Title : Role of blood management in optimizing perioperative outcomes in patients with secondary anemia undergoing hysterectomy for abnormal uterine bleeding: A Proposed Randomized Control Trial

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I. Background/Introduction:

According to the World Health Organization (WHO), 30.2 % of the world's population of nonpregnant women are anemic (1), with a higher percentage of anemia being encountered in patients seeking surgical management of abnormal uterine bleeding (AUB). Age, gender, socioeconomic factors, nutrition, and certain pathologic states are associated with iron depletion and associated iron deficiency anemia. Uterine fibroid (or leiomyoma) is the most common diagnosis associated with hysterectomy, accounting for approximately 31% of all procedures performed. Abnormal uterine bleeding and endometriosis are the second and third most common diagnoses associated with hysterectomy, explaining 14% and 11%, respectively (2). Based on the diagnoses recorded in the medical record by providers, 48.7% of patients were presumed to have dysfunctional uterine bleeding (DUB) and 9% were presumed to have bleeding secondary to uterine fibroids. In this population of women with AUB, 350 (92.3%) had a hemoglobin concentration recorded. Thirty-five percent were anemic with a hemoglobin of <12g/dL and 13.7% had moderate to severe anemia with a hemoglobin of <10 g/dL (3).

In addition to the high incidence of secondary anemia in patients with abnormal uterine bleeding and fibroids, surgeries for abnormal uterine bleeding and fibroids such as hysterectomy and myomectomy can involve a significant blood loss (4,5). The overall rate of postoperative blood transfusion for hysterectomy in the cited study was 13.3% (5). The need for packed red blood cell transfusion is one of the known complications of surgery and is increased in women who are noted to be anemic preoperatively. Blood transfusions are associated with increased adverse surgical outcomes. Higher rates of morbidity and mortality have been reported in patients receiving one unit of packed red blood cells compared with patients who did not undergo transfusion (6). The WHO recommends, in compliance with their guide for optimal clinical use, "that before surgery every reasonable measure should be taken to optimize the patient's own blood volume" (7). Pre-operative hemoglobin less than 10.6 g/dL versus greater than or equal to 13.1 g/dL had five times the odds of transfusion (5).

Anemia is a modifiable risk factor that can be assessed and optimized pre-operatively. Prior studies have evaluated preoperative blood management strategies in oncology patients, patients undergoing general surgery procedures, and orthopedic surgery. A systematic review of the management of perioperative anemia showed varying results in change in hemoglobin levels after blood management intervention, but all studies were able to show a decrease in postoperative blood transfusions (8). A randomized control trial evaluating oral iron supplementation preoperatively in patients undergoing colorectal surgery reported reduced blood transfusion rates in the group receiving this intervention (9). Froessler et al studied perioperative IV iron intervention in patients undergoing major abdominal surgery in a randomized control trial with using blood transfusions as a primary endpoint. They concluded that perioperative IV iron reduced the need for blood transfusion and was also associated with higher postoperative hemoglobin and shorter hospital stay (10). A blood management protocol implemented in the perioperative period also noted a decrease in perioperative blood transfusion and postoperative anemia in the orthopedic population. The interventions used in their blood protocol management included erythropoietin, ferric carboxymaltose, and tranexamic acid (11).

A Blood management protocol was recently developed at the Cleveland Clinic whereby either confirmed or suspected anemic patients with abnormal uterine bleeding scheduled for surgical management are referred to Blood Management for assessment of laboratory studies (CBC, Ferritin, iron, TIBC, %Sat) and a care plan is development. Several factors are considered in designing a treatment plan including current blood loss, anemia symptoms, scheduled or upcoming procedures, and others. Treatment plans may include observation alone or oral iron versus intravenous iron. Iron deficiency is calculated using the Ganzoni calculation for patients receiving intravenous iron. Per the Blood Management Protocol: An anemia screening lab panel will be ordered, in combination with a referral to the Blood Management clinic via WHI Blood Management Referral Smartset. This order set will automatically preselect the lab panel — complete blood count (CBC), iron, total iron binding capacity (TIBC) and ferritin — and the referral to the Blood Management clinic. The patient will automatically receive information in the after-visit summary regarding the Blood Management clinic referral. Any correctable causes of anemia will be addressed preoperatively by the Blood Management group. Measures used may include the use of intravenous iron or oral iron. See Algorithm in Table 2.0.

Using Ganzoni Formula Calculator: http://www.al-nasir.com/www/PharmCalc/mob_exec_calc.php?ID=ganzoni

Clinical data for calculator:
a) Current hemoglobin
b) Weight in kg
c) Target hemoglobin (see table below)

Ganzoni Target Hemoglobin	**Female**
High Blood Loss* (> 3 gm/dL)	13 gm/dL

Low Blood Loss* (1-2 gm/dL)	12 gm/dL
Non-surgical*	12 gm/dL
Unknown*	12 gm/dL

*High blood loss defined as expected drop in hemoglobin > gm/dL postoperatively i.e. CABG, Valve, AAA, lower extremity joint replacement,multi-level spine w/instrumentation; Low blood loss expected drop hemoglobin 1-2 gm/dL i.e. hysterectomy, simple colectomy, laparoscopic or robotic assisted procedures; Non-surgical is medical iron deficiency treatment; Unknown are default targets.

There is currently limited information regarding the role of blood management in the benign gynecologic population and specifically, in patients who are scheduled to undergo surgery for fibroids and/or abnormal uterine bleeding. A thorough search through PubMed and clinicaltrials.gov did not reveal any studies on this issue. In 2019 at CCF only 2% of gyn patients at Main Campus were referred to blood management, but 12.6% of the main campus gyn population had a Hb of <10.0 g/dL. The overall goal of this study is to evaluate the role of preoperative blood management in optimizing surgical outcomes by reducing the co-morbidities associated with postoperative blood transfusion.

Specific Aims/Objective:

The primary objective of this study is to compare the change in baseline hemoglobin levels in patients in the study (Blood Management Protocol) and control ("usual care")
group who are undergoing hysterectomy for abnormal uterine bleeding. Change in baseline hemoglobin levels is defined as the difference of the hemoglobin level obtained within 72 hours prior to surgery and the hemoglobin level at 4 weeks postoperatively.

Our secondary objectives include 1. To evaluate the perioperative outcomes between the two groups including OR times, EBL, peri-operative transfusion rates, length of hospital stay, complications including intra-operative injuries, postoperative infection rates, readmission, and re-operation; 2. to assess patient satisfaction regarding their experience with the Blood Management protocol and extra outpatient infusion visits required using a patient questionnaire **(**PATSAT 35, Attached); and 3. to compare the quality of patient health and recovery between the two groups using the RAND-36 (Attached) assessment tool. The REDCap database will include potential identifiers to enable online surveys. The included potential patient identifiers include: date of birth, surgery date, and subject email (they provide for the study.)

Data variables that will be collected in the study are visible in the following table.

Patient Demographics:
• MRN • Age/ Date of Birth
• BMI

• Race
• Gravidity/Parity • Prior abdominal surgery • Prior cesarean section • Diabetes • Hypertension • Current Smoker • Former Smoker • Menopause status
• Type of surgery: Hysterectomy or myomectomy
Type: Vaginal, laparoscopic, open, laparoscopic assisted vaginal hysterectomy, robotic • Surgery date, discharge date
• Surgery date/ Discharge date
• Subject email
Primary objectives:
• Change in hemoglobin levels
o Baseline Hemoglobin (pre-op)
o Post Op Hemoglobin level
Secondary objectives:
• Operative time
• Blood Loss
• Perioperative transfusion rate
• Length of hospital stay
• Intraoperative Complications
o Intraoperative injuries
o Post-operative infection rates
o Readmission
o Reoperation
• Patient Satisfaction
• Quality of Health and Recovery
• Number of infusions received
• Days on PO iron therapy

Table 1.0 -- Data Collection Variables

We anticipate that patients undergoing blood management protocol will have a faster return to normal recovery and better quality of life scores during recovery using the RAND-36 assessment questionnaire compared to patients undergoing usual care. We also plan to evaluate additional cost of blood management treatments for oral iron, IV iron, and blood transfusion in regards to feasibility, and from a health care utilization standpoint.

Methods and Study Design:

This will be a prospective randomized control trial conducted in a single large-referral center where anemic patients undergoing hysterectomy for fibroids or abnormal uterine bleeding will be recruited and randomized to undergo Blood Management protocol or usual care.

Inclusion criteria are anemic patients (defined as Hgb ≤ 11g/dL within 30 days of initial MIGS consult visit), greater than 18 years of age, with abnormal uterine bleeding, or fibroids undergoing hysterectomy by laparoscopic, robotic, vaginal or open routes. Exclusion criteria are malignancy, pregnancy, sickle cell anemia or other blood dyscrasias, women who received blood transfusions in 30 days prior to surgery, women receiving EPO therapy, women who have undergone gastric bypass surgery, and women on therapeutic/full anticoagulation. Patients undergoing hysteroscopic myomectomy alone without will not be included in the study.

Women meeting the above inclusion criteria who are undergoing elective surgery (hysterectomy) at the Cleveland Clinic Main Campus will be randomly allocated to receive pre-surgical optimization blood management referral versus usual care - defined as expectant management with no therapy, or PO iron therapy at the primary surgeon's discretion. Randomization following a computer generated number sequence and allocation will occur in person. Patients will be screened from multiple minimally invasive gynecologic providers with high volume surgical practices at a large teaching institution, and consented on their initial preoperative visit. (These MIGS surgeons are Dr. Rosanne Kho, Dr. Mark Dassel, Dr. Cara King, Dr. Lindsey Valentine.) Patients will be randomized to receiving a blood management referral or usual care. Patients will be randomized with permuted block randomization with block size 2 and stratified on care providers. Blood management work up protocol is visible in Table 1. Patients receiving usual care will receive anemia management provided by the primary physician that may include no treatment, continued observation, or oral iron recommendations in the pre-operative time.

The intervention will include pre-surgical optimization blood management referral based on pre-operative Hb levels ≤11.0. Currently it is not standard of care at the Cleveland Clinic to send all patients with Hb ≤11.0 due to secondary anemia to blood management. It is done currently at the provider/surgeons preference alone and not through a research protocol or guidelines. At the initial consultation visit a CBC will be drawn, patients will be given a consent form for the study and asked to review it. If a Hb ≤11.0 within 30 days of consultation visit is documented in EPIC, they will be consented and randomized at the consultation visit. All patients after initial consultation visit will be immediately sent to the lab for blood draw if they have not had Hb drawn within 30 days. Lab draw includes: CBC + differential, iron studies: iron, TIBC, ferritin, optional B12. If the initial consult visit occurs at Fairview or Hillcrest Hospital, the patient's follow up preoperative visit will be scheduled at the main campus where consent will be obtained. The blood management team then will receive the referral from primary surgeon's office via EPIC in-basket. Blood management coordinator will assess patient, arrange treatment, and orders will be cosigned by surgeon/referring provider. Blood management may further assess for symptoms of PICA, restless legs, and cold intolerance as symptomatic indicators of anemia. The Rand 36 study will be administered at either the consultation or the pre-operative visit. The PATSAT 35 will be administered at the postoperative visit only. Postoperative Hb levels will be collected by a CBC at the post-operative visit. All postoperative visits will be scheduled at the main campus. All surveys and consents will be obtained at visits that occur at the main campus.

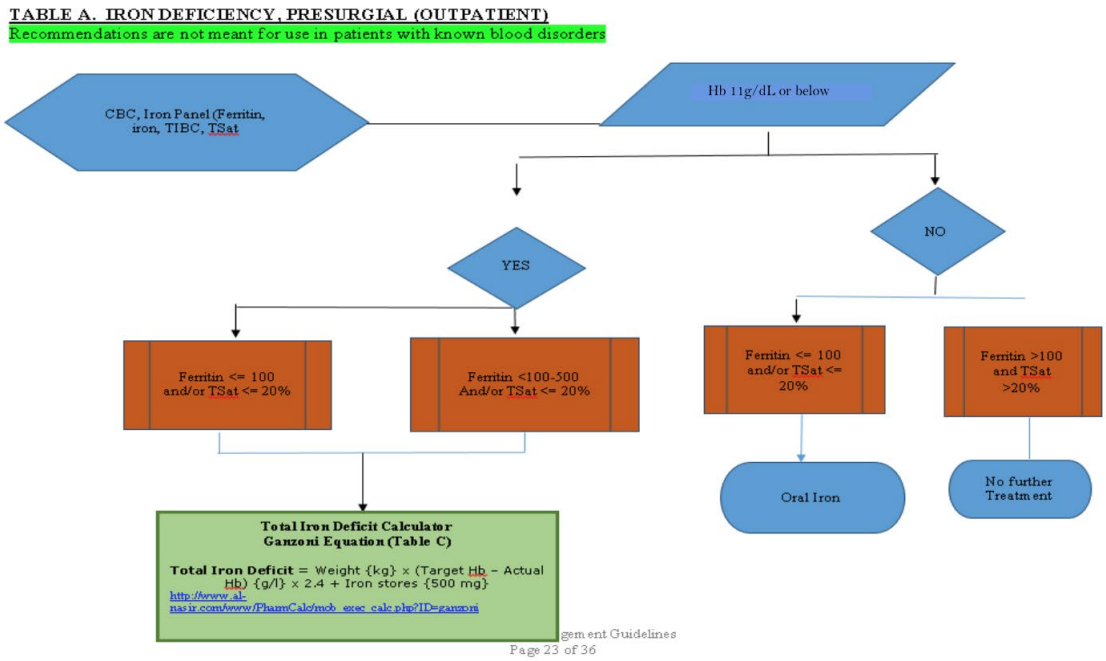

Table 2: Blood Management Preoperative Iron Deficiency Algorithm

Blood loss intraoperatively will be measured as accurately as possible with suction device recording and quantitative blood loss and tapes/packs by weighing instead of only visual assessment.

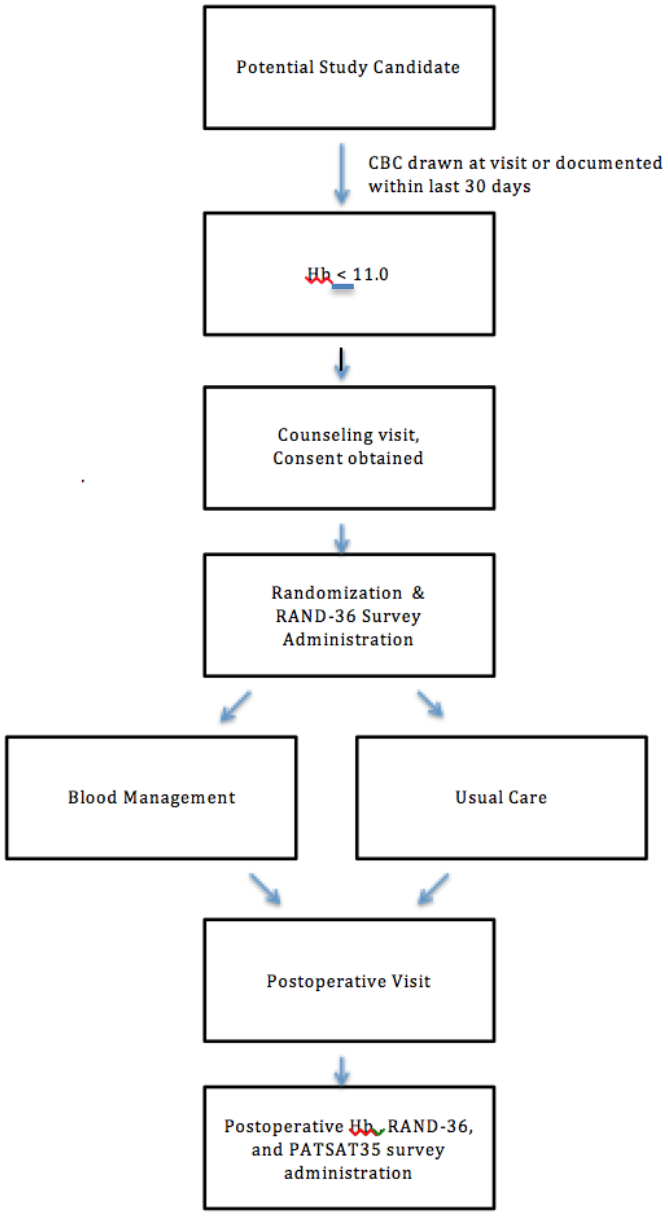

Image: 1.0 -- Patient Flow Sheet

Justification for Sample Size:

Power Calculation:

Sample size was calculated to have 80% power to detect a difference between groups using a T-test at a significance level of 0.05. We assume that patients at 4 weeks will have a standard deviation in hemoglobin values of 1.2 g/dL (8) to detect a 1 g/dL difference between groups, we

will need 48 patients total (24 per group) if the groups are of equal size. Assuming a 20% dropout rate, 60 patients total (30 per group) will be the target enrollment.

Cost and Payments to Subjects
The patients will have no additional costs due to participating in the study beyond the usual insurance copays and standard costs for appointments.

Quality Control Procedure:
Information will be provided to all department members involved in administration of the study. Follow up, data entry, and patient follow up will be closely followed by the research team (resident, fellow, staff physicians, MIGS NP's, Lead research nurse)

Process of Consent
Patients would be consented for participation in the study at their primary surgeon's office when shared decision making for proceeding with surgery is performed. Patients will receive no difference in care based on their participation in the study apart from the study protocol

Risks and Discomfort of the Project
The study has been designed to minimize as much risk as possible, and participants will be subjected to no more than minimal or standard risk for undergoing the intervention. Breach of confidentiality is a small risk. Physical risk are rare and unanticipated but would be limited to transfusion reaction to the IV iron therapy. There are no psychological risks for patients who participate in this study. Participants can also benefit from their participation in this study due to their altruistic motivation for partaking in research study they have contributed to scientific advancement.

Analysis plan
Approximately normally-distributed continuous measures will be summarized using means and standard deviations and will be compared using two-sample t-tests. Continuous measures that show departure from normality and ordinal measures will be summarized using medians and quartiles and will be compared using Wilcoxon rank sum tests. Categorical factors will be summarized using frequencies and percentages and will be compared using Pearson's chi-square tests or Fisher's Exact tests. All analyses will be done using SAS (version 9.4, The SAS Institute, Cary, NC) and a $p < 0.05$ will be considered statistically significant.

Timetable:
The IRB will be submitted in April 2020. Upon approval of the IRB, it is estimated that data analysis can begin shortly after. It is estimated that it will take 6 months to enroll the 60 patients required. The study will be registered on clinicaltrials.gov after approval of the IRB and prior to enrollment.

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