Acute Normovolemic Hemodilution Is Safe in Neurosurgery

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Key words
- Autologous blood
- Hemodilution
- Neurosurgery
- Red blood cell transfusion

Abbreviations and Acronyms
ANH: Acute normovolemic hemodilution
PTT: Partial thromboplastin time
SAH: Subarachnoid hemorrhage

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■ OBJECTIVE: **To determine the safety of acute normovolemic hemodilution (ANH) for patients undergoing neurosurgical procedures.**

■ METHODS: **A group of 100 patients undergoing neurosurgical procedures was assigned prospectively to receive ANH. A group of 47 patients who underwent craniotomy for aneurysm clipping and standard anesthetic management was used as a control. Procedures conducted under ANH were performed without significant variations in physiologic parameters.**

■ RESULTS: **Compared with controls, intraoperative blood loss, operative time, incidence and grade of complications, and length of hospital stay were similar between the two groups. Although the ANH group showed a difference in prothrombin levels before and after hemodilution procedures, the levels were still considered within physiologic parameters. Platelet counts and partial thromboplastin time (PTT) levels indicated no significant variations in either group. During the ANH procedure, a considerable reduction of brain oxygen extraction was observed in individuals with worse preoperative neurologic status ($P < 0.05$), indicating potential benefit. Among patients with cerebral aneurysm, patients with good initial clinical grades had better clinical results as indicated by Glasgow Outcome Scale scores ($P < 0.02$).**

■ CONCLUSIONS: **ANH is a safe procedure for patients undergoing neurosurgical procedures. Further studies are necessary to confirm the improvement in brain oxygen extraction and the clinical impact. Nonetheless, patients undergoing aneurysm clipping with good clinical grades seem to profit from ANH.**

INTRODUCTION

Hemodilution has been advocated in many medical situations, such as trauma and orthopedic and cardiac surgery, to prevent infections (e.g., acquired immunodeficiency syndrome or hepatitis) or undesired immunologic side effects. In 18%–90% of cases, hemodilution decreases the need for homologous blood transfusion in various surgical procedures (8, 9, 12, 23, 25, 28–30, 34, 39). Normovolemic hemodilution consists of replacing a patient's entire blood supply simultaneously with noncellular fluids, such as colloids or crystalloids (17). This procedure can be employed safely in surgeries associated with potential significant blood loss, with a reduced need for homologous transfusions (19). It also promotes a 24% increase in cardiac output after the hematocrit level has been downsized to the acceptable range of 27%–30% without compromising tissue oxygenation (18). However, normovolemic hemodilution should not be performed in patients with hemoglobin values < 11 g/dL; patients with clinical conditions compromising hepatic, renal, pulmonary, and cardiac functions; or patients in whom low concentrations of clotting factors are detected (33).

The literature supports the use of colloids as opposed to crystalloids (11, 19). Colloids present potential risks of hypersensitivity reaction and platelet dysfunction. Also, in case of fluid overload, it is easier to remove crystalloids with the aid of diuretics.

Several mechanisms have been proposed to support the benefits of normovolemic hemodilution, such as increased cardiac performance with a decrease in afterload (14, 18). Additionally, it was shown that cardiac output increases 16%–50% in anesthetized patients with hematocrit levels of 20%–25% (33). Experimental evidence also showed increased brain and coronary flow (18), and some authors recommend that patients with coronary disease should not be submitted to hemodilution (2). Normovolemic hemodilution reduces blood viscosity and peripheral vascular resistance and increases blood flow. In that sense, venous return and cardiac output vary according to the patient's oxygen transport capacity. Also, a heart rate increase should be interpreted as hypovolemia, requiring action. In our series, the hemodynamic parameters remained stable during surgery, reflecting the efficacy in amount of volume replacement.

In pediatric patients, acute normovolemic hemodilution (ANH) has been used as an alternative to homologous blood transfusions in craniosynostosis operations (3, 38) and has been used more recently for spinal procedures associated with

Table 1. Average Volume Withdrawal and Replacement in Patients Submitted to Normovolemic Hemodilution

Volume Removal (mL)		
Planned to be removed	1277 ± 526	
Removed	1013 ± 347	$P < 0.0005$
Volume of crystalloid replacement (mL)		
Planned	3039	
Used	2740 ± 1067	$P > 0.05$
Other (mL)		
Colloid (n = 13)	731 ± 300	
Blood	852 ± 308	

significant blood loss, such as instrumentations and laminectomies (4, 5). Despite the potential unwarranted blood loss related to most neurosurgical procedures, the literature concerning ANH is scarce, and evidence is lacking regarding benefits or even appropriateness of the use of hemodilution for preventing complications. We report the safety of normovolemic hemodilution as a volemic substitute to homologous transfusions during a prospective series of neurosurgical procedures and analyze the impact of these procedures on hemodynamic variables, clotting functions, perioperative morbidity, and early neurologic outcomes. We compared the same variables in a group of patients undergoing standard fluid management.

METHODS

Patients were prospectively assigned to two groups at a single neurosurgical center. The first group consisted of 100 consecutive neurosurgical patients receiving normovolemic hemodilution. This group comprised 53 cases of ruptured intracranial aneurysms undergoing surgical repair and 47 brain tumors undergoing resection. A second group of consecutive cases was a control group for the subset of ruptured aneurysms and was assigned to receive standard fluid management. This group was created to compare the impact of ANH on early outcome of patients with subarachnoid hemorrhage (SAH) undergoing craniotomy for aneurysm repair, a cerebrovascular condition in which mechanisms of vascular regulation could be impaired. Approval from the institutional review board regarding human subjects was obtained and informed consents were signed by the patients or their legal guardians.

To be included in this trial, patients had to have a baseline hemoglobin > 12 g/dL and a pathologic condition requiring a neurosurgical procedure, such as vascular or complex tumor surgeries, with potential blood loss during the operation. Preoperative assessment included a complete work-up to rule out cardiac ischemia and abnormalities on a baseline electrocardiogram. Patients with an obstructive or restrictive pulmonary condition, renal disease, severe high blood pressure, hepatic cirrhosis, and clotting abnormalities were excluded from the trial.

Baseline parameters were measured in all patients, including weight, hemoglobin, and hematocrit. During surgery, an anesthesiologist monitored hemodynamic (blood pressure, heart rate) and respiratory parameters (total volume, oxygenation, and carbon dioxide) using standard protocol.

First Group: Acute Normovolemic Hemodilution

The hemodilution procedure was initiated with general anesthesia and removal of half the target volume using the following formula by Gross (7):

$$V = EBV \times ([Hi - Hf]/Hav)$$

where V = volume of blood to be removed, EBV = estimated blood volume (body weight in kg × 70 mL/kg), Hi = patient's initial hematocrit level, Hf = patient's target hematocrit level following hemodilution, and Hav = patient's average hematocrit level (average of Hi and Hf).

Blood was drawn from suitable peripheral venous access, central venous access, or arterial line. Simultaneously, a crystalloid infusion was started to maintain normovolemia in the proportion of 3:1. Alternative use of colloid was considered, in the proportion of 1 mL for 1 mL of blood removed (33), but crystalloid replacement was used as the first choice in all cases. Having removed half of the blood volume target, physiologic parameters and hematocrit and hemoglobin levels were measured. Also, depending on patients' stability, additional blood removal up to the target volume was performed. The new he-

Table 2. Hemoglobin and Hematocrit Levels During Hemodilution

	Initial	Interval Measurement	End of Hemodilution	End of Surgery	*P*
Hb (g/dL)	13.46 ± 1.23	11.58 ± 1.26	10.15 ± 1.43	10.74 ± 1.11	<0.05
Ht (%)	40.92 ± 3.65	35.45 ± 3.71	30.96 ± 4.20	33.18 ± 3.29	<0.05
SBP (beats/min)	131.4 ± 17.5	103.2 ± 20.8	104.1 ± 14.1	117.2 ± 16.6	<0.05
DBP (beats/min)	80.42 ± 12.9	67.9 ± 14.5	66 ± 11.5	76.4 ± 12.7	<0.05
HR (beats/min)	89 ± 11	88 ± 15	85 ± 16	86 ± 13	>0.05

DBP, diastolic blood pressure; Hb, hemoglobin; HR, heart rate; Ht, hematocrit; SBP, systolic blood pressure.

Table 3. Coagulation Factors Before and After Surgery Among Patients Receiving Acute Normovolemic Hemodilution

	Initial	End of Surgery	*P*
Prothrombin (seconds)	12.66 ± 0.67	13.3 ± 1.01	<0.025
% Prothrombin	91.21 ± 8.88	86.23 ± 10.54	<0.025
Platelets (per μL)	318,592 ± 88,205	315,769 ± 79,700	>0.05
PTT (seconds)	26.06 ± 2.41	27.23 ± 3.28	>0.05

PTT, partial thromboplastin time.

matocrit level remained > 30%, and the hemoglobin level was > 10 g/dL. At the end of the hemodilution procedure, a complete blood work-up was done again.

Bags with removed blood were identified in sequence and stored at room temperature to be reinfused in case of significant blood loss during surgery. Reinfusion would begin with the last bag. The initial bags containing the highest concentration of blood cells and clotting factors were used last in case of reinfusion. At the end of the operation, the surgeon decided whether or not reintroduce the stored residual blood, taking into account the baseline disease and blood loss during surgery. After the procedure, removed blood bags not replaced were stored at the blood bank and used in the same patients during the postoperative period, depending on their need

Cerebral extraction of oxygen was measured in 22 patients by comparing the difference between peripheral arterial blood and jugular bulb venous blood with the following formula (32):

$$\text{Extraction } O_2 = (CaO_2 - CvO_2)/CaO_2 \times 100$$

$$CaO_2\ (mL/dL) = 1.36 \times Hb\ (g/dL) \times (SaO_2) + 0.003 \times PaO_2\ (mm\ Hg)$$

$$CvO_2\ (mL/dL) = 1.36 \times Hb\ (g/dL) \times (SaO_2) + 0.003 \times PvO_2\ (mm\ Hg)$$

Second Group: Standard Fluid Management

A control group was assigned to compare early clinical outcomes in patients with SAH caused by ruptured intracranial aneurysms. This outcome measure was not prone to analysis in tumor surgery owing to the high heterogeneity of clinical pictures related to lesion location, size, and histopathology. Physiologic parameters and hematocrit and hemoglobin levels of the control group were measured at the beginning of the procedures, during the procedures, and at the end of the procedures. A complete blood work-up was conducted at the end of the process.

Outcome Evaluation

In both groups, perioperative mortality and morbidity were analyzed. Also, during baseline and subsequent procedures, physiologic parameters of blood pressure and heart rate and hematocrit and hemoglobin levels were measured. Patients with SAH were classified clinically using the grading system of Hunt and Hess (10), and outcomes were evaluated 3 months after the procedure with the Glasgow Outcome Scale (37). In addition, χ^2 and Fisher tests were used for statistical analysis. Differences were considered significant if the probability level (P value) was < 0.05.

Table 4. Brain Oxygen Extraction Before and After Normovolemic Hemodilution Procedure

	Initial (%)	End of Surgery (%)	*P*
Whole group (n = 22)	27.05 ± 15.58	24.56 ± 10.66	>0.05
Group 1 (n = 15)	17.75 ± 6.06	20 ± 8.58	>0.05
Group 2 (n = 7)	46.97 ± 9.2	34.31 ± 7.94	<0.05

RESULTS

Of the 147 patients assigned to the study, 98 were male and 49 were female, with ages ranging from 11–79 years old (average age 60 years old). Pathologic conditions in these patients included 47 intracranial tumors (patients were undergoing elective neurosurgical operations) and 100 ruptured intracranial aneurysms.

In the patients submitted to acute normovolemic hemodilution, the average blood withdrawal was 1013 mL, and average crystalloid replacement was 2740 mL (**Table 1**). Initial hemoglobin level was 13.4 g/dL, and hematocrit was 40.9% ± 3.6. After hemodilution, hemoglobin was 10.1 g/dL ± 1.4, and hematocrit was 30.9% ± 4.2. **Table 2** summarizes the hemodynamic and laboratory variables in this group during the procedure.

A difference in the blood pressure of patients undergoing hemodilution was noted at the end of the operation, albeit still within appropriate range for this type of operation. As expected, there was no variation in cardiac rate, considering preoperative conditions and the procedure employed. Also, coagulation factors, prothrombin, platelets, and partial thromboplastin time (PTT) results all were within physiologic parameters.

To maintain adequate hematocrit and hemoglobin levels during the postoperative period, five (9.5%) patients receiving ANH required homologous blood replacement, with an average volume of 560 mL ± 357; this was not statistically different from the control group, in which eight (17%) patients required homologous blood transfusion with an average volume of 787.5 mL ± 747. A significant difference within acceptable physiologic parameters was observed in prothrombin levels before and after operations among ANH patients. Platelets and PTT levels showed no significant differences (**Table 3**).

In 22 patients undergoing aneurysm surgery, brain oxygen extraction was calculated before and after the normovolemic he-

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Table 5. Clinical Grades Among Patients with Cerebral Aneurysms

Clinical Grade (Hunt and Hess Classification)	Not Hemodiluted	Hemodilution Completed	Total	*P*
I	23	24	47	>0.05
II	10	10	20	>0.05
III	11	18	29	>0.05
IV	3	1	4	>0.05
Total	47	53	100	>0.05

modilution procedure (**Table 4**). Among these patients, 15 (group 1) had an initial average oxygen extraction of 17.7%, which did not vary significantly throughout the process. The remaining patients (group 2) with worse neurologic conditions had higher initial levels of oxygen extraction (average 47.9%). Within this subset of patients, a significant improvement of this variable to a lower range of oxygen extraction (34.3%) was noted at the end of the surgery ($P < 0.05$).

Subgroup of Intracranial Ruptured Aneurysms

In the subgroup of 100 patients with cerebral aneurysms, 53 underwent hemodilution; their clinical characteristics are summarized in **Table 5**. Baseline Hunt and Hess scores were similar between groups. Among patients submitted to ANH, patients with initial good clinical grades (Hunt and Hess I) had significantly better clinical results as shown by Glasgow Outcome Scale scores ($P < 0.02$). There was no significant variation in results within other groups (**Table 6**).

DISCUSSION

ANH can be used safely in surgeries associated with potential significant blood loss, reducing the need for homologous transfusions (19). ANH also promotes a 24% increase in cardiac output after the hematocrit level has been reduced to the acceptable range of 27%–30% without compromising tissue oxygenation (18). Normovolemic hemodilution consists of a deliberate removal of blood, with replacement provided by infusion of noncellular fluids such as colloids or crystalloids (17). Colloids could present potential risks of hypersensitivity reaction and platelet dysfunction. Also, in case of fluid overload, it is easier to remove crystalloids with the aid of diuretics (11, 19).

Several mechanisms have been proposed to support the benefits of ANH, such as an increase in cardiac performance with a decrease in afterload (14, 18). Experimental evidence also showed an increase in brain and coronary flow (18), although some authors recommend that patients with coronary disease should not be submitted to hemodilution (2). Additionally, it has been shown that cardiac output increases 16%–50% in anesthetized patients with hematocrit levels of 20%–25% (33). In the present series, hemodynamic parameters remained within acceptable ranges during surgery, reflecting the efficacy of the amount of volume replaced.

The decrease in blood viscosity after hemodilution increases the microcirculation flow, with a more uniform distribution of oxygen to the tissues (27, 36). Clinical and experimental studies report that reduction of viscosity protects against ischemic injury to the brain (11, 14, 35). Reduction of viscosity has been used extensively by neurosurgeons to prevent delayed ischemic injury owing to cerebral vasospasm after aneurysmal SAH (1, 13, 15, 20, 26, 31).

In the present study, data regarding oxygen extraction improvement in patients with previously increased oxygen extraction should be interpreted carefully. In this scenario, patients with worse neurologic conditions present with increased oxygen extraction as a result of reduced cerebral perfusion. The observed improvement owing to the decrease of oxygen extraction could be a reflex of the mechanical ventilation or related to the decompression effect of the craniotomy, rather than a result of the hemodilution itself (6, 21). Additional studies are required to show a beneficial influence of the hemodilution on the oxygen extraction and whether these effects may have any clinical repercussion. However, in this circumstance, the consequences of the hemodilution had no deleterious effect. The increase in the capillary blood flow did not induce problems to the surgical wound, such as difficulties with homeostasis and scarring process, as shown in previous series (18). Also, variations observed in coagulation test values did not present clinical repercussions.

One of the first studies employing hemodilution in neurosurgery was a case-control series of 100 patients with brain tumors and aneurysms (16). In this study, the average blood removal was 649 mL, and the need for autologous blood transfusion occurred in 24% of the cases. The average volume of transfused blood was > 10 times less than the hemodiluted group (120 mL vs. 1344 mL). Also, there was a difference in the amount of blood loss during surgery (333 mL for hemodiluted patients vs. 995 mL for the control group).

The benefits of hemodilution in neurosurgery are controversial (22); however, it has been used in craniostenosis operations (24) of pediatric patients. The present study

Table 6. Outcome Analysis of Patients with Cerebral Aneurysms

	Clinical Grade							
	I		II		III		IV	
GOS	NH	H	NH	H	NH	H	NH	H
1	18	24	9	8	5	5	1	0
2	5	0	1	2	3	10	0	0
3	0	0	0	0	2	3	2	1
4	0	0	0	0	1	0	0	0
P	<0.02		>0.05		>0.05		>0.05	

GOS, Glasgow Outcome Scale; H, hemodilution completed; NH, not hemodiluted.

in adults recorded and analyzed all significant hemodynamic and metabolic parameters to make conclusions relevant for clinical practice. Despite a few differences between initial and final values, all the parameters remained within the expected levels for this kind of operation. Regarding the group of 100 patients undergoing aneurysm clipping, there was a significant benefit in clinical outcomes for patients with good clinical grades (Hunt and Hess I) after hemodilution. There were no complications related to hemodilution, showing the safety of the procedure for aneurysm surgery.

The present study may be limited because of the number of patients. The small trial size restricted comparisons between subgroups of patients. Regardless, no benefit has been shown in other clinical grades of patients with SAH as of yet, and additional studies should be conducted to confirm the lack of clinical repercussions related to hemodilution.

CONCLUSIONS

Normovolemic hemodilution is a safe and useful method that can be employed to decrease the need for homologous blood transfusion in patients undergoing neurosurgery. The impact of hemodilution on hemodynamic and laboratory variables was not significant, and no clinical repercussions were observed. Also, oxygen extraction did not worsen during the experiment, and a decrease was shown in a subset of patients with initial increased extraction, although a clear relationship of this to hemodilution cannot be established as of yet. Patients with good clinical grade after aneurysmal SAH had better outcomes when submitted to hemodilution during aneurysm clipping.

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Clinicopathological Analysis of Rhabdoid Meningiomas: Report of 12 Cases and a Systematic Review of the Literature

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BACKGROUND: **Rhabdoid meningioma (RM) is a rare subtype of meningioma, classified as World Health Organization grade III with a poor prognosis. Here we present our experience on RM and review relevant literature in an attempt to investigate the clinical features, treatment, and prognosis of these tumors.**

METHODS: **Twelve patients underwent surgical treatment for intracranial RMs between 2003 and 2008 in our department. The clinical data, radiological manifestations, pathological findings, treatments, and prognoses of the patients were analyzed retrospectively; 58 other cases reported previously by other institutions also were summarized and reviewed.**

RESULTS: **These cases (6 men and 6 women, mean age 44.3 years old, ranging from 21 to 78 years old) constituted 0.28% of all meningioma patients admitted at our department during the same period. The mean duration of symptoms was relatively short at 1.6 months. There was no significant clinical manifestation noted, and the radiologic findings fell into 3 types of images. In the follow-up period of over 30 months, 7 patients died; 5 patients had recurrence and 2 patients died of unknown causes.**

CONCLUSIONS: **RM is a rare subtype of malignant meningioma featuring an increased tendency for recurrence and possible metastasis. It is still difficult to make a correct preoperative diagnosis. The overall prognosis for these patients is extremely poor, and the role of various adjuvant treatments needs to be further studied.**

Key words
- Diagnosis
- Prognosis
- Rhabdoid meningioma

Abbreviations and Acronyms
EMA: Epithelial membrane antigen
GFAP: Glial fibrillary acidic protein
H&E: Hematoxylin and eosin
MRI: Magnetic resonance imaging
RM: Rhabdoid meningioma
VP: Ventriculoperitoneal
WHO: World Health Organization

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INTRODUCTION

Malignant rhabdoid tumor is an aggressive form of tumor originally described by Beckwith and Palmer (6) in 1978, primarily as a kidney tumor that occurs mainly in children. Having cytological features resembling rhabdomyoblasts, this kind of tumor lacks skeletal muscle differentiation. Later, rhabdoid tumors outside the kidney were reported in many tissues, including the liver, soft tissue, and central nervous system (19, 32), with an extremely poor prognosis. In 1998, Kepes et al. (19) and Perry et al. (32)