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# *Effectiveness of Acute Normovolemic Hemodilution to Minimize Allogeneic Blood Transfusion in Major Liver Resections*

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***Background:*** **Liver resection is a major operation for which, even with the improvements in surgical and anesthetic techniques, the reported rate of blood transfusion was rarely less than 30%. About 60% of transfused patients require only 1 or 2 units of blood, a blood requirement that may be accommodated by the use of acute normovolemic hemodilution (ANH).**

***Methods:*** **The efficacy, hemodynamic effects, and safety of ANH were investigated in a randomized, active-control study in patients with American Society of Anesthesiologists status I–II who were undergoing major liver resection with fentanyl–nitrous oxide–isoflurane anesthesia. Patients were randomized to the ANH (n = 39) or control group (n = 39). Patients in the ANH group underwent hemodilution to a target hematocrit of 24%. The indication for blood transfusion was standardized. In both groups transfusion was started at a hematocrit of 20%. The primary efficacy endpoint was the avoidance of allogeneic blood transfusion in the intraoperative period and first 72 h after surgery. Various laboratory and hemodynamic parameters as well as postoperative morbidity were monitored to define the safety of ANH in this patient population.**

***Results:*** **During the perioperative period, 14 control patients (36%) received at least one unit of allogeneic blood compared with 4 patients (10%) in the ANH group ($P < 0.05$). The hemodilution process was not associated with significant changes in patients' hemodynamics. Morbidity was similar between the control and the ANH groups. Postoperative hematocrit levels and biochemical liver, renal, and standard coagulation test results were similar in both groups.**

***Conclusions:*** **Acute normovolemic hemodilution in patients with American Society of Anesthesiologists status I–II undergoing major liver resection may allow a significant number of patients to avoid exposure to allogeneic blood.**

CONCERNS about the risks associated with allogeneic blood transfusion have led to the development of a variety of blood-conserving techniques intended to minimize the need for allogeneic transfusion during surgery.[1,2] Among these, acute normovolemic hemodilution (ANH) has become accepted.[3,4] The procedure entails the removal of blood from the patient immediately before operation and simultaneous replacement with appropriate volume of crystalloid or colloid fluids. ANH reduces hematocrit so that blood shed during the operative procedure results in less erythrocyte mass loss. The removed blood is then reinfused as autologous whole blood after the procedure is completed.[5] The procedure is simple and inexpensive and has the advantage that fresh autologous blood is readily available. The resultant reduction in allogeneic blood transfusion may conserve resources and protect the patient from exposure to the risks of allogeneic blood transfusion.[6] Numerous studies of its efficacy, however, have produced conflicting results,[3] perhaps because of the heterogeneity of the surgeries in which it was used, differences in study protocol, and differences in the definition of outcome variables. Previous mathematical analyses of ANH have shown that it may be effective in diminishing the need for allogeneic blood transfusion and that its efficacy depends on surgical blood loss, initial patient hematocrit, and the "transfusion trigger" (the hematocrit at which blood is to be transfused).[7–9] Recent analysis by Weiskopf[10] suggested that surgical blood loss should be 0.7 or more of the patient's blood volume for ANH to result in the saving of at least one unit of blood.

Liver resection is a major operation for which, even with the improvements in surgical and anesthetic techniques, the risk of major intraoperative blood loss and the resultant blood transfusion remain. In several series of liver resections over the past decade, blood loss ranged between 20 and 10,000 ml, and the reported rate of blood transfusion was rarely less than 30%.[11–16] About 60% of the transfused patients required only 1 or 2 units of blood,[12,16] a blood requirement that could have been accommodated by the use of ANH.

We therefore sought to determine the efficacy of ANH in decreasing exposure to allogeneic transfusion in adults undergoing elective liver resection. Since the extent of liver resection has been shown to correlate with surgical blood loss and blood transfusion requirements,[13] in this prospective, randomized trial we included specifically patients who underwent major hepatic resection. Moreover, coagulation and renal variables as well as postoperative morbidity were also compared between the groups.

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## Materials and Methods

*Patients*

The trial was approved and monitored by the Research Ethics Committee of the Hadassah University Medical Center, and written informed consent was obtained from each patient. Over a 3-yr period, 78 consecutive patients (age > 18 yr) who were scheduled to undergo elective major hepatic resection (hepatectomy or extended hepatectomy[17]) for primary or metastatic tumors were studied prospectively. Patients were eligible for the study if they had a preoperative hematocrit greater than 36%,[10] were American Society of Anesthesiologists (ASA) physical status I or II, had no cardiovascular or pulmonary disease, and showed no evidence of severe hepatic metabolic disorder (bilirubin > 1.5 times upper limit of normal or aspartate aminotransferase or alanine aminotransferase > 2 times upper limit of normal).

*Protocol*

Study patients received a standardized general anesthetic. General anesthesia was induced with fentanyl, thiopental, and vecuronium, and after tracheal intubation was maintained with isoflurane in a 50% oxygen–nitrous oxide balance. Additional fentanyl and vecuronium were administered as appropriate. The surgical technique was also similar for all patients. Minute ventilation was titrated to maintain normocarbia. Hypothermia was prevented during surgery by using a heating blanket and perfusion warming. In addition to the standard monitors, intraoperative monitoring included intraarterial (*via* radial artery catheter) and central venous (*via* an internal jugular catheter) pressure monitoring and electrocardiogram (5-lead) with continuous ST-segment trends that were reviewed and verified for possible ischemic episodes[18] by an investigator who was blinded to patient group assignment.

On admission to the operating room, patients who met inclusion criteria were randomly assigned (random numbers) to one of two groups: control group or ANH group. For patients undergoing ANH, the hemodilution process was initiated immediately after tracheal intubation. ANH was performed *via* a high-flow (8.5 French) internal jugular introducer to a target hematocrit of 24%. The volume of blood removed was calculated from preoperative hematocrit, target hematocrit after hemodilution, and the patient's estimated blood volume according to a formula previously described.[7,19] The blood, which was removed into standard citrate–phosphate–dextrose blood storage bags, was simultaneously replaced by colloid solutions (6% hydroxyethylstarch [200/0.5], 20 ml/kg, followed by 5% albumin), which was administered *via* two large bore peripheral veins, in quantities approximately 1.1 times the volume of blood removed.[20–22] The hemodilution process took about 40 min. Additional blood-conserving techniques, *i.e.*, preoperative autologous blood donation and intraoperative use of cell salvage, were not implemented in the current study.

During the intraoperative period, patients in both groups received continuous crystalloid (Ringer's lactate solution) infusion: 4 ml · $kg^{-1}$ · $h^{-1}$ during the prehepatic resection phase until completion of parenchymal transection (relative fluid restriction was applied to maintain low central venous pressure, *i.e.*, < 5 cm $H_2O$[11,23]) and 10 ml · $kg^{-1}$ · $h^{-1}$ during the posthepatic resection phase until the end of the operation. Intermittent fluid boluses (500 ml) were administered to maintain urine output greater than 0.5 ml · $kg^{-1}$ · $h^{-1}$ and systolic blood pressure greater than 90 mmHg. Subsequent volumes of blood were replaced with Ringer's lactate solution in a 3:1 volume replacement. Subsequent blood loss was estimated by assessment of the suction bottles, sponges, and the surgical drapes and gowns by an anesthesiologist who was not aware of the patient's group assignment. Arterial blood was sampled every 30 min, and when clinically indicated, for measurement of arterial blood gases and hematocrit. Fraction of inspired oxygen was increased from 0.5 to 1.0 when the transfusion trigger was reached. The transfusion threshold for all types of erythrocytes (autologous or allogeneic) was hematocrit less than 20%. To ensure uniformity, transfusion guidelines were also established for administration of fresh frozen plasma (prothrombin time, activated partial thromboplastin time > 1.5 times normal), cryoprecipitate (fibrinogen concentrations < 100 mg/dl), and platelets (< $50 \times 10^3/\mu l$) in the presence of continuous uncontrolled bleeding with no evidence of clot formation.[2] The anesthesiologist making decisions regarding transfusion was not blinded to patient group assignment. Autologous blood was reinfused when a minimal hematocrit value was reached or after completion of liver resection and hemostasis, in the reverse order of collection. In the ANH group, allogeneic blood was administered only after all autologous blood was transfused. Patients were monitored in the postanesthesia care unit until the first postoperative day, and thereafter discharged to the surgical unit.

Postoperative surveillance included hematology, biochemical liver, renal, and standard coagulation tests (prothrombin time, activated partial thromboplastin time), and postoperative morbidity and mortality. Measurements were routinely determined and reviewed on admission to the recovery room and daily until the third postoperative day and every other day until discharge. Additional samples were drawn when clinically indicated. Electrocardiography was performed on admission to the recovery room, on the first and third postoperative day, and on the day of discharge. Additional electrocardiography and measurements of cardiac enzymes were determined when clinically indicated. Adverse outcomes, as listed in Results, were detected by the examining physician and validated by one of the other inves-

**Table 1. Clinical Characteristics**

| | ANH (n = 39) | Control (n = 39) |
|---|---|---|
| Sex (M/F) | 14/25 | 17/22 |
| Age (yr) | 58 ± 12 | 55 ± 14 |
| Weight (kg) | 66 ± 12 | 70 ± 11 |
| Height (cm) | 163 ± 7 | 165 ± 9 |
| ASA I/II | 16/23 | 14/25 |
| Tumors | | |
| Primary liver cancer | 3 | 2 |
| Metastasis | 28 | 26 |
| Benign | 8 | 11 |
| Duration of operation (min) | 293 ± 61 | 321 ± 79 |
| Estimated blood loss (ml) | 750 (100–7,000) | 890 (100–7,500) |
| Intraoperative urine output (ml) | 879 ± 512 | 811 ± 476 |

Values are mean ± SD. There were no significant differences between the groups in all parameters.

* Data presented as median (range).

ANH = acute normovolemic hemodilution; ASA = American Society of Anesthesiologists physical status.

tigators, both of whom were not aware of the patients' group assignment.

*Study End-points*

The two prospectively defined endpoints were (1) the avoidance of exposure to at least 1 unit of allogeneic blood transfusion, as indicated by the proportion of patients in each group who did not receive at least one allogeneic erythrocyte transfusion during the intraoperative period and first 72 h after surgery, and (2) documenting the safety profile of ANH as assessed by comparing mortality, morbidity, and laboratory values reported in the ANH group with those variables in the control group.

*Statistical Analysis*

Categorical data were analyzed using the chi-square test or Fisher exact test. Differences between the means of two groups and the median units transfused were compared using Student *t* test and Mann–Whitney test, respectively. Data within each group were analyzed using analysis of variance for repeated measurements. When appropriate, *post hoc* analyses were performed with the Newman-Keuls test. Analysis was performed using Statistical Analysis System software (version 6.12; SAS Institute, Cary, NC). $P < 0.05$ was considered to represent statistical significance. Results are expressed as the mean ± SD. A power analysis for allogeneic blood transfusion as an outcome, with 80% power to detect a 25% reduction in this outcome, and significance ≥ 0.05, assuming 36% incidence of blood transfusion, indicated that 39 patients were required in each group.

## Results

During the study period, 78 patients were included. Both groups (n = 39 per group) were comparable with regard to sex ratio, age, weight, height, and ASA physical status (table 1). In both groups the most common indication for resection was metastatic cancer, and in approximately two third of the patients, a standard right or left hepatectomy was performed. Preoperatively, all patients had normal liver, renal, and standard coagulation test results (data not shown).

*Hemodilution Procedure*

In the hemodilution group, the amount of collected blood was 2,020 ± 412 ml, and the mean volume of 6% hydroxyethylstarch plus albumin infused was 2,210 ± 458 ml (table 2). The reduction in hematocrit from 40.5 ± 2.7 to 23.5 ± 1.2% was not associated with significant changes in mean arterial blood pressure, heart rate, central venous pressure, or blood lactate concentrations. There was a slight but statistically significant prolongation in the time from induction of anesthesia to skin incision in the hemodilution group (43 ± 5 *vs.* 40 ± 6 min in the ANH and control groups, respectively).

**Intraoperative Parameters.** There were no significant differences in anesthetic and operative times between the two groups (table 1). The median estimated surgical blood loss was 750 and 890 ml for the ANH and control groups, respectively. Mean respective values were 1,442 ± 1,827 (range, 100–7,000 ml) and 1,528 ± 1,822 (range, 100–7,500 ml). Central venous pressure increased, although not significantly, from preoperative values of 7 ± 4 and 7 ± 5 mmHg to 10 ± 6 and 10 ± 7 mmHg with skin closure in the ANH and control groups, respectively. During parenchymal resection,

**Table 2. Hematocrit and Hemodynamic Parameters with Hemodilution**

| | ANH* | | Control* | |
|---|---|---|---|---|
| | Before | After | Before | After |
| Mean arterial blood pressure (mmHg) | 76 ± 14 | 73 ± 10 | 81 ± 11 | 76 ± 12 |
| Heart rate (beats/min) | 73 ± 11 | 68 ± 14 | 75 ± 9 | 73 ± 11 |
| Central venous pressure (mmHg) | 7 ± 4 | 6 ± 3 | 7 ± 5 | 7 ± 5 |
| Hematocrit (%) | 40.8 ± 2.7 | 23.5 ± 1.2† | 41.6 ± 3.2 | 40.9 ± 2.8 |
| Lactate (mM) | 1.3 ± 0.4 | 1.2 ± 0.3 | 1.2 ± 0.6 | 1.2 ± 0.6 |

Values are mean ± SD.

* Measurements were recorded after induction of anesthesia and at the end of the hemodilution process in the acute normovolemic hemodilution (ANH) group and before skin incision in the control group. † $P < 0.05$ difference with respect to the value before ANH and compared with the control group.

**Table 3. Perioperative Laboratory Values**

| | After Induction of Anesthesia | PACU | POD 1 | POD 3 | POD 7 |
|---|---|---|---|---|---|
| Hematocrit (%) | | | | | |
| ANH | 40.5 ± 2.7 | 30.5 ± 6.9* | 31.7 ± 5.2* | 30.7 ± 5.1* | 31.9 ± 4.6* |
| Control | 41.6 ± 3.2 | 29.1 ± 7.3* | 30.5 ± 6.1* | 31.1 ± 5.4* | 31.7 ± 4.1* |
| Creatinine (mM) | | | | | |
| ANH | 70 ± 11 | 64 ± 14 | 67 ± 14 | 71 ± 19 | 75 ± 16 |
| Control | 72 ± 15 | 62 ± 13 | 69 ± 18 | 73 ± 21 | 70 ± 15 |
| PT (s) | | | | | |
| ANH (%) | 10.9 ± 1.8 | 14.4 ± 2.6* (64) | 15.1 ± 3.1* (67) | 13.2 ± 2.5 (30) | 11.2 ± 1.3 |
| Control (%) | 11 ± 1.6 | 15.2 ± 2.4* (74) | 15.9 ± 2.9* (77) | 13.4 ± 2.8 (33) | 11.4 ± 1.1 |
| pH | | | | | |
| ANH (%) | 7.41 ± 0.02 | 7.39 ± 0.04 (8) | 7.4 ± 0.02 | NA | NA |
| Control (%) | 7.40 ± 0.02 | 7.39 ± 0.05 (10) | 7.39 ± 0.02 (2) | NA | NA |

Values are mean ± SD. There were no significant differences between the groups in all parameters.

* $P < 0.05$ compared with value obtained after induction of anesthesia.

PACU = postoperative anesthesia care unit; POD = postoperative day; ANH = acute normovolemic hemodilution; PT = prothrombin time; % = percentage of patients with abnormal test results; NA = not available.

central venous pressure in the ANH and control groups was 7 ± 2 and 6 ± 3 mmHg, respectively. None of the patients in the two groups required the administration of fluid bolus to keep urine output greater than 0.5 ml · $kg^{-1}$ · $h^{-1}$. No ST-segment changes were observed during the operation in both groups.

**Perioperative Laboratory and Outcome Parameters.** Hematocrit, creatinine, prothrombin time, and arterial pH values were similar in both groups in the postoperative period (tables 3 and 4). Also, the highest postoperative values for bilirubin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase were comparable between the groups (data not shown).

Overall, 14 patients (36%) in the control group compared with 4 patients (10%) in the ANH group received allogeneic blood transfusion ($P = 0.014$, Fisher exact test). There were no significant differences between the groups in the median number of units of allogeneic blood transfused. The number of units of allogeneic blood transfused for the ANH and control groups and the fractional surgical blood loss in patients receiving allogeneic blood transfusion are shown in figures 1 and 2, respectively. Five patients in the control group compared with three patients in the hemodilution group received fresh frozen plasma, cryoprecipitate, or platelets ($P > 0.05$). None of the patients died in the perioperative period. The overall complication rate was similar in the two groups.

**Table 4. Outcome Variables**

| | ANH | Control |
|---|---|---|
| Transfusion of packed erythrocytes | | |
| No. of patients transfused* (%) | 4† (10) | 14 (36) |
| Median units transfused (range) | 0 (0–13) | 0 (0–16) |
| Postoperative complications (%) | | |
| Intraabdominal infection | 1 (2.5) | 3 (7.7) |
| Wound infection | 1 (2.5) | 4 (10.3) |
| Biliary leak | 3 (7.7) | 2 (5.1) |
| Small bowel obstruction | 1 (2.5) | 0 |
| Intraabdominal bleeding | 2 (5.1) | 0 |
| Pneumonia | 1 (2.5) | 1 (2.5) |
| Others | 3 (7.7) | 2 (5.1) |
| Total | 9 (23) | 8 (20) |

* All blood obtained by acute normovolemic hemodilution (ANH) was returned and is not included in this analysis. † $P < 0.05$ compared with control group.

## Discussion

The major finding of the current study is that ANH in adults undergoing elective major liver resection is a method for significantly reducing exposure to allogeneic blood. Although previous studies have demonstrated the efficacy of this technique in children[24] and adults[25,26] undergoing liver resection, these studies were not controlled randomized trials. Moreover, criteria for blood transfusion were not defined,[24,25] and none of the studies reported central venous pressure at the time of parenchymal resection, a parameter that has been shown to affect surgical bleeding during major hepatic resec-

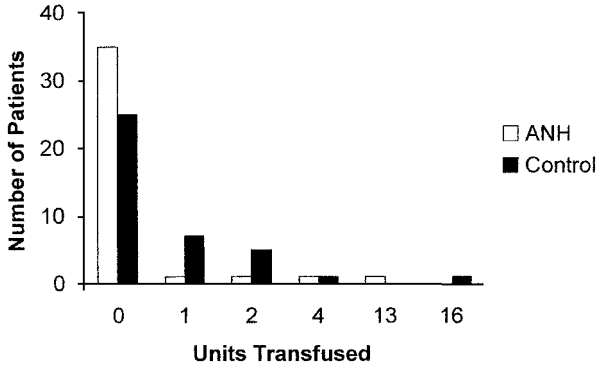


**Fig. 1. The number of units of allogeneic blood transfused for the acute normovolemic hemodilution and control groups.**

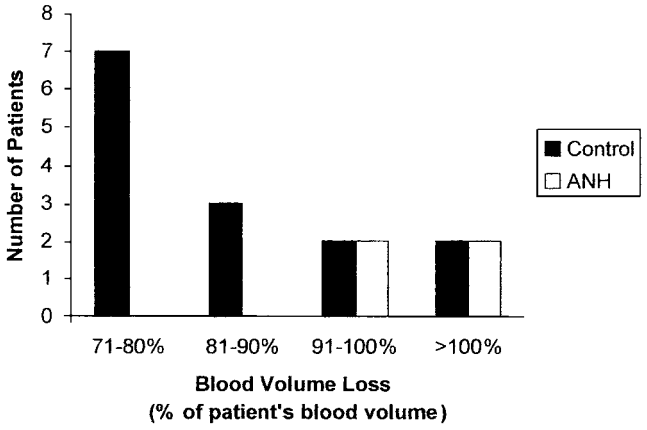


**Fig. 2. Fractional surgical blood loss for all patients receiving allogeneic blood transfusion.**

tions.[11,23] Finally, recent advances in surgical and anesthetic care made the applicability of findings from earlier studies to current practice uncertain. We therefore undertook this prospective, randomized study that recruited similar patients who were scheduled to undergo major liver resection. Although the anesthesiologist making the decision about the need for transfusion was not blinded to the patients' group assignment, the indication for blood transfusion was standardized. Also, during the postoperative period, adverse outcomes were detected by the examining physician, who was not aware of the patient's assignment.

Recent mathematical analysis predicted that hemodilution may be efficacious if surgical blood loss is greater than 70% of the patient's blood volume.[10] Patients presenting for major liver resections may be appropriate candidates for ANH because expected blood loss may be substantial.[11–16,27] The overall mean surgical blood loss in our current series of patients was 1,442 ± 1,827 ml and 1,528 ± 1,822 ml, with a median value of 800 ml (range, 100–7,000 ml) and 900 ml (range, 100–7,500 ml) in the ANH and control groups, respectively, and is comparable to previously reported blood loss associated with major liver resections.[12,25,26,28] In a selected group of patients in whom surgical blood loss was greater than 0.7 of the patient's blood volume, the median blood loss was 3,800 and 3,350 ml in the ANH and control groups, respectively. In addition, 7 of the 14 transfused patients in the control group received 1 unit of blood, a blood requirement that could have been accommodated by the use of ANH.[9,20] Presumably, the surgical blood loss as a fraction of blood volume in these patients was within "the window of efficacy" as suggested by Weiskopf.[10] However, in contrast to the latter mathematical analysis,[10] in which the assumption was that hemodilution proceeds until the trigger hematocrit, in the current study a different approach was used: the hemodilution was undertaken to a hematocrit of 24%, while the transfusion trigger was 20%. Although less efficacious, we have chosen this approach, as did other investigators previously,[20,28–32] because during liver resections, a sudden extensive bleeding may occur with an acute and rapid decrease in hematocrit below the lowest acceptable value. In addition, the mathematical model also assumes that euvolemia is maintained. This may be difficult in the clinical situation because intraoperative estimates of blood loss are inaccurate.[33] Because we did not measure blood volume, it may be argued that isovolemia was not maintained. In the current study, blood removed during the hemodilution process was replaced by colloid solutions in quantities approximately 1.1 times the volume of blood removed, as previously suggested.[20–22] Also, surgical blood loss was replaced with crystalloid solution in a 3:1 volume replacement, and patients in both groups received continuous crystalloid infusion with additional intermittent fluid boluses when indicated, according to predetermined criteria. Finally, heart rate did not increase and central venous pressure did not change significantly during hemodilution and thereafter, and urine production was comparable in the two groups and did not decrease to less than 0.5 ml · kg$^{-1}$ · h$^{-1}$ throughout the operation, suggesting that patients in the ANH group were not hypovolemic. In addition, the finding of no change in heart rate during hemodilution in the current study is comparable to previous reports[34–36] that showed an increase in cardiac output with hemodilution without a significant heart rate change. This may be caused in part by the effect of anesthetic agents, since previous studies[36,37] showed that ANH in awake patients was associated with higher values of heart rate than those measured in anesthetized patients.

Although previous mathematical models[7–10] suggest that ANH can save erythrocytes that would otherwise be lost during surgery, they emphasize that limited (posthemodilution hematocrit > 24%) normovolemic hemodilution is of minimal value. In the current study, the amount of blood removed was 2,020 ± 412 ml. A recently published metaanalysis reported that the mean volume of blood removed in 24 randomized controlled trials of ANH was 936 ml. In addition, the investigators also found that, in trials in which the volume of blood withdrawn was less than 1,000 ml, the reduction in the likelihood of transfusion failed to reach statistical significance, whereas in studies in which more than 1,000 ml of blood was removed, a statistically significant reduction in the likelihood of transfusion was found. A protocol that targets a low posthemodilution hematocrit level, in the range from 24% to as low as 20%, might therefore enhance the effectiveness of hemodilution.[7–9]

The perioperative morbidity rate was similar in the two groups and was comparable to that previously reported by other investigators,[11–16] indicating that ANH is well tolerated in this patient population. Although Sejourne *et al.*[26] found that alterations in blood coagulation

were greater in hemodiluted patients undergoing liver resection than in those without hemodilution, we observed no difference in standard coagulation tests between groups. Rehm *et al.*[20] recently showed that ANH used during certain conditions reduces the surgical loss of erythrocytes. With retransfusion of the removed autologous blood after termination of surgery, a higher hematocrit should therefore be expected.

Previous studies reported higher rates of postoperative infections in patients who received perioperative allogeneic transfusions than in those who were not transfused or who received only autologous blood.[38,39] In the current study, the rate of infections was not significantly higher in the control group (8 patients, 3 of whom received transfusion) compared with the hemodilution group (3 patients, none of whom received allogeneic transfusion). With a reduction of only 1 unit of allogeneic blood transfusion (in 7 of 14 transfused patients), no real benefit was to be expected. No adverse cardiac, renal, or neurologic outcomes were observed in the ANH group. However, the occurrence of zero events does not imply the risk is zero. For a sample size of 39 patients, the maximum incidence (with 95% confidence) of an adverse event is 7.4%. Also, in this study we included only ASA I–II patients. This careful patient selection may have contributed to the zero incidence of adverse outcome. ANH has been used previously in the elderly and in patients undergoing cardiac surgery; however, most of the published studies were seriously flawed.[35] Moreover, several recent studies suggested that anemia in the presence of cardiovascular disease may be associated with increased risk of organ dysfunction and mortality.[40,41] In the present state of knowledge, it seems clear that caution should be exercised in patients with coronary artery disease or aortic stenosis, since their normal compensatory mechanism is impaired. Moreover, ANH is best avoided in patients with vascular disease in whom the prevalence of ischemic heart disease is very high.

In summary, in 39 ASA I or II patients undergoing major liver resection, ANH was used as a method for autologous blood transfusion. By this method, the need for allogeneic blood transfusion was reduced significantly. As ANH is a relatively cheap and simple method of autologous transfusion, these data suggest that ANH should be considered in this patient population. The resultant decrease in allogeneic blood use may help to alleviate the blood shortage that blood banks are facing.

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