PROTOCOL

Pediatric Outcomes and Recovery with Peri-Operative Iron Supplement Evaluation (PORPOISE)

[H25-00010]

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Contents

1.0 BACKGROUND INFORMATION AND RATIONALE

1.1 Background

Varus-derotation osteotomy (VDRO), which may sometimes involve a pelvic osteotomy, is a surgical procedure designed to prevent or address hip displacement in children.[1] Many children undergoing this complex surgery have cerebral palsy or other neuromotor disorders and require the procedure to alleviate or improve seating issues, patient care (including toileting), contractures, and pain.[1] Patients with developmental hip dysplasia may also be candidates for this surgery. VDRO is typically a lengthy procedure, lasting 4 hours or more, with the risk of blood transfusion ranging from 10% to 25% or higher (32% at BC Children's Hospital in the past 2.5 years).[2,3] The post-operative complication rate in VDRO surgery for those with neuromotor conditions can approach 50%.[4] Patients with neuromotor conditions, including cerebral palsy, are known to be at an elevated risk of malnutrition, as indicated by laboratory findings such as low iron or anemia.[5–7] Malnutrition and anemia in pediatric patients undergoing significant procedures, such as scoliosis surgery and VDRO, can affect surgical outcomes, including the need for transfusions and the length of stay.[8,9]

Patients undergoing VDRO, with or without pelvic osteotomy, often have multiple, complex medical conditions and require a multidisciplinary team approach to care.[10] Malnutrition, while noted to be an important contributor to morbidity in these patients, is not often highlighted as a primary component of the perioperative care team.[10] It can also be challenging to quantify and requires expertise in nutrition to employ tools such as the Subjective Global Nutrition Assessment (SGNA) score validated in neuromotor conditions.[11] Yet, the impact of optimizing diet before surgery can be profound. Integrating perioperative nutrition management into the care pathway of these patients may improve their outcomes.

Patient blood management (PBM) programs are recognized as standard care in the adult peri-operative population; however, their implementation in pediatrics remains limited.[12,13] There are few studies on the prevalence of iron-deficiency anemia in Canadian children, and historical research has indicated rates ranging from 12% to 64%, often without considering medically complex patients who are known to be at high risk of malnutrition.[14,15] Pre-operative anemia raises the risk of in-hospital mortality for pediatric patients undergoing non-cardiac surgery.[16] While a comprehensive intra-operative PBM strategy can often be effectively planned through collaboration among anesthesia, surgery, nursing, and perfusion teams, the pre-operative PBM of patients is influenced by numerous factors. These include a lack of laboratory testing, concerns about compliance with iron supplementation, late referrals to the pre-anesthesia consult clinic, and challenges in caring for complex patients, often living at considerable distances from tertiary pediatric centres.[12,13,17] The lack of service integration and collaboration among those caring for pediatric surgical patients

means that the opportunity to optimize a patient's nutrition for improved surgical outcomes may be missed.

At BC Children's Hospital (BCCH), we treat an average of 30-35 patients per year with VDRO. Of these patients, it is standard of care for a dietitian to consult on the patients who have neuromotor conditions, including cerebral palsy, for specific nutritional optimization. Consultations occur alongside surgical visits, during which weight and height are measured, growth chart tracking is performed, a nutrition-focused physical exam is conducted, and a review of their oral or enteral diet, including supplements, is carried out. No intervention is recommended if the child is growing well, and their diet is adequate. Possible interventions may include recommending supplements (most commonly calcium/Vitamin D and occasionally a multivitamin), optimizing tube feeds, and providing diet education. Iron supplementation is not recommended because blood work is not performed. Hemoglobin levels may be ordered in the days leading up to surgery or may be deferred until after the induction of anesthesia based on individual patient circumstances, and results typically are not available in time to optimize care if the patient is anemic. Typical waitlists for VDRO are 6-12 months, so there would time to correct iron deficiency anemia if it was detected from the beginning of the pre-op process.[18]

1.2 Aim of Study

We aim to establish a multidisciplinary pathway that extends the standard of care offered to patients with neuromotor conditions to *all* patients scheduled for VDRO that incorporates comprehensive nutrition management and iron deficiency anemia assessment and management. The goal is to determine whether patients with nutritional optimization will experience improved care, including a decreased risk of adverse outcomes. Subsequently, we plan to apply this care pathway to our complex patient population undergoing other extensive surgical procedures, including neuromuscular scoliosis surgery. In the long term, we intend to integrate this nutrition program into a multidisciplinary and comprehensive perioperative approach that addresses nutrition, pain management, and prehabilitation, with engagement from nutrition, anesthesia, surgery, nursing, and physiotherapy.

1.3 Study Rationale

The *primary objective* of this project is to study the integration of blood management into the nutritional care of patients having VDRO surgery and determine whether it improves patient outcomes, including exposure to transfusion, anemia, iron levels, hospital length of stay and surgical complications such as surgical site infection.

The *secondary objective* is to develop a multidisciplinary perioperative nutritional and prehabilitation program for patients scheduled for elective VDRO that promotes collaboration among nutrition, anesthesia, surgery, nursing, and physiotherapy at BC Children's Hospital. We will evaluate the operational feasibility of the program and evaluate its acceptability among patients and their families, based on self-reported measures of compliance and satisfaction, and feedback from follow-up interviews.

An *additional objective* is to extrapolate the learnings from this project to other elective surgical interventions, such as neuromuscular scoliosis surgery, where nutritional optimization may also improve outcomes. We aim to establish which surgical outcome(s) will provide a feasible and clinically meaningful measure of benefit so future implementations can be constructively evaluated. This project also benefits patient populations and their families by providing nutritional care and education to those who may lack the financial or other resources needed to access this resource. Equitable access to nutritional management for medically complex patients at BCCH will ensure that all patients with major orthopedic surgery have the same building blocks needed to recover and rehabilitate.

1.4 Hypothesis

Primary Outcome: A comprehensive nutritional prehabilitation intervention for iron deficiency anemia before pediatric VDRO surgery will decrease the risk of requiring a blood transfusion, as shown by a decreased incidence of blood transfusions, in the perioperative period.

Secondary Outcomes: This nutritional program with the addition of treatment for iron deficiency will have a positive impact on other perioperative surgical outcomes, including resolution of anemia, increased iron levels, lower incidence of surgical site infection and pressure wounds, and decreased hospital length of stay. The program will also be feasible and acceptable to families.

2.0 STUDY DESIGN, METHODOLOGY, AND ANALYSIS PLAN

2.1 Research Design

We will conduct a prospective observational study of children and their families undergoing a comprehensive medium-term nutritional prehabilitation program over a period of 24 months and compare outcomes against a historical cohort from February 2022 to December 2024. We will determine if including pre-operative PBM in the nutritional intervention for patients undergoing VDRO has a statistically significant impact on measurable perioperative outcomes.

2.2 Participants

Inclusion Criteria

- Patients scheduled for VDRO and/or pelvic osteotomy surgery (*prospective cohort*)
- Patients who had VDRO and/or pelvic osteotomy surgery between February 2022 and December 2024 (*historical cohort*)
- Ages 0-18 years old

Exclusion Criteria

- Patients who have undergone a major surgical intervention in the last 3 months *
- Patients who have received a nutritional intervention that includes iron testing and treatment within the last 3 months
- Patients in whom oral/enteral iron supplementation is contraindicated
- Patients who have a bleeding disorder
- Patients taking erythropoietin
- Patients who cannot read and understand English**

*Major surgical interventions include stimulating, complex or invasive elective or emergency procedures, defined as anesthesia with skin incision or painful manipulation.

**Patients and families who cannot read and understand English will be excluded as the surveys and interviews are conducted in English. These patients will still have access to the same nutrition management and interventions as study participants.

Note that we will include patients who do or do not have a diagnosis of a neuromotor condition. We may not include patients who are enrolled in other conflicting research studies.

2.3 Methodology

Enrollment

Prospective cohort: Patients who meet eligibility criteria will be approached for recruitment by research team members in the orthopedic clinic at BC Children's Hospital.

Historical cohort: No patients will be approached for enrollment or consent.

Consenting

Prospective cohort: Parents or caregivers of participants will provide written informed consent, while their children who are 7 years old and above may provide written assent.

Waiver of Consent (*historical cohort*)

For the purposes of historical data matching, we are including a request for waiver of consent for the historical control participants under TCPS Article 5.5A. No patients (or parent/guardian) who is part of the historical group will be approached for inclusion in the study; historical participant selection will be performed using the propensity score matching approach described in the data analysis plan below. This is justified as it fulfils the following six points:

a. *Identifiable information is essential to the research.*
    i. No identifiable information will be used for analysis. The variables collected from past VDRO and/or pelvic osteotomy surgery patients will include age, sex, GMFCS score, ASA physical status score, and procedure booking code for propensity score matching, as well as our study outcomes, including perioperative blood transfusion requirements, perioperative blood lab results, length of hospital stay, and details of any surgical site infection, pressure wounds, or return to hospital.
b. *The use of identifiable information without the participants' consent is unlikely to adversely affect the welfare of individuals to whom the information relates.*
    i. The alteration to consent requirements is unlikely to adversely affect the welfare of participants as no intervention is being implemented. We request only the use of their non-identifiable data. We do not anticipate being able to discern individual participant identity from aggregated non-identifiable data.
c. *The researchers will take appropriate measures to protect the privacy of individuals and to safeguard the identifiable information.*
    i. All electronic data safeguards are described in section 3.1. All participants will be provided with a participant ID that is unrelated to any identifying information (i.e. date of birth). Participants will be linked to their ID in a separate password-protected document.
d. *The researchers will comply with any known preferences previously expressed by individuals about any use of their information.*
    i. Any preferences identified on patient charts regarding use of patient information and participation in research will be respected and adhered to. Patients who have expressed that they do not want their information used for research purposes will not be enrolled in the study.
e. *It is impossible or impracticable to seek consent from individuals to whom the information relates.*
    i. It is impracticable to carry out the research and address the research question properly if prior consent is required. If past VDRO and/or pelvic osteotomy patients cannot be contacted and consent cannot be achieved, our ability to conduct propensity score matching will be less effective. This will make it challenging to determine if the nutrition intervention is effective. Additionally, consenting past

patients would require us to collect their contact information, identifying patients to more members of the research team.

f. The researchers have obtained any other necessary permission for secondary use of information for research purposes.

i. We will obtain permission from the BCCH Department of Anesthesia and the Department of Orthopedic Surgery following submission to the REB.

Nutrition Intervention (prospective cohort)

All patients who are enrolled in the study will have standard blood work conducted according to PBM recommendations[13] to evaluate for iron deficiency. They will have their blood tested at the time of surgical decision, prior to their nutrition management, and again prior to surgery, with two tubes containing 1 to 2 ml each (2 to 4 ml total) taken at each test. This patient population regularly has blood work done prior to surgery, but some patients may be getting one more blood test than they typically would. Iron deficiency and iron deficiency anemia are diagnosed via insufficient serum Ferritin levels, anemia is diagnosed via low hemoglobin levels in a hematology profile (complete blood count).[18] Etiology of anemia can be further supported by MCV; microcytic anemia is associated with iron deficiency.[18] Transferrin saturation is also tested in cases where ferritin, an acute-phase reactant, is high due to inflammation.[19] CRP is tested to help with interpretation of possible inflammation status. In children, Ferritin <12 mcg/L is diagnostic of iron deficiency and Ferritin 12-20 mcg/L indicates possible iron deficiency, as per the Government of British Columbia guidelines.[18] In adults, Ferritin < 15 mcg/L is diagnostic of iron deficiency and Ferritin 15-30 mcg/L is diagnostic of probably iron deficiency.[19] The Government of British Columbia guideline fails to differentiate between infants/toddlers and school-aged children and we are including patients who may be considered adults or who may be menstruating in our study.[18] Therefore, we will consider iron supplementation for blood Ferritin < 20 mcg/L for participants aged 0 to 2 years old and < 30 mcg/L for participants aged 3 years or older.[18,19] Cases where Ferritin is < 100 mcg/L, but Transferrin saturation is <20% will also be considered for iron supplementation.[19] In addition to standard nutritional care and standardized family education, patients determined to be iron deficient, or anemic, will receive a prescription from a physician or nurse practitioner for iron supplementation following the BC guidelines for management of iron deficiency, as well as education on non-pharmacological methods to enhance iron intake.[18]

Feramax (or other iron polysaccharide complex) will be prescribed as it is most used in practice due to its fewer gastrointestinal side effects, ability to be taken with food, and lack of requirement for stomach acid for absorption, making it suitable for patients receiving gastrojejunostomy feedings. The typical dose of iron for pediatric patients with deficiency is 3-6 mg/kg, up to a maximum of 150 mg/day. Other possible nutritional interventions may include

recommending supplements (most commonly calcium/Vitamin D and occasionally a multivitamin), optimizing tube feeds, and providing dietary education.

Standard nutrition care will depend on the results of the nutrition assessment, as well as underlying conditions, and will be performed regardless of iron supplementation. The intervention will be at the discretion of the dietician but may include components of the following non-exhaustive list.

a. Diet education regarding general healthy diet and nutrition for bone health (for generally healthy orally fed patients).
b. Recommendations for vitamin and mineral supplements as needed (based on estimated intake from diet or tube feeds. This may include a multivitamin, calcium and/or Vitamin D.
c. Optimization of tube feeds (if the child is tube fed).
d. High protein or high energy diet education if the child is underweight, but capable of achieving their nutritional needs by increasing oral intake.
e. Addition of oral nutrition supplements (i.e., Pediasure or Ensure) to promote weight gain in orally fed children.
f. Discussion surrounding enteral feeding (for children who are orally fed, but severely malnourished and cannot meet their nutritional needs by mouth). The cardiac surgeon may refer the patient to general surgery, or the family may ask their pediatrician for a referral.

Family Web-Surveys (prospective cohort)

Families will be sent REDCap surveys via email to assess (1) the family's satisfaction with the nutrition program and (2) their compliance with iron supplementation (if applicable). Surveys will be built using a Research Electronic Data Capture (REDCap) database[20] hosted at the BC Children's Hospital Research Institute.

The family satisfaction surveys will be completed at three time points: 1) one week after the dietitian consultation, 2) the week prior to surgery, and 3) the week after surgery.

For patients prescribed iron supplementation, they will complete a REDCap survey each month to assess their compliance, including their child's tolerance of the iron supplements.

Family Interviews (prospective cohort)

During their postoperative stay, while the family is at the hospital for the child's VDRO surgery, they will be invited to participate in an optional semi-structured interview. The interview guide will be based on overall preliminary web-survey results. We aim to obtain more detailed feedback and potential improvements to the program from a patient and family perspective. Interviews will be recorded and transcribed for analysis.

Study Procedures (prospective cohort)

i. Families will be approached by research assistants in the orthopedic clinic at BCCH when deciding to have surgery.
ii. They will be informed about the study, invited to participate, and asked to provide parent/caregiver consent and, if applicable, child assent.
iii. The parent/guardian's email address will be collected for online survey link distribution.
iv. Patients will meet with the clinical dietitian and the surgeon, where they will receive a requisition for blood work.
v. Participants will have their blood work done prior to initiating nutrition intervention for iron deficiency.
vi. Participants will receive comprehensive nutrition consultation and management from the clinical dietitian, communicated by phone.
vii. During the months leading up to their procedure, families will receive follow-up from their dietitian and follow their nutrition intervention to their best of their ability. They will be encouraged to reach out to their dietitian with any question or concerns. Patients prescribed iron supplementation will take the dosage they are prescribed to the best of their ability.
viii. Families will be emailed REDCap surveys to complete at the time points listed above.
ix. When families attend BCCH for the patient's VDRO surgery, they will be invited to participate in an interview.
x. Patients will have their blood re-tested preoperatively or following the induction of anesthesia during their procedure.

2.4 Renumeration

Families who are part of the prospective cohort will each be provided with a $25 Starbucks gift card as renumeration for participating in the study. Families who chose to participate in the interviews will be provided with an additional $25 Starbucks gift card.

2.5 Data Analysis Plan

Sample Size

Data from the 2012-2023 period from our local American College of Surgeons Pediatric National Surgical Quality Improvement Program (P-NSQIP) registry were queried for Current Procedural Terminology Codes 27147, 27151, 27156, and 27165, resulting in 304 cases. This cohort had a median (interquartile range [IQR]) age of 7.8 (5.2-10.9) years and included 59 males (19%). Patients, including 96 patients (32%) with a neuromuscular disorder and 165 (54%) with cerebral palsy, underwent surgical procedures lasting a median (IQR) of 3.6 (2.5-

4.4) hours of surgical time; American Society of Anesthesiologist Physical Status was I for 48, II for 87, III for 153, and IV for 5 patients, with the rest not specified. The median (IQR) length of hospital stay was 5 (4-7) days, with 7 exceeding 30 days. Nutritional support was provided to 79 children (26%). A blood transfusion of median 12.2 (9.2-15.0) ml/kg was transfused in 45 children (15%).

We will recruit a convenience sample of participants over a two-year period: n~50-60, based on 60-70 patients and assuming an 80% recruitment rate for a low-risk study; this recruitment rate would align with our previous experience in a similar longitudinal survey study.[21] As we plan to match each participant in the prospective cohort to two participants in the historical control group, we expect to observe approximately 5 participants in the intervention group (10% prevalence) and 15 participants in the matched cohort (15% prevalence) requiring a blood transfusion.

Statistical Analysis Plan

Historical data for matching will be extracted by a BCCH Surgical Clinical Reviewer from the P-NSQIP portal or by a research assistant from the Cerner electronic medical record (EMR). Prospective data will be extracted from the EMR and augmented by family-reported satisfaction and tolerance data from REDCap surveys. Data will be inspected for missingness to explore its patterns and inform to which degree this missingness can be corrected using multiple imputation by chained equations.[22,23] Data will be analyzed using R 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria). Transfusion rates between the baseline period and the intervention period will be compared using Fisher's exact test.

Propensity score methods will be implemented; this approach helps to reduce confounding when a treatment effect is estimated from observational sources rather than randomized trials.[24] We will estimate propensity scores for each patient as the confounder-adjusted probability for transfusion using a logistic regression model. We plan to match participants for five variables: 1) age, 2) sex, 3) gross motor function classification system (GMFCS) score, 4) ASA physical status score, and 5) procedure booking code. Results will be reported as marginal risk ratios and differences between intervention periods (historical cohort and prospective cohort, in which iron deficiencies were corrected) using the *weightit* package in R. Risk data will be reported as odds ratios (ORs) with 95% confidence intervals.

Semi-structured interviews will be transcribed, verified, and analyzed using a grounded theory-based qualitative approach.[25] Recurring patterns and themes will be systematically identified using thematic analysis in NVivo (Lumivero, Denver, CO) based on an inductive-deductive approach;[26] data will be analyzed while establishing codes and linking these codes through axial coding, enabling us to identify relationships between categories and key concepts.

3.0 DATA MANAGEMENT

3.1 Platform

All participants who are part of the prospective cohort will be assigned a participant ID, which is a sequential number based on the recruitment order. The connection between participants and their IDs will be stored in a password-protected master tracking log. This tracking log file will reside on a separate encrypted server from the study database in a folder accessible only to the research team. All electronic data will be maintained on PHSA and UBC-approved servers. Collected study data will be maintained by the BCCHR REDCap team on their encrypted databases. Other study files created by the researchers will be housed within the research team's shared drive on their secured and encrypted servers. Access to both data locations is restricted to the research team through their log-in credentials.

3.2 Data Sharing

Summarized results will be presented at scientific conferences and published in peer reviewed journals. At the time of publication, de-identified study results may be made available in a publicly accessible location.

To advance scientific knowledge and promote transparency within research, our team supports data sharing with the wider scientific community. It is our hope that data yielded from this study will support collaborative research efforts and continue to improve patient care and outcomes.

Per our local Research Ethics Board (REB) requirements, at the time of consent, all eligible patients will be informed of the potential future use of their deidentified data and provided with an opportunity to opt out of future use.

Data (of consenting participants) and documentation necessary to facilitate study reproducibility and program expansion will be shared, including deidentified raw data, data dictionaries, and project methodology. Study data will be available for 5 years following publication, in accordance with UBC data retention guidelines.

Data will be made available through the University of British Columbia's Dataverse Collection, hosted on the multidisciplinary, Canadian research repository, Borealis. A DOI will be assigned upon publication. Access to clinical patient data will be subject to ethical review and approval by the Research Ethics Board (REB) at the University of British Columbia and de-identified to ensure confidentiality. Requests for clinical patient data may be made directly to the PI or through Dataverse. Data sharing will be contingent on signing a Data Sharing Agreement.

3.3 Future Use of Data

In an effort to advance scientific knowledge and promote transparency within research, our team supports data sharing with the wider scientific community. It is our hope that data yielded from this study will support collaborative research efforts and continue to improve patient care and outcomes.

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3.4 De-Identification

Any potentially identifiable data fields collected during the data collection process are flagged within the REDCap platform as identifiers. The policy regarding flagged identifiers in the REDCap project will be set so that all fields marked as identifiers are removed from the data set upon export.

3.5 Data Lifecycle

Data will be kept for a minimum of 5 years following the date of publication. Any data required to be submitted along with a manuscript as a requirement for publication in a peer-reviewed journal will be de-identified.

Once the project's data has reached its effective lifespan, hard copies will be securely destroyed using the on-site PHSA approved secure document shredding service. Digital data will be deleted and wiper from the servers as per BCCHR Secure Data Erasure SOP 2020.

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