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Running head: UNKNOWN ANEMIA IN HEALTHY ADULT

Anemia of Unknown Origin in an Otherwise Healthy ASA 1 18-Year-old Male

By

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PERMISSION

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Abstract

Title: Anemia of Unknown Origin in an Otherwise Healthy ASA 1, 18-Year-old Male.

Background: An 18-year-old male undergoing an elective facial reconstructive surgery presented with a starting hemoglobin of 8g/dl. While the patient remained stable throughout the case and had no postoperative complications, the topic of blood transfusions and acceptable hemoglobin levels was posed.

Purpose: To evaluate and conclude current recommendations on blood transfusion triggers and alternate ways to manage blood loss while providing the best possible care within the operating room setting.

Process: Systematic search was conducted utilizing CINAHL and PubMed for research articles that were published in recent years that pertained to intraoperative fluid and blood loss management. Information from the review of literature was synthesized to develop evidence-based recommendations for healthy individuals within the perioperative setting.

Results: The literature shows positive results when a more restrictive transfusion protocol is instituted in healthy patients. The transfusion trigger should be between 7- 8 g/dl or if the patient becomes unstable. A balanced fluid replacement of crystalloids and colloids are recommended to replace blood loss. Pre-operative optimization is also recommended for patient with existing anemia.

Keywords: Blood transfusion, intra-operative fluid management, crystalloid, colloid, transfusion reactions, healthy, ASA 1-2

Background

The World Health Organization defines anemia as an insufficient circulating red cell mass, with a hemoglobin (Hgb) concentration of <13g/dl for men and <12g/dl for women (WHO, 2011). The concept of anemia has been around for over a century from when William Hewson first discovered that there was a large amount of red blood cells in circulation and concluded that they must contain some clinical importance. Since then, research has been discovering means in which to identify the amount of RBCs in the body through staining and advancements in microscopes (Uthman, 1998).

Historically, there were several crude measures in which health care providers treated anemia. In 1884, saline infusions replaced milk as the fluid of choice due to the large number of adverse reactions observed. Between 1924-1926, George Minot and William Murphy successfully treated pernicious anemia with large quantities of raw liver. Since then, many more advancements have been discovered to identify and treat anemia. According the Red Cross, the first successful human to human blood transfusion was completed by James Blundell in 1818. In 1907, the concept of cross-matching blood between donors was introduced by Ludvig Hektoen in order to decrease adverse reactions (Red Cross, 2017).

Hemoglobin is required for the transport of oxygen from the lungs to the tissues, the transfer of CO₂ from tissues to the lungs, buffering hydrogen ions formed in the erythrocyte from conversion of CO₂ to bicarbonate, and nitric oxide metabolism. It is made up of four protein molecules and is a component of red blood cells. Even a minor decrease in Hgb values can alter the bloods ability to maintain homeostasis (Thomas & Lumb, 2012).

The prevalence of anemia increases significantly with age. Males aged 17-49 have only a prevalence of 1.5% with female rates of 12.2%. The rate increases for males to 11% between 65-85 years of age, but decreases for females to 10.2% within the same age group. The incidence increases to 26.1% (males) and 20.1% (females) after the age of 85. In individuals from outside of North America and Europe, there is a much higher risk of iron deficiency anemia (Clevenger & Richards, 2015).

Within the pre-operative setting, one-third of all patients will present with some type of anemia, regardless of procedure being performed. There is also a much higher prevalence of pre-operative anemia in patients undergoing colorectal surgery. The prevalence increases anywhere from 39% to 75% within this group of patients. Anemia is commonly seen with increased frailty as evidence by 40% of all nursing home residents experiencing anemia. (Clevenger & Richards, 2015).

Anemia can often be expected in certain patient populations. This project will investigate the case of a healthy, asymptomatic 18-year-old male with significant anemia undergoing elective maxiofacial surgery. Anemia in this patient population is extremely rare especially when no signs or symptoms of anemia are present.

Case report

The case being explored was a healthy, 18-year old male undergoing an elective facial osteotomy for cosmetic reasons. He was 6' 1" and weighed 75kg. He had no past medical history and was classified as an ASA 1 with seasonal allergies. Current medication regimen included zyrtec and occasional ibuprofen. A preoperative examination included vital signs which were as follows: blood pressure 133/67, heart rate, 57, respiratory rate 18, temperature 36.5C, and oxygen saturation 98%. Laboratory data included a CBC with a Hgb 8.0 g/dl, hematocrit (Hct) 31%, and platelets of 481 K/uL. The remaining labs, including a complete metabolic panel and coagulation studies, were within normal limits.

The surgeon requested a nasal 8.0 ETT. He presented with a Mallampati II and a recessed mandible. Pre-oxygenation was completed for 5 minutes with the following medication regimen completed: 2 mg versed, 100 mcg fentanyl, 5mg Rocuronium, 150 mg Propofol, 8 mg Decadron, 4 mg Zofran, and 200 mg succinylcholine. Following neosynephrine spray to both nostrils, nasal intubation was obtained after two attempts utilizing a MAC 4 blade via the left nostril. A large amount of blood was suctioned during and following the intubation attempts, totaling 50 mL. The tube was taped at a depth of 30 cm measured at the left nare after end tidal carbon dioxide wave form was present and bilateral breath sounds were auscultated. An oral gastric tube was placed to decompress the stomach and remove any blood that may have entered the stomach during intubation. A volume control mode of ventilation was selected with the following settings: respiratory rate 12, tidal volume 600 ml, PEEP 4 cmH20, and FIO2 40%.

Depth of anesthesia was maintained using Desflurane 8% with doses of fentanyl, Dilaudid, and Rocuronium. 1g of Ofirmev was also given prior to incision. The patient was placed in the supine position with the arms tucked at his side. The intraoperative course began

with large amounts of blood loss following incision. After several doses of narcotics, 5mg Labetalol was given for a systolic blood pressure greater than 140 mmHg. No additional doses of Labetalol was required as the patient's blood pressure remained within 20% of baseline throughout the remaining course of the procedure. A repeat Hgb and Hct was obtained after 750 mLs of estimated blood loss, which revealed a Hgb of 7.1 g/dl and Hct of 26.1%. The patient remained stable and the decision was made to maintain fluid status with lactated ringers and 500mL of 5% Albumin. Transfusing PRBC's was discussed if significantly more blood loss was encountered or if the patient became symptomatic. The remaining intraoperative course proceeded uneventfully. Prior to extubation, Neostigmine 4mg and Glycopyrrolate 0.6mg was administered after 4/4 twitches were observed. The patient was extubated without incidence after the oropharynx was suctioned. Postoperatively, the patient reported no PONV and pain was treated with small doses of fentanyl. Fluid totals at the end of the case were as follows: EBL 1.25 L, crystalloid fluid total was 2.5 L, and 500 ml of Albumin. A follow up Hgb and Hct was drawn on arrival to the general floor which revealed a Hgb/Hct value of 6.7 g/dl and 26.4% respectively. The patient's vital signs remained close to baseline with no signs of hypovolemia or hypoxia. The patient was admitted to the medical/surgical floor overnight for observation and was discharged home the following day. A consult was made with the patient's primary physician to assess the patient's underlying anemia. The patient was subsequently diagnosed with celiac disease.

Discussion

Anemia

The WHO (2011) defines anemia as an insufficient circulating red cell mass, with a hemoglobin (Hgb) concentration of <13g/dl for men and <12g/dl for women. There are many forms and causes of anemia. The most common causes of anemia are iron deficiency, issues with the hemoglobin molecule, acute blood loss, and the presence of chronic disease.

Types of Anemia

Iron Deficiency Anemia

Iron deficiency anemia in adults is caused by chronic blood loss usually through the GI tract, through menstruation, or the bodies inability to absorb iron. Chronic blood loss may be too great for the body to adequately replace proper hemoglobin. Through the GI tract, the body is only able to absorb so much iron and can therefore produce RBCs with too little Hgb. Normally, iron enters the epithelial cell within the duodenal mucosa in a ferrous form. It enters through an apical or brush border membrane transport protein termed the divalent metal transporter. Iron flow into the blood plasma is regulated by a protein called hepcidin. In diseases such as celiac disease, both chronic blood loss and decreased iron absorption can lead to anemia (Freeman, 2015). Celiac disease was the diagnoses given to this patient and deemed the reason for the anemia.

Aplastic Anemia

Aplastic anemia occurs when the bone marrow stops producing the three hematopoietic cell lines, RBCs, WBCs, and platelets. Chemotherapy, irradiation, radiation, and other forms of

treating cancer along with viral illnesses like hepatitis or AIDS may also cause the marrow to not replace the mature red blood cells. In a majority of cases, the cause is idiopathic and no source can be identified. While the exact mechanism is unknown, it is thought that the exposure to any of the above stressors will lead to the production of cytokines by activated T cells. This will then lead to the suppression of normal stem cell growth and affect the creation of mature blood cells. Onset of symptoms is often delayed after treatment because existing blood cells remain viable. Treatment includes bone marrow replacement, blood transplantation, or immunosuppressive therapy (Grossman & Porth, 2014).

Hemolytic Anemia

Hemolytic anemia describes a wide range of acquired and inherited disorders that are characterized by the premature destruction of red cells, the retention of iron and other products of hemoglobin destruction, and an increase in erythropoiesis. We can further classify hemolytic anemia as intravascular, hemolysis, extravascular hemolysis, intrinsic, or extrinsic/acquired. Intravascular anemia occurs with mechanical injury, toxic factors, or as a result of complement fixation in transfusion reactions. Hemoglobinemia, hemosiderinuria, hemoglobinuria, and jaundice are seen with this type of anemia. Extravascular hemolysis occurs when red cells become less deformable, thus making it difficult for them to cross the splenic sinusoids. Jaundice is then seen after the abnormal cells are sequestered and phagocytized by macrophages in the spleen (Grossman & Porth, 2014).

Inherited hemolytic anemias show many different clinical manifestations due to the different causes of damage. Hereditary spherocytosis is an autosomal dominant trait and is the most common inherited disorder. This trait leads to a gradual loss of the membrane surface,

which causes the RBC to take a spherical shape that cannot easily transverse the spleen (Grossman & Porth, 2014).

Sickle cell disease is an abnormality within the Beta chain of the hemoglobin molecule. When an infected Hgb gene or HbS becomes deoxygenated or has a low oxygen tension, the HbS will take on a sickle shape. The cell may return to its normal shape after oxygenation, but repeated assaults will cause the HbS to retain the sickle shape. When enough of the hemoglobin molecule takes the sickle shape, chronic hemolytic anemia and blood vessel occlusion can occur. Blood vessel occlusion can be severe and very painful. The spleen is especially susceptible because it has low oxygen tension and sluggish blood flow. This predisposes individuals to numerous infections, especially in neonates and children (Grossman & Porth, 2014).

When severe, hypoxia can occur in other vital organs leading to pain from ischemia and can eventually lead to significant organ damage. The leading cause of death related to sickle cell anemia is acute chest syndrome, which is an atypical pneumonia resulting from pulmonary infarct. Diagnosis can be made from a simple blood test that is subjected to electrophoreses to detect HbS. While there is no definitive treatment for sickle cell anemia, medications such as hydroxyurea can limit the formation of HgS. However, side effects can occur with long term use. Most treatment goals are aimed at preventing sickling from occurring. Triggers include hypoxia, infections, cold exposure, dehydration, acidosis, and physical exertion. Other means to prevent attacks are to treat infections, hydrate, oxygenate, keep up to date with immunizations, and blood transfusions (Grossman & Porth, 2014).

Intrinsic hemolytic anemia can be caused by a deficiency of glucose-6-phosphate dehydrogenase, which is expressed only on the X chromosome. It leads to direct oxidation of Hgb to methemoglobin which then becomes unable to transport oxygen. This process will also

lead to denaturing of the Hgb molecule and lead to hemolysis two to three days after the triggering event. It affects nearly 400 million people and is most prevalent in Mediterranean and African populations. This condition can be diagnosed through a G6PD assay test (Nantakomol et al., 2013).

Acquired hemolytic anemias are caused by exogenous factors that cause direct membrane destruction or antibody-mediated lysis. Various drugs, chemicals, toxins, and infections can lead to destruction of red cell membranes. Mechanical factors such as vasculitis, burns, and prosthetic heart valves can also lead to hemolysis. Changes to microcirculation as seen in DIC or thrombotic thrombocytopenic purpura will create turbulence, leading to destruction of the cell. Acquired hemolytic anemias can be broken down further into warm or cold reacting antibodies. Warm-reacting antibodies react with antigens on the cell membrane that lead to spherocytosis and subsequent phagocytic destruction in the spleen. Cold-reacting antibodies occur in distant parts of the body where the temperature may drop below 30 degrees Celsius. The destruction occurs as the result of complement activation. Clinical presentation presents as pallor, cyanosis of the body, and Raynaud's phenomenon (Grossman & Porth, 2014).

Thalassemia is a group of inherited disorders of the Hgb molecule. There are three different categorizations within the Thalassemia diagnosis. Minor, which is the most common, has either an alpha or beta globulin mutation. Anemia is often only modest and can result in hypochromic and microcytic red blood cells. Thalassemia intermedia shows more prominent microcytosis and hypochromia along with greater anemia. The most severe form is thalassemia major. This is a severe, life threatening anemia. If not corrected, most patients will not survive childhood. In order to survive, many transfusions of red blood cells will need to be completed to correct anemia. Patients often display three defects including ineffective erythropoiesis,

hemolytic anemia, and hypochromia with microcytosis. These three deficits greatly reduce the bodies oxygen carrying capacity (Hines & Marchall, 2012).

Pernicious Anemia

Pernicious anemia occurs when the body is unable to absorb vitamin B12 due to atrophic gastritis. It is a form of megaloblastic anemia that is thought to result from immunologically mediated destruction of gastric mucosa. Megaloblastic anemia produces large, oval shaped red cells that have immature nuclei and show cellular destruction. The life span of these cells is significantly decreased compared to healthy cells. Clinical manifestations can be seen as anemia and mild jaundice with elevated MCV. Demyelination of the dorsal and lateral columns of the spinal cord may lead to paresthesia of the feet and fingers and alter proprioception. It can lead to dementia and confusion in advanced cases. The diagnosis can be made with the Schilling test and can be treated with B12 administrations either orally or IM (Grossman & Porth, 2014)

Fanconi Anemia

Auerbach (2009) describes Fanconi anemia as a genetically and phenotypically heterogeneous recessive disorder characterized by diverse congenital malformations, progressive pancytopenia, and predisposition to both hematologic malignancies and solid tumors. Hematologic abnormalities occur in most patient by the age of seven and bone marrow failure is seen in 90% of patient by the age of 40. A chromosome breakage test or cytometric flow analysis test is recommended if there is a genetic predisposition to this kind of anemia or if the patient is showing signs and symptoms. Blood transfusion is indicated as a short-term treatment with blood and marrow stem cell transplant, androgen therapy, synthetic growth factors, and gene therapy available for long term management.

Acute Blood Loss

Acute blood loss can be seen in the hospital setting which can result in anemia. This can be anything from a GI bleed to severe trauma such as a motor vehicle accident. The severity of the anemia is relative to the initial Hgb/Hct and the amount of blood lost. Treatment is specific to each individual patient based on their clinical presentation and medical history. Surgery is often required in these circumstances and intraoperative management may be difficult due to the presence of co-morbidities and the patient's acute situation (Hines & Marchall, 2012).

Anemia & Chronic Disease

Anemia related to chronic conditions refers to any disorder that can affect the formation or function of the Hgb. For example, chronic kidney disease decreases the amount of erythropoietin that is released. With limited erythropoietin, the bone marrow will not make adequate levels of RBCs, resulting in anemia (Hines & Marchall, 2012).

Clinical Presentation

Anemia can present as fatigue, which can be extreme, weakness, pale skin, headache, dizziness, decreased level of consciousness, cold hands or feet, brittle nails, chest pain, dyspnea, faintness, dim vision, and unusual cravings such as dirt or ice. Under general anesthesia, patients are unable to communicate these symptoms and thus anesthesia providers must rely on clinical presentation. Anemia may be suspected when there are low oxygen saturations (<90%), an increase in heart rate, a decrease in blood pressure, or if pulsus paradoxus is observed (Grossman & Porth, 2014). Hamzaoui, Monnet, and Teboui (2013) describe pulsus paradoxus as a fall of systolic blood pressure of greater than 10 mmHg during inspiration. While we need to rule out common causes of pulsus paradoxus, such as cardiac tamponade or acute asthmatic attack, it can

be a useful tool to indicate if severe hypovolemia is present. Another limitation with this sign is that it is not specific to RBCs, but to volume status as a whole. Additional testing and clinical judgment would need to be considered in order to diagnosis anemia.

Weiskopf et al. (2003) performed a study in which healthy, awake patients had their Hgb lowered to 5g/dl. This was performed with simultaneous removal of whole blood and immediate transfusion of either Albumin or autologous platelet-rich plasma to create an isovolemic anemia. It concluded that there was a linear relationship between lowered Hgb and an increase in heart rate (HR). It found that for each 1g/dl of Hgb loss there was an increase in heart rate of 4 beats per minute. It also discussed that the increase in heart rate may not be seen with patients who are anesthetized due to medications, including opioids, that decrease the sympathetic response that should occur with corresponding anemia. However, these patients may present with unexplained tachycardia post operatively.

In chronic cases, ventricular hypertrophy can occur and may lead to high output cardiac failure as the heart attempts to compensate for hypoxia. As described above with different anemias, jaundice may be seen with increased levels of bilirubin along with petechia and purpura leading to small hemorrhagic spots or purplish skin. In addition, anemia could be a cause of any unexplained acidosis (Grossman & Porth 2014).

Lab

Hemoglobin, as discussed earlier, is the protein that is responsible for carrying oxygen. Hgb values delineates the amount of Hgb that is circulating within the body and is described in grams per deciliter. Hematocrit will usually coincide with Hgb. Meaning as one increases, the other will also increase. However, Hct measures all RBCs within the blood and its number is

expressed as a percentage compared to whole blood. In a healthy adult, a normal Hct is between 41.5-50.4% (AACC, 2015). Mean corpuscular volume (MCV) and mean corpuscular hemoglobin concentration (MCHC) will also reveal more specific causes of anemia. MCV reflects the size of red cells and the MCHC signifies the concentration of hemoglobin within each cell (Grossman & Porth, 2014). We will also later discuss that preoperative testing is not indicated for healthy patients undergoing elective procedures. The occurrence of anemia, that is not previously diagnosed based on other symptoms, is extremely unlikely within this population (Olson, Stone, & Lubarsky, 2005).

Recommendations

When to Transfuse

There has been much debate on what the optimal transfusion trigger is when encountering anemia in the perioperative setting. In the past or what is now referred to as a liberal transfusion protocol, the threshold is between a Hgb of 9-10 g/dl. This protocol was established in an attempt to maintain as close to normal physiologic levels as possible (Carson et al., 2016).

Currently, literature is recommending a more restrictive transfusion protocol with the trigger being around 7 g/dl. However, there are additional factors that need to be considered before making, or not making the decision to transfuse blood. The main factors to be considered, besides Hgb, is whether or not the patient is hemodynamically stable and is the expected blood loss going to overcome our estimated allowable blood loss. Past medical history is also a major factor, as the trigger point would be much higher for someone with a severe cardiac history (Grossman & Porth 2014). This project will focus on patients with ASA scores of 1 and 2.

The American Association of Blood Banks (AABB) conducted a large literature review that investigated 31 RCTs which amounted to 12,587 participants through 7 decades. They ultimately compared patient outcomes based on liberal transfusion protocol (trigger at 9-10g/dl) or restrictive (7-8g/dl). The data showed no difference in adverse clinical outcomes, including 30- day morbidity and mortality, strokes, rebleeding, or myocardial infarction. In addition, the restrictive transfusion group actually showed slightly better outcomes due to a decrease in transfusion related issues (Carson et al, 2016).

The AABB also provided specific guidelines for patients with pre-existing comorbidities. It recommended a threshold of 7g/dl for hospitalized adults who are hemodynamically stable. In patients undergoing orthopedic surgery or cardiac surgery with preexisting cardiovascular disease, the threshold should be 8g/dl as long as hemodynamic stability remains. The AABB also stated that patients with acute coronary syndrome, severe thrombocytopenia, and chronic transfusion-dependent anemia should not follow these guidelines. The AABB did not provide specific guideline for these individuals (Carson et al., 2016).

Olson, Stone, and Lubarsky (2005) performed a retrospective study that looked at over 14,000 ASA 1-2 patients who presented for elective surgery. Of these patients, only 0.8% had a starting Hgb of less than 9g/dl. Four of these patients did require transfusions, but all were due to preexisting conditions or intraoperative blood loss. The study recommended a restrictive transfusion protocol and to not transfuse unless Hgb was less than 7g/dl or if the patient became hemodynamically unstable. It even recommended that no preoperative lab testing is required if no preexisting conditions were identified.

Carson and Patel (2014) observed outcomes looking at patients who refused/were unable to receive blood products and found that only after Hgb levels dropped below 5g/dl was there a

significant increase in morbidity and mortality. While this study did not have a large enough sample size to change practice, it shows that the transfusion trigger could be even lower than current recommendations. An additional study conducted by Carson et al. (2016) demonstrated no increase in 30-day morbidity and mortality among patients placed in a restrictive versus liberal transfusion protocol group. It did identify that there was a decrease in hospital length of stay and an increase in patient satisfaction scores. It also revealed that when side effects of blood administration were factored into the 30-day mortality and morbidity that the restrictive protocol provided a safer option. It also showed a decrease in acquired transfusions by 43% (Carson & Patel, 2014).

Blood Transfusion and Side Effects

In the past, research determined the best treatment for blood loss and anemia was to transfuse blood. As discussed earlier, the literature shows that this is not always the best treatment due to the potential side-effects. However, in certain situations, the need for a blood transfusion is required to increase intravascular volume and the blood's oxygen carrying capabilities despite the potential side effects.

Blood is often transfused at a ratio of 1:1 with blood loss. On average, one unit of PRBCs will increase Hgb values by an average 1g/dL or 2-3% for Hct (Grossman & Porth, 2014). In today's practices, providers typically replace blood loss with PRBCs, but in some major trauma areas or military bases whole blood may be used. The major drawback to a blood transfusion is the side effects that could occur. A retrospective study completed by Hendrickson et al. (2016) identified that transfusion reactions of varying degrees could occur in up to 59% of transfusions, although they are often underreported and only carry a documented rate of about 5%. Since

many of the early signs of transfusions are reported by the patient, making an early diagnosis may be difficult within the OR setting where about 50% of transfusions occur.

Blood transfusion reactions can be broken down into *acute reactions* which occur within minutes to hours or *delayed reactions* which can occur days to months after the transfusion. Signs and symptoms of a reaction include the following: fever, chills, tachycardia, dyspnea, nausea, vomiting, chest tightness, hypotension, bronchospasm, anaphylaxis, shock, pulmonary edema, and CHF (Carson et al., 2016).

Hemolytic reactions occur when the recipient's antibodies are found within the donor blood. This can either be an ABO incompatibility or an incompatibility related to another blood group antigen. This leads to a severe hemolytic, immune mediated reaction. Serious issues such as DIC or renal failure along with death can occur if unrecognized or untreated. Since antibody testing has been mandated, this type of reaction has decreased although reactions are still seen due to mislabeling errors. Allergic reactions can also be seen due to plasma proteins. Reactions can be as severe as anaphylaxis or as minor as itching (Hendrickson et al., 2016).

Transfusion related acute lung injury (TRALI) carries the largest mortality rate of any transfusion reaction. It causes acute, non-cardiogenic pulmonary edema. While the exact mechanism is unknown, there is a significant increase in capillary leak causing the edema. Circulatory overload is also a risk due to the amount of PRBCs that may be given. Overload can manifest as nonspecific dyspnea or agitation in individuals with CHF or cardiac insufficiency being the most sensitive (Carson et al., 2016).

Delayed reactions are often underreported due to the onset of symptoms. They often present as unexplained fever or with a decreased Hct. It is caused by a recall secondary immune

response to donor red cell antigens. Treatment is often not necessary as the symptoms are not life threatening (Carson et al., 2016).

When large volumes of blood or massive transfusion protocols are initiated, there are additional issues that may arise. Citrate toxicity may occur due to the addition of the product to prevent clots while in storage. Hyperkalemia can occur especially in units that have been in storage for an extended period of time. Fresh units carry less than 0.5 mEq of potassium but blood units nearing expiration (42 days) may have as much as 5-7 mEq of potassium. Coagulopathies may also develop due to hemodilution and other factors such as hypothermia, acidosis, and shock. Conversely, the AABB found there was no difference in morbidity and mortality in patients who received fresh versus near expiration of PRBCs (Carson et al., 2016).

Measures to manage these reactions is specific to each reaction but usually involves supportive measures. This includes treating symptoms, replacing electrolytes, and vigilant preparation prior to transfusion. The best treatment is early recognition and cessation of the blood product (Refaai & Blumberg, 2013).

Fluid Management and Side Effects

Intraoperative fluids are administered with almost every case and there are many options to choose from. Most cases begin with a crystalloid solution with 0.9% normal saline or lactated ringers (LR) as the most popular options. Both are isotonic solutions with LR having the closest composition to ECF. Hourly maintained rate can be calculated using the 4-2-1 rule, along with replacing NPO deficit and insensible loss. The replacement of blood is often calculated at a 3:1 ratio when using crystalloid components. Crystalloid fluid has a limited half-life of around 20-60 minutes and only about 1/5 of the fluid remains in the intravascular space (Strunden, Heckel,

Goetz, & Reuter, 2011). Issues associated with 0.9% NS is hyperchloremic metabolic acidosis due to the chloride component. Another side effect of using large of amounts of crystalloids is hemodilution. Lahsae, Ghaffaripour, & Hejr (2013) discussed how Hgb and Hct are affected by crystalloid fluid replacement. Within their limited study group (50 patients) they found an average decrease of 1% of Hgb and Hct per 158 to 160ml of fluid. Patients identified in this study were ASA 1-2 and had no preexisting medical issues that would affect these levels. Average starting Hgb drawn pre-operatively was 13.47. The second draw, one hour into the procedure, was 12.08. The third, an hour post operatively, was 11.69. The average amount of crystalloid given was 2,118ml and average case was 105 minutes.

Colloids

An alternative to crystalloid solutions is a group of high molecular weight substances categorized as colloids. Colloids have an intravascular half-life of 3-6 hours, depending on the patient and specific agent being used, because it does not easily cross the capillary membrane. Colloids will also affect the oncotic pressure within the vascular space, drawing fluid into the vascular space further increasing volume. Colloids should replace blood loss at a 1:1 ratio and should be considered when 3-4 L of crystalloid solution is given. They will result in a more rapid fluid resuscitation when compared to crystalloid solutions. Colloids can be broken down into two separate categories, natural (albumin) or artificial (Hespan) (Mitra & Purva, 2009).

Albumin, the principal natural colloid, comes in either 5% or 25% solutions, and is manufactured from pooled donor plasma. 5% is often used within the perioperative setting and as much as 80% of the solution stays within the intravascular space. It is also indicated in patients with liver failure or liver transplant due to its active oncotic properties. 25% can increase volume by as much as five times the original amount given and the effects can be seen

for as long as 24 hours. 25% may be used when individuals have excessive ECF and are requiring intravascular expansion or when hypoalbuminemia is present (Butterworth, Mackey, Wasnick, 2013). Advantages of albumin is that it is natural occurring and has a smaller side effect profile when compared to other colloids. A disadvantage of albumin is the cost as it is more expensive when compared to other colloids. It can also cause fluid overload, especially when the 25% solution is used, when compared to other colloids and crystalloid solutions. There is a theoretical risk of disease transmission as it is from human donors, but is rarely seen (Mitra & Purva, 2009).

Dextran is an artificial colloid that is made up of highly branched polysaccharide molecules. It has similar volume expansive properties as albumin at a cheaper price, but has a much larger side effect profile. It has the largest rate of anaphylactic reactions amongst colloids, it coats RBCs leading to interference with cross-matching, is seen in precipitation of acute renal failure, and can lead to coagulation abnormalities. It can cause ARF through accumulation of dextran molecules in the renal tubules leading to a plug. Coagulation abnormalities stem from decreased platelet adhesiveness, decreased factor VIII and increased fibrinolysis (Mitra & Purva, 2009).

Hydroxyethyl starches (HES) are either prepared as 6% or 10% and mixed with 0.9% NS or LR. The volume expansion of 6% HES is similar to 5% albumin with 10%, the volume expansion will be slightly greater. Advantages of HES compared to Albumin is it's reduced cost. In addition, larger volumes can be given (50ml/kg) when compared with dextrans. Like dextrans, HES also comes with a significant side effect potential. It can delay coagulation by reducing factor VIII, impair platelet function, and prolong partial thromboplastin and activated partial thromboplastin time. In larger doses, it can lead to pruritus from deposits in skin and other

tissues. Renal impairment can also result in osmotic nephrosis like lesions in both proximal and distal renal tubules. Anaphylactoid reactions are also a risk when administering HES products. When mixed with 0.9% NS, hyperchloremic metabolic acidosis can result with large amounts (Mitra & Purva, 2009). These side effects are associated with first and second generation products, but there is still some debate about third generation products such as Voluven and it's safety profile. Voluven's volume expansion properties should be comparable to other HES products, but it is made up of a smaller molecule and is associated with less plasma accumulation (Nagelhout & Plaus 2014). This product has less effect on coagulation and is associated with a decrease in intraoperative blood loss when compared with 2nd generation products (Mitra & Purva, 2009). A systematic review performed by Jartog, Kohl, & Reinhart (2011) found that there is no adequate evidence to support that Voluven has a safer renal profile than other HES products and that it may even have less volume expansion properties than expected.

Preoperative optimization

The optimal manner in which to prevent the need for a transfusion is to have your patient optimized prior to surgery, if possible. Due to the different causes of anemia, as discussed earlier, certain treatments are available to increase Hgb. Iron supplementation can be prescribed if iron deficiency anemia is present. Ferrous sulfate is cheap, but absorption can be affected by gastric content and acidity. IV iron is also available if iron loss exceeds absorption, if the patient is unable to tolerate treatment, or patients undergoing chemotherapy. If treatment is successful, Hgb levels should increase by about 1 g/dl every two to three weeks. If anemia is due to B12 or folate deficiency, supplementation should be initiated. Oral folate tablets are available and cobalamin IM injections may be needed to correct deficiencies. Treatment is often well tolerated within these individuals. The final treatment is erythropoietin. Erythropoietin can be utilized in

patients with anemia of chronic disease, chronic renal insufficiency, and other hematological disease. Erythropoietin, normally released in response to low oxygen levels within the blood, stimulates bone marrow to produce more red blood cells. Goal for therapy should be for a Hgb of around 12 g/dl. Erythropoietin has been known to increase tumor progression and should be used cautiously with patients at risk (Patel & Carson, 2009).

While there is no exact cut off for canceling a case based on low hemoglobin, any value below normal in an otherwise healthy adult should be investigated further. The lower the starting hemoglobin, the greater the 30-day morbidity and mortality especially when starting values are below 7 g/dl (Patel & Carson, 2009). If co-morbidities are present, the threshold would be at an even higher number. Increased risk is always associated if the patient is not properly optimized prior to surgery. If they are not, the surgery should be postponed or canceled in the elective population. Unfortunately, anesthesia providers don't always have this luxury in emergent cases.

Conclusion

Based on the information obtained in this independent project, a different approach to this case study should have been taken. The first and probably most significant change would have been to cancel the case because it was elective and non-emergent. The patient's anemia should have been investigated further and Hgb measures should have taken place prior to surgery.

Interestingly, preoperative labs were not warranted in this patient. The patient's underlying anemia may have never been detected and the patient would have continued on an uneventful surgical course. The literature shows that this was an extreme outlier and will not occur often. However, vigilance and continued clinical observation would have led to a similar diagnosis if the patient had deteriorated. In regards to fluid management and the decision to not transfuse, the literature supported the above anesthesia/surgical plan. Some recommendations do state that the trigger should be around 7 g/dl, but the majority of researchers found that a transfusion is not warranted if vital signs and clinical presentation continue to be stable.

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Appendix

The following PowerPoint presentation will be presented at the 2017 fall North Dakota Association of Nurse Anesthetists meeting in Bismark, ND.


Anemia in a Healthy Patient
Andrew Rook, SRNA



Anemia Presentation

- Fatigue
- Pale skin
- Dizziness/feeling of faint
- Decreased LOC
- Cold hands/feet
- Chest pain
- Dyspnea
- Unusual cravings such as dirt or ice
- Low O2 sats (<90%)
- Increase In HR
- Decrease in BP
- Pulsus paradoxus


(Grossman & Porth, 2014)



Fluid Administration: A Historical Perspective

- 1739 William Hewson observed "Ruddy Globules" under microscopic and due to the large number decided that they must be important
- 1852 Karl Vierordt found fewer RBCs in what was deemed an "Anemic" patient
- 1818 1st human to human blood transfusion
- 1884 saline infusions replaced milk as fluid of choice
- 1907 Ludvig Hektoen introduced the concept of cross-matching blood


(Urthma, 1998)



Prevalence

- Age
 - 17-49- Male: 15% Female: 12.2%
 - 65-85- Male: 11% Female: 10.2%
 - >85- Male: 26.1% Female: 20.1%
- Individuals presenting for colorectal surgery (39%-75%)
- Frailty- Nursing home patient carry a 40% rate
- Individuals from outside of North America and Europe

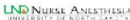
(Clevenger & Richards, 2015)



Hemoglobin Physiology

- Transport of oxygen from lung to the tissues
- Transfer of CO2 from tissues to the lungs
- Buffering hydrogen ion formed in erythrocytes from conversion of CO2 to bicarbonate
- Nitric oxide metabolism


(Thomas & Lumb, 2012)



Types of Anemia

- Iron Deficiency
 - Chronic blood loss through GI or inability to absorb iron
- Aplastic Anemia
 - Bone marrow stops producing RBCs along with WBCs and platelets
- Hemolytic Anemia
 - Wide range of acquire and inherited disorders
 - Characterized by premature destruction of RBCs, retention of iron, and increased erythropoiesis
 - Sickle cell disease and thalassemia

(Grossman & Porth, 2014)



Types of Anemia continued

- **Fanconi Anemia**
 - Heterogenous recessive disorder
 - Hematologic abnormalities seen in most by age 7 with complete bone marrow failure by age 40
- **Pernicious Anemia**
 - Body is unable to absorb vitamin B12
- **Acute blood loss**
- **Anemia of Chronic disease**
 - CKD

(Grossman & Porth, 2014)

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Anesthetic Course

- **Induction**
 - Versed 2mg
 - Fentanyl 100mcg
 - Rocuronium 5mg
 - Propofol 150mg
 - Succinylcholine 200mg
- **Technique**
 - 7.0 ITT placed nasally, MAC 4, 12 attempts after rocuronium spray administered
 - 50ml EBL
- **Vent Settings**
 - VC, RR 12, TV 600, PEEP 4cmH2O, FiO2 40%
- **Maintenance**
 - Desflurane 8%
 - Fentanyl 50-100mcg Prn
 - Dilaudid 1mg
 - Rocuronium Prn
 - Ofirmev 1g
- **Anti-emetics**
 - Zofran 4mg
 - Decadron 4mg
- **Reversal**
 - Neostigmine 4mg
 - Glyco 0.6mg

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Case Information

- **Surgical Procedure**
 - Elective facial osteotomy
- **Pertinent Patient Information**
 - 38 year old, male
 - 75kg 73in
 - ASA 1
 - Seasonal Allergies

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Intraoperative issues

- After 750ml EBL additional H&H ordered
 - Hgb 7.1g/dl & Hct 26.1%
 - Vital signs stable
- I/O
 - EBL total 1.25L
 - 2.5L LR
 - 500 ML's 5% Albumin
 - 350 ML's UO
- **Total Anesthesia Time**
 - 3 hours 20 min

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Pre-operative Evaluation

- No pertinent medical/surgical HX
- Pre-op VS
 - BP: 133/67, HR: 57, RR 18, O2 Sat: 99% on RA, and temp. 36.5C
- **Pertinent labs**
 - Hgb: 8.0 g/dl
 - Hct: 31%
 - Pts 481 K/uL
- Airway evaluation
 - Mallampati II, recessed mandible, and full ROM

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PACU

- Awake extubation was completed with no issues
- Pain level 3/10
 - Additional Prn fentanyl ordered
- No PONV or intraoperative awareness reported
- Transferred to Med/Surg floor
 - Discharged the following day
 - Repeat H&H revealed 6.7 g/dl and 26.4%

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Preoperative Evaluation for Anemia

- CBC
 - Hemoglobin/Hematocrit
 - Differentiate etiology of anemia
 - Not recommended on healthy individuals presenting for elective surgery
- Age
- Medical history
 - Cancer
 - Kidney disease
 - Etc.
- Ethnic Background
- Surgery being performed
(Olson, Stone, & Lubarsky, 2005).

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Colloid Fluid

- High molecular weight substance
- Replace blood loss 1:1 ratio
- Can increase IV volume by as much as 5X the volume given
- IV 1/2 life of 3-6 hours
- Natural
 - Albumin- More expensive, small risk of disease transmission
 - Smaller side effect profile when compared to other colloids
- Artificial
 - Much cheaper
 - Larger side effect profile- reduce coags, renal impairment, & anaphylactoid reactions
- Does not replace oxygen carrying capacity
(Mitra & Purva, 2009)

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Intraoperative Treatment Options

- Crystalloid
- Colloid
- Blood
- Preoperative management
 - Iron
 - B12
 - Folate
 - Erythropoietin

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Blood

- Replace blood loss 1:1 ratio
- PRBCs should increase Hgb by 1g/dl and Hct 3%
- Side effects can occur in up to 59% of transfusions
 - SE include: fever, chills, tachycardia, dyspnea, N/V, bronchospasm shock, pulmonary edema, and CHF
 - Only a documented rate of about 5%
 - TRALI carries largest mortality rate- Non-cardiogenic pulmonary edema
 - Massive transfusions can lead to citrate toxicity and hyperkalemia

(Carson et al., 2016)

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Crystalloid Fluid

- LR & 0.9% Normal Saline
- 4-2-1 rule
- Replace blood loss 1:3
- Intravascular half life of 20-60minutes
- Only about 1/5 of the volume remains within the intravascular space
- Side effects
 - Hyperchloremic metabolic acidosis
 - Hemodilution
 - * 1% decrease in Hgb and Hct per 100ml of fluid
- Does not help oxygen carrying capacity
(Lahassee, Ghaffaripour & Heir, 2013)

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Transfusion Triggers

- Restrictive- Hgb 7-8g/dl
- Liberal- Hgb 9-10g/dl
- Allowable blood loss
 - More blood loss predicted
- Past medical history
- Surgery being performed
- Vital signs
(Grossman & Porth, 2014)

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Transfusion Triggers Cont.

- AABB looked at 31 RCTs (12,587 participants)
- Found no increase in adverse clinical outcomes
 - (30 day M&M, strokes, rebleeding, or MI)
- Actually showed slightly better outcomes when transfusion reactions were included. (Carson et al., 2016)

- Retrospective study looking at 14,00 ASA 1-2 patients for elective surgery
 - 0.8% had starting Hgb <9g/dl
 - All had preexisting conditions
 - Only four required blood transfusions
 - Again, all had preexisting conditions

(Olson, Stone, & Lubarsky, 2005)

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Conclusion

- Restrictive transfusion protocol (7-8g/dl) has a less adverse effects than a more liberal protocol
- Blood loss can be effectively managed through other fluids
- Routine labs do not need to be drawn on healthy individuals presenting for elective cases
- If labs not optimized prior to elective case- Cancel case and reassess the patient

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Transfusion Triggers Cont.

- Carson and Patel (2014) looked at a group that refused/were unable to receive blood products
- Significant increase in N&M wasn't observed until Hgb levels dropped below 5g/dl
- Showed that triggers points could eventually be lower (Carson & Patel, 2014)

- Another study conducted by Carson et al. demonstrated no increase in 30 day M&M when a restrictive transfusion protocol was used
 - Decrease in hospital length
 - Increase in patient satisfaction
 - Decreased transfusion reactions by 43%

(Carson et al., 2016)

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Preoperative Management

- Iron supplementation- ferrous sulfate/IV iron
 - Iron deficiency anemia
- B12 or folate deficiency
- Erythropoietin
 - May be needed for any type of bone marrow suppression
- Cancel procedure if Patient is not optimized
 - Not always an option

(Patel & Carson, 2009)

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Thank You
Any questions?

