Selecting Patients for Acute Normovolemic Hemodilution during Hepatic Resection: A Prospective Randomized Evaluation of Nomogram-Based Allocation

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BACKGROUND: Acute normovolemic hemodilution (ANH) decreases transfusion rates but adds to the complexity of anesthetic management during hepatectomy. A randomized controlled trial was conducted to determine if selecting patients for ANH using a transfusion nomogram improves management and resource use compared with selection using extent of resection.

STUDY DESIGN: One hundred fourteen patients undergoing partial hepatectomy were randomized to a clinical arm (ANH used for resection of $\geq$3 liver segments) or a nomogram arm (ANH used for predicted probability of transfusion $\geq$50% based on a previously validated nomogram). The primary end point was appropriate management, defined as avoidance of ANH in patients at low risk or use of ANH in patients at high risk for allogeneic red blood cell transfusions.

RESULTS: Between September 2009 and May 2011, 58 patients were randomized to the clinical arm and 56 to the nomogram arm. Demographics, diagnoses, extent of resection, blood loss, and incidence and grade of complications did not differ between the 2 groups. There were no differences in perioperative transfusions or laboratory values. Nomogram-based allocation did not change appropriate management overall (80% vs 76% in the clinical arm; $p = 0.65$), but did result in comparable perioperative outcomes and a trend toward decreased ANH use (30% vs 47%; $p = 0.09$), particularly in low blood loss (estimated blood loss $\leq$400 mL) cases (12% vs 25%; $p = 0.04$).

CONCLUSIONS: Although allocation of intraoperative management using a transfusion nomogram did not improve appropriate management overall, it more effectively identified low blood loss cases and reduced ANH use in patients least likely to benefit. (J Am Coll Surg 2013;217: 210–220. © 2013 by the American College of Surgeons)

During the past 3 decades, hepatic resection has been widely used to treat primary and metastatic liver tumors. Recent advances in anesthetic management and operative technique have allowed for large hepatic resections to be performed with fewer complications and reduced hemorrhage.[1,2] Despite improvements, the need for perioperative allogeneic packed red blood cell (PRBC) or fresh frozen plasma (FFP) transfusion remains high, with 30% to 40% of patients requiring perioperative transfusion, even at large-volume centers.[3,4] The risks associated with allogeneic transfusions are well known and include transmission of blood-borne infections,[5,6] immune-related transfusion reactions,[7] and complications related to immunosuppression, such as increased perioperative morbidity[8] and worse long-term oncologic outcomes.[9-12]

Driven by the realization of increased cost and adverse outcomes associated with blood transfusions, strategies

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Abbreviations and Acronyms

ANH = acute normovolemic hemodilution
EBL = estimated blood loss
FFP = fresh frozen plasma
INR = international normalized ratio
PBRC = packed red blood cell

have been sought to reduce their use. These have been extensively reported in the orthopaedic and cardiac surgical literature and include reinfusion of washed shed blood (Cell Saver),[13,14] preoperative autologous blood donation,[15,16] and acute normovolemic hemodilution (ANH).[17,18] The benefits of ANH over autologous preoperative transfusion include decreased risk of administration error, reduced cost, and elimination of the need to cool and store blood. Acute normovolemic hemodilution does have limitations, including need for specialized equipment and training, increased operating room time, and theoretical dilution of coagulation factors during volume expansion.

The authors previously conducted a randomized controlled trial of ANH vs standard perioperative management in patients undergoing major hepatic resections (>3 liver segments).[19] Patients in the ANH arm had higher postoperative Hgb levels and required fewer intraoperative allogeneic transfusions. For patients with greater blood loss, the effect was more dramatic, with reductions in both intra- and postoperative RBC and FFP requirements. Criticisms of this study include the relatively high proportion of patients treated with ANH with no benefit and the unpredictability of blood loss and transfusion requirements related solely to the amount of liver resected. It is clear that a better means of identifying patients at high risk for transfusion is required, especially as hepatic resection continues to evolve and major hepatectomy is performed less frequently.

Recent efforts have been made to improve prognostication of transfusion requirement to better allocate the resources needed for ANH. Sima and colleagues[4] proposed a nomogram that used preoperative variables to predict the likelihood of perioperative red blood cell transfusion in patients undergoing liver resection. Allotting points based on preoperative Hgb and platelet level as well as details about the operation, including planned number of segments to be resected, primary vs metastatic disease, and need for extrahepatic resection, a score was created that predicted the percent probability of transfusion.

The aim of the current study was to determine if nomogram-based allocation of ANH was superior to allocation using extent of resection alone in patients undergoing partial hepatectomy. A trial was designed in which patients were randomized to different management strategies: a clinical arm (patients assigned to ANH or standard intraoperative management based on extent of resection) or a nomogram arm (patients assigned to ANH or standard intraoperative management based on the nomogram-predicted transfusion risk). The primary aim was to assess the impact of the nomogram on appropriate management by assessing its ability to target ANH to patients most likely to benefit.

METHODS

Patients scheduled for partial hepatectomy for any liver lesion, with or without a concomitant procedure, were approached for enrollment in an Institutional Review Board–approved prospective randomized controlled trial. Preoperative assessment, operation, and perioperative care all took place at Memorial Sloan-Kettering Cancer Center.

Patient eligibility

Inclusion criteria were all adult (older than 18 years) patients undergoing hepatectomy with a preoperative Hgb concentration $\geq$11 mg/dL in male and $\geq$10 mg/dL in female patients, as recorded within 14 days of registration. Exclusion criteria are listed in Table 1. In addition, patients participating in preoperative autologous donation or those receiving erythropoietin were excluded from the study.

Study design

We predicted that a nomogram-based allocation would more appropriately select patients for ANH when compared with selection based on extent of resection alone for patients undergoing partial hepatectomy. Patients were randomized to the clinical arm, where the decision to use ANH was based solely on the hepatic resection extent ($\geq$3 segments),[19] or a nomogram arm, in which ANH was performed only when the probability of requiring a transfusion was

Table 1. Patient Exclusion Criteria

Active coronary artery disease, unless a cardiac stress study shows no reversible ischemia and normal left ventricular function within 30 days of operation
History of cerebrovascular disease
Congestive heart failure
Uncontrolled hypertension
COPD
Renal dysfunction (creatinine > 1.8)
Abnormal coagulation parameters (international normalized ratio >1.5 not on warfarin, or platelet count <100,000 K/mL)
Presence of active infection
Evidence of hepatic metabolic disorder (bilirubin >2 mg/dL, ALT >75 U/L in the absence of biliary tract obstruction)
Preoperative autologous blood donation
Erythropoietin use

ALT, alanine aminotransferase.

≥50%, based on a previously validated transfusion prediction model (Fig. 1).

The primary end point was appropriate management, defined as avoiding the use of ANH in patients at low risk for a transfusion (ie, unlikely to benefit from the procedure) and enlisting ANH for patients at high risk for a transfusion (ie, more likely to benefit). This concept is easy to articulate but in practice is complicated by a certain level of uncertainty about the impact of the intervention. Specifically, if a patient receives ANH and is not transfused, one must consider whether ANH prevented a transfusion that would otherwise have been required (appropriate management) or because a transfusion would have been unnecessary even without ANH (inappropriate management). In an effort to account for this, the estimated blood loss (EBL) was used to stratify the probability that a transfusion would have been required. Based on analysis of past data from the hepatopancreatobiliary service database at Memorial Sloan-Kettering Cancer Center, a cutoff EBL of >600 mL was found to represent an inflection point above which the need for perioperative transfusions increased significantly. Therefore, for all patients treated with ANH and not transfused, assignment to ANH was considered inappropriate if the blood loss was <600 mL, given the low likelihood that a transfusion would have been necessary. On the other hand, if the EBL was >600 mL, management with ANH was considered appropriate, given the higher risk of needing blood. By contrast, when patients in the ANH group required allogeneic transfusions, the management allocation was considered appropriate because such patients were identified as high risk, but the intervention was ineffective. Similarly, patients assigned to standard care and not transfused were considered appropriately managed, and those who required an allogeneic transfusion in the standard arm were misallocated and, therefore, managed inappropriately.

Using this definition of appropriate management, we retrospectively calculated that 50% of the patients in the service database would be appropriately managed if randomized to the clinical arm and speculated that nomogram-based allocation would increase this to 70%. This design would require randomizing 220 patients (110 to each arm) and would provide >80% power (type I error of 5%, chi-square test) to test this hypothesis. An interim analysis was also planned halfway through the enrollment using O'Brien-Fleming boundaries. The 2 allocation strategies were compared for appropriateness of management as well as rate of transfusion, postoperative complications, and overall use of ANH. The intent-to-treat principle was followed where all randomized patients were included in the analysis and in the treatment groups to which they were randomized. Data are presented as the mean ± SD or the median (range).

Preoperative and intraoperative management

The general management approach has been described previously.[2,19] Briefly, all patients were seen in a surgical clinic where a preoperative assessment was performed, x-rays and pathology were reviewed, and an operative

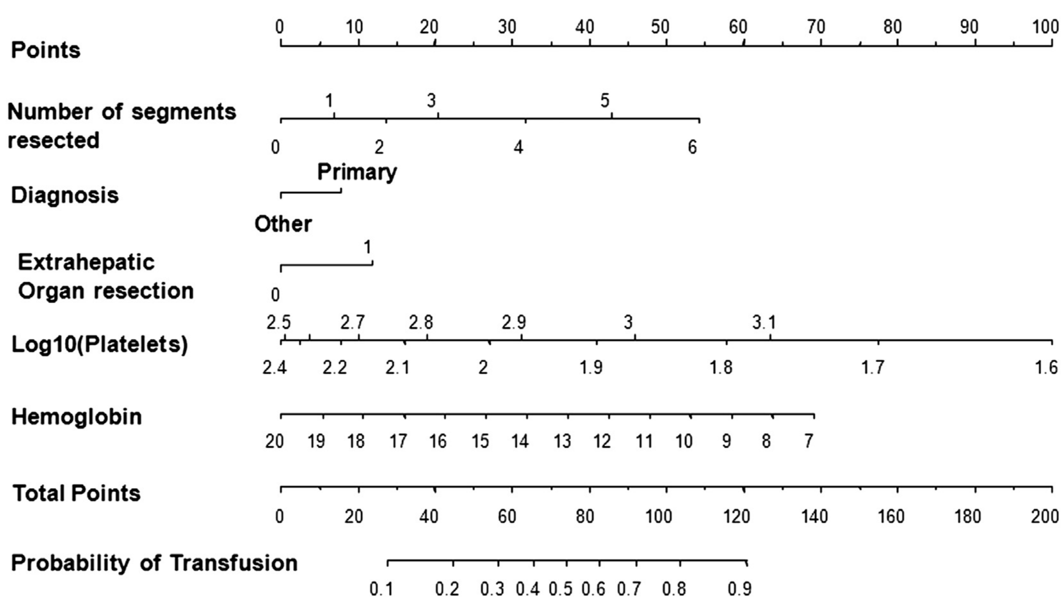

Figure 1. A previously created and validated nomogram (from Sima and colleagues[4]) was used to determine probability of allogenic red blood cell transfusion during or after hepatectomy. Patients randomized to the nomogram arm received acute normovolemic hemodilution if their probability exceeded 50%.

plan was formulated. If sufficient comorbidities existed, and in all patients older than 65 years of age, referral for general medical clearance or additional cardiopulmonary workup was made. All patients had preoperative complete blood counts, comprehensive and coagulation panels, chest x-rays, and electrocardiograms, in addition to appropriate imaging related to assessment of cancer extent. Before operation, cases were reviewed at a multidisciplinary conference where extent of disease and fitness for surgical resection were discussed.

At operation, after determination of resectability, patients were randomized to the clinical arm or the nomogram arm, and then assigned to either ANH or standard management based on the criteria described previously.

Patients were explored through a midline, right subcostal, or bilateral subcostal incision at the discretion of the operating surgeon. The abdomen was thoroughly explored, and the liver was assessed via bimanual palpation; inspection and palpation of the porta hepatis and retroperitoneum were performed to assess for the presence of suspicious lymphadenopathy. Suspicious lesions were biopsied and frozen section was performed when appropriate. Intraoperative ultrasound was used routinely to identify lesions missed on preoperative imaging, as well as to determine the proximity of lesions to vascular structures. In most cases, inflow vascular control was obtained after mobilization of the liver before parenchymal transection.

As described previously, all patients were managed with a combination of fluid restriction and pharmacologic manipulation to keep central venous pressure $\leq$5 mmHg.[2,20] All patients had continuous monitoring of heart rate, blood pressure, central venous pressure, electrocardiogram, end-tidal CO_2, oxygen saturation, temperature, and urine output. Serial arterial blood gases and serum Hgb values were monitored every 30 minutes during the procedure. All data were recorded prospectively for later analysis. For all patients, surgical blood loss during the operation was replaced with crystalloid in a 3:1 ratio.

If the operation was aborted before randomization due to unanticipated anatomic abnormalities, extensive extrahepatic disease, or unresectability, the patient was removed from the trial and replaced.

Acute normovolemic hemodilution protocol

For patients in the ANH arm, hemodilution was performed as described previously.[19,21] Briefly, allowable blood loss was calculated using the formula: $VL = EBV \times (H_0 - H_F)/H_{AV}$, where VL = allowable blood loss, EBV = estimated blood volume, H_0 = patient's initial Hgb, H_F = patient's minimum allowable Hgb, and H_{AV} = average of initial and minimal allowable Hgb. The volume of blood was withdrawn to a target Hgb of 8.0 g/dL using a central venous catheter with a maximum allowable phlebotomized volume of 3 L—that is, they did have central venous pressures—in all patients or only those randomized to ANH. Removed blood was placed into standard blood-collection bags (Baxter-HC/Fenwal Autologous Blood Collection Kit) and stored at room temperature in the operating room labeled with the patient's name, medical record number, date, beginning and completion times of blood removal, and name of phlebotomist. All bags were clearly numbered indicating the order of removal and marked with the phrase "NOT TO LEAVE THE OR." During collection, a tilt rocker scale was used to gently mix and weigh the blood (Biomixer 323; National Hospital Specialties). Blood removed was replaced 50% with 5% albumin in quantities 1.1 times the volume of blood removed and 50% with crystalloid solution in a 3:1 replacement ratio.

Transfusion protocol

A predetermined trigger for intraoperative transfusion was chosen at $\leq$7.0 g/dL. For ANH patients, this was treated with reinfusion of autologous blood given in reverse order from which it was drawn; allogeneic blood was used only after all autologous blood was reinfused. If autologous blood remained or the transfusion trigger was not reached, it was transfused back to the patient at the end of the case. Per protocol, blood was intended to be returned to patients 8 hours after pheresis even if the operation was not yet completed, although this was never required.

Postoperatively, Hgb and international normalized ratio (INR) were measured daily for 7 days until values normalized or the patient was discharged. If Hgb was $<$8.0 g/dL or $>$8.0 g/dL, with symptoms such as tachycardia, shortness of breath, or fatigue, the patient would receive allogeneic PRBC transfusion. If the INR was $>$1.8 or $\leq$1.8, with evidence of bleeding or need for an invasive procedure, the patient would receive FFP. Transfusions were also given or held at the discretion of the primary surgeon when clinically indicated.

Postoperative care

All patients had standard posthepatectomy treatment on a general care floor or, when indicated, an ICU. Laboratory values were checked daily while inpatient and monitoring of fluids and postoperative complications was done by the primary surgical team. Complications were graded in severity using a score of 1 to 5, as described previously.[22]

RESULTS

From September 2009 to May 2011, 123 patients were registered. Nine patients were excluded for unresectability (n = 6), protocol violation (n = 2), or error in randomization (n = 1). In total, 114 patients were randomized to either the clinical arm (58 patients) or the nomogram-based arm (56 patients; Fig. 2). The trial was terminated at the interim analysis for futility based on the primary end point of appropriate management.

Preoperative characteristics

Patient demographics and preoperative data are listed in Table 2. The groups were well matched, although patients in the clinical group trended toward slightly older age (60.8 vs 57 years). The majority of resections were performed for metastatic colorectal cancer (62%); 18% were performed for primary liver cancer, which likely explains the high preoperative chemotherapy rate observed in both groups. Pertinent preoperative laboratory values, including Hgb and INR, were similar between groups and well within normal ranges.

Perioperative outcomes

Intraoperative variables were similar between the groups (Table 3). There were no differences in extent of resection, with a mean of 2.7 ± 1.2 segments resected in each group. Forty percent of patients underwent concomitant extrahepatic procedures, including colectomy (14 patients), bile duct resection (3 patients), and diaphragm resection (3 patients). Twenty-one patients had hepatic artery chemoinfusion pumps placed at the time of hepatectomy. Estimated blood loss was not different between the 2 groups (mean 552.2 ± 575.9 mL). Those submitted for ANH had a greater EBL when compared with the standard group (844.8 ± 762.4 mL vs 367.4 ± 302.8 mL, respectively; $p < 0.001$), reflecting their identification as patients at higher risk for transfusion in both arms. Resuscitation with crystalloid and albumin was done per protocol and did not differ between groups.

Acute normovolemic hemodilution

In accordance with the trial design, patients in the clinical arm were assigned to ANH based on the anticipated number of liver segments (≥3) to be resected at the outset of the case. A total of 28 patients (47%) in the clinical arm received ANH for a planned median of 4 segments to be removed (Table 4). One patient received ANH and subsequently underwent resection of only 2 segments, and 3 patients treated with standard management required more extensive resections than planned. Patients in the nomogram arm had a probability of perioperative transfusion score generated using a previous published nomogram (Fig. 1).[4] Those with a score predicting a transfusion probability of ≥50% were assigned to receive ANH, and others received standard management. Mean calculated nomogram score was 42%, with 17 patients (30%) undergoing ANH for a score ≥50%.

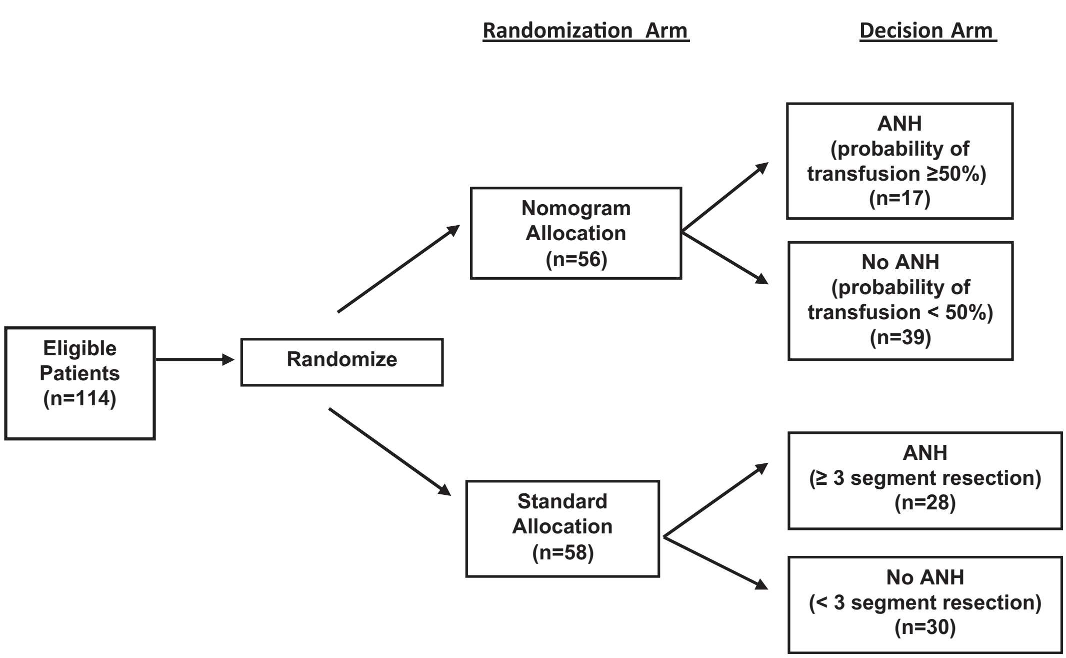

Figure 2. Randomization schema. ANH, acute normovolemic hemodilution.

Table 2. Comparison of Preoperative Characteristics

Characteristic	Clinical (n = 58)	Nomogram (n = 56)
Age, y	60.8 ± 13.7	57 ± 11.9
Race, n		
White, non-Hispanic	39	50
Asian-Pacific Islander	6	2
Black, non-Hispanic	2	1
Hispanic	5	3
Sex, male/female, n	27/31	25/31
1 or more comorbidity, n	28	20
BMI, mean ± SD	30.0 ± 6.1	29.2 ± 6.4
ASA classification, n		
1	0	0
2	21	31
3	36	25
4	1	0
Preoperative chemotherapy (within 6 mo), n	23	30
Metastatic/primary tumor, n	44/14	42/14
Diagnosis, n		
Metastatic colorectal	37	34
Metastatic other	6	9
HCC	8	4
Biliary cancer	4	5
Benign tumor	2	4
Preoperative Hgb, g/dL, mean ± SD	13.1 ± 1.6	13.1 ± 1.3
Preoperative INR, mean ± SD	1.06 ± 0.3	1.06 ± 0.3
Preoperative platelet count, ×1,000/μL, mean ± SD	227 ± 76.1	237 ± 72.2
Preoperative bilirubin, mg/dL, mean ± SD	0.6 ± 0.2	0.7 ± 0.2

BMI, body mass index (calculated as kg/m^2); HCC, hepatocellular carcinoma; INR, international normalized ratio.

Details about the ANH procedure for all patients are listed in Table 4; there were no differences between the randomization arms. For all patients treated with ANH, a mean volume of 2,139 ± 778 mL blood was withdrawn during a mean time of 40 ± 27.6 minutes. There were no complications directly related to ANH, and all patients were reinfused with their autologous blood at the end of the case.

Postoperative complication rates were similar, with 40 complications occurring in 18 patients. The most common complications were infections, occurring in 8 and 6 patients in the nomogram and clinical arms, respectively. Other complications included cardiac (1 vs 2 patients) and thrombotic events in (2 vs 1 patient) in the nomogram and clinical arms, respectively. There was 1 perioperative death within 30 days in the clinical arm.

Perioperative laboratory values

Preoperative laboratory values were available for all enrolled patients. There were no differences in starting Hgb (13.1 ± 1.6 g/dL vs 13.1 ± 1.3 g/dL), INR (1.06 ± 0.3 vs 1.06 ± 0.3), or platelet count (227 ± 76.1 K/μL vs 238 ± 72.2 K/μL) between the clinical and nomogram arms, respectively. There were no significant differences in postoperative Hgb, platelet count, or INR for the 7 days after operation and at return visit approximately 14 days after discharge.

Transfusion data and appropriate management

Of the entire cohort, 17 patients (15%) required transfusion of either allogeneic FFP or PRBC during the perioperative period (Table 5). Ten patients (8.8%) received a median of 2 U (range 1 to 3 U) PRBC and 11 (9.6%) received a median of 3 U (range 2 to 6 U) FFP; 4 patients received both. There were no differences in overall PRBC transfusions between the clinical and nomogram arms (6 vs 4 patients, respectively; $p = 0.79$). All patients were transfused within the guidelines of the protocol, with the exception of 3 patients in the nomogram arm and 4 in the clinical arm who were not transfused PRBC for an Hgb <8.0 at the discretion

Table 3. Comparison of Operative and Perioperative Results

Result	Clinical (n = 58)	Nomogram (n = 56)	p Value
No. of segments removed, mean ± SD	2.7 ± 1.2	2.7 ± 1.2	0.95
Nomogram score, mean ± SD	0.42 ± 0.2	0.42 ± 0.2	0.99
Extrahepatic operation, n	20	25	0.34
OR time, min, mean ± SD	254 ± 89	271 ± 101	0.36
Starting Hgb, g/dL, mean ± SD	11.1 ± 2.9	11.8 ± 2.4	0.13
Starting pH, mean ± SD	7.38 ± 0.04	7.38 ± 0.05	0.51
Intraoperative fluid given, mL, mean ± SD	4,138 ± 271	3,873 ± 279	0.51
Crystalloid, mL	3,564 ± 208	3,465 ± 231	0.74
Colloid, mL	578 ± 59	402 ± 53	0.12
EBL, mL, mean ± SD	528.4 ± 500	575.9 ± 648	0.66
Urine output, mL, mean ± SD	433 ± 291	380 ± 321	0.36
Postoperative complications, n			
Any	17	16	0.77
≥Grade 3	13	14	

EBL, estimated blood loss; OR, operating room.

of the treating surgeon ($p = 0.87$). Intraoperatively, 3 patients undergoing ANH in the nomogram arm and 2 in the clinical arm required transfusion of autologous blood, as per the protocol transfusion guidelines; however, there were no intraoperative allogeneic PRBC transfusions in either arm.

The primary end point of the trial was allocation to appropriate management, defined as use of ANH when blood transfusion was more likely to be needed (EBL > 600 mL) and avoiding it when the likelihood was low. In the clinical arm, 14 patients (24.1%) had inappropriate management, with 12 patients undergoing unnecessary ANH and 2 patients receiving blood transfusions after routine anesthetic care. This was similar in the nomogram arm, where 8 patients (14%) with EBL < 600 mL and no blood transfusions underwent unnecessary ANH, and 3 patients in the standard management group subsequently needed a postoperative transfusion. There was no significant difference between the 2 arms with respect to the primary end point ($p = 0.65$). With this finding at the interim analysis, the trial was terminated.

Of note, although overall appropriate management was similar between the 2 randomization groups, ANH was used more frequently in the clinical arm compared with the nomogram arm ($p = 0.09$). Median EBL for the entire cohort was 400 mL (range 50 to 2000 mL); there were 33 patients in the nomogram arm and 28 patients in the clinical arm, with EBL less than this median value (ie, low blood loss cases; $p = 0.57$). In this subgroup of patients with EBL less than the median, ANH was used less frequently in those randomized to the nomogram arm (12.1%) compared with those in the clinical arm (25%; $p = 0.04$; Fig. 3).

When focusing on those who underwent hemihepatectomy or greater (n = 36), there were similar transfusion rates in both patients randomized to the clinical arm and nomogram arm (35% vs 38%, respectively). Again, there was a trend toward decreased ANH use in the nomogram-based allocation arm, with ANH used in 81% of patients compared with 100% in the clinical arm. There were no statistical differences in appropriateness of management.

DISCUSSION

Despite technical and anesthetic advancements during the past 3 decades, major hepatectomy remains a challenging operation with potential for high blood loss and frequent need for intraoperative and postoperative transfusions. It has long been known that allogeneic blood transfusions carry some element of risk, including transmission of

Table 4. Hemodilution Data for Patients Receiving Acute Normovolemic Hemodilution

Variable	Clinical (n = 58)	Nomogram (n = 56)	p Value
ANH performed	28	17	0.09
Mean blood removed, mL, mean ± SD	2149 ± 767	2119 ± 831	0.91
Mean duration of ANH, min, mean ± SD	35 ± 16	49 ± 38	0.09
Post-ANH starting Hgb, mean ± SD	8.4 ± 2.9	8.8 ± 2.4	0.28

ANH, acute normovolemic hemodilution.

Table 5. Intraoperative and Perioperative Transfusion Data

Variable	Clinical	Nomogram	p Value
Lowest postoperative Hgb, g/dL, mean ± SD	9.9 ± 1.7	9.6 ± 1.5	0.29
Highest postoperative INR, mean ± SD	1.41 ± 0.25	1.42 ± 0.28	0.9
Patients requiring autologous blood transfusion, intraoperative, n	2	3	0.7
Patients requiring allogenic postoperative blood transfusion, n	4	6	0.79
Units per transfused patient, mean ± SD	1.8 ± 0.75	2 ± 1.2	0.77
Transfusion blood after 7 d, n	2	3	0.71
Patients requiring any transfusion postoperatively, n	6	9	0.79

INR, international normalized ratio.

bacteria and viruses, hemolytic transfusion reactions, and transfusion-associated lung injury.[5,6,23] An increasingly recognized sequelae of transfusions is development of relative immunosuppression.[24,25] This has been implicated in the increased morbidity observed after major operations requiring blood transfusion, as well as worse oncologic outcomes in colon,[9,10] breast,[11] lung,[12] and gastric cancers.[26]

In a study looking at morbidity after hepatectomy, nontransfused patients had significantly fewer postoperative complications compared with those who received blood transfusions.[8] This observation appeared to be dose related, as a greater number of units transfused were associated with a higher rate of complication. These findings do not apply only to transfusion of PRBC, as similar results have been reported for platelets and FFP.[27] Postoperative transfusion is also associated with decreased long-term survival after resection of both primary[28] and metastatic hepatic malignancies. A retrospective analysis by Kooby and colleagues[8] found that patients undergoing hepatic metastasectomy for colorectal cancer who received multiple units of PRBC had worse disease-specific survival compared with nontransfused controls.

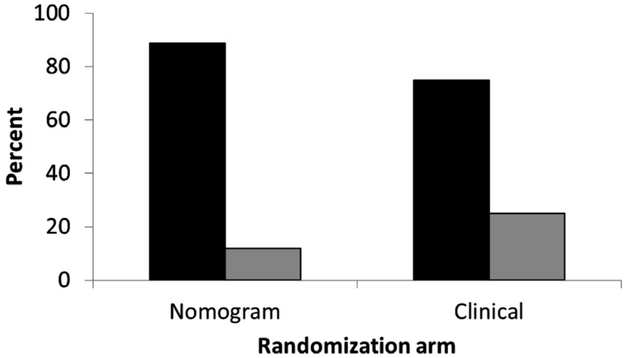

Figure 3. Patients were dichotomized around the median estimated blood loss of 400 mL. Patients who had low blood loss operations were less likely to receive hemodilution when allocated using the nomogram (p = 0.04). Black bar, standard; gray bar, acute normovolemic hemodilution (ANH).

The short and long-term morbidity associated with allogeneic transfusions has prompted the development of blood-conservation strategies to prevent perioperative anemia, including use of intraoperative Cell Saver and preoperative autologous donation.[15,16] The latter involves preoperative phlebotomy and storage of a patient's own PRBC to be used, if needed, intraoperatively. Although this approach gained popularity in the early 1990s, the morbidity of preoperative donation is 12 times higher than elective donation, and more than half of all units donated are never needed and are discarded.[29] There is also a substantially increased incidence of clerical errors and higher associated cost.

Recent data have demonstrated the safety and efficacy of ANH in liver resection.[19] This technique involves the collection of whole blood after induction of general anesthesia, followed by volume replacement using a combination of crystalloid and colloid. The phlebotomized blood is anticoagulated and stored at room temperature in the operating room and transfused to the patient as needed during the operation. At the end of the case, the unused blood is given back to the patient and none is discarded. There are numerous theoretical and practical benefits to ANH vs preoperative autologous donation. Because the blood is withdrawn at the time of operation, there is the ability to rapidly re-expand the intravascular space, decreasing the morbidity associated with donation. Blood is also stored in the operating room at room temperature, avoiding the associated costs of cross matching, preservation, and storage. Clerical mistakes are avoided because the blood never leaves the patient's side and, finally and perhaps most importantly, blood is never discarded.

Acute normovolemic hemodilution is not without drawbacks, however, including the need for anesthetic expertise and the associated cost of phlebotomy and potential for added operating room time. Additionally, the efficacy of ANH in preventing transfusion[19] is greater when blood loss is higher, and given the improvements in the conduct of hepatic resection during the past several years, most patients will not benefit from its use. Given the reduction in blood loss associated with hepatic resection over time, the authors' current practice has been to reserve ANH use for resections likely to be associated with high blood loss.[19,21] Unfortunately, preoperative prediction of high intraoperative blood loss is difficult, with most authors relying solely on the number of segments resected as a surrogate; however, with the rising use of parenchymal-sparing resections, preoperative portal vein embolization, and 2-stage hepatectomy, the number of segments alone is an imperfect predictor. In a recent publication by Sima and colleagues,[4] a statistical nomogram was created based on multiple preoperative variables that accurately predicted the need for intraoperative transfusion. It was clear from this analysis that extent of hepatic resection, which is generally known before the procedure, is not the only predictor of blood loss and the need for allogeneic transfusions. The goal of the current study was to determine if use of this nomogram might improve allocation of ANH to patients with higher blood loss operations and/or those otherwise at high risk of requiring intraoperative or postoperative transfusion.

To address this issue, a randomized controlled trial was designed in which patients were assigned to ANH or standard anesthetic management based on either the number of planned segments resected (clinical arm) or a nomogram-predicted probability of transfusion of >50% (nomogram arm). The primary end point was appropriate management, defined broadly as targeting of ANH to patients at higher risk for transfusions and avoiding its use in patients at lower risk; as part of this definition, a blood loss cutoff value (600 mL) was used to ensure that the level of transfusion risk justified the treatment allocation (ie, ANH vs standard management) in both randomization arms. The findings of the study showed that both the nomogram and clinical arms resulted in the same level of appropriate management, with the majority of patients receiving intraoperative care that, in general, was commensurate with their EBL. As a result, the early stopping rule for futility was invoked during the planned interim analysis, and the study was stopped.

Although the nomogram did not improve overall management, it was not without some merit with respect to resource use. Specifically, there was a trend toward decreased ANH use in the nomogram compared with the clinical arm (30% vs 47%; $p = 0.09$), which appeared to result entirely from better identification of low blood loss cases. When focusing on resections with very low blood loss (<400 mL), nomogram-based allocation appropriately reduced the proportion of unnecessary ANH (12% vs 25%; $p = 0.04$), highlighting the potential of the statistical model to better identify patients at risk for substantial blood loss and therefore more likely to benefit from hemodilution.

In line with our original hypothesis, there were some patients undergoing resection of 1 or 2 segments with high blood loss, elevated predictive nomogram scores, and transfusion requirements (Table 6). Although blood loss and ANH use were predictably higher in the patients that underwent more extensive partial hepatectomy (ie, greater number of segments), these data show that the predictive nomogram can be useful, even for more limited resections, and highlight the limitations of relying on extent of resection alone.

Although it has been practiced since the 1970s, many are reluctant to introduce ANH into standard practice due to low yield in terms of transfusions prevented per hemodilution performed. In our original trial, it was estimated that 40% of patients underwent unnecessary ANH based on the subsequent low operative EBL. In the current study, the transfusion nomogram appeared to be particularly effective for identifying this subgroup of patients, thereby improving resource use. With the cost of phlebotomy, storage, and volume expansion averaging \$40 to \$50 per unit,[30] a hospital-wide adoption of this strategy can result in substantial cost savings and possibly more widespread adoption. As highlighted in this study, the transfusion rate for major hepatectomy has decreased steadily during the past decade. As such, it is imperative to develop methods to target blood-conservation strategies like ANH to patients most likely to benefit.

An obvious limitation of this study is the inability to blind the surgeons and the postoperative care team to the randomization, possibly biasing management.

Table 6. Blood Loss and Acute Normovolemic Hemodilution by Number of Segments Removed

	No. of segments removed				
Variable	**22**	**34**	**21**	**27**	**9**
Median EBL, mL (range)	250 (25−900)	225 (25−1,500)	400 (80−2,500)	600 (50−1,800)	2,000 (500−3,000)
Median nomogram score (range)	0.28 (0.13−0.80)	0.30 (0.15−0.87)	0.37 (0.16−0.70)	0.58 (0.25−0.83)	0.64 (0.55−0.81)
ANH, %	9	3	38	85	100
Transfused (allogenic and autologous), %	14	3	0	33	44

ANH, acute normovolemic hemodilution; EBL, estimated blood loss.

Although this might have influenced perioperative care, strict transfusion triggers were in place to minimize deviation from the protocol. There were 7 failures to transfuse when triggers were met, which were equally distributed between the 2 arms and did not alter the overall results. Additionally, it remains to be determined if the management approach and the findings of the current study can be readily adapted to other centers.

CONCLUSIONS

Acute normovolemic hemodilution decreases the need for allogeneic blood transfusions without the waste and dangers of preoperative autologous donation. It does increase the complexity and cost of the operation and is unnecessary in most patients. Allocation of ANH using a preoperative predictive transfusion nomogram can prevent unnecessary hemodilution use in low blood loss hepatic resections, where benefit is least likely.

Author Contributions

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Analysis and interpretation of data: Frankel, Krone, Jarnagin, Gönen

Drafting of manuscript: Frankel, Jarnagin, Gönen

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