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A Prospective Trial of Acute Normovolemic Hemodilution in Patients Undergoing Primary Cytoreductive Surgery for Advanced Ovarian Cancer

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Abstract

Objectives: Our objective was to determine the safety and efficacy of acute normovolemic hemodilution (ANH) to reduce the requirement for allogenic red blood cell (RBC) transfusions in patients undergoing primary cytoreduction for advanced ovarian cancer.

Methods: Patients undergoing primary cytoreduction for advanced ovarian cancer were enrolled in a prospective trial assessing ANH at time of surgery. Intraoperative blood withdrawal was performed to a target hemoglobin of 8.0 g/dL. A standardized transfusion protocol first using autologous then allogenic blood was applied intraoperatively and throughout hospitalization according to institutional guidelines. The primary endpoint was to determine the overall rate of allogenic RBC transfusions in the intra- and postoperative periods. A predetermined allogenic

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Conflict of Interest Statement

Outside the submitted work, Dr. Dennis Chi is on the Medical Advisory Boards of Bovie Medical Co. and Verthermia Inc. The other authors have no conflicts of interest to disclose.

RBC transfusion rate <35% was deemed a meaningful reduction from a 50% transfusion rate in historical controls.

Results: Forty-one patients consented to participate. Median blood withdrawn during ANH was 1650 mL (range, 700–3000). Cyto-reductive outcomes were as follows: 0 mm, 30 (73%); 1–10 mm, 8 (20%); and >10 mm, 3 (7%) residual disease. Estimated blood loss was 1000 mL (range, 150–2700). Fourteen patients (34%) received allogenic RBC transfusions intra- or postoperatively, meeting the primary endpoint. No patients were transfused outside protocol guidelines. The rate of grade 3 complications (20%) and anastomotic leaks (7%) were similar to historical controls and met predefined safety thresholds.

Conclusions: For patients with advanced ovarian cancer undergoing primary cyto-reductive surgery, ANH appears to reduce allogenic RBC transfusion rates versus historical controls without increasing perioperative complications. Further evaluation of the technique is warranted.

Keywords

acute normovolemic hemodilution; blood transfusion; ovarian cancer; primary cyto-reduction; surgery; prospective trial

Introduction

In appropriately selected patients with advanced ovarian cancer, primary cyto-reduction maximizes long-term survival [1]. Given the extensive nature of these procedures, cyto-reduction is often associated with significant blood loss and subsequent need for allogenic red blood cell (RBC) transfusion [2]. RBC transfusions have been linked to a variety of negative outcomes in patients undergoing major surgery. These include increased risk of infection, immune suppression, and at least in some cases, inferior cancer survival [3–8]. Patients with ovarian cancer would likely benefit from new strategies that reduce the need for perioperative allogenic RBC transfusions associated with primary cyto-reductive surgery.

Acute normovolemic hemodilution (ANH), a technique performed immediately prior to a procedure at high risk for blood loss, has been shown to reduce the need for allogenic transfusion [9]. During ANH, whole blood is removed from the patient and replaced with a crystalloid/colloid mixture to maintain euvolemia. The harvested blood, which has a greater red cell mass than the blood lost intra-operatively, is reinfused as needed during the procedure, with all removed blood returned at the completion of the operation. Several studies have evaluated the ability of ANH to reduce the need for perioperative allogenic transfusions, with mixed results, depending on the circumstances [5,10–12]. ANH has been particularly promising in patients undergoing major hepatic surgery, as well as other procedures with moderate-to-high blood loss (i.e., at least 1000 mL) [13,14].

Primary cyto-reductive surgery for ovarian cancer is an ideal setting to evaluate ANH, as the procedure is associated with moderately high blood loss. As the technique has not yet been described in this setting, we designed a pilot study to evaluate ANH in patients planned to undergo primary cyto-reduction at our institution, with the intent of proceeding to a randomized trial if results were favorable. Our primary objective was to determine if ANH

reduces the requirement for allogenic RBC transfusions in patients undergoing primary cytoreduction for advanced ovarian cancer versus historical benchmarks. Our secondary objective was to evaluate the safety of ANH in this setting.

Materials and Methods

IRB Approval and Patient Population

Patients planning to undergo primary cytoreductive surgery for presumed advanced ovarian cancer were approached for enrollment on an Institutional Review Board approved prospective pilot study.

Patient Eligibility

All patients between 18 and 69 years of age with a high preoperative suspicion of advanced primary epithelial ovarian, fallopian tube, or primary peritoneal carcinoma (stage IIIC or IV), as determined by CT or MRI of the abdomen and pelvis, and planned for exploratory laparotomy and primary surgical cytoreduction were eligible for enrollment. Patients were required to have a serum hemoglobin ≥ 10 mg/dL within 30 days of registration. Exclusion criteria are listed in Table 1. Patients underwent standard preoperative preparation for cytoreductive surgery according to institutional standards.

ANH Protocol

ANH was performed according to a predefined protocol. Following induction of anesthesia, a large bore peripheral IV and radial arterial line were placed. All patients underwent standard continuous intraoperative monitoring. Arterial blood gases and serum hemoglobin were drawn at 1-hour intervals for the duration of the procedure.

The volume of blood to be removed during ANH was calculated using an established formula based on preoperative hemoglobin, target hemoglobin after hemodilution, and the patient's estimated blood volume. The attending anesthesiologist for the surgical procedure was responsible for this calculation, the intraoperative blood recovery, and administration:

$$V_L = EBV \times H_0 - \frac{H_F}{H_{AV}} \text{ where } V_L = \text{allowable blood loss, EBV} = \text{estimated blood volume, } H_0$$

= patient's initial hemoglobin, H_F = patient's minimum allowable hemoglobin, and H_{AV} = the average of the initial and minimal allowable hemoglobin. H_F was defined as 8.0 g/dL, and V_L was capped at 3 L.

Blood was withdrawn and stored in standard collection bags (Baxter-HC/Fenwal Autologous Blood Collection kit) at room temperature. During collection, a tilt rocker scale (Biomixer 323, National Hospital Specialties) was used to rock, mix, and weigh the blood. To maintain euvolemia, half of the blood volume removed was replaced with colloid (5% albumin) at a 1:1 ratio and half was replaced with crystalloid at a 1:2 ratio. Additional crystalloid fluid boluses were administered throughout the case to maintain euvolemia.

Transfusion Protocol

Hemoglobin was checked hourly during the procedure. Blood was returned to patients in reverse chronological order from which it was removed if the intraoperative transfusion trigger (Hgb <7.0) was reached or at the completion of the operation. If cytoreductive surgery was aborted, the target Hgb was not reached, or the operation was not completed by the eighth hour post-phlebotomy, all blood was re-infused. Allogenic blood was only given after all autologous blood had been returned to the patient. The same transfusion triggers were used to determine the need for allogenic blood transfusions during the procedure.

Postoperative Management

All patients received standard postoperative management. Routine laboratory studies, including comprehensive metabolic panel, complete blood count and coagulation profile, were obtained daily postoperatively. During postoperative hospitalization, patients were transfused with 2 units of allogenic blood for an Hgb <8.0 g/dL or Hgb 8.0 g/dL with hemodynamic changes, such as hypotension, tachycardia, and oliguria according to longstanding standard institutional protocols. The postoperative transfusion threshold was set according to the institutional standard at the time of trial initiation and was the prevailing practice in the historical cohort used to establish the baseline allogenic transfusion rate. Patients were followed for 30 days postoperatively to evaluate for complications. Complications were classified and graded according to institutional standards, as described by Martin *et al.* [15].

Outcomes

The primary objective of our study was to determine the rate of allogenic RBC transfusions during and after primary cytoreductive surgery for advanced ovarian, fallopian tube, and primary peritoneal carcinoma and compare this rate to a historical baseline estimate. An allogenic RBC transfusion was defined as any transfusion of allogenic RBCs occurring during the operating procedure or subsequent hospitalization. The secondary objective was to quantify the rate of grade 3 or higher complications (and anastomotic leaks in particular) during the 30-day postoperative period.

Historical data were used to establish baseline estimates for primary and secondary outcomes. In the year prior to opening the study, the rate of allogenic RBC transfusions in patients undergoing primary cytoreductive surgery meeting study criteria at our institution was 50%. In a prospectively maintained database of patients undergoing cytoreductive surgery for advanced ovarian cancer at our institution from 1/01 to 2/04, the rate of major complications (grade 3) was reported as 20% [2]. The baseline rate of anastomotic leaks was estimated to be 6%, a rate consistent with the literature available at the time of study design [16–18].

Statistical Analysis

We hypothesized that the allogenic RBC transfusion rate would decrease from a historical baseline of 50% to 25% with the use of ANH. This risk reduction hypothesis was based on the results of a prior institutional ANH protocol that evaluated a procedure (partial hepatectomy) with similar estimated blood loss to that of ovarian cancer cytoreduction [14].

A sample size of 41 patients would allow us to demonstrate a meaningful reduction in the transfusion rate (defined as a reduction from 50% to 25%) using a one-sample, one-sided binomial proportion test with a power of 93% and type I error of 3% if the actual rate were less than 35%. As this trial was designed as a pilot study for a possible larger randomized trial, we intended to consider proceeding with the randomized trial if the allogenic RBC transfusion rate with ANH was less than or equal to 34% (14/41 patients). If more than 14 patients received allogenic RBC transfusions, then the study would be deemed negative, supporting the hypothesis that the transfusion rate was statistically equivalent to the 50% baseline rate. An interim safety analysis assessing the rate of transfusions outside of study guidelines, overall major complications, and anastomotic leaks was planned following accrual of the first 20 patients. An early stopping threshold would be triggered if the overall rate of major complications (grade 3) and/or anastomotic leaks was more than twice the rate reported in the baseline reference data (>40% and >12%, respectively). The same safety thresholds were used upon completion of the study to determine whether a prospective trial comparing ANH to standard intraoperative management was advisable.

Results

Forty-one patients with presumed advanced ovarian, fallopian tube, or primary peritoneal cancer consented to ANH at the time of planned primary cytoreduction. Demographic characteristics for the patients are listed in Table 2. All patients underwent primary cytoreductive surgery with the goal of optimal debulking. Complete gross resection was achieved in 30 patients (73%), 1–10 mm residual disease was achieved in 8 patients (20%), and >10 mm residual disease remained in 3 patients (7%). Cytoreductive procedures are listed in Table 3. Most patients (68%) required at least one colon and/or rectal resection.

Hemodilution was initiated prior to skin incision and lasted a median of 44 minutes (range, 19–165 minutes). If ANH was not completed by the time the surgeon intended to begin a step in the procedure in which bleeding could be reasonably anticipated, further surgical progress was delayed or attention turned elsewhere until ANH was complete. Blood withdrawal was rarely a cause of intraoperative delay (20%), with all but one delay occurring in the first 17 cases. The median volume of blood withdrawn was 1650 mL (range, 700–3000 mL). The median intraoperative fluid administered was 7750 mL (range, 3000–14500 mL) and consisted of a mixture of crystalloid (median, 6000 mL) and colloid (median, 1750 mL). Systolic blood pressure did not vary significantly from the beginning to the end of the procedure.

The median estimated blood loss was 1000 mL (range, 150–2700 mL). Fourteen patients (34%) received allogenic RBC transfusions intraoperatively (5%) or postoperatively (29%), meeting the predetermined primary endpoint for a statistically meaningful reduction in the allogenic transfusion rate (Table 4). No patients were transfused outside protocol guidelines. The median hemoglobin triggering a postoperative RBC transfusion was 7.3 g/dL. The rate of grade 3 complications (20%) was similar to historical controls, meeting predefined safety thresholds.

Two (7%) of 28 patients developed leaks at the colorectal anastomosis. This rate was below our predetermined safety threshold (<12%) and is consistent with leak rates in the literature. In one case, the leak was identified on postoperative day 7, soon after the removal of a pelvic drain placed near the anastomosis site. As the drain output was clear and minimal prior to removal, it was hypothesized that the drain could have disrupted the anastomosis, resulting in the leak. In the other case, the leak was identified on postoperative day 14. No risk factors were identified in this case. An additional patient underwent a distal pancreatectomy at the time of her cytoreduction. A pancreatic fistula was identified on postoperative day 10 and managed with drain placement. Complication categories and distribution by grade are listed in Table 5.

Discussion

A growing body of literature has demonstrated the feasibility and safety of ANH to reduce the rate of perioperative allogenic RBC transfusions. Our results provide the first evidence suggesting this benefit also extends to patients undergoing primary cytoreductive surgery for ovarian cancer. We observed a relative 32% reduction in allogenic RBC transfusions versus the historical baseline rate of 50%. In a meta-analysis of 63 studies and 3819 patients, Zhou *et al.* showed that ANH was associated with a 26% reduction in the risk of allogenic RBC transfusions versus standard care (RR 0.74; 95% CI, 0.63–0.88), a reduction in infection risk (RR 0.64; 95% CI, 0.42–0.97), and no impact on perioperative complications [9]. Numerous studies have demonstrated a meaningful reduction in transfusion risk with ANH for moderate-to-high blood loss procedures, which is consistent with the 1000 mL median blood loss observed in our study cohort. Although modeling studies have called into question whether ANH can substantially reduce transfusion risk in all but the most extreme blood loss procedures, we believe that any strategy consistently reducing allogenic transfusion risk by the magnitude observed in our pilot study would be welcomed [19].

Other investigators at our institution have previously observed reduced transfusion rates with ANH for patients undergoing hepatic resection but no impact on transfusion rates for patients undergoing pancreaticoduodenectomy (PD) [14,20]. More concerning than the lack of a transfusion benefit in the PD trial was a dramatic increase in the risk of duodenal anastomotic leak observed in the ANH arm (21.5% versus 7.7%; $P = 0.045$). The authors of the randomized trial speculated that the increased risk of anastomotic leak may have been due to the 2 L increase in fluid administration in the ANH arm [21]; however, a follow-up trial evaluating liberal versus restrictive fluid administration during PD did not demonstrate a similar association [22]. One randomized trial composed primarily of patients undergoing colorectal anastomoses for rectal cancer also did not demonstrate an increased risk of anastomotic leak with ANH despite a similar increase in fluid administration in the ANH arm [13]. There are no other studies addressing the safety of ANH in this setting. Therefore, the integrity of bowel anastomoses was a paramount concern for our pilot study. Despite the majority of patients (68%) in our cohort undergoing colon and/or rectal resections, we did not identify an increased risk of anastomotic leak. It is conceivable that there is a variable impact of fluid overload on colorectal anastomoses versus PD anastomoses. Fortunately, our results also confirm the overall safety of ANH during cytoreductive surgery, as complications rates were consistent with historical thresholds, despite relatively high

volumes of fluid administered intraoperatively. The only potential harm noted in our study was a 20% risk of procedural delays due to prolonged blood withdrawal. While the magnitude of this delay was not specifically quantified, the overall impact was subjectively deemed to be minimal by participating surgeons and potentially worthwhile given the lower allogenic transfusion risk.

The role of evidence-based perioperative care is rapidly expanding, to the great benefit of patients. Our results, which admittedly should be interpreted cautiously due to a lack of a control arm, suggest ANH could be a promising strategy to improve perioperative outcomes. Our appreciation of the negative impact that allogenic RBC transfusions have on perioperative outcomes continues to increase [5]. This knowledge could have had a subtle impact on transfusion rates in our cohort. Given the lack of a randomized design, it is possible that transfusion rates decreased from historical rates to observed levels independent of the study intervention. Rigorous transfusion guidelines were implemented at our institution prior to the year when baseline transfusion estimates were determined, although these guidelines have evolved further since that time. Using contemporary transfusion thresholds of hemoglobin less than 7 g/dL and transfusing only one unit PRBCs at a time would likely reduce the transfusion rates even lower, with or without ANH. We did not adjust the transfusion guidelines for the study as this would have impacted our ability to compare our results to the historical transfusion rate.

Our pilot study suggests that ANH can be safely performed in patients undergoing primary cytoreduction for ovarian cancer. ANH is one of many options to reduce the chance of a patient requiring an allogenic RBC transfusion. Other strategies include improved attention to hemostasis, implementation of institutional transfusion protocols, preoperative administration of tranexamic acid, and the use of cell saver devices [23–25]. ANH may be especially appealing when blood loss is estimated to be substantial (i.e., greater than 1 L) but its utility must be balanced against the added complexity required to perform the procedure. Future studies will hopefully confirm the role of ANH as a mechanism to reduce allogenic blood transfusions for patients undergoing cytoreductive surgery for ovarian cancer.

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Highlights

- Acute normovolemic hemodilution (ANH) reduces RBC transfusion rates during ovarian cancer surgery vs. historical controls
- ANH can be performed safely for patients undergoing cytoreductive surgery for ovarian cancer
- ANH appears to be a promising strategy to reduce RBC transfusion rates during cytoreductive surgery for ovarian cancer

Table 1:**Exclusion Criteria**

Serum albumin <3 g/dl
GOG performance status >2
Active coronary artery disease (unless normal cardiac stress test within 30 days of enrollment)
History of cerebrovascular disease
Renal insufficiency with serum creatinine >1.6 mg/dL
Uncontrolled hypertension
Restrictive or obstructive pulmonary disease
Congestive heart failure
Active infection
Pregnancy
Refusal to accept allogenic or autologous blood transfusion
Autologous blood transfusion within last 30 days or plan to donate autologous blood prior to surgery
Plan for exploratory laparoscopy prior to laparotomy for assessment of disease resectability
Surgeon has high suspicion (>50% chance) that cytoreductive surgery will be aborted due to inability to achieve optimal cytoreduction to <1 cm residual disease

GOG, Gynecologic Oncology Group

Table 2.

Patient Demographics and Preoperative Characteristics (N= 41)

	Median	Range
Age, years	58	33 – 73
Median body mass index, kg/m ²	25.5	19.7 – 41.2
Median preoperative laboratory values		
Hemoglobin, g/dL	12.4	10.1 – 14.3
Platelets, K/ μ L	333	169 – 699
Albumin, g/dL	4.2	3.0 – 4.8
Creatinine, mg/dL	0.7	0.4 – 1.0
	Number of Patients	Percent
ASA score		
Score = 2	30	73%
Score = 3	11	27%
Race		
White	36	88%
Asian	4	10%
Unknown	1	2%

Table 3.

Intraoperative and Acute Normovolemic Hemodilution Characteristics (N = 41)

Procedures performed	Number of Patients (%)
Oophorectomy +/- hysterectomy	41 (100%)
Omentectomy	40 (98%)
Pelvic lymphadenectomy	28 (68%)
Para-aortic lymphadenectomy	28 (68%)
Rectosigmoid resection	26 (63%)
Colon resection	11 (27%)
Diaphragm resection/stripping	30 (73%)
Liver resection	9 (22%)
Splenectomy	13 (32%)
Distal pancreatectomy	4 (10%)
Partial gastrectomy	4 (10%)
Thoracic/mediastinal lymph node resection	9 (22%)
Diameter of largest residual disease (%)	
>10 mm	3 (7%)
1 – 10 mm	8 (10%)
Complete gross resection	30 (73%)
FIGO stage (%)	
IA	1 (2%)
IIB	1 (2%)
IIIA	2 (5%)
IIIB	1 (2%)
IIIC	21 (51%)
IVA	1 (2%)
IVB	13 (32%)
IVB (endometrial)	1 (2%)
Median blood loss, mL (range)	1000 (150 – 2700)
Median hemodilution time, minutes (range)	44 (19 – 165)
Median blood volume removed, mL (range)	1650 (700 – 3000)
Median intraoperative fluid given, mL (range)	
Total	7750 (3000 – 14500)
Crystalloid	6000 (1500 – 10500)
Colloid	1750 (500 – 4000)
Median systolic blood pressure, cm H₂O (range)	
Start of procedure	105 (70 – 200)
End of procedure	100 (70 – 138)
Intraoperative urine output, mL (range)	780 (150 – 2550)

FIGO, International Federation of Gynecology and Obstetrics

Table 4:

Transfusion and Postoperative Outcomes (N= 41)

Allogenic RBC transfusion (total)	Number of Patients (%)
Patients (%)	14 (34%) [†]
Units	25
Allogenic RBC transfusion (intraoperative)	
Patients (%)	2 (5%)
Units	6
Median length of stay, days (range)	8 (3 – 29)
30-day complications (%)	
Any grade	29 (71%)
grade 3	8 (20%) [†]
Anastomotic leak	2 of 28 (7%) [†]

RBC, red blood cell

[†]Endpoint below predetermined thresholds for safety and efficacy

Table 5.

Complications by Type and Grade

Type	G1	G2	G3	G4	G5	Total
Infection	7 [*]	4	4	0	0	15
Hematologic	0	12	0	0	0	12
Gastrointestinal	0	7	4	0	0	11
Pulmonary	3	2	0	0	0	5
Wound	5	0	0	0	0	5
Urinary	2	0	0	0	0	2
Cardiac	0	0	0	0	0	0
Total	17	25	8	0	0	50 [†]

[†]71% of patients (n = 29) developed a complication, with some patients having more than one complication

^{*}Number of patients with a complication, by grade