

A Prospective Randomized Comparison of Three Blood Conservation Strategies for Radical Prostatectomy

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Background: Preoperative autologous blood donation is a standard of care for elective surgical procedures requiring transfusion. The authors evaluated the efficacy of alternative blood-conservation strategies including preoperative recombinant human erythropoietin (rHuEPO) therapy and acute normovolemic hemodilution (ANH) in radical retropubic prostatectomy patients.

Methods: Seventy-nine patients were prospectively randomized to preoperative autologous donation (3 U autologous blood); rHuEPO plus ANH (preoperative subcutaneous administration of 600 U/kg rHuEPO at 21 and 14 days before surgery and 300 U/kg on day of surgery followed by ANH in the operating room); or ANH (blinded, placebo injections per the rHuEPO regimen listed previously). Transfusion outcomes, perioperative hematocrit levels, postoperative outcomes, and blood-conservation costs were compared among the three groups.

Results: Baseline hematocrit levels were similar in all groups ($43\% \pm 2\%$). On the day of surgery hematocrit decreased to 34%

$\pm 4\%$ in the preoperative autologous donation group ($P < 0.001$), increased to $47\% \pm 2\%$ in the rHuEPO plus ANH group ($P < 0.001$), and remained unchanged at $43\% \pm 2\%$ in the ANH group. Allogeneic blood exposure was similar in all groups. The rHuEPO plus ANH group had significantly higher hematocrit levels compared with the other groups throughout the hospitalization ($P < 0.001$). Average transfusion costs were significantly lower for ANH ($\$194 \pm \192) compared with preoperative autologous donation ($\$690 \pm \128 ; $P < 0.001$) or rHuEPO plus ANH ($\$1,393 \pm \204 , $P < 0.001$).

Conclusions: All three blood-conservation strategies resulted in similar allogeneic blood exposure rates, but ANH was the least costly technique. Preoperative rHuEPO plus ANH prevented postoperative anemia but resulted in the highest transfusion costs. (Key words: Epoetin alfa; erythropoietin; hemodilution; preoperative autologous donation.)

CONCERNS over allogeneic blood transfusion risks have made preoperative autologous donation (PAD) of blood a standard of care for major elective surgical procedures;¹⁻³ however, PAD has several limitations. Recent studies have demonstrated that PAD is not cost-effective because of wastage rates of approximately 40%.⁴⁻⁶ Additionally, 10-20% of patients who predonate blood also require allogeneic blood.^{3,7,8} Mathematical modeling and clinical studies have also confirmed that PAD results in preoperative anemia and promotes a more liberal transfusion policy.^{9,10}

Acute normovolemic hemodilution (ANH)^{7,11,12} or the preoperative use of recombinant human erythropoietin (rHuEPO)¹³⁻¹⁵ have been reported to reduce allogeneic blood exposure in patients undergoing major elective surgery. Despite previous studies suggesting that the efficacy and safety of ANH is equivalent to PAD in patients undergoing radical retropubic prostatectomy,^{7,12} ANH has been underused, in part because the technique is poorly understood and its benefits are controversial.^{11,16-17} Recombinant human erythropoietin has been used to augment autologous blood collection and has recently been approved for perioperative use in the United States, Japan, and Canada.¹⁴ We report a prospec-

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tive, randomized study evaluating the efficacy and transfusion outcomes of three blood-conservation techniques (ANH, alone or with preoperative rHuEPO therapy, and PAD) in patients undergoing radical retropubic prostatectomy.

Materials and Methods

Patients

This protocol was approved by the institutional review board, and all patients provided informed consent. Eligible patients were of physical status I, II, or III per the American Society of Anesthesiologists classification system.¹⁸ Laboratory inclusion criteria were hematocrit (Hct) level between 36% and 45%, serum iron to total iron-binding capacity ratio (transferrin saturation) $\geq 15\%$, and serum ferritin ≥ 50 ng/ml. Exclusion criteria consisted of history of any primary hematologic disease, seizure disorder, therapy with androgens or cytotoxic or immunosuppressive drugs within 1 month of study entry, uncontrolled hypertension with diastolic blood pressure > 100 mmHg, unstable angina, myocardial infarction within 6 months preoperatively, recent drug or alcohol abuse, autoimmune hemolysis or ongoing blood loss, active inflammatory disease except for osteoarthritis, blood transfusion within 1 month of study entry, and refusal of blood transfusions.

Study Design and Procedures

After obtaining informed consent, patients were randomized to one of three blood-conservation treatment groups according to a computer-generated random numbers table. The treatment groups were (1) PAD of 1 U weekly for 3 weeks (3 U total), terminating at least 7 days before surgery (PAD group); (2) preoperative administration of erythropoietin (Procrit, Epoetin alfa, Ortho Biotech, Raritan, NJ) 600 U/kg subcutaneously at 21 and 14 days preoperatively and 300 IU/kg on the day of surgery followed by ANH in the operating room (rHuEPO plus ANH group); and (3) ANH (patients received blinded, placebo injections of albumin diluent at the same time points as the injections in the rHuEPO plus ANH group and ANH in the operating room). All patients received oral iron supplementation (Niferex-150 capsules, Central Pharmaceuticals, Seymour, IN) twice daily preoperatively beginning at study entry. The study medications (rHuEPO and placebo) were prepared in a blinded fashion (identical volume and appearance),

and investigators and patients were unaware of treatment assignment in the ANH groups.

Complete blood count with differential and an iron profile (serum iron level, total iron-binding capacity, ferritin level, and transferrin saturation) were obtained 21 days preoperatively, before study entry (baseline). The complete blood count was repeated at 7 days preoperatively, on admission to the hospital the day of surgery, in the postanesthesia care unit, and on postoperative days 1, 4, and 14. Patient vital signs (blood pressure, heart rate, and respirations) were monitored at each preoperative donation or study drug injection.

All patients were medicated with midazolam in the preoperative holding area and received a standardized general anesthetic consisting of thiopental, sufentanil, isoflurane, and vecuronium. After tracheal intubation, patients underwent ventilation with nitrous oxide, 67% in oxygen. Intraoperative monitoring included continuous monitoring of leads II and V₅ of the electrocardiogram and automated ST-segment analysis. Blood pressure monitoring was obtained with a radial artery catheter and central venous pressure monitoring *via* a catheter placed in the internal jugular vein after tracheal intubation. Oxygen saturation was continuously monitored with a pulse oximeter.

The ANH groups underwent moderate hemodilution according to previous reports after anesthesia induction.⁷ Hemodilution was discontinued if a target Hct level of 28% was reached or a blood volume of 2,000 ml was removed. The approximate blood volume to be removed was calculated by the following formula¹⁹:

$$V = \text{EBV} \times \frac{H_i - H_f}{H_{av}}$$

where V = volume of blood to be removed; EBV = patient's estimated blood volume (body weight in kg \times 70 ml/kg), H_i = patient's initial Hct level, H_f = patient's target Hct level after hemodilution or 28% for this study, and H_{av} = patient's average Hct level (average of H_i and H_f).

Onset of surgery was not delayed by hemodilution. Hemodilution was performed in conjunction with prepping and draping of the patient and pelvic lymph node dissection. The first 1,000 ml of blood withdrawn during ANH was replaced with an equal volume of 6% hydroxyethyl starch (Hespan, Du Pont Merck, Wilmington, DE). Subsequent blood removed *via* ANH was replaced with crystalloid solution (Ringer's lactate, 3:1 volume replacement). The first 1,000 ml of surgical blood loss in the

PAD group was replaced with colloid solution. Hct levels were determined every 30 min, or more frequently at the anesthesiologist's discretion. All blood obtained from hemodilution was returned before discharge from the operating room. If all the autologous blood collected during ANH was returned to the patient and the Hct level was $< 25\%$ in the operating room or during the postoperative period, allogeneic blood was transfused. Patients in the PAD group received stored autologous (PAD) blood intraoperatively or postoperatively if Hct level was $< 25\%$. If the Hct level was $< 25\%$ and all PAD blood had been returned, allogeneic blood was transfused.

At 30 days and 1 yr postoperatively, patients were contacted *via* telephone to determine any postoperative complications after hospital discharge.

Data Analysis and Cost Determinations

Blood volumes were estimated by nomogram based on height, weight, and gender.²⁰ Baseline and the day of surgery erythrocyte volumes were calculated by multiplying each patient's blood volume by baseline or day-of-surgery percentage HCT level. The overall erythrocyte loss for each patient was calculated using the model previously reported by Goodnough *et al.*^{21,22} and described in Appendix 1.

The erythrocyte volume "saved" by the autologous interventions was estimated by a previously reported mathematical model using each patient's blood volume, estimated surgical blood loss, the volume of ANH, the Hct level and volume of each PAD donation, and the perioperative Hct levels.^{9,22-25} These calculations are detailed in Appendix 2.

Blood costs were estimated as the sum of blood acquisition, laboratory, administration, and overhead costs for our institution (table 1). For preoperatively donated autologous blood and for allogeneic blood, the acquisition costs reflected the cost of purchasing blood from the regional blood center. Laboratory costs reflected those of the blood type, antibody screen, and cross-match performed on the day of surgery. Administration costs included those related to equipment such as blood administration sets, storage, and labor for infusion. For the autologous blood units obtained by hemodilution, acquisition costs reflected those of supplies and the labor (15 min/U) of a registered nurse to assist during the hemodilution process.⁷ Fringe-benefit rates used in labor costs were 30% of the hourly wage and overhead costs were 50% of total direct costs. The cost of erythropoietin was calculated at \$0.01/U.^{14,26}

Table 1. Direct Costs of Collecting, Testing, and Processing Predonated Autologous (PAD), Hemodiluted Autologous (ANH), and Allogeneic Blood*

	Cost per Unit (\$)		
	PAD	ANH	Allogeneic
Acquisition costs	115.00	19.00	75.50
Laboratory costs	23.00	0	23.00
Administration	13.00	0	13.00
Overhead	75.00	9.00	55.50
Total blood cost	226.00	28.00	167.00

* Costs of PAD, ANH, and allogeneic blood based on costs of blood at Barnes-Jewish Hospital, St. Louis, MO. Costs of ANH also based on information presented by Monk *et al.*⁷

Statistical Analysis

The sample size for this study was designed to evaluate the ability of rHuEPO to increase preoperative Hct levels if used in a once-weekly dosing regimen. We decided preoperative administration of rHuEPO would only be useful if patients experienced an Hct increase of at least 3%, which is the approximate Hct increase after the administration of one unit of packed erythrocytes. We estimated a standard deviation of 4%. With a sample size of 25 patients per treatment arm, the analysis was expected to have at least an 80% power to detect a 3% increase in preoperative Hct levels compared with changes in the other two arms of the study. A *P* value of 0.05 was used for statistical significance. Secondary efficacy outcomes included transfusion outcomes, the erythrocyte volume saved by each autologous intervention, and the blood-conservation costs related to each autologous intervention, drug therapy, and blood-replacement therapy.

Changes in Hct level within a group were analyzed with paired two-sided *t* tests. Hematologic variables, transfusion costs, and demographic data were compared among groups using analysis of variance. Because of the extreme skewness of the distribution of the number of units of allogeneic blood transfused, the Kruskal-Wallis test was applied to these data. Proportions were compared with a two-sided Fisher exact test. Differences were considered significant at *P* < 0.05 . Data are expressed as mean \pm SD (unless otherwise specified).

Results

Of 79 patients enrolled, 76 completed the study (PAD = 26, ANH = 26, rHuEPO plus ANH = 24), and statistical analysis was performed on data from these

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Table 2. Clinical Characteristics of the Three Treatment Groups

Characteristic	PAD (n = 26)	ANH (n = 26)	rHuEPO + ANH (n = 24)
Age (yr)	62 ± 4	61 ± 7	63 ± 7
Weight (kg)	85 ± 12	89 ± 13	85 ± 11
Height (cm)	178 ± 6	179 ± 6	177 ± 10
ASA physical status [N (%)]*			
Class 1	2 (8)	8 (31)	4 (17)
Class 2	21 (81)	12 (46)	18 (75)
Class 3	3 (11)	6 (23)	2 (8)
Patients' estimated blood volume (ml)	5,393 ± 492	5,301 ± 602	5,341 ± 547
Baseline (21 pre) estimated RBC volume (ml)	2,278 ± 217	2,379 ± 295	2,303 ± 234
Day of surgery estimated RBC volume (ml)	1,845 ± 256†‡	2,339 ± 299	2,507 ± 270‡
Estimated surgical blood loss (ml)	1,467 ± 567	1,346 ± 508	1,227 ± 468
Estimated (calculated) RBC (ml) lost during hospitalization	921 ± 195	950 ± 244	794 ± 194
Anesthesia time (min)	233 ± 39	221 ± 46	222 ± 34
Duration of hospitalization (days)	4 ± 1	4 ± 1	4 ± 0

PAD = preoperative autologous donation; ANH = acute normovolemic hemodilution; rHuEPO = recombinant human erythropoietin; RBC = red blood cell. Values are mean ± SD unless otherwise stated.

* American Society of Anesthesiologists (ASA) classification system.

† Significantly different from both ANH groups, $P < 0.05$.

‡ Significantly different from baseline RBC volume within a group.

patients. Two patients (one each in the ANH and rHuEPO plus ANH groups) were withdrawn on cancellation of their procedures after determination of metastatic carcinoma in pelvic lymph nodes. One rHuEPO plus ANH patient was withdrawn because the surgical procedure was canceled after a positive preoperative stress test.

Patient clinical characteristics are shown in table 2. There were no significant between-group differences at baseline (study entry). All patients had normal serum iron, ferritin, and transferrin saturation levels indicating adequate baseline iron stores.

Perioperative Hct values are shown in figure 1. Baseline (21 days preoperative) Hct values were similar ($P = 0.21$) among all treatment groups. In the PAD group, the day-of-surgery Hct level was significantly lower than baseline ($P < 0.001$). In the ANH group, preoperative Hct levels remained unchanged ($P = 0.5$). However, Hct levels were significantly higher in the ANH group *versus* the PAD group at 7 days preoperatively, on the day of surgery, and in the postanesthesia care unit ($P < 0.05$). The rHuEPO plus ANH patients showed a significant increase in Hct level preoperatively ($P < 0.001$). Inter-group comparisons showed higher Hct level levels for the rHuEPO plus ANH group at every measurement after baseline ($P < 0.001$).

Perioperative hemodynamic values for the groups are shown in table 3. There were no differences in blood pressure or heart-rate values among the groups at any

time point from study entry (baseline, 21 days preoperative) to discharge from the hospital. There were no ST-segment changes on the electrocardiogram during the intraoperative and postanesthesia care unit periods.

Table 4 highlights the characteristics of the hemodilution process. Similar ANH blood volumes were collected

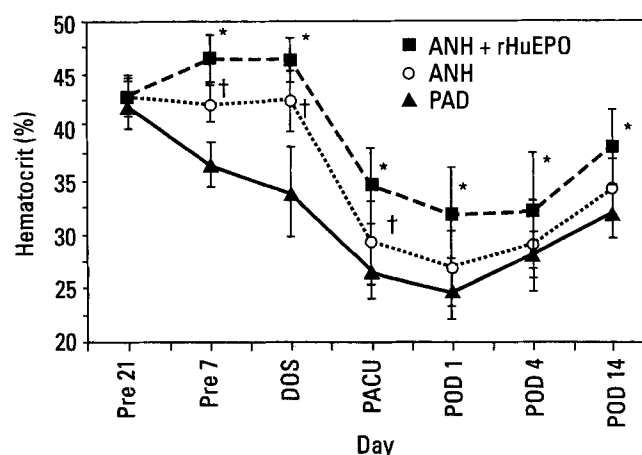


Fig. 1. Perioperative hematocrit levels in patients undergoing preoperative autologous blood donation (PAD group), acute normovolemic hemodilution (ANH group), or preoperative recombinant human erythropoietin therapy combined with acute normovolemic hemodilution (ANH + rHuEPO group). Values are mean ± SD. * $P < 0.001$ was statistically significant compared with the PAD and ANH groups; † $P < 0.05$ was significant compared with the PAD group. Pre = preoperative day; DOS = day of surgery; PACU = postanesthesia care unit; POD = postoperative day.

Table 3. Perioperative Hemodynamic Values for the Three Treatment Groups

	PAD (n = 26)	ANH (n = 26)	rHuEPO + ANH (n = 24)
Mean blood pressure (torr)			
Baseline (21 pre)	106 ± 13	109 ± 15	105 ± 11
Day of surgery	102 ± 13	105 ± 13	106 ± 10
OR × 1 h	84 ± 8	84 ± 8	80 ± 10
PACU	106 ± 16	103 ± 16	106 ± 16
Discharge	94 ± 10	94 ± 13	94 ± 8
Heart rate (bpm)			
Baseline (21 pre)	78 ± 14	79 ± 15	77 ± 14
Day of surgery	79 ± 12	79 ± 13	77 ± 13
OR × 1 h	58 ± 9	59 ± 8	56 ± 7
PACU	87 ± 19	77 ± 16	85 ± 17
Discharge	80 ± 11	80 ± 9	75 ± 10

PAD = preoperative autologous donation; ANH = acute normovolemic hemodilution; rHuEPO = recombinant human erythropoietin; OR × 1 h = 1 h after induction of anesthesia; PACU = postanesthesia care unit; Discharge = day of discharge from hospital.

Values are mean ± SD. Baseline values were taken 21 days prior to surgery; day of surgery values are prior to induction of anesthesia.

in both groups, but patients treated with rHuEPO had higher post-ANH Hct levels. Mean anesthesia times were not prolonged by ANH and were similar to the PAD mean anesthesia time (table 2). The volume of intravenous crystalloid fluid administered during surgery was also similar in all treatment groups (3,716 ± 794 ml [PAD] vs. 3,863 ± 892 ml [ANH] vs. 3,810 ± 523 ml [rHuEPO plus ANH]; $P = 0.5$).

Blood-transfusion outcomes are detailed in table 5. Because of low Hct level on the third donation visit, one PAD patient predonated only 2 U. Although only 57 of 77 units (74%) of PAD blood were reinfused, all ANH-collected blood was returned in the operating room. Overall, 23 of 26 PAD patients (88%) were transfused with stored blood from the blood bank (PAD or allogeneic units) compared with 5 of 26 ANH patients (19%; $P < 0.001$) and only 1 of 24 rHuEPO plus ANH patients (4%; $P < 0.001$). However, there were no differences in the allogeneic transfusion outcomes among the groups.

Table 5 presents the average direct costs for blood-conservation support. Significantly different among all groups ($P < 0.001$), the direct costs per group were \$194 ± \$192 for ANH, \$690 ± \$128 for PAD, and \$1,393 ± \$204 for rHuEPO plus ANH. The cost of the rHuEPO therapy was \$1,275 ± \$165.

The relationship between the day-of-surgery Hct levels and subsequent transfusion of blood from the blood bank (PAD or allogeneic blood) is illustrated in figure 2. None of the 25 patients with Hct level ≥ 45% on the day

of surgery required transfusion (rHuEPO plus ANH group = 20; ANH group = 5). Conversely, both patients (PAD group) with Hct level < 30% required stored blood transfusions, as did 90% (eight of nine) of patients with Hct level between 30 and 35%. Ninety-six percent (25 of 26) of PAD patients and 23% (6 of 26) of ANH patients had day-of-surgery Hct level < 40%. No patients in the rHuEPO plus ANH group had an Hct level < 40% on the day of surgery ($P < 0.05$).

The patient benefit attributed to the autologous interventions was also calculated (fig. 3). Although the net erythrocyte volume generated by blood predeposit for PAD patients was 104.8 ± 3.8 ml (median, 144.5 ml), some patients realized a net loss of erythrocyte volume because 26% of PAD units were discarded (range, -304.7-611.6 ml). The PAD blood was not discarded until the patient was discharged from the hospital, and no patient in the PAD group required allogeneic blood after the PAD blood was discarded. The calculated benefit attributed to ANH was 140.5 ± 43.2 ml (median, 144.4 ml) of erythrocyte volume saved. As all ANH blood was reinfused, this resulted in a net gain of erythrocyte volume (range, 42.4-202.9 ml). There was no significant difference in the benefit attributed to the autologous intervention between the PAD and ANH groups ($P = 0.96$). The benefit of the autologous intervention for patients in the rHuEPO plus ANH group was calculated to be a total "savings" in erythrocyte volume of 317.1 ± 3.8 ml (median, 323.0 ml; range, 62.4-486.4 ml), of which 151.5 ± 43.7 ml (median, 154.4 ml) was attributed to ANH and 165.6 ± 101.1 ml (median, 167.2 ml) was attributed to the increase in erythrocyte mass from rHuEPO therapy in the preoperative period. The savings of erythrocyte volume were significantly greater in the rHuEPO plus ANH group than in the PAD ($P = 0.002$) or the ANH ($P < 0.001$) groups.

Duration of hospitalization was similar among groups (table 2). One PAD patient had a myocardial infarction on postoperative day 15. This patient had predonated 3 U, 2 of which were infused before hospital discharge. Nadir Hct level was 25.3% on postoperative day 1, and discharge Hct level was 28.4%. One patient in the PAD group developed pneumonia requiring readmission to the hospital 4 days after discharge. One patient in the ANH group was rehospitalized 1 month after surgery with a wound infection. He died 12 months after surgery as a result of metastatic carcinoma of the prostate. No other deaths, pulmonary thromboembolic events, deep venous thromboses, or cardiovascular complications were reported.

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Table 4. Characteristics of the Hemodilution Process

Characteristic	ANH (n = 26)	rHuEPO + ANH (n = 24)
Hematocrit (%)		
Pre-ANH	43 ± 3	47 ± 2†
Post-ANH	28 ± 1	32 ± 3†
Blood collected by hemodilution		
Volume (ml)	1,958 ± 141	1,981 ± 98
Median number of units*	4 ± 0	4 ± 0
Pre-ANH estimated whole blood volume (ml)	5,301 ± 602	5,340 ± 547
Percentage of the patient's blood volume removed during ANH (%)	36	37
Duration of hemodilution (min)	57 ± 5	58 ± 11
RBC volume "saved" by hemodilution (ml)	141 ± 43	152 ± 44

ANH = acute normovolemic hemodilution; rHuEPO = recombinant human erythropoietin; RBC = red blood cell.

Values are mean ± SD.

* For blood collected by ANH, a unit equals 500 ml whole blood.

† $P < 0.05$ versus ANH + placebo.

Discussion

Hemodilution as a "point of care" strategy in the operating room obviates the need for blood testing and eliminates costly blood wastage because all blood collected during ANH is returned. The potential risks of PAD or allogeneic blood are reduced or eliminated.^{10,27} Although autologous blood collected by PAD carries a lower risk for transmission of infectious disease, it still carries risks associated with the storage of blood.²⁸⁻³¹ A recent report describing PAD in Canada found an overall error rate of 1 of 149 U to 1 of 322 U.²⁹ Most of these errors were administrative (*i.e.*, late receipt of a unit at the hospital or administration of allogeneic blood if PAD blood was available). Although extremely rare, administrative error resulting in the transfusion of blood to the wrong recipient has also been reported with stored blood.²⁸⁻³⁰ These reports emphasize the fact that PAD

blood is not risk-free and should only be administered if a patient exhibits a transfusion trigger. Blood obtained during ANH remains in the operating room with the patient and is returned before leaving the operating room, thereby eliminating the administrative risks associated with the storage of blood. We demonstrated that 88% of patients in the PAD group received stored blood (allogeneic plus autologous) compared with 4% in the rHuEPO plus ANH group and 19% in the ANH group. This finding corroborates the predictions of Cohen and Brecher⁹ and the conclusions of Kanter *et al.*¹⁰ that PAD exposes patients to a markedly higher likelihood of receiving a transfusion of stored blood. Other advantages of ANH include patient convenience, ability to schedule surgery without delay, and the provision of fresh whole autologous blood for transfusion on the day of surgery.¹¹

Hemodilution conserves blood because the Hct level is

Table 5. Transfusion Outcomes for the Three Treatment Groups

Outcome	PAD (n = 26)	ANH (n = 26)	rHuEPO + ANH (n = 24)
Median number of units deposited prior to hospitalization (range)	3 (2-3)	NA	NA
Median number of units obtained by ANH* (range)	NA	4 (3-4)	4 (3-4)
Median number of units transfused (range)			
Predonated autologous	2 (0-3)	NA	NA
ANH	NA	4 (3-4)	4 (3-4)
Allogeneic	0 (0-2)	0 (0-3)	0 (0-1)
Patients exposed to allogeneic blood (%)	4 (15%)	5 (19%)	1 (4%)
Direct costs for blood conservation (\$)	690 ± 128†	194 ± 192†	1,393 ± 204†

PAD = preoperative autologous donation; ANH = acute normovolemic hemodilution; rHuEPO = recombinant human erythropoietin; NA = not applicable.

Values are mean ± SD.

* For blood collected by ANH, a unit equals 500 ml whole blood.

† Significantly different from the other two groups, $P < 0.001$.

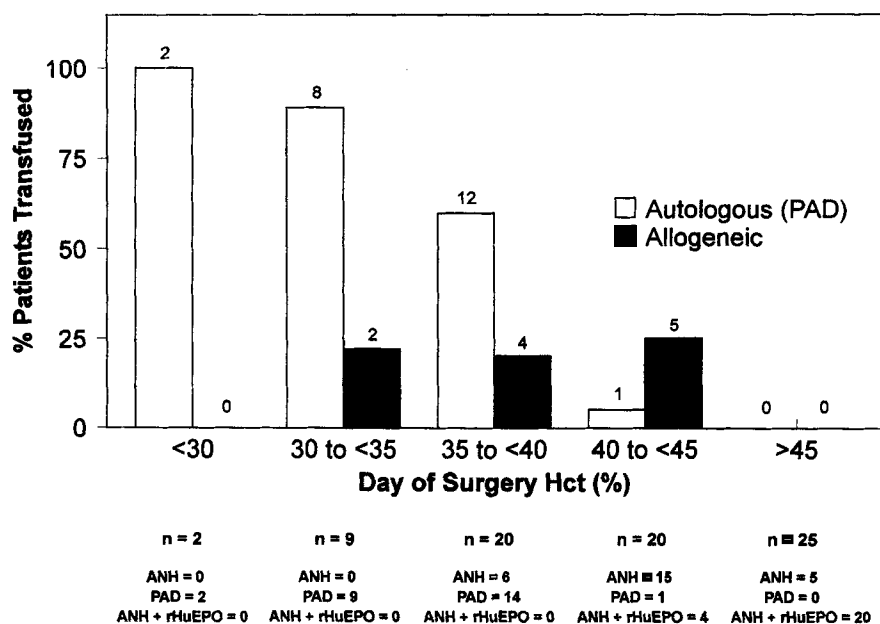


Fig. 2. The relationship between day of surgery hematocrit (Hct) levels and the percentage of patients transfused with blood from the blood bank (allogeneic or predonated autologous blood). The total number of patients (n) at each Hct level is indicated. The number of patients in each blood conservation group is presented below each n value. PAD = predonation of 3 U of blood; ANH = acute normovolemic hemodilution; ANH + rHuEPO = preoperative recombinant human erythropoietin therapy combined with acute normovolemic hemodilution.

reduced before surgical blood loss, so that for a given volume of whole blood lost, a smaller volume of erythrocytes is lost.^{7,11} The benefit of ANH has been questioned previously because the predicted savings in erythrocyte volume are modest unless extreme hemodilution (*i.e.*, nadir Hct levels $\leq 20\%$) is used.^{16,17,23} Analysis of the erythrocyte volume savings from each autologous intervention in our study demonstrated that the contribution from ANH was similar to that of PAD and equivalent to approximately 1 U of blood for each technique (fig. 3). In PAD patients, Hct levels decreased preoperatively despite adequate serum iron levels and oral iron supplementation; 96% of PAD patients had day-of-surgery Hct levels $< 40\%$ (fig. 2). Previous studies have shown that the primary limitation to replenishing the erythrocyte volume lost during PAD is an absence of compensatory erythropoiesis.^{32,33} Along with the net loss in erythrocyte volume from untransfused PAD units, the cost of PAD blood also affects its overall usefulness. In contrast, all blood collected by ANH was returned, resulting in not only a gain in erythrocyte volume for every ANH patient, but also the avoidance of additional expenses for unused and discarded units. These results indicate that ANH is a reasonable alternative to PAD as an autologous blood strategy for radical prostatectomy. However, the modest benefit of only 1 U of blood with either ANH or PAD suggests that transfusion outcomes might be similar even if no blood conservation interventions were used.

Hemodilution was not associated with intraoperative hemodynamic instability (table 3) or an increased incidence of adverse events in our patients. These findings suggest that ANH is safe and well tolerated in men undergoing prostatectomy. The safety of hemodilution has recently been documented in a study evaluating intraoperative hemodynamic changes in 250 men undergoing this procedure.³⁴ This study also concluded that intraoperative ANH was safe and did not increase postoperative morbidity or mortality rate.

Previous studies have reported dosing regimens in which rHuEPO was administered daily or twice weekly.^{13-15,35-37} Our results also indicate that rHuEPO is effective if administered once weekly. A once-weekly dosing of 600 U/kg rHuEPO has also been shown to exhibit greater baseline-to-presurgery hemoglobin increase more than 300 U/kg daily administration, with comparable efficacy and less cost, as 47% less rHuEPO is used.³⁸ The cost of rHuEPO therapy potentially could be further reduced by eliminating the day-of-surgery dose of rHuEPO, reducing the preoperative dose of rHuEPO, or both.

Previous studies have evaluated the combination of preoperative rHuEPO therapy and PAD in nonanemic patients scheduled for orthopedic surgery.^{15,39,40} These studies demonstrated that the use of rHuEPO accelerated erythropoiesis and increased the mean number of PAD units collected per patient. Likewise, our findings indicate that perioperative rHuEPO is beneficial in patients with normal Hct level if the preoperative increase in

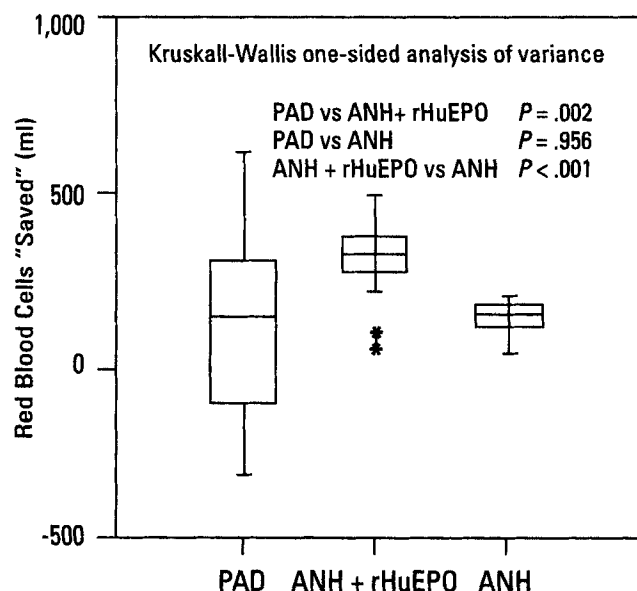


Fig. 3. Box-and-whisker plot showing the relationship between the blood-conservation interventions and the subsequent erythrocyte volume "saved" by each intervention. The blood-conservation interventions were either predonation of 3 U blood (PAD), acute normovolemic hemodilution (ANH), or preoperative recombinant human erythropoietin plus acute normovolemic hemodilution (ANH + rHuEPO). Horizontal lines = the median value; box margins = the 25th to 75th percentile; bars = 1.5 times the interquartile range and would encompass 95% of values in normally distributed data.

erythrocyte mass is coupled with ANH. These two blood-conservation strategies are synergistic in their efficacy.

In addition to reducing allogeneic blood transfusions, treatment with rHuEPO was associated with significantly higher perioperative Hct level levels. All rHuEPO-treated patients had day-of-surgery Hct level $\geq 40\%$, mean nadir Hct levels exceeding 30% on postoperative day 1, and mean discharge Hct level $> 35\%$ (fig. 1). There are no universally accepted transfusion guidelines based on Hct levels, but recent reports suggest that postoperative Hct levels $< 28\%$ may predispose elderly or high-risk patients to myocardial ischemia.^{41,42} The 1–2% incidence of postoperative myocardial infarction in patients undergoing radical prostatectomy suggests that this patient population is at risk for postoperative ischemic complications.^{43,44}

Our data also indicate that a patient's day-of-surgery Hct level can be used to predict allogeneic transfusion risk. The two patients in the PAD group with Hct levels $< 30\%$ undergoing radical retropubic prostatectomy required transfusion of stored blood; none of the patients with day-of-surgery Hct level $\geq 45\%$ were transfused (fig. 2). Figure 2 also illustrates that the percentage

of patients requiring transfusion increased as day-of-surgery Hct level decreased, suggesting that a patient's baseline Hct level could be used to make an informed decision on preoperative rHuEPO therapy and the type of blood conservation strategy to be used. This conclusion is supported by the findings of Sowade *et al.*³⁵ who found preoperative Hct level to be an independent predictor of allogeneic transfusion in patients undergoing elective open-heart surgery.

In conclusion, our study indicates that preoperative rHuEPO therapy combined with intraoperative ANH increases perioperative Hct levels and minimizes postoperative anemia. However, an equivalent transfusion outcome at lower cost can be achieved with ANH compared with either PAD or rHuEPO plus ANH therapy in patients undergoing radical retropubic prostatectomy.

Appendix 1: Calculation of Erythrocyte Loss

The erythrocyte volume lost during the hospital admission was calculated by multiplying the patient's blood volume by the difference between admission Hct level and discharge Hct level. The erythrocyte volume transfused during the hospital admission was added to the erythrocyte volume lost to determine the overall erythrocyte lost during the hospitalization.²¹ The formulas used in the calculations are: erythrocyte volume lost = (patients blood volume) (admission Hct level – discharge Hct level) + erythrocyte volume transfused, where erythrocyte volume transfused = (number of allogeneic blood units transfused) \times 200 ml + (number of predonated autologous units transfused) \times 177 ml.²²

Appendix 2: Calculation of Erythrocyte "Saved" by the Autologous Intervention

In the calculation of the erythrocyte saved for each patient, we calculated the volume of blood loss to reach the minimum allowable Hct. Blood was assumed to be replaced during surgery to maintain a minimum Hct value once it was reached. The model allowed for availability of both ANH blood and PAD blood units (177 ml/red cell unit) and for the transfusion of allogeneic blood units (200 ml/red cell unit).²²

If ANH was used this volume was calculated after the hemodilution. This volume was subtracted from the estimated blood volume, and the remaining estimated blood loss was compared with a calculated maximum allowable blood loss (which was based on the erythrocyte volume actually transfused). If the remaining blood loss was less than the maximum allowable blood loss, this would result in the final Hct being above the minimum allowable Hct. If the remaining blood loss exceeded the maximum allowable blood loss, the resulting final calculated Hct would be below the minimum allowable Hct. Although the study was designed to not allow a patient's Hct to fall below the minimum allowable Hct, calculations were based on the estimated blood loss. Because of the inaccuracies inherent in estimating the blood loss, the computer model was constructed to allow for over- or

underestimates of the actual blood loss. Over- or underestimates in the blood loss would result in final calculated Hcts being below or above the minimum allowable Hct, respectively.

For modeling purposes a surgical procedure was divided into two phases.

Phase I

Phase I encompasses the blood loss that occurs once surgery is started until the patient reaches a minimum Hct at which transfusion would begin. Such a volume is calculated by:

$$V_L = EBV \times \ln(Hct_0/Hct_{min})$$

where V_L = volume lost, EBV = estimated blood volume, Hct_0 = the Hct at the start of surgery, and Hct_{min} = the final Hct (in this case the minimum Hct allowable or the transfusion trigger). If acute normovolemic hemodilution is used the starting Hct would be the Hct after the completion of the dilution or:

$$Hct_F = Hct_0 \times e^{(-V_{ANH}/EBV)}$$

where in this case Hct_F = the Hct after the drawing of the ANH blood and V_{ANH} = the volume of blood drawn during ANH.

Phase II

After the minimum Hct is reached, it is assumed that the patient would be transfused with red cells so as to maintain the minimum allowable Hct and normovolemia throughout the remainder of phase II.

The maximum allowable blood loss during this phase that could occur without a resulting Hct being below the minimum allowable Hct can be calculated as²³:

$$\text{Maximum blood loss} = \text{Erythrocyte}_T/Hct_{min} = (\text{Erythrocyte}_{ANH} + \text{Erythrocyte}_{ALLO} + \text{Erythrocyte}_{PAD})/Hct_{min}$$

where Erythrocyte_T = the sum of erythrocyte ml infused during the hospitalization, Erythrocyte_{ANH} = the volume of erythrocytes in the ANH blood reinfused, $\text{Erythrocyte}_{ALLO}$ = the volume of erythrocytes in the allogeneic units infused, and Erythrocyte_{PAD} = the volume of erythrocytes in the PAD units available for reinfusion.

The erythrocyte volume of the ANH blood is calculated by:

$$V_{ANH} \times Hct_{ANH}$$

where Hct_{ANH} = the average Hct of the ANH blood drawn and calculated by²⁴:

$$Hct_{ANH} = (Hct_0 \times EBV) \times (1 - e^{-V_{ANH}/EBV})/V_{ANH}$$

If the blood loss was greater than the maximum allowable blood loss, the final Hct would then be:

$$Hct_F = Hct_{min} \times e^{(-V_{excess}/EBV)}$$

where in this case Hct_F = the final Hct and V_{excess} = the volume of blood loss that exceeds the maximum allowable blood loss. If the blood loss was less than the maximum allowable blood loss, the red cell volume remaining to be transfused would be added to the patients blood volume and the final Hct calculated.

The red cell volume "saved" by PAD, ANH, or rHuEPO was calculated by running multiple computer simulations for each patient with

or without each of these interventions. These types of models have recently undergone clinical validation.²⁵

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