continued provision of efficient and effective diagnosis of treatable anemias and treatment with intravenous iron are considered essential services during this period of elective healthcare limitations [6]. Specifically, we are targeting surgical and obstetric patients, and other at-risk populations.

Anemia

Anemia is one of the most common conditions encountered in perioperative and non-perioperative settings. It is present in up to 75% of elective surgical patients [7], 30% of obstetric patients [8,9], and 27.5% of emergency department patients [10]. Numerous studies have demonstrated an association between untreated anemia and increased morbidity and mortality. There is an increased risk of morbidity in patients even with mild-moderate anemia [11,12]. A hemoglobin of less than 8 g/dL is associated with a 10-fold increase in mortality [11]. In obstetric patients, peripartum anemia is associated with numerous adverse neonatal outcomes including low birth weight, pre-term birth, neonatal anemia and postpartum depression [13].
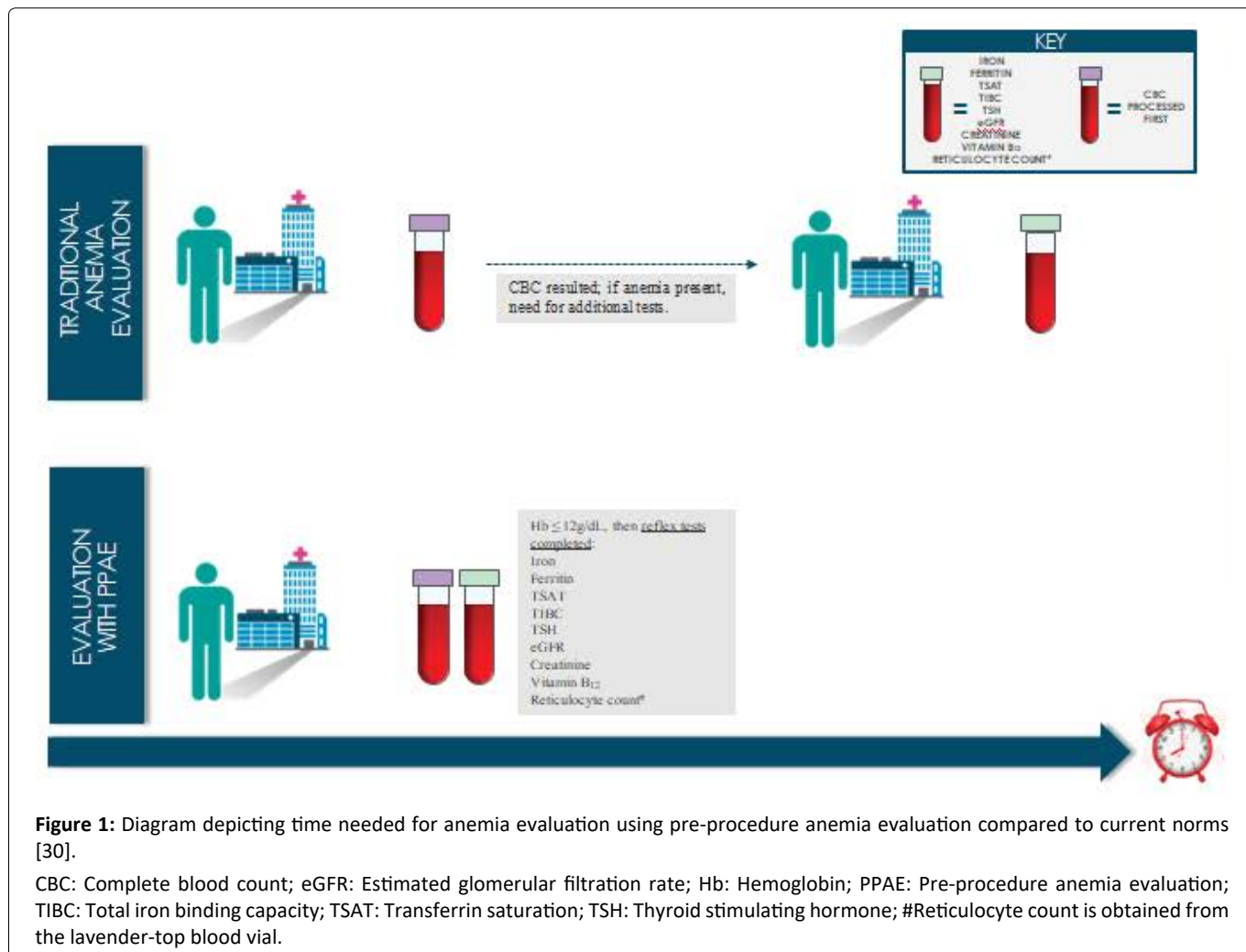
Historically, blood transfusions are used as the default therapy for anemia in the perioperative period and for severe reductions in hemoglobin concentrations. However, several studies have shown that blood transfusions are associated with postoperative complications such as infections, need for intensive care and prolonged hospital length of stay [14,15]. In fact, the severity of anemia is directly correlated with worse outcomes, such as the likelihood of readmission

within 30 days [16]. In obstetric patients, alloimmunization from exposure to antigens on transfused red blood cells is of particular concern. If a fetus carries these antigens, maternal antibodies can attack fetal red blood cells, causing hemolytic disease of the newborn, or even hydrops fetalis leading to intrauterine fetal demise [17]. Antepartum anemia is a leading risk factor for postpartum blood transfusion [18]. With 11.4% of maternal mortality attributed to postpartum hemorrhage [19], blood component shortage may lead to an increase in poor outcomes, as seen in resource-limited settings [20]. This underscores the importance of using alternative means to improve hematologic parameters in pregnant patients. Furthermore, blood transfusions are only a temporizing therapy that does not treat the underlying cause of anemia or replete iron stores to allow the bone marrow to produce red blood cells. The half-life of red blood cells is 57-59 days [21], so inherently, if the underlying cause of anemia is not addressed, patients re-develop anemia and remain transfusion-dependent. In addition to adverse outcomes, blood transfusion is expensive, poorly reimbursed and is a financial burden on hospitals [22,23].

The correlations among anemia, blood transfusions and associated negative outcomes have led to several studies on the treatment of anemia. Many have advocated for and developed patient blood management programs [24,25]. These efforts encourage healthcare providers to minimize blood transfusions by employing strategies to optimize hematopoiesis, reduce blood loss, and optimize anemia tolerance [26,27].

Anemia is a serious but treatable medical condition, rather than simply an often-ignored laboratory abnormality. Anemia should be considered an indication for rescheduling surgery until fully evaluated and ideally treated [28]. Common underlying causes of readily treatable anemia are iron or vitamin B_{12} deficiencies. Associated conditions contributing to anemia include hypothyroidism, malabsorption, malnutrition, blood loss and chronic kidney disease. Worldwide, iron deficiency is the most common etiology of anemia [7] including in the obstetric population [29]. A recent study showed that 37% of surgical patients had anemia, 70% of which were diagnosed with iron deficiency [30]. Treatment is especially beneficial in the elderly, pregnant patients, those patients having surgeries associated with significant blood loss, patients who refuse blood transfusions, and when perioperative anticoagulation is planned. It is important to reiterate that anemia, like any other disease, should be treated. Addressing chronic conditions can improve both perioperative and long-term outcomes [30].

Several studies have evaluated the use of oral and intravenous iron or erythropoietin stimulating agents to treat anemia in the perioperative period. Intravenous iron is significantly more effective and better tolerated than oral iron supplements in treating iron deficiency anemia (IDA) [6]. Iron infusion is a safe and well-recognized treatment for IDA in pregnant patients, particularly during late pregnancy [31,32]. Currently available intravenous iron preparations are safer and better tolerated than older intravenous formulations [33-35]. In a German study, administration of intravenous

Okocha et al. J Clin Anesth Pain Manag 2020, 4(2):156-164

Open Access | Page 157 |

Figure 1: Diagram depicting time needed for anemia evaluation using pre-procedure anemia evaluation compared to current norms [30].

CBC: Complete blood count; eGFR: Estimated glomerular filtration rate; Hb: Hemoglobin; PPAE: Pre-procedure anemia evaluation; TIBC: Total iron binding capacity; TSAT: Transferrin saturation; TSH: Thyroid stimulating hormone; #Reticulocyte count is obtained from the lavender-top blood vial.

iron showed decreased red blood cell transfusions in a select group of surgical patients. A limitation of that study is that patients were assessed a median of three days before surgery [36]. Although the optimal effect of iron infusion is seen at 3-4 weeks post-infusion [36], individual patient response to intravenous iron can vary based on bone marrow capacity. In one study of intravenous iron, 97% of patients doubled their reticulocyte counts within 48 hours of the infusion, with an increase in hemoglobin concentrations of 0.5 to 2.4 g/dL by post-infusion day 7 [30,37]. Another study showed an average increase of 2.5 g/dL among pregnant women 6 weeks after iron infusions [30]. However, one of the barriers to treatment of IDA is timely diagnosis.

Significant blood loss leads to more severe anemia. The use of tranexamic acid as an antifibrinolytic has been studied in the trauma and obstetric populations to limit hemorrhage. Although tranexamic acid and erythropoietin are associated with the risk of venous thromboembolism in some settings [38,39], this is far from universal as tranexamic acid has demonstrated safety in many patient populations [40,41].

Anemia Evaluation

At our institution, one of the authors (BJS) developed a testing protocol that allows for diagnosis and evaluation of common etiologies of anemia in one visit. The anemia test-ing protocol, the pre-procedure anemia evaluation (PPAE), was implemented in January 2017, and has been shown to effectively and efficiently diagnose anemia including IDA [30], thereby allowing for expedited treatment (Figure 1). The PPAE order set includes reflex anemia testing when a hemoglobin concentration is less than or equal to 12 g/dL on the complete blood count. Although the World Health Organization defines anemia as a hemoglobin less than 13 g/dL for men and less than 12 g/dL for women [42], we had designed the hemoglobin trigger for reflex testing on our PPAE at 12 g/dL or lower to simplify the process [30]. The diagnostic tests in the reflex testing evaluate the different etiologies of anemia and include reticulocyte count, serum iron concentration, transferrin saturation, serum ferritin concentration, total iron-binding capacity, thyroid-stimulating hormone concentration, creatinine concentration, estimated glomerular filtration rate and vitamin B_{12} concentration. The PPAE process has been described in detail elsewhere [30]. Using the PPAE to diagnose anemia limits patient visits to a single appointment, eliminating the need for patients to return for further testing. It is even possible to diagnose anemia, delineate the underlying cause and provide treatment with just one patient visit. This is especially important during the COVID-19 pandemic.

Treatment of Anemia

IDA is diagnosed when an anemic patient has a serum fer-

Table 1: Intravenous iron products, recommended dosing, adverse effects and costs [44,63-65,69].

Iron preparation	Dose	Adverse effects	Drug cost per 1000 mg[a]
Iron sucrose	200 to 300 mg every 2 days Infusion time: 15 minutes	Headache, muscle cramps, vomiting, diarrhea, nausea	$300-400
Ferric carboxymaltose	750 mg (weight ≥ 50 kg) or 15 mg/kg (weight < 50 kg) every 7 days Infusion time: 15 minutes	Nausea, transient hypertension, flushing, hypophosphatemia, dizziness.	$800-1000
Ferric gluconate	125 mg every 2 days Infusion time: 1 hour	Nausea, vomiting, diarrhea, hypotension, muscle cramps, hypertension, dizziness, dyspnea, chest pain	$150-250
Ferumoxytol	510 mg, 3-8 days apart Infusion time: 15 minutes	Diarrhea, headache, nausea, dizziness, hypotension, constipation, peripheral edema	$1800-2000
Low molecular weight iron dextran[b]	100 mg daily (20 mg/kg, maximum 1000 mg) Infusion time: 1 hour	Hypersensitivity reaction, nausea, vomiting, injection site thrombosis or phlebitis	$300-400
Ferric derisomaltose	1000 mg (weight ≥ 50 kg) or 20 mg/kg (weight < 50 kg) Infusion time: 20 minutes	Rash, nausea, hypophosphatemia	Not available[c]

[a]Associated costs such as personnel, consumables and capital equipment costs and patient-related costs such as lost wages and transportation not included; [b]Test dose recommended before first therapeutic dose; [c]Approved in the United States February 2020, data not available.

Figure 2: Sample order set for intravenous iron therapy.

ritin concentration less than 30 ng/mL or transferrin saturation less than 20% [43]. When IDA is diagnosed, evaluation of underlying conditions causing IDA is necessary. Algorithms for determining etiology have been described elsewhere [44]. Our preoperative clinic processes provide guidance to address medical conditions that require follow up. We either initiate and complete appropriate diagnostics and therapies, or partner with primary care physicians and specialists. Timely identification of IDA and treatment with intravenous iron to optimize hemoglobin and prevent transfusions are recommended [45].

The current practice at our institution utilizes the PPAE to evaluate patients suspected of being anemic, pregnant patients or those planning procedures with significant blood loss. Within hours, iron deficiency can be determined, allowing for timely treatment with iron infusion [30]. Various iron preparations are available (Table 1). Figure 2 shows a sample order set for intravenous iron therapy. The dose of intravenous iron is based on the calculated iron deficit using the Ganzoni formula:

Total iron dose (mg iron) = lean body weight (kg) (target hemoglobin - actual hemoglobin) (g/dL) 2.4 + 500 mg

Vitamin B_{12} is administered if pernicious anemia is diagnosed and erythropoietin injections are given when chronic kidney disease or anemia of chronic disease is present, and

in select circumstances such as for patients who refuse blood [46].

Safety of Intravenous Iron

Intravenous iron is a safer alternative than blood transfusions in iron-responsive anemia in light of the myriad of life-threatening acute complications from acute hemolytic transfusion reaction, transfusion-related acute lung injury and transfusion-associated anaphylaxis and infection [47,48]. Intravenous iron is also a more socially and economically responsible treatment of anemia given the current blood shortage and pandemic. There have been no demonstrable increase in rates of infection, severe gastrointestinal, cardiovascular, neurologic, respiratory or thromboembolic adverse events in patients given intravenous iron [49]. Ferric carboxymaltose is safe even at higher doses than available with other preparations, allowing for fewer clinic visits [50,51]. Ferric carboxymaltose is particularly favorable in this COVID-19 pandemic as total iron deficits can be replenished with only one or two visits. For example, a 750 mg weekly dose of ferric carboxymaltose, in contrast to the 200 mg alternate day dosing of iron sucrose, reduces the number of clinic visits from 8 to 2, in a patient with an iron deficit of 1500 mg.

In the past, there was a relatively high risk of anaphylaxis with older, high molecular weight dextran iron infusions. The carbohydrate shell that stabilizes the iron core to prevent pain
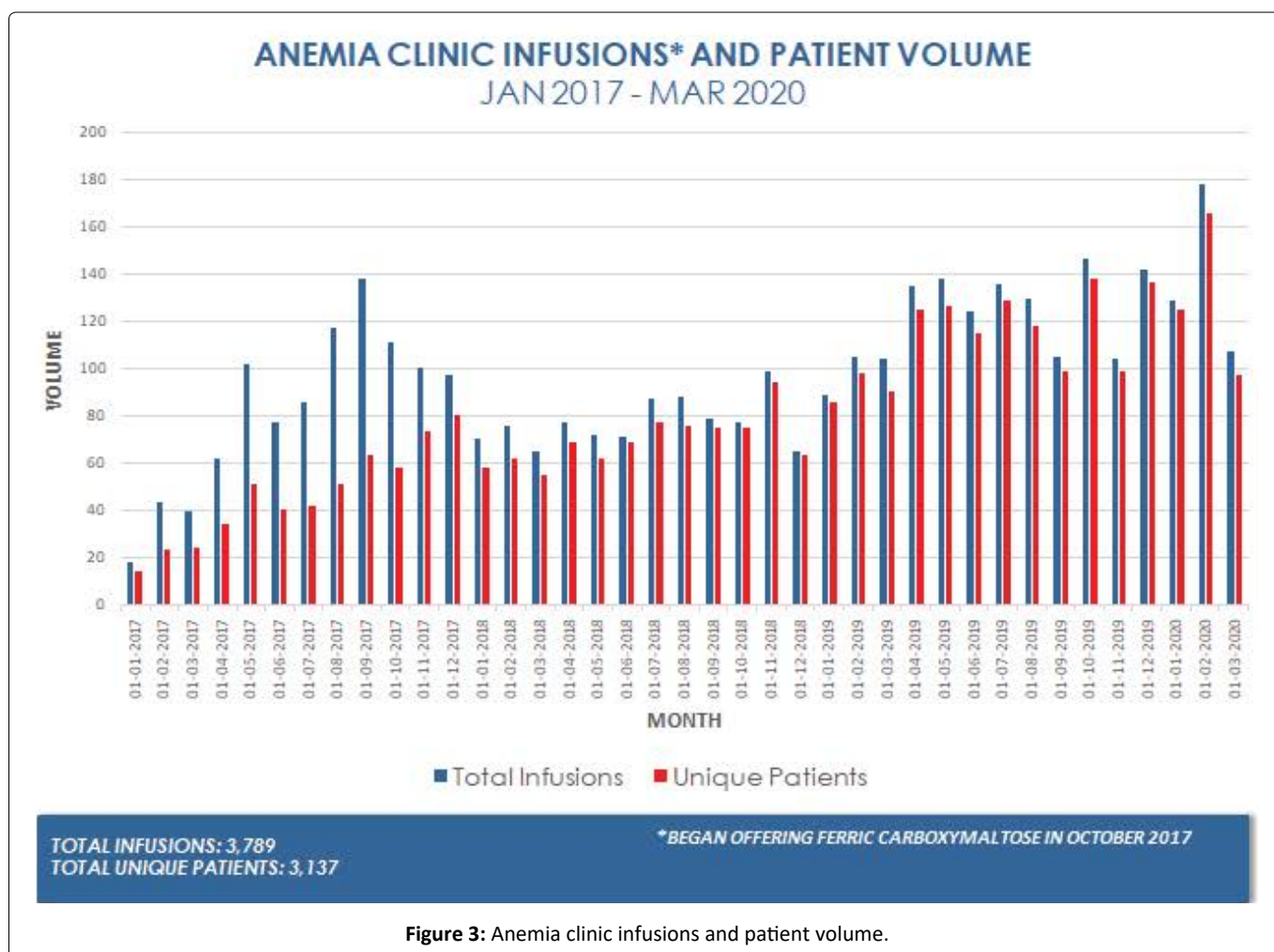

Figure 3: Anemia clinic infusions and patient volume.

with infusion and hemodynamic instability from rapid release of elemental iron have been implicated in infusion reactions ranging from anaphylaxis to a mild infusion reaction characterized by rash, myalgias, dizziness and palpitations without ventilatory or hemodynamic compromise [52]. However, infusion reactions are rare with current preparations [49]. Among the older formulations, iron sucrose has the lowest rate of anaphylaxis and continues to be used widely today due to its safety profile and cost [53]. Ferric carboxymaltose, with the most stable carbohydrate shell among the newer formulations, has the lowest rate of anaphylaxis. Other complications of intravenous iron infusions include skin staining from extravasation and hypophosphatemia. Painless, but potentially permanent, light brown skin staining has been reported [54-58]. Flushing the cannula with normal saline before and af-

ter infusion, and checking for site infiltration helps avoid skin staining [54,55]. Laser treatments can treat the stains without subsequent hypopigmentation or scarring [56]. Intravenous iron can cause hypophosphatemia within 1-3 weeks [49,59] as a result of renal phosphate wasting [60]. Two studies show that only ferric carboxymaltose causes severe hypophosphatemia, while iron sucrose causes mild hypophosphatemia of no clinical significance. The only consequence of hypophosphatemia in these studies was persistent fatigue [61-63]. Other, more severe consequences of hypophosphatemia such as cardiac arrhythmias may theoretically develop but have not been reported. High-risk patients should be monitored for low serum phosphate concentration and repletion with phosphate supplements as indicated [62]. In the last three years, our anemia clinic has safely administered more than 3,700

SAMPLE ANEMIA CLINIC DISCHARGE SUMMARY

If you have any questions or non-emergency concerns related to your iron infusion, please contact the Preoperative Clinic at XXX-XXX-XXXX between 7:30am and 5:30pm (Monday - Friday). If this is an emergency, visit your nearest emergency department or call 911.

Please understand that this content is intended to be used as supplemental information and does not substitute for the advice of your physician.

Today you received an iron infusion. Sometimes this medication can cause a decrease in your phosphate levels. This typically occurs 1-3 weeks after the infusion.

Symptoms that may indicate your phosphorus level is too low include:

• Changes in your mental state (for example, anxiety, irritability, or mild confusion)
• Bone issues, such as pain, fragility
• Fatigue
• Loss of appetite
• Muscle weakness

We recommend you increase phosphorus in your diet by consuming:

• Protein-rich foods such as
• Meats (especially white/light as opposed to dark chicken, turkey and pork)
• Fish
• Nuts
• Whole grains (wheat, oats, rice)
• Quinoa
• Sunflower and pumpkin seeds
• Peas, beans, lentils
• Soy
• Dairy products
• Chocolate
• Colas

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Figure 4: Sample of discharge instructions given to patients after intravenous iron infusion.

Okocha et al. J Clin Anesth Pain Manag 2020, 4(2):156-164

Open Access | Page 161 |

intravenous iron infusions (Figure 3), with only one patient reporting skin staining. When ferric carboxymaltose is administered, patients are warned about hypophosphatemia and phosphate-rich diets are recommended (Figure 4).

Of note, low molecular weight iron dextran is a formulation with a recommended dosing regimen that requires multiple visits to effectively replete iron stores since large intravenous doses have been associated with an increased incidence of adverse effects [63-65]. However, two studies suggest that doses of 1000 mg can be given in a single visit, though this is not FDA approved, and they reported a not insignificant number of adverse events [64,65].

Efficacy of Intravenous Iron

Iron deficiency anemia can be treated with oral iron which is inexpensive and readily available; however, oral iron therapy requires several weeks to months to have an effect. Oral iron is rarely effective because compliance with treatment is low due to patients' inability to tolerate oral iron preparations [30]. Furthermore, even when patient adherence to oral iron therapy is confirmed, oral iron is less effective than intravenous iron in improving hemoglobin concentration [66]. Intravenous iron infusions are used to expeditiously raise hemoglobin concentrations before surgery, during pregnancy and before delivery. This strategy can be applied to all hospitalized and ambulatory patients with IDA as a blood conservation strategy during blood shortages. Numerous studies have shown robust hemoglobin responses as high as 1.55 g/dl within two weeks even among patients with cancer in whom the etiology of anemia is multifactorial [45,66,67]. A randomized controlled trial of anemic patients undergoing elective cardiac surgery goes even further to show that a combination treatment using ferric carboxymaltose, erythropoietin, folic acid, and vitamin B_{12} just one day before surgery reduced blood transfusions [68]. Thus, iron infusion can rapidly increase hemoglobin and decrease the need for blood transfusions for patients with IDA to preserve our blood bank supply. Specific examples at our institution where intravenous iron effectively raised hemoglobin concentrations within a short timeframe are numerous. A few examples of patients with significant elevations in hemoglobin concentrations within days after intravenous iron infusions are shown in Table 2. Data presented in Table 2 is from institutional review board (IRB)-approved studies that include subsets of anemic obstetric and surgical patients treated in our anemia clinic with intravenous iron.

Conclusion

The COVID-19 pandemic has significantly impacted our national blood supply. Prompt and effective treatment of anemia conserves resources. With the poor outcomes and significant financial burden associated with blood transfusion, and the ineffective treatment of IDA using oral iron, we argue that intravenous iron should be considered first-line therapy [22]. Although outpatient intravenous iron administration with newer iron preparations may be expensive, this practice is a cost-effective treatment of IDA since one must consider costs beyond simply the drug itself. The repeat visits required with the less-expensive, older iron formulations carry significant health system costs related to supplies, equipment and personnel and patient-related costs such as number of venipunctures and lost time from work and family [22].

Intravenous iron is the most efficient treatment of IDA. Streamlined testing utilizing a protocol such as the PPAE allows for prompt diagnosis of anemia, and determination of iron deficiency if present. Diagnosis and treatment can be completed with only 1-2 patient encounters and has long term benefits. This strategy reduces workload on healthcare providers, limits exposure of patients to SARS-CoV-2, and conforms to compliance with travel restrictions. Therefore, we advocate that iron infusions are essential, time-sensitive medical treatments that warrant implementation and continuation by providers in both surgical and non-surgical specialties during the COVID-19 pandemic. Although the FDA has issued updated guidance aimed at acutely increasing the potential donor pool, the safety of this practice is yet to be determined. The uncertainty of the severity and duration of the pandemic, and the reluctance of individuals to leave their homes suggest that reductions in our blood supply may persist for some time. We encourage institutions and providers to adopt tests such as the PPAE for timely diagnosis of IDA, especially in advance of resumption of elective surgeries or ongoing procedures with high blood utilization, and to institutionalize the use of intravenous iron therapy for IDA. We recommend implementing these changes not only for the current COVID-19 blood shortage, but because future resource limitations are unpredictable.

Table 2: Characteristics of sample patients with significant elevations in hemoglobin concentrations following intravenous iron infusions[a].

Age (yrs)	Sex	ASA-PS	Comorbidities	Procedure	Initial Hb (g/dL)	Post iron infusion Hb (g/dL)	Hb change (g/dL)	Time interval (days)
33	F	2	Fibroids	Myomectomy	7.4	9.5	2.1	14
45	F	3	Lung cancer, Myasthenia gravis	Lung lobectomy	10.2	12.6	2.4	15
40	F	2	Pregnancy	Vaginal delivery	8.5	10.8	2.3	19
37	F	2	Twin pregnancy	Vaginal twin delivery	9.6	11.4	1.8	10
31	F	2	Gastric bypass	Cesarean delivery	8.1	9.7	1.6	14

ASA-PS: American Society of Anesthesiologists Physical Status; F: Female; Hb: Hemoglobin.
[a]No reported adverse effects or need for blood transfusions.

Acknowledgments

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Open Access | Page 163 |

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Okocha et al. J Clin Anesth Pain Manag 2020, 4(2):156-164

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