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Anesthesia Considerations for Intraoperative Blood Transfusion

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ANESTHESIA CONSIDERATIONS FOR INTRAOPERATIVE BLOOD TRANSFUSION

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ABSTRACT

Title: Anesthesia Considerations for Intraoperative Blood Transfusion

Background: Bleeding during surgery is inevitable. Blood transfusions are commonly administered intraoperatively in effort to maintain adequate oxygenation of vital organs; however, blood transfusions are not without considerable risk. Hence, anesthesia professionals should be made aware of when blood transfusion may be of more benefit than harm.

Purpose: The purpose of this independent study is to provide a case report as well as an extensive review of the current evidence on administering blood transfusions during the intraoperative period for the surgical patient.

Process: A review of the literature was performed using PubMed and the Cochrane Library databases from the University of North Dakota's Health Sciences Library. Each reference was carefully selected for inclusion in this review, which was conducted between September 2016 and February 2017.

Results: Anesthesia professionals must ensure patients are optimized prior to surgery in effort to minimize blood loss and prevent the need for intraoperative blood transfusion. Current literature supports restrictive versus liberal transfusion. Specific guidelines regarding intraoperative transfusion are vague and leave much room for anesthesia professionals judgement. In the event that massive transfusion of blood products is required, it is recommended to transfuse a high ratio of fresh frozen plasma (FFP)/red blood cell (RBC) and platelet (PLT)/RBC.

Implications: Morbidity and mortality of patients may be decreased if anesthesia providers are knowledgeable about surgical transfusion practices.

Keywords: Blood transfusion, massive transfusion, transfusion ratios, survival, mortality, surgery, and noncardiac surgery.

Anesthesia Considerations for Intraoperative Blood Transfusion

The Joint Commission (2012) identified RBC transfusion as one of the most overused interventions performed in the United States. Blood loss during surgery is likely; the degree can vary depending on the surgery and individual patient factors. Thus, it is of no large surprise that most RBC transfusions in the United States occur in surgical patients (US Department of Health and Human Services, as cited by Qian et al., 2013). Certainly, intraoperative blood transfusion may be life-saving at times; however, blood transfusion is not a benign intervention. Blood transfusions have been associated with immunomodulation, which may cause several other complications. In addition, blood transfusions contribute significantly to healthcare costs. In 2010, the cost of a single unit of red blood cells (RBCs) from acquisition to transfusion was estimated to be between $1,600 - $2,400 (Wu et al., 2010). Addressing surgical blood management will not only affect patient safety, but healthcare costs as well (Ferraris et al., 2011).

Estimated blood loss for a radical nephrectomy is approximately 500ml. However, if the renal vein or inferior vena cava (IVC) is involved, the complexity of the surgery is increased and the chances of intraoperative complications, such as bleeding, are greater. A team approach, which includes cardiothoracic surgery, may be utilized if the tumor significantly involves the IVC as the patient may require cardiopulmonary bypass under hypothermia as the ICV is clamped (Jaffe, Schmiesing, and Golianu, 2014).

The decision to transfuse blood must not be made frivolously. Rather, the benefits versus the risks of transfusion must be carefully considered based on the individual patient and particular situation. In the following pages, a case report of an elderly man with renal malignancy, which required intraoperative blood transfusion, while undergoing a radical robotic nephrectomy is presented. A review of literature regarding transfusion practice during the intraoperative period for surgical patients will then be presented.

Purpose

The purpose of this independent project is to review a case report and provide anesthesia professionals with evidence-based research regarding blood transfusion in the noncardiac surgical patient. By understanding when intraoperative transfusion is warranted, morbidity and mortality rates associated with intraoperative blood transfusion may be reduced. Thus, anesthesia professionals may improve surgical patient outcomes by being knowledgeable in appropriate transfusion practices.

Case Report

A 65-year-old, 110 kg, 175 cm, Caucasian male presented for a right radical robotic (possibly open) nephrectomy for the treatment of primary kidney cancer with metastasis to the lung. The surgery was elective with the intent as being cytoreductive rather than curative. Prior to surgery, the patient had a coil placed in his right renal artery to decrease the potential for intraoperative bleeding. He denied having any allergies. His medical history was significant for hypertension, diabetes mellitus type 2, and a cerebrovascular accident (CVA) in 2013. Surgical history included tonsillectomy, bronchoscopy, and an endobronchial ultrasound. There was no history of anesthetic complications. Current medications included aspirin, fish oil, tamsulosin, insulin glargine, lisinopril, amlodipine, and clonidine.

The patient was considered an American Society of Anesthesiologists physical status level three. He was a Mallampati class II with full neck range of motion and no notable dental history or viable issues. His preoperative electrocardiogram (EKG) showed normal sinus rhythm. Preoperative vital signs were: blood pressure 166/72, heart rate 72, respirations 20, pulse oximetry 90% on room air, and temperature 36.9° Celsius. His preoperative labs were as follows: hemoglobin 14.2 g/dL, hematocrit 42.5%, platelets 187,000 per mcL, PT 10.4 seconds, PTT 23.8 seconds, INR 0.97, BUN 25 mg/dL, creatinine 1.56 mg/dL, CO2 20 mEq/L, Na 138 mEq/L, Cl 100 mEq/L, K 3.7 mEq/L, and glucose 149 mg/dL. The patient's blood type was AB positive without antibodies. Two units of RBCs had been typed and cross matched prior to surgery and were available.

In the preoperative holding room, a 20-gauge peripheral intravenous (IV) catheter was started in the patient's right antecubital area. A 1L bag infusion of lactated ringer's solution was begun and midazolam 2mg was given IV. The patient was transported to the operating room (OR) by a registered nurse, certified registered nurse anesthetist, and a student registered nurse anesthetist. Upon arrival to the OR, the patient was assisted to the operating table and standard non-invasive monitors were applied.

The patient was pre-oxygenated via face mask at 8 liters per minute (LPM) for approximately three minutes. For induction, fentanyl 50mcg, lidocaine 50mg, propofol 200mg, and cisatracurium 20mg were given. The patient was intubated via direct laryngoscopy using a Macintosh 3 blade. A grade I view was obtained and a 7.5mm cuffed endotracheal tube (ETT) was visualized passing through the vocal cords without difficulty. After intubation, bilateral breath sounds were auscultated. End-tidal carbon dioxide ($ETCO_2$) monitoring was present and the ETT was secured in place with tape. The patient was placed on mechanical ventilation and desflurane was initiated with end-tidal concentrations of 6-7%. Initial fresh gas flows were 1 LPM of air and 1 LPM of oxygen. A nasopharyngeal temperature probe was inserted into the right nare and a bispectral index (BIS) monitor was applied to his forehead. The left radial artery was cannulated with a 20-gauge arterial line without ultrasound guidance and a 16-gauge peripheral IV catheter was inserted in the left hand. A 1L bag of 0.9% sodium chloride with blood tubing on a fluid warmer was attached to the newly placed IV. A Foley catheter was inserted by the registered nurse.

The patient was repositioned in the left lateral decubitus position with a sandbag and the kidney rest up. An upper Bair hugger was placed across his thorax and arms as he was sterilely prepped, draped, and the robot was positioned into place. Prior to incision cefazolin 2g as well as famotidine 20mg, metoclopramide 5mg, dexamethasone 10mg, and ondansetron 4mg were given.

Approximately three hours into the operation, general surgery was consulted due to the tumors proximity and adherence to the hepatic flexure of the bowel. Three options were presented: have general surgery assist and perform a bowel resection, abort the surgery as it was not intended to be curative, or have urology continue attempting to dissect the tumor away from the bowel. At that time, the decision for urology to proceed without general surgery was made. After another hour passed, the urologist decided to convert to an open radical nephrectomy due to tumor size and involvement with surrounding tissues. The robot was removed from position as the surgeon scrubbed and sterilely donned a gown and gloves. At that point, the patient remained hemodynamically stable with negligible blood loss. Mild hypoglycemia (75 mg/dL) had been corrected with dextrose 25g.

Roughly 30 minutes after converting to an open procedure, the surgeon notified the anesthesia team about blood loss and he determined that the IVC had been inadvertently incised. The blood bank was immediately called and the 2 units of RBCs that had been typed and cross matched were sent to the OR. In the meantime, the surgeon attempted to contain the bleeding by holding his fingers over the opening in the IVC, while anesthesia rapidly infused the two liters of crystalloid that were hanging.

The previously consulted general surgeon came to assist, while waiting for the vascular surgeon to arrive. A transesophageal echocardiogram (TEE) was performed by the anesthesiologist, which showed an empty left ventricle. Simultaneously, several units of RBCs were transfused, as well as infusion of several liters of crystalloid and colloid. IV boluses of epinephrine, phenylephrine, ephedrine, and vasopressin were given as well as calcium gluconate 4g, and a total of 300mEq of sodium bicarbonate. Eventually, phenylephrine and epinephrine infusions were initiated and the desflurane was stopped due to severe hemodynamic instability. Two subsequent doses of cisatracurium, 10mg each, were given to prevent any patient movement. After receiving no sedation for an extended period, the patient's BIS reading was between 3-10.

A total of 12 units of RBCs, 3 units of PLT, and 1 unit of FFP were transfused in the OR. Total estimated blood loss in the OR was approximately 8,000ml and the patient's estimated total blood volume was 8,260ml. Total urine output at the end of surgery was 430ml.

Once the bleeding was controlled, the patient was transferred to the critical care unit (CCU). The anesthesia team determined that the patient would remain intubated upon transfer. The transfusions of blood products and infusions of vasopressors were continued as the patient was transferred to the CCU. Upon arrival to the CCU, the patient cardiac arrested. One round of cardiopulmonary resuscitation was performed. A single lumen right femoral central line was placed by the general surgeon for increased IV access and care was turned over to the critical care physician.

Two days after the surgery, the patient was extubated. On the third postoperative day, he was transferred out of the CCU to a general floor. The patient's mental status had returned to baseline; he was alert and oriented to person, place, and time.

Literature Search

An online review of current evidence was completed using the University of North Dakota's Health Sciences Library website. The criteria for inclusion were: publication date within the past 5 years, availability in English, and human subjects. Knowing that significant vasculature, such as the IVC, may be involved during a nephrectomy, the initial focus was blood loss and transfusion during a radical nephrectomy as well as associated morbidity and mortality. However, several preliminary searches involving such focus were without avail. Failed searches performed on PubMed included the medical subject heading (MeSH) terms: *nephrectomy (adverse effects, complications, mortality), robotic, kidney neoplasms, renal cell carcinoma, bleeding, blood transfusion, hemorrhage, blood component transfusion,* and *vena cava* in various combinations. Similar searches were performed on CINAHL using CINHAL headings without success. A research and education librarian from the Library of Health Sciences at the University of North Dakota was contacted for assistance with the literature search. Likewise, the searches by the librarian yielded insufficient results.

The scope of the literature review was broadened to include intraoperative transfusion of patients undergoing general noncardiac surgery and associated morbidity and mortality. PubMed was searched with the MeSH terms *blood transfusion (standards, surgery)* and *surgical blood loss*. The search yielded 13 articles, one of which was selected for inclusion. A link of similar articles was provided which contained 104 results. When the inclusion criteria were applied (publication date within the past 5 years, availability in English, and human subjects), 41 results remained, six of which were selected for review. One article of particular interest contained a link to similar articles; inclusion criteria remaining, 402 articles were available for review. Thirteen applicable articles were carefully selected.

Additional journal articles were found by reviewing the reference lists of the aforementioned articles. Articles which met the inclusion criteria were selected, except for certain recurring references or more specific articles of interest, which had publication dates outside of the past 5 years. The average publication date of the older selected articles (5) was 6.6 years. Each selected article was found by typing in the title in the search field of PubMed or the Cochrane Library. After the above selection process and careful consideration of each article, a total of 23 articles were selected for inclusion in this literature review.

Discussion

It is well known that RBCs are needed to carry oxygen to the tissues. In a state of anemia, less oxygen is readily available to be exchanged and the body attempts to compensate by increasing cardiac output. The elderly, such as the patient presented in the case report, have less physiological reserve and may be unable to compensate adequately. Additionally, the workload of the heart is greater, which may be deleterious to an already ailing heart. Blood is transfused in effort to increase hemoglobin concentration; subsequently, increasing oxygen delivery while decreasing the demand on the heart (Carson et al., 2016).

Patients may be anemic for various reasons: iron deficiency, renal disease, cancer, and perhaps the most common reason intraoperatively, surgical blood loss. Blood transfusion is the most common treatment for anemia and despite the expense, may be overused (Glance et al., 2011; Mastracci et al., 2012, Smilowitz et al., 2016). The overuse of blood transfusion may negatively impact the health of surgical patients (Qian et al, 2013). Adverse effects, such as immunomodulation, may be particularly detrimental in already immunocompromised patients, such as those with malignancy. Consequently, it is important to understand when transfusion is in the best interest of the patient versus when it is not. Various researchers have explored this matter in attempt to determine best practice guidelines.

The elderly patient in this case report had renal disease, cancer, and underwent a right radical nephrectomy which placed him at an increased risk for preoperative anemia and significant blood loss. He had not yet started radiation/chemotherapy, which would have caused him to become substantially immunocompromised, increasing the risks associated with blood transfusion. His history of chronic hypertension may have resulted in a rightward shift in his cerebral autoregulation curve; resulting in higher mean arterial pressure (MAP) required to maintain constant cerebral blood flow. Also, his history of a previous CVA and diabetes placed him at an increased risk of poor neurological outcomes in the event of decreased perfusion to the brain.

Transfusion Thresholds: Blood Loss and Anemia

Wu et al. (2010) retrospectively examined 239,286 older patients (>65 years) at the Veteran Affairs (VA) hospitals with the intent of determining an association between intraoperative blood transfusion and 30-day postoperative mortality. The study included eight surgical specialties: general, vascular, orthopedics, urology, noncardiac thoracic, neurosurgery, otolaryngology, and plastic surgery. It was found that patients benefited from transfusion if they had "substantial" operative blood loss (>500ml) or a low preoperative hematocrit (<24%). However, transfusion in patients who did not have substantial blood loss or had a preoperative hematocrit between 30-35.9% had an associated increase in mortality.

Based on the framework of the previously discussed study, Wu et al. (2012) again retrospectively studied 46,608 older patients (>65 years) who received an intraoperative transfusion when undergoing major noncardiac surgery at a VA hospital. In this study, the relationship between hospital rates of transfusion in patients experiencing significant (>500ml) blood loss and 30-day mortality was examined. The researchers found that hospitals which transfused patients with significant blood loss had lower risk adjusted 30-day postoperative mortality rates.

Likewise, in a retrospective observational study, Chen et al. (2015) examined 424,015 older patients (>65 years) who received an intraoperative blood transfusion while undergoing noncardiac surgery at a VA hospital. The relationship between intraoperative blood transfusion and 30-day risk adjusted postoperative mortality was examined at a hospital-level. The study concluded that hospitals which transfused patients with an indication for transfusion (preoperative hematocrit <24% or surgical blood loss >500 ml), had lower risk adjusted 30-day postoperative mortality rates.

Smilowitz et al. (2016) also conducted a retrospective cohort study of 3,050 patients undergoing major orthopedic surgery: hip, knee, and spine surgery. The average patient age was 60.8 years and approximately 41% of the subjects were male. Patients with a higher preoperative hemoglobin had higher associated mortality risk with transfusion, while those with lower preoperative hemoglobin levels did not: the hazard ratio of patients with no preoperative anemia (hemoglobin 12 or > in women, 13 or > in men) was 4.39 versus 0.81 in patients with moderate/severe anemia (hemoglobin <9).

Likewise, Saager et al. (2013) also researched preoperative anemia and the association with 30-day postoperative mortality rates. The American College of Surgeons National Surgical

Quality Improvement Project (ACS-NSQI) database was used to perform a retrospective analysis. A total of 574,860 noncardiac surgical patients, which underwent propensity matching, were included in the study. Trauma and pediatric patients are not included in the database and were subsequently not included in this study or others using the ACS-NSQIP database. Approximately 25% of patients had baseline anemia; anemia in this study was defined as hematocrit <36% in women and <39% in men. Preoperative anemia was independently associated with increased postoperative mortality rates. Saager et al. (2013) suggests that transfusion of blood prior to surgery may be preferable to intraoperative transfusion as "allogeneic blood transfusion compromises the immune system as well and might cause a second hit to an already weakened immune system when performed in the intraoperative period" (p 914).

Low Volume Transfusion

Bernard, Davenport, Chang, Vaughan, and Zwischenberger (2009) queried the ACS-NSQIP database to evaluate the effect of low volume intraoperative blood transfusion (1 to 2 units) of RBCs on morbidity and mortality of patients undergoing general surgery. The study was a prospective, systematic study that included 125,177 patients undergoing noncardiac general surgery. The mean age of patients included in the study was 52.9 years, approximately 40% of which were male. The study concluded that transfusion of merely 1 or 2 units of RBCs intraoperatively increases morbidity and mortality.

Similarly, Ferraris et al. (2011), also utilized the ACS-NSQIP database to conduct an exploratory observational study of patients undergoing noncardiac, nonvascular thoracic surgery. Patients were further divided into three groups based on type of surgery: lung/pleura/chest wall, nonvascular within the mediastinum, and esophageal operations. A total of 8,728 patients, which were propensity-matched, were included in this study. The effect of small amounts (1 or 2 units) of intraoperative RBC transfusion on 30-day morbidity and mortality was evaluated. The results of this study were much like those of Bernard et al. (2009); overall, morbidity and mortality were increased with transfusion of 1 or 2 units of RBCs.

Ferraris, Davenport, Saha, Austin, and Zwischenberger (2012), also used the ACS-NSQIP to compare patients undergoing noncardiac operations who received 1 unit of RBCs intraoperatively versus both patients who did not receive an intraoperative transfusion and those who received more than 1 unit of RBCs. A total of 941,496 patients, which were propensity-matched, were included in this longitudinal, uncontrolled observational study. The findings supported an association between intraoperative transfusion of 1 unit of RBCs and morbidity, especially infectious complications such as wound infections, pneumonias, and sepsis.

Lastly, Glance et al. (2011) performed a retrospective analysis using the ACS-NSQIP database to observe the association between intraoperative transfusion of 1 or 2 units of RBCs and morbidity and mortality in patients with “severe” baseline anemia (hematocrit <30%) undergoing noncardiac surgery: general, vascular, and orthopedic surgery. The study included 10,100 patients. Patients who received 1 or 2 units of RBCs intraoperatively were compared to those who did not receive a transfusion. Transfused patients experienced a higher 30-day mortality rate in this observational study.

Transfusion within 72 Hours

Abdelsattar, Hendren, Wong, Campbell, and Henke (2015), studied the effect of blood transfusion within 72 hours of surgery on 30-day mortality in patients greater than 18 years undergoing vascular or general abdominal surgery. Information obtained for the study stemmed from the Michigan Surgical Quality Collaborative (MSQC), which includes 52 hospitals. A total of 2,243 patients who received a RBC transfusion within 72 hours were included in this propensity score matched observational study. Overall, patients which received a postoperative blood transfusion had increased rates of 30-day mortality; paradoxically, an exception to these findings was an associated decreased risk of myocardial infarction.

Ferraris, Hochstetler, Martin, Mahan, and Saha (2015), used the ACS-NSQIP database to evaluate the effect that blood transfusion within 72 hours of surgery had on operative outcomes. The records from more than 300 acute care hospitals were analyzed. The intent of this observational study was to identify patients which may be “helped” from transfusion versus those that would be “harmed”. Patients undergoing cardiothoracic, vascular, neurosurgery, or general surgery were included in the study. Patients who underwent cardiac surgery were excluded from analysis. A total of 470,407 patients were included in the study, 32,953 of which received a transfusion within 72 hours of surgery. Predicted operative mortality was calculated for each patient based on various preoperative variables such as age, ASA class, preoperative illness (pneumonia, sepsis), steroid use, preoperative cancer diagnosis, preexisting bleeding disorder, etc. It was discovered that patients which were the most “high-risk” did not have significant risk with blood transfusion; however, “low-risk” patients had a substantially increased risk of morbidity associated with blood transfusion. The researchers posit that careful preoperative evaluation of transfusion risk and proper intervention prior to elective procedures may decrease morbidity and mortality associated with blood transfusion.

Cancer and Immunomodulation

Al-Refaie, Parsons, Markin, Abrams, and Habermann (2012) specifically looked at the effect of blood transfusion on cancer surgery outcomes. The ACS-NSQIP was utilized to identify 38,926 patients >18 years of age who underwent surgical resection for thoracic, abdominal, or pelvic neoplasms. Approximately 60% of patients included in this prospective study received only 1 or 2 units or RBCs. Overall, intraoperative blood transfusion was found to have adverse effects on surgical outcomes, including 30-day postoperative mortality. Unlike other studies, such as those performed by Wu et al. (2010) and Chen et al. (2015), blood transfusion was shown to have adverse effects despite a low or normal hematocrit level.

Ferraris, Ballert, and Mahan (2013) utilized the ACS-NQIP database to retrospectively explore the relationship between intraoperative blood transfusion and the development of systemic inflammatory response syndrome (SIRS). Patients who underwent outpatient procedures were excluded from the study. A total of 553,288 patients were included in the study, 40,378 of which received an intraoperative blood transfusion. The development of SIRS may increase the risk of patients developing serious complications such as respiratory failure and multiple organ dysfunction. After propensity-matching of risk factors, transfused patients had increased rates of morbidity, including SIRS, and mortality. Most patients in this study received 1 or 2 units of RBCs. The researchers conclude that limiting intraoperative transfusion may improve patient outcomes by decreasing the risk of developing SIRS.

Blood Loss Prevention

Some bleeding during surgery is to be expected; however certain precautions may be taken to decrease the occurrence of major bleeding. For non-emergent surgeries, such precautions should be initiated long before the patient arrives in the OR. Prudent anesthesia professionals should carefully review previous medical records as well as conduct a thorough interview of the patient. Information obtained should include history of previous blood transfusions, drug-induced or congenital coagulopathies, thrombotic events, as well as risk factors for organ ischemia (American Society of Anesthesiologists Task Force on Perioperative Blood Management, 2015).

Anticoagulation medications should also be discontinued as appropriate; the risk of thrombosis versus the risk of bleeding must always be carefully considered. The American Society of Anesthesiologists Task Force on Perioperative Blood Management (2015) has developed the following specific guidelines regarding anticoagulation therapy:

> In consultation with an appropriate specialist, discontinue anticoagulation therapy (i.e. warfarin, anti-Xa drugs, antithrombin agents) for elective surgery.
>
> - Transition to shorter acting drugs (i.e. heparin, low-molecular-weight heparin) may be appropriate in selected patients.
> - If clinically possible, discontinue non-aspirin antiplatelet agents (i.e. thienopyridines such as clopidogrel, ticagrelor, or parsugrel) for sufficient time in advance of surgery, except for patients with a history of percutaneous coronary interventions.
> - Aspirin may be continued on a case-by-case basis. (p. 245)

Additionally, erythropoietin and/or iron may be administered to treat iron deficiency anemia and reduce the chance of requiring an intraoperative blood transfusion. Autologous blood may also be donated prior to surgery (American Society of Anesthesiologists Task Force on Perioperative Blood Management, 2015).

For the case report patient, precautions were taken preemptively to decrease the chance of significant blood loss prior to surgery. The patient had undergone embolization of the right renal artery in the catheterization laboratory. Preoperative labs including hemoglobin, hematocrit, platelets, as well as coagulation studies were within normal range prior to surgery. Two units of blood had been typed and cross matched for the patient and were readily available in the blood bank. A second peripheral IV was inserted for additional vascular access and a 0.9% sodium chloride infusion on blood tubing and a fluid warmer was begun in preparation for the event that transfusion was indicated. A radial arterial line was placed for vigilant hemodynamic monitoring. Prior to the patient arriving to the OR, a fluid table was prepared and used for guidance of fluid administration and urine output was monitored throughout the case. The room was routinely scanned for blood loss contained in canisters and saturated laparotomy pads. Vasopressors, such as ephedrine, phenylephrine, and vasopressin were given as needed to maintain a MAP greater than 70. A less invasive approach at surgery was initially attempted with the da Vinci robot; however, despite best attempts of the surgeon after several hours of dissecting the surgery was converted to an open approach.

Intraoperative Transfusion Management

As Ferraris et al. (2015) stated, “Blood transfusion can be both good and bad, depending on the clinical situation” (p. 608). Identifying when intraoperative blood transfusion will be “good” for patients versus “bad” is important and may be an indicator of surgical quality (Wu et al., 2012). Certainly, blood transfusion may be life-saving at times, especially in the case of an actively hemorrhaging patient, such as was in the presented case. As discussed previously, in a study by Chen et al. (2015) and Wu et al. (2012), patients with an indication for transfusion, preoperative hematocrit <24% or surgical blood loss >500ml, had a lower 30-day risk-adjusted mortality if they received a blood transfusion intraoperatively.

However, in the absence of massive bleeding or symptomatic anemia, despite the theoretical benefits of blood transfusion, it has not proven to be advantageous (Smilowitz et al., 2016). Much debate over the ideal transfusion trigger has persisted in recent years. Not surprisingly, there has been a wide variation in transfusion practices (Abdelsattar, et al., 2015; Ferraris et al., 2012; Qian et al., 2013).

Current literature supports restrictive versus liberal transfusion. Dose-dependent increases in morbidity and mortality have been observed with blood transfusion (Ferraris et al., 2012; Johnson et al., 2016). Transfusion of even small amounts, 1 or 2 units, of blood intraoperatively has been associated with adverse surgical outcomes (Bernard et al., 2009; Ferraris et al., 2011; Ferraris et al., 2012; Glance et al., 2011). In a recent Cochrane review, which included a wide variety of patients (surgical, critical care, acute blood loss/trauma, cancer) initiation of blood transfusion at a restrictive threshold (hemoglobin 7 to 8 g/dL) did not have adverse effects on 30-day mortality, cardiac morbidity, or infection when compared to initiation at a liberal threshold (hemoglobin 9-10 g/dL) (Carson et al., 2016). Transfusion guidelines published by The American Society of Anesthesiologist's Task Force on Perioperative Blood Management (2015) remain unspecific and leaves much room for anesthesia professionals discretion:

> The determination of whether hemoglobin concentrations between 6 and 10 g/dl justify or require red blood cell transfusion should be based on potential or actual ongoing bleeding (rate and magnitude), intravascular volume status, signs of organ ischemia, and adequacy of cardiopulmonary reserve. (p. 251)

Currently, no specific algorithm can be recommended; however, restrictive transfusion of RBCs may be safely implemented (The American Society of Anesthesiologist's Task Force on Perioperative Blood Management, 2015).

Massive Transfusion

In the event of major surgical bleeding, as was seen in the case report, massive transfusion may be required. Halmin et al. (2016) identified major surgery as the most common indication for massive transfusion. Hence, the effects of massive transfusion on morbidity and mortality of the patient is of interest. It is also important to understand that not all massive transfusion protocols are the same. Blood component products at various facilities may be released in different volumes. Research regarding best component ratios during massive transfusion must be understood to develop protocols that will best improve patient outcomes.

Massive transfusion has also been associated with morbidity and mortality. Turan et al. (2013) used the ACS-NSQIP database to prospectively collect data and examine complications as well as 30-day mortality rates in patients undergoing noncardiac surgery who received massive transfusion (5 RBC units). A total of 5,143 patients were included in the study. An association between massive transfusion and adverse patient outcomes was found. With each unit transfused, patients were estimated to have a 5% decreased chance of being discharged alive.

Johnson et al. (2016) performed a retrospective analysis of medical and surgical patients who received high-dose transfusion (>10 units throughout hospitalization) and the association with patient morbidity and mortality. Approximately 3,500 patients met inclusion criteria; certain patient populations, such as those with hematologic malignancies were excluded from the study. Patients were further stratified into eight groups based on transfusion volume: 0, 1-9, 10-19, 20-29, 30-39, 40-49, 50-75, and >75 units. Overall, mortality increased in a linear fashion as transfusion volume increased; approximately 10% for every 10 units of RBCs or 50% mortality for 50 units of transfused RBCs. However, surgical patients had decreased morbidity and mortality compared to massively transfused non-surgical patients. This disparity may be attributable to the cause of bleeding being correctable with surgical intervention in the surgical population.

Similarly, Brown et al. (2012) performed a multicenter prospective cohort study using the Inflammation and the Host Response to Injury Large Scale Collaborative Program to evaluate adult patients with blunt injury and hemorrhagic shock who were between 18 and 90 years of age and received massive transfusion (10 or more units of RBCs within 24 hours of admission). A total of 604 patients met inclusion criteria. The study found an association between high early ratios of blood products (FFP/RBC 1:1.5 and PLT/RBC 1:9) and decreased patient mortality in the first 24 hours. Similarly, Holcomb et al. (2011) retrospectively examined ratios of PLT/RBC transfusion in 643 massively transfused trauma patients (10 units or more of RBCs within 24 hours of admission) and mortality. The findings from this study support early transfusion of high ratio (defined in this study as 1:1) PLT/RBC transfusion in massively transfused patients.

Conversely, Sharpe et al. (2012) prospectively collected data to evaluate the effect of the number of RBC transfused on FFP/RBC and PLT/RBC ratio transfusion in 165 surgical trauma patients at Presley Regional Trauma Center. Activation of this protocol is based on clinician judgement rather than physiologic criteria. The protocol at this facility released 10 units of RBCs, 10 units of plasma, and 10 single-donor platelet units. Patients who were taken directly to surgery and received at least 10 units of RBCs by operation completion were included in the analysis; a total of 135 patients met the criteria. The average patient was 36 years of age and male. Sharpe et al. (2012) discovered that the more RBC units transfused, the less likely high component ratios were received by the end of the surgery. The reason for a lower ratio of product transfusion with increasing number of RBC units transfused was not clear. Patients who received a higher number of RBC units and lower FFP/RBC transfusion ratio had an increased mortality risk.

The facility at which this case took place had a massive transfusion protocol (MTP) policy in place. The policy stated four reasons for activating the MTP: life-threatening trauma, unexpected surgical/obstetrical blood emergencies, surgeries expected to require massive transfusion, or others as determined (Sanford, 2016). The patient presented in this case report obviously met the criteria for massive transfusion. The MTP was not initiated until the vessel had been repaired. Prior to the vessel being repaired, several units of RBCs were transfused. Upon initiation of this facility's MTP, packs of blood products are to be released every 45 minutes. The first pack is to contain: 4 units of RBCs, 4 units of FFP, and 1 unit of PLT. Cryoprecipitate requires time to be thawed and is initially released in the second MTP pack (Sanford, 2016).

Despite best efforts to prevent significant blood loss in the presented patient, massive bleeding was encountered. The bleeding was immediately recognized by the surgeon and quickly communicated to the anesthesia staff. Transfusion was without question indicated in the situation. The previously prepared units of RBCs as well as several additional units were transfused as urologic, general, and cardiothoracic surgeons repaired the IVC. Once the vessel was repaired, the MTP was activated and units of platelets and FFP were transfused along with more RBCs.

Although not following high component ratio initially, as is supported by current literature, the patient had a good outcome. Perhaps this can be partially attributed to the fact that prior to repair of the IVC, the majority of transfused blood rapidly escaped from the vasculature, as was evidenced by the TEE. Once, the vessel was repaired, transfusion of other blood products was initiated. Considering this, perhaps the blood products which were retained intravascularly had a higher ratio, which was sufficient in preventing hemodilution associated with high transfusion of RBCs without other components.

Evidence Based Practice Recommendations

Specific protocols or algorithms for intraoperative blood transfusion cannot be recommended at this time. Current transfusion guidelines, leave much room for practitioner discretion. Based on the current literature, restrictive transfusion is favorable, as transfusion of small perhaps discretionary amounts of blood has been shown to have adverse effects. If massive transfusion is required in the surgical patient, it is recommended to transfuse a “high” ratio of FFP/RBC and PLT/RBC. There is no clear-cut definition of high component ratios. In research, a high ratio of FFP/RBC has varied (1:1 - 1:2); however, a high ratio of PLT/RBC has ranged even more (1:1 - 1:9) (Brown et al., 2012; Holcomb et al., 2011; Sharpe et al., 2012). As such, massive transfusion protocols vary from facility to facility. It is advisable that anesthesia professionals be familiar with the MTP at the facility in which they practice.

Overall, the literature regarding the risk of bleeding in patients undergoing a radical nephrectomy and blood transfusion in cancer patients undergoing resection is extremely limited. Given the known potential involvement of vasculature with renal carcinoma and the risks of blood transfusion, especially in the immunocompromised, it is advisable that more research be performed on this topic. With more research, specific guidelines for this patient population may be developed to improve patient safety and enhance outcomes.

Conclusion

Some bleeding during surgery is expected. Severe bleeding during surgery may lead to several complications, including death. However, transfusion of blood may also increase patient morbidity and mortality. Hence, it is important that anesthesia professionals are knowledgeable about the current literature regarding blood transfusion in the surgical patient. Intervention starts with prevention; it is vital that anesthesia professionals work collaboratively with other members of the healthcare team to ensure patients have been optimized prior to undergoing elective surgery to decrease the chance of significant surgical bleeding. Preparation of patients may need to begin days or weeks prior to surgery. Secondly, it is important that anesthesia professionals identify when blood transfusion is warranted. Anesthesia professionals must carefully weigh the risks and benefits of blood transfusion for each patient individually to achieve best patient outcomes.

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Appendix A

Anesthesia Considerations for Intraoperative Blood Transfusion

Ana Dahl, SRNA

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Introduction

- The majority of RBC transfusion occurs in surgical patients (U.S. Department of Health and Human Services, as cited by Qian et al., 2013).
- Blood transfusion has been identified as one of the most overused interventions in the U.S. (Joint Commission, 2012).
- While life-saving at times, blood transfusion has been associated with increased morbidity and mortality rates.
- RBCs are expensive: acquisition to transfusion of a single unit costs between $1,600-2,400 (Wu et al., 2010).
- Appropriate surgical blood management may not only affect patient safety, but healthcare costs as well (Ferraris et al., 2011).

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Case Information

- Right radical robotic (possibly open) nephrectomy for primary kidney cancer with metastasis to the lung
- 65 year-old
- 110kg, 175cm
- Male
- ASA 3
- No known allergies

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Preoperative Evaluation

- Past Medical History
  - HTN
  - DM 2
  - CVA (2013)
- Surgical History
  - Tonsillectomy
  - Bronchoscopy
  - Endobronchial ultrasound
- Anesthesia History
  - No history of anesthetic complications
- Home medications
  - Aspirin
  - Fish oil
  - Tamsulosin
  - Insulin glargine
  - Lisinopril
  - Amlodipine
  - Clonidine

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Preoperative Evaluation Continued

- Pertinent Labs/EKG
  - Hemoglobin 14.2 g/dL
  - Hematocrit 42.5%
  - Platelets 187 per mcL
  - PT 10.4 seconds
  - PTT 23.8 seconds
  - Blood type: AB positive without antibodies
    - 2 units of RBCs typed and cross matched
  - EKG: Normal sinus rhythm
- Preoperative VS
  - BP 166/72
  - HR 72
  - RR 20
  - SaO2 90% on RA
  - T 36.9° C
- Airway Evaluation
  - Mallampati II
  - Full neck ROM
  - No notable dental history or viable issues

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Anesthetic Course

- Technique: GETA
- Induction
  - Standard non-invasive monitors
  - Preoxygenated with 100% O2 via face mask for approximately three minutes
  - Fentanyl 50mcg, lidocaine 50mg, propofol 200mg, cisatracurium 20mg
  - Macintosh 3 blade, 7.5mm cuffed ETT
- Maintenance
  - Desflurane 1.0 MAC
  - Initial FOF 1LPM air and 1LPM O2
  - Arterial line and additional 16-gauge IV
  - NS and LR infusions, cefazolin 2g, famotidine 20mg, metoclopramide 5mg, dexamethasone 10mg, ondansetron 4mg, dextrose 25g for mild hypoglycemia, and PRN fentanyl, hydromorphone, phenylephrine, and ephedrine

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Intraoperative Issues

Difficult Tumor Dissection

- Approximately 3 hours into the operation, a general surgeon was consulted due to the tumors proximity to the hepatic flexure of the bowel
- Approximately 4 hours into the surgery, it was converted to an open procedure due to tumor size and involvement with surrounding tissues
  - At this time, the patient remained hemodynamically stable with negligible blood loss
- Approximately 30 minutes after converting to an open procedure, significant surgical bleeding was encountered
  - The IVC had been inadvertently incised by the surgeon

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Intraoperative Issues Continued

Massive Blood Loss

- Previously consulted general surgeon assisted, while waiting for the vascular surgeon
- TEE was performed by the MDA, which showed a nearly empty LV
- Several units of RBCs and other products were transfused
  - 12 units RBCs, 3 units PLTs, 1 unit FFP, and 1L 5% albumin
  - Estimated total blood loss was 8,000ml; patients estimated TBV was 8,260ml
  - Massive transfusion protocol initiated **after** repair of the IVC
- Medications
  - Boluses of epinephrine, phenylephrine, ephedrine, and vasopressin
  - Infusions of phenylephrine and epinephrine
  - Calcium gluconate 4g and 300mEq of sodium bicarbonate
  - Desflurane discontinued due to severe hemodynamic instability
  - Two subsequent doses of cisatracurium were given, 10mg each

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Postoperative Care

- The patient bypassed PACU; transferred directly to the CCU
  - Transfusion of blood products and infusions of phenylephrine and epinephrine continued
- Upon arrival to the CCU, the patient cardiac arrested
  - One round of CPR was performed
  - A single lumen right femoral central line was inserted
  - Care was turned over to the critical care physician
- Two days after surgery the patient was extubated and on the third postoperative day was transferred to a general floor A&O x3.

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Discussion

Intervention Starts with Prevention: Preventing Blood Loss

- Preparation may need to begin several days/weeks before elective surgery
- Careful review of medical records and a thorough interview
- Discontinue anticoagulation medications as appropriate. The ASA Task Force on Perioperative Blood Management (2015) recommends:
  - Consult an appropriate specialist and discontinue anticoagulation therapy
    - Transition to shorter acting drugs, such as heparin or LMWH, may be appropriate
    - Discontinue non-aspirin antiplatelet agents (i.e. clopidogrel, ticagrelor). Exception, history of PCI
    - Aspirin may be continued on an individual patient basis
- Erythropoietin and/or iron may be administered or autologous blood may be donated prior to surgery

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Discussion Continued

Transfusion Thresholds: Blood Loss & Anemia

- Wu et al. (2010) Retrospective Study
  - 239,286 older patients (>65 years), undergoing noncardiac surgery
- Chen et al. (2015) Retrospective Study
  - 424,015 older patients (>65 years), undergoing noncardiac surgery
    - Both studies looked at intraoperative blood transfusion in relation to 30-day postoperative mortality rates
    - Benefit from intraoperative transfusion if "substantial" operative blood loss (>500ml) or low preoperative hematocrit (<24%)
- Wu et al. (2012) Retrospective Study
  - 46,608 older patients (>65 years), undergoing noncardiac surgery
  - Relationship between hospital rates of transfusion in patients with substantial blood loss (>500ml) and 30-day postoperative mortality rates
  - Hospital which transfused patients with substantial blood loss had lower risk-adjusted 30-day postoperative mortality rates

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Discussion Continued

Low Volume Transfusion

- Bernard, Davenport, Chang, Vaughan, and Zwischenberger (2009) Prospective Study
  - 127,177 adult patients (average age 52.9 years), undergoing noncardiac general surgery
- Ferraris et al. (2011) Exploratory Observational Study
  - 8,728 propensity-matched adult patients, undergoing noncardiac nonvascular thoracic surgery
    - Both studies looked at the effect of low volume intraoperative transfusion (1-2 units) on morbidity and mortality
    - Increased morbidity and mortality was associated with low volume intraoperative transfusion

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Discussion Continued

Transfusion within 72 Hours

- Abdelsattar, Hendren, Wong, Campbell, and Henke (2015) Prospective Observational Study
  - 2,243 propensity-matched adult patients (>18 years), undergoing vascular or general abdominal surgery
  - Blood transfusion within 72 hours of surgery and 30-day postoperative mortality
  - Increased postoperative mortality; paradoxical exception, decreased risk of MI
- Ferraris, Hochstetler, Martin, Mahan, and Saha (2015) Observational Study
  - 470,407 adult patients, undergoing noncardiac surgery
  - Predictive operative mortality and associated risk of blood transfusion
  - "High-risk" patients did not have significant risk with blood transfusion; however, "low-risk" patients had substantially increased risk

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Discussion Continued

Cancer and Immunomodulation

- Al-Refaie, Parson, Markin, Abrams, and Habermann (2012) Prospective Study
  - 38,926 adult patients (>18 years), undergoing surgical resection of thoracic, abdominal, or pelvic neoplasms
  - Intraoperative blood transfusion and association with outcomes
  - Adverse effects of intraoperative blood transfusion, including increased 30-day postoperative mortality rates
  - Unlike other studies, adverse effects were found despite a low preoperative hematocrit level
- Ferraris, Ballert, and Mahan (2013) Retrospective Study
  - 553,288 propensity-matched adult surgical patients,
  - Blood transfusion and the development of systemic inflammatory response syndrome (SIRS)
  - Transfused patients had increased morbidity, including SIRS, and morality

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Discussion Continued

Massive Transfusion

- Turan et al. (2013) Prospective Study
  - 5,143 adult patients, undergoing noncardiac surgery
  - Association between massive transfusion (5 RBC units) and patient outcomes
- Johnson et al. (2016) Retrospective Study
  - Approximately 3,500 medical and surgical patients
  - Association between high-dose transfusion (>10 units throughout hospitalization) and morbidity and mortality
    - Mortality increased with increase in RBC units transfused

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Discussion Continued

- Brown et al. (2012) Prospective Cohort Study
  - 604 blunt injury/hemorrhagic shock patients, age 18-90 years, which received massive transfusion
- Holcomb et al. (2011) Retrospective Study
  - 643 massively transfused trauma patients
    - Both studies defined massive transfusion as 10 or > units of RBCs in 24 hours)
    - High early ratios (FFP/RBC 1:1.5 and PLT/RBC 1:9 or 1:1 respectively) were associated with better patient outcomes
- Sharpe et al., (2012) Prospective Study
  - 165 surgical trauma patients
  - More units of RBCs transfused = lower component ratios
  - Lower component ratios increased mortality rates

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Discussion Continued

Case Report Discussion

- The patient was "optimized" prior to surgery
- Additional IV access and invasive hemodynamic monitoring (arterial line) had been initiated prior to the start of surgery. A type and crossmatch was completed preoperatively.
- Despite, best efforts, significant blood loss was encountered
- The blood loss was quickly communicated to anesthesia
- Although not following a high component ratio initially, as supported by current literature, the patient had a positive outcome

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Discussion Continued

Intraoperative Transfusion Management

"Blood transfusion can be both good and bad, depending on the clinical situation." (Ferraris et al., 2015, p. 608)

- Blood transfusion has been shown to be beneficial if there is an indication for transfusion; however, in the absence of massive bleeding or symptomatic anemia, it has not proven to be advantageous (Smilowitz et al., 2016)
- There has been debate over the ideal transfusion trigger and subsequently, transfusion practices have varied widely (Abdelsattar et al., 2015; Ferraris et al., 2012; Qian et al., 2013)

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Discussion Continued

- Current literature supports restrictive versus liberal transfusion.
  - As discussed previously, transfusion of even small amounts of blood (1-2 units) has been associated with adverse surgical outcomes (Bernard et al., 2009; Ferraris et al., 2011; Ferraris et al., 2012; Glance et al., 2011)
  - In a recent Cochrane review (Carson et al., 2015), which included a wide variety of patients (surgical, critical care, trauma, cancer, etc.), transfusion at a restrictive threshold (7-8 g/dL) was not associated with adverse effects when compared to initiation at a liberal threshold (9-10 g/dL).

"The determination of whether hemoglobin concentrations between 6 and 10g/dl justify or require red blood cell transfusion should be based on potential or actual ongoing bleeding (rate and magnitude), intravascular volume status, signs of organ ischemia, and adequacy of cardiopulmonary reserve." (ASA Take Force on Perioperative Blood Management, 2015, p. 251)

Recommendations

- While current transfusion guidelines leave much room for practitioner discretion, based on current literature restrictive transfusion trigger is favorable
- If massive transfusion is required, it is recommended to transfuse a "high" ratio of FFP/RBC and PLT/RBC
  - There is no clear-cut definition of high component ratios. In research the definition varies (Brown et al., 2012; Holcomb et al., 2011; Sharpe et al., 2012):
    - FFP/RBC 1:1 -1:1.5
    - PLT/RBC 1:1 – 1:9

Recommendations Continued

- Massive transfusion protocols are not all the same. It is advisable that anesthesia providers be familiar with the protocol at the facility in which they practice.
- Despite the known potential involvement of vasculature with renal carcinoma, there is extremely scarce data regarding the risk of bleeding and associated blood loss in patients undergoing a radical nephrectomy. It is recommended that research be performed on this topic

Conclusion

- While blood transfusion may be life-saving at times, it has also been associated with increased morbidity and mortality.
- It is important that anesthesia professionals be knowledgeable about current literature regarding transfusion in the surgical patient.
- Intervention starts with prevention
  - Optimize patients prior to elective surgery
- The risks versus the benefits of transfusion must be carefully weighed for each patient to achieve best outcomes.

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Thank You
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