Cover Page for ClinicalTrials.gov

Document: Study Protocol

Official Study Title:

Reducing Red Blood Cell Transfusion Requirements for Adults

Undergoing Surgical Resection of the Liver – A Quality Improvement Project

Document Date:

June 30, 2025

Reducing red blood cell transfusion requirement for hepatectomy – a quality improvement project

Sean Bennett, Jeannie Callum, Anne Cao, Jennifer Fleming, Christopher Haley, Anthony Ho, Diederick Jalink, Jordan Leitch, Glenio Mizubuti, Sulaiman Nanji, Rachel Phelan, Steve Tresierra

BACKGROUND

Hepatectomy commonly results in blood loss significant enough to require red blood cell (RBC) transfusion. Blood transfusion has been shown in various scenarios to have been associated with inferior immediate- and longer-term outcomes, including cancer recurrence. In an observational study, a median follow-up of 45 months in 1469 hepatectomy patients, of whom 43% had had blood transfusion within 7 days of surgery, revealed that transfusion was independently associated with cancer recurrence [adjusted hazard ratio (HR) 1.29 (1.07-1.57)] and all-cause mortality [HR 1.42 (1.04-1.96)].[1] Blood products are also expensive. Blood conservation is a priority highlighted by the Choosing Wisely campaign.[2]

The PRICE-2 randomized controlled trial (RCT) by Martel et al investigated the effect of hypovolaemic phlebotomy (HP) prior to liver resection on transfusion need and operative conditions.[3] HP consisted of removing blood from the patient via a central or large bore peripheral venous line the equivalent of 1 unit (7-10 mL/kg of lean body weight) of whole blood after induction of general anesthesia (GA) and before liver resection began. Instead of concurrently replacing the phlebotomized blood with crystalloid (euvolemic phlebotomy), the PRICE-2 investigators used vasopressors [type(s) and quantities not disclosed] instead to maintain a normal blood pressure (BP) to mitigate the effect of the hypovolemia. When liver

resection was completed, the phlebotomized blood was always re-infused into the patient during the closing phase of surgery and before emergence from GA. The control group received usual care.

The PRICE-2 investigators found that allogeneic RBC transfusion between the time of surgery and the first 30 days postoperatively was less in the cohort that had received HP (53 RBC units were transfused within the HB group of 223 patients, compared with 86 units within the usual care group of 223 patients – a saving of 33 units per 223 patients, or 0.15 unit/patient on average), and the blinded surgeons perceived that intraoperative conditions were better in the HP group. Each red cell transfusion is estimated to cost between US$522-1183 in 2010 (US$774-$1183 in 2025), suggesting this intervention could save between $116 to $177 per case. In addition, Canada has experienced numerous blood shortages due to an imbalance between demand and supply. The composite adverse outcomes were similar between cohorts although the estimated blood loss was significantly less and Grade A bile leak happened significantly more in the HP group. The authors considered the Grade A bile leak to be of little clinical significance and also attributed the increased incidence to chance. Specifically, there was no difference in acute kidney injury between groups. The authors did not report arterial blood gas and lactate levels (important for detecting metabolic differences), urine output, and hemodynamic results such as central venous pressure which previously had been linked to blood loss in hepatectomy. The type of crystalloid used, though assumed to be Ringer's lactate, was not specified; neither were the quantities infused in either cohort.

At the Kingston Health Science Centre (KHSC), ~30 hepatectomies for cancer are performed/year. Based on 0.15 RBC unit/patient saved,[3] KHSC can reduce RBC consumption by hepatectomy patients of 9 units/2 years, and approximately 8 of those 60 patients would have

avoided a RBC transfusion. Even more importantly, cancer recurrence and mortality rates could potentially be reduced. Tai et al's observed that the unadjusted 5-year disease-free survival rates without and with peri-operative transfusion were 43% (95% CI 39-46%) and 29% (95% CI 25-33%), respectively. With HP, of the 8 patients who would have avoided RBC transfusion each 2 years in Kingston, 1 extra patient could be disease-free in 5 years.

PROBLEM STATEMENT

Patients undergoing liver resection for primary or secondary liver cancer often requires RBC transfusion. Transfusion is costly and may be associated with short- and/or long-term complications, including cancer recurrence and reduced survival.

AIM STATEMENT

1. To decrease RBC transfusion during and immediately after liver resection at KHSC;
2. To determine intra- and post-operative metabolic sequelae from hypovolemic phlebotomy, not reported in PRICE-2;
3. To standardize a hypovolemic phlebotomy protocol at KHSC for hepatectomy, not detailed in PRICE-2;
4. To determine if reduction in RBC transfusion will reduce cancer recurrence and all-cause mortality over 5 years in patients undergoing hepatectomy for cancer at KHSC;
5. To compare with a historical cohort of hepatectomy patients in the past 2 years.

STUDY OBJECTIVES

Primary Objective

To reduce intraoperative transfusion rates by 38% (based on PRICE-2[3]) in elective hepatectomies for cancer at KHSC upon implementation of a standardized hypovolemic phlebotomy protocol.

Secondary Objectives

1. Improved physiologic monitoring during hepatic resection.
    a. Intraoperative assessment of changes in arterial blood gases (specifically pH, PaO_2, $PaCO_2$), urine output and lactate levels relative to the volume of blood removed. This information not reported in PRICE-2.
2. Standardize intraoperative protocols for vasopressor management.
    a. Evaluate the effect of standardized fluid and vasopressor management protocols on intraoperative blood loss and hemodynamic stability. This information not reported in PRICE-2.
3. Postoperative Outcomes and Recovery
    a. Track postoperative complications and 90-day morbidity and mortality and length of hospital stay. Compare long-term recurrence of liver cancer to a historical cohort (not reported in PRICE-2).

HYPOTHESES

Implementation of a standardized hypovolemic phlebotomy (HP) protocol at KHSC during hepatic resection for cancer will reduce intraoperative blood product use and adoption of standardized physiological parameter documentation will improve patient outcomes and reduce resource overuse.

Reduction in RBC transfusion will translate into lower cancer recurrence and all-cause mortality over 5 years.

STUDY DESIGN

This will be a single-center prospective before-after quality improvement (QI) study evaluating the implementation of a standardized hypovolemic phlebotomy protocol in adult

patients undergoing hepatic resection. To define usual care outcomes, we will conduct a retrospective chart review of previous liver resections before the introduction of HP at KGH. By comparing prospective outcomes against this baseline, our study aims to evaluate whether a structured hypovolemic phlebotomy approach leads to measurable improvements in intraoperative management and perioperative outcomes.

Population

Adults aged ≥18 years undergoing elective hepatic resection at KGH.

Inclusion Criteria

The inclusion criteria are as follows:

1. Liver resection in this study is defined according to the PRICE-2 trial, involving 3 or more liver segments, such as right posterior sectionectomy (of segments VI and VII) as well as central resections involving segments IVb and V.
2. Alternatively, in patients with known liver cirrhosis, resection of a full segment was included.

Exclusion Criteria

The exclusion criteria are adapted from the PRICE-2 trial. Patients will be excluded if theoretically vasoconstriction or cardiac stimulation from vasopressors may exacerbate their underlying conditions:

1. A current cardiac condition (e.g. MI within the last 6 months, hypertrophic cardiomyopathy, severe valvular disease, or other unstable coronary syndromes), history of cerebrovascular disease (CVA within the past 6 months or severe carotid stenosis with more than 70% occlusion)
2. Peripheral vascular disease

3. A current pregnancy
4. Surgical plan including intention to use cell salvage during surgery
5. A documented, patient-declared refusal to undergo phlebotomy and transfusion.
6. Met the following preoperative risk markers for bleeding or transfusion:
    a. Preoperative hemoglobin <100 g/L
    b. GFR <60 mL/min
    c. Platelet count <100 x 10^9/L.
    d. Uncorrectable coagulopathies or other decompensated cardiac or respiratory conditions that would contraindicate acute volume depletion
    e. Are undergoing emergency surgery

CHART REVIEW

We will conduct a retrospective chart review for baseline process assessment to identify patients who underwent hepatic resection involving ≥3 segments at KGH prior to Aug 2025. Data extracted will include demographics (age, sex), indication for resection, baseline risk factors (preoperative hemoglobin, platelet count, GFR, ASA classification), pre-operative anemia optimization (diagnostic testing, intravenous iron, oral B12 administration) operative variables (type and extent of resection, estimated blood loss, total fluid administered, vasopressor use including agent, dose, duration and any intraoperative transfusions of blood products). Postoperative outcomes will also be collected, including hemoglobin levels, total length of hospital stay, ICU admission (if applicable), total intraoperative blood product usage, 30- and 90-day mortality, and post-operative complications (cardiac events, bleeding, AKI, infection). The same exclusion criteria as the intervention group will be applied. For comparative analysis, the

data will be de-identified and stored in a secure database. The longer-term survival data will constitute a follow-up study.

PDSA CYCLES

These experiments will be conducted prior to wider implementation of the protocol to refine it based on feedback and outcomes. Each cycle will be based on a single process change with rapid feedback to evaluate the impact of such a change on the system.

1. Cycle 1: Pilot the existing PRICE-2 protocol in elective liver resection patients at KHSC, assess protocol adherence and any issues with administration of HP, pre-operative team huddle to clarify team roles.
2. Cycle 2: Introduce and implement a standardized lab work [i.e., arterial blood gases (ABG)/lactate] timing checklist and compare compliance rates across various surgical teams. Evaluate feasibility and uptake, modify checklist to integrate into existing perioperative checklist.
3. Cycle 3: Adjust vasopressor usage thresholds according to real-time correlation data for MAP and lactate levels, monitor adherence and post-operative outcomes.

Process Measures

To assess how well the intervention is being implemented, the following outcome measures will be assessed:

1. % of elective hepatic resections where HP was implemented – to gauge protocol uptake

2. Compliance with vasopressor guidelines – evaluate adherence to standardization of intervention
3. Compliance with blood draw and lab work timing checklist – ensuring that physiologic monitoring is done at the correct timing

Balancing Measures

To assess and address any challenges presented by the intervention to improve patient care without compromising safety and efficiency.

1. Efficiency impact – measure time added to OR workflow in minutes
2. Workflow disruption – surveys of anesthesiologists and surgeons to gauge perceived burden on staff with intervention
3. Incidence of HP intolerance – ensure intervention for systemic improvement is not at the cost of patient safety

STAKEHOLDER ENGAGEMENT STRATEGY

Members of the QI team will include anesthesiologists, surgeons, internists (transfusion and hepatology), registered nurses, quality improvement leads, clinical research facilitators, statisticians, and other affiliated staff. The HP protocol will be introduced at an initial meeting, with monthly debriefs for feedback and evaluate implementation issues. Anonymous surveys and suggestion forms will be available between meetings to capture real-time feedback to adjust interventions in between PDSA cycles, and to facilitate continuous engagement across stakeholders.

LOCAL CONTEXT/BARRIERS TO INTERVENSION

KHSC has a formal code transfusion protocol but does not currently have a protocol in place for intra-operative HP administration.

SUSTAINABILITY

If this HP intervention is implemented for future liver resections, the checklists will be embedded into LUMEO and other pre-operative documentation.

STUDY INTERVENTION

The study intervention will consist of HP in addition to the current standard of care at KHSC. As per the PRICE-2 protocol, HP involves removing 7-10 mL/kg (of estimated lean body weight) of whole blood from the patient depending on tolerability, which is approximately 10% of total blood volume. Administration of HP will be in concordance with KHSC standards and precautions for handling of blood products, utilizing whole blood collection bags labelled with the patient's identifying information. Phlebotomy will be preferably conducted using the central venous catheter, although other vascular access routes may be considered at the discretion of the anesthesiologist. To prevent the influx of air or contaminants, the tubing system should remain sealed. The blood collection bags (standard issue by KHSC blood bank) will be gently shaken periodically during phlebotomy to ensure mixing of the blood with the citrate phosphate dextrose adenine. Hemodynamic changes following phlebotomy will be managed using vasopressors [phenylephrine +/- norepinephrine at the discretion of the attending anesthesiologist(s)] instead of IV fluid replacement. The goal is to maintain a MAP of ≥65 mmHg following HP, if MAP <65 mmHg or signs of hypoperfusion occur. The serum lactate level is checked immediately upon placement of an arterial line to establish a baseline. Upon completion of phlebotomy, the lactate level is again checked. If it is >3 mmol/L, Ringer's lactate boluses are allowed at the discretion

of the anesthesiologist. ABG and lactate level will be checked again immediately prior to exit from the operating room.

The full volume of phlebotomized blood will be returned prior to the end of the surgery following completion of hepatic resection, irrespective of the amount of intraoperative blood loss. If a patient requires more blood than the volume withdrew as per HP protocol, the anesthesiologist will administer Ringer's lactate +/- blood products. The Ottawa Criteria for Appropriate Transfusion in Hepatectomy[4] will be followed in the operating room, and the Association for the Advancement of Blood and Biotherapies Guidelines[5] will be followed in the postoperative setting (hemoglobin trigger <70 g/L or symptoms of anemia). If significant bleeding is ongoing, RBC transfusion will begin before the threshold is breeched. As per usual care, a CVP ≤ 5cm H2O will be targeted. For patients with a body mass index (BMI) >30, the volume of blood for phlebotomy will be adjusted using the Devine formula for ideal body weight using sex, height and current weight using MDCalc.

Serial urine output documentation, ABG (arterial pH, PaO_2, $PaCO_2$) and lactate measurements will be performed at pre-defined intraoperative timepoints. These include (1) at baseline immediately after induction and prior to HP, (2) immediately post HP to evaluate physiologic response to acute blood volume changes, and (3) at the end of resection as a predictor for postoperative morbidity and mortality.

The criteria for intolerance to HP will be defined as follows:

(1) vasopressor administration has surpassed 12 mcg/min for norepinephrine or 30 mcg/min for phenylephrine and the patient is persistently hypotensive (e.g. MAP ≤65 mmHg),

(2) evidence of tissue hypoperfusion or acidosis (e.g. elevated lactate >3 mmol/L, base deficit >4-6 mmol/L, pH <7.25).

If the patient has met any of the above criteria, this will be documented as HP intolerance and will prompt immediate evaluation for autologous blood reinfusion and small volume fluid resuscitation.

The anesthetic techniques used, including the use of thoracic epidural analgesia, will be at the discretion of the attending anesthesiologist.

REFERENCES

1. Tai YH, Wu HL, Mandell MS, et al. The association of allogeneic blood transfusion and the recurrence of hepatic cancer after surgical resection. Anaesthesia 2020; 75:464-471.
2. Callum JL, Waters JH, Shaz BH, et al. The AABB recommendations for the Choosing Wisely campaign of the American Board of Internal Medicine. Transfusion 2014; 54:2344-2352.
3. Martel G, Carrier FM, Wherrett C, et al. Hypovolaemic phlebotomy in patients undergoing hepatic resection at higher risk of blood loss (PRICE-2): a randomised controlled trial. Lancet Gastroenterol Hepatol 2025; 10:114-124.
4. Bennett S, Tinmouth A, McIsaac DI, et al. Ottawa criteria for appropriate transfusions in hepatectomy: using the RAND/UCLA appropriateness method. Ann Surg 2018; 267:766-74.
5. Carson JL, Guyatt G, Heddle NM, et al. Clinical practice guidelines from the AABB: red blood cell transfusion thresholds and storage. JAMA 2016; 316:2025-35.