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**The Use of Acute Normovolemic Hemodilution in Clipping Surgery for Aneurysmal Subarachnoid Hemorrhage**

*Ping Chen¹, Ying Wang¹, Xin-Huang Zhang¹, De-Zhi Kang²-⁴, Xian-Zhong Lin¹, Qing-Song Lin²-⁴*

**BACKGROUND:** The occurrence of coronavirus disease 2019 (COVID-19) has overwhelmed the blood supply chain worldwide and severely influenced clinical procedures with potential massive blood loss, such as clipping surgery for aneurysmal subarachnoid hemorrhage (aSAH). Whether acute normovolemic hemodilution (ANH) is safe and effective in aneurysm clipping remains largely unknown.

**METHODS:** Patients with aSAH who underwent clipping surgery within 72 hours from bleeding were included. The patients in the ANH group received 400 mL autologous blood collection, and the blood was returned as needed during surgery. The relationships between ANH and perioperative allogeneic blood transfusion, postoperative outcome, and complications were analyzed.

**RESULTS:** Sixty-two patients with aSAH were included between December 2019 and June 2020 (20 in the ANH group and 42 in the non-ANH group). ANH did not reduce the need of perioperative blood transfusion (3 [15%] vs. 5 [11.9%]; P = 0.734). However, ANH significantly increased serum hemoglobin levels on postoperative day 1 (11.5 ± 2.5 g/dL vs. 10.3 ± 2.0 g/dL; P = 0.045) and day 3 (12.1 ± 2.0 g/dL vs. 10.7 ± 1.3 g/dL; P = 0.002). Multivariable analysis indicated that serum hemoglobin level on postoperative day 1 (odds ratio, 0.895; 95% confidence interval, 0.822–0.973; P = 0.010) was an independent risk factor for unfavorable outcome, and receiver operating characteristic curve analysis showed that it had a comparable predictive power to World Federation of Neurosurgical Societies grade (Z = 0.275; P > 0.05).

**CONCLUSIONS:** ANH significantly increased postoperative hemoglobin levels, and it may hold the potential to improve patients’ outcomes. Routine use of ANH should be considered in aneurysm clipping surgery.

**INTRODUCTION**

Aneurysmal subarachnoid hemorrhage (aSAH) is a severe cerebrovascular disease, with a high incidence of 9.1–22.7 cases per 100,000 people per year. Early clipping surgery within 72 hours from initial bleeding is recommended in current guidelines. Of patients with aSAH, 19%–62% required allogeneic blood transfusion during hospitalization, and neurological clipping was suggested to be an independent predictor of transfusion. Allogeneic blood transfusion may increase the risk for vasospasm and unfavorable outcome in patients with aSAH. Despite that situation, ensuring adequate blood preparation is still critical to ascertain the safety of clipping surgery. However, blood shortage has a long-term impact on surgical procedures, with potentially massive blood loss, including aneurysm clipping. During the pandemic of coronavirus disease 2019 (COVID-19), blood shortage has been rapidly aggravated and has become a global health care problem as a result of city lockdown management. There is also concern about the well-known problems of allogeneic blood

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**Key words**
- Acute normovolemic hemodilution
- Clipping
- Functional outcome
- Subarachnoid hemorrhage

**Abbreviations and Acronyms**

- ANH: Acute normovolemic hemodilution
- aSAH: Aneurysmal subarachnoid hemorrhage
- CI: Confidence interval
- COVID-19: Coronavirus disease 2019
- FFP: Fresh frozen plasma
- OR: Odds ratio
- ROC: Receiver operating characteristic
- WFNS: World Federation of Neurosurgical Societies
transfusion, such as an immunomodulatory effect. Moreover, the transmission of coronaviruses via allogeneic blood transfusion is also a potential problem during the COVID-19 pandemic. Therefore, efforts to minimize allogeneic blood transfusion are warranted.

Acute normovolemic hemodilution (ANH), a blood conservation technique, has been used in many kinds of surgeries. For ANH, autologous blood was collected immediately before the procedure while euvolemia was maintained with crystalloid/colloid replacement, and the harvested blood was returned to patients before the completion of surgery. ANH was suggested to be associated with a significant reduction of perioperative allogeneic blood transfusion. However, whether ANH reduces allogeneic blood transfusion in early clipping surgery remains largely unknown. Besides, the association between ANH and the functional outcomes has not yet been clarified.

The primary aim of this study was to investigate whether ANH reduces the need for perioperative blood transfusion in early clipping surgery. The secondary aim was to determine the association between ANH and postoperative outcome.

METHODS

Study Design and Participants
A single-center retrospective cohort study was conducted. Adult patients with a diagnosis of aSAH who underwent clipping surgery within 72 hours from initial bleeding were eligible for enrollment. Patients in the ANH group received 400 mL of autologous blood collection immediately before surgery. Patients in the non-ANH group did not undergo autologous blood collection before surgery and received allogeneic blood transfusion as needed. The main exclusion criteria were 1) age <18 years; 2) combined with other intracranial lesions; 3) combined with a systemic disease, such as uncontrolled hypertension, abnormal coagulation status, or cardiac insufficiency; 4) preoperative serum hematocrit level <28% or hemoglobin level <10.0 g/dL; 5) preoperative blood donation; 6) receiving erythropoietin perioperatively; 7) underwent coiling surgery or declined surgery; 8) underwent clipping surgery after 72 hours from ictus; and 9) declined to sign the consent form.

This study adheres to the applicable STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines. Data were retrieved from a quality control database in which data of patients with aSAH were prospectively entered and saved as the previous report in our hospital. Written informed consent was obtained from all patients or their relatives if the patient could not sign the form by themselves. This study was approved by the ethics committee of our hospital.

Patient Management, ANH Protocol, and Blood Transfusion
Clinical management of aSAH followed the guidelines of the American Heart Association and the American Stroke Association. All patients in the ANH group received 400 mL of autologous blood collection. Euvolemia was maintained by transfusing 200 mL colloid and 600 mL crystalloid. All patients underwent continuous vital monitoring. Perioperative blood transfusion followed the guidelines of the American Society of Anesthesiologists. The intraoperative transfusion trigger was set at a hemoglobin level <7.0 g/dL for all patients in our institution. Autologous blood from ANH was returned to patients if the transfusion trigger was reached or reinfused when the surgery was completed or if the surgery was not completed within 8 hours. The allogeneic blood might be required only after all the autologous blood had been applied. A hemoglobin level <8 g/dL or a hemoglobin level ≥8 g/dL with hemodynamic changes was identified as the postoperative transfusion indication. The fresh frozen plasma (FFP) transfusion trigger was set at an international normalized ratio >1.8 or the need for an invasive procedure or intraoperative excessive microvascular hemorrhage.

Statistical Analysis
Clinical outcome at discharge was assessed and dichotomized as favorable outcomes (modified Rankin Scale score 0–2) and unfavorable outcomes (modified Rankin Scale score 3–6). Continuous variables were expressed as mean ± standard deviation, and analyzed by Student t test or Mann-Whitney U test. Categorical variables were expressed as frequency (percentage), and assessed by the χ² test or Fisher exact test. Multivariable logistic regression analysis included all variables significant at P < 0.10 in univariate analysis for the risk factors associated with allogeneic blood transfusion and the predictors associated with unfavorable outcomes. Predictive performances of the independent factors for unfavorable outcomes were analyzed using the receiver operating characteristic (ROC) curve method. Area under the curve analysis was performed using the Z test. P ≤ 0.05 was considered significant. Statistical analysis was performed with SPSS version 20 (IBM Corp., Armonk, New York, USA).

RESULTS
Since the first case of COVID-19 was diagnosed in December 2019, >80,000 cases have been confirmed in mainland China, and 353 cases had been reported in Fujian province by the end of June 2020. During this period, 119 patients with aSAH were admitted to our hospital. All these patients were excluded from COVID-19 infection by throat swab nucleic acid amplification test at admission. As summarized in Figure 1, 57 patients were excluded from the final analysis, and 62 patients were included (20 in the ANH group and 42 in the non-ANH group).

Demographic and Perioperative Surgical Results
The age and gender were well matched (Table 1). The average number of patients with aSAH who were admitted to our hospital per month during the COVID-19 pandemic was not significantly different from that in the previous report (17 patients/month vs. 17.9 patients/month). No patient with posterior circulation aneurysm underwent clipping in this cohort. A pterional keyhole approach was used except in 3 patients who developed brain herniation and received classic decompressive hemicraniectomy (1 [5%] vs. 2 [4.8%]; P = 0.967). A total of 12 patients experienced intraoperative aneurysm rupture, 4 in the ANH group and 8 in the non-ANH group (4 [20%] vs. 8 [19.0%]; P = 0.929; Table 2). No patient underwent assistant coiling surgery either before or during the clipping surgery. ANH did not extend the length of surgery compared with the
non-ANH group (209.8 ± 88.1 min vs. 180.4 ± 58.7 minutes; \( P = 0.187; \) Table 2). The estimated blood loss seemed higher in the ANH group, but it was not significant (545.0 ± 611.5 mL vs. 380.5 ± 357.3 mL; \( P = 0.187; \) Table 2). The hemodynamics was maintained stably in both groups, because the mean arterial pressure was maintained around 80 mm Hg in both groups, and the occurrence of mean arterial pressure <60 mm Hg was not significantly different between the 2 groups (Table 2).

There was no significant difference in the rate and severity of postoperative complications between the 2 groups (Table 2). Vasospasm was the most common complication, and it occurred more frequently in the ANH group than in the non-ANH group (5 [25%] vs. 19 [45.2%]; \( P = 0.126; \) Table 2). The rate of intracranial infection was higher but not significantly in the ANH group (2 [10%] vs. 2 [4.8%]; \( P = 0.433; \) Table 2). No patient developed myocardial ischemia or infarction in the entire cohort. There was no significant difference in the rate and severity of postoperative complications between the 2 groups (Table 2).

Perioperative Routine Laboratory Examination and Transfusion Data
As expected, the intraoperative hemoglobin levels decreased more sharply but not significantly in the ANH group (11.9 ± 1.7 g/dL vs. 12.4 ± 1.6 g/dL; \( P = 0.271; \) Table 2). There were no significant differences in the routine laboratory test result between the 2 groups, except for the serum hemoglobin level on postoperative day 1, which was dramatically higher in the ANH group than in the non-ANH group (11.5 ± 2.5 g/dL vs. 10.3 ± 2.0 g/dL; \( P = 0.045; \) Table 2). On postoperative day 3, serum hemoglobin level was consistently and significantly higher in the ANH group (12.1 ± 2.0 g/dL vs. 10.7 ± 1.3 g/dL; \( P = 0.002; \) Table 2).

ANH did not reduce the frequency and volume of allogeneic blood transfusion. In the entire cohort, 8 patients received allogeneic red blood cell transfusion: 3 in the ANH group and 5 in the non-ANH group (3 [15%] vs. 5 [11.9%]; \( P = 0.734; \) Table 2). Three patients in each group received postoperative allogeneic blood transfusion (3 [15%] vs. 3 [7.1%]; \( P = 0.328) and 1 patient with favorable outcome in each group received allogeneic blood transfusion (1 [5%] vs. 1 [2.4%]; \( P = 0.545) . Two patients in the ANH group received a total of 650 mL FFP transfusion and 4 patients in the non-ANH group had overall 1500 mL FFP transfusion (2 [10%] vs. 4 [9.5%]; \( P = 0.535; \) Table 2). A total of 9 patients underwent intraoperative autologous blood salvage: 4 in the ANH group and 5 in the non-ANH group (4 [20%] vs. 5 [11.9%]; \( P = 0.645; \) Table 2). For the entire cohort, the requirement of allogeneic blood transfusion was associated with intraoperative aneurysm rupture (7 [87.5%] vs. 5 [9.3%]; \( P < 0.001; \) Table 3) and length of surgery (277.3 ± 88.0 minutes vs. 176.9 ± 57.6 minutes; \( P = 0.014; \) Table 3). However, intraoperative aneurysm rupture was the only independent risk factors (odds ratio [OR], 0.024; 95% confidence interval (CI), 0.002–0.272; \( P = 0.003; \) Table 3).

Postoperative Outcome
For the entire group, 16 patients (25.8%) had unfavorable outcomes. The incidence of unfavorable outcomes was slightly lower in the ANH group, but the difference was not significant (ANH, 4 [20%] vs. non-ANH, 12 [28.6%]; \( P = 0.471) . Hemoglobin levels on postoperative day 1 were significantly higher in patients with
favorable outcomes than in patients with unfavorable outcomes (Figure 2A and B). Another 5 variables that may affect the functional outcomes were entered in the univariate and multivariable analysis: age, gender, World Federation of Neurosurgical Societies (WFNS) grade, Fisher grade, and estimated blood loss. As shown in Table 4, WFNS grade and postoperative day 1 hemoglobin levels were the 2 independent risk factors for unfavorable outcome (WFNS grade: OR, 36.442, 95% CI, 2.175–610.481, \(P = 0.012\); postoperative day 1 hemoglobin levels: OR, 0.895, 95% CI, 0.822–0.973, \(P = 0.010\)). ROC curve analysis for postoperative day 1 hemoglobin levels to predict discharge outcome was represented as area under the curve \(= 0.838\) (95% CI, 0.719–0.956), and the sensitivity and specificity were derived as 65.2% and 93.7%, respectively, based on the best threshold of 10.9 g/dL for postoperative day 1 hemoglobin levels (Figure 2C). The predictive value of postoperative day 1 hemoglobin levels was not significantly different compared with that of WFNS grade (\(Z = 0.275; P > 0.05\); Figure 2C). The hospital length of stay was not different between the 2 groups (15.3 ± 13.0 days vs. 12.5 ± 5.4 days; \(P = 0.367\)).

**DISCUSSION**

Blood shortage is a historical problem that may influence routine clinical practice, especially major surgery with a potential requirement of blood transfusion, including clipping surgery for aneurysm.4,7 During the COVID-19 pandemic, the blood supply chain has been dramatically disrupted because of global curtailment strategies.9,10 The severe crisis of blood shortage has overwhelmed health care practice worldwide.18 Apart from blood shortage, the underlying adverse effects of allogeneic blood transfusion, such as immunomodulatory effects, transfusion reactions, and mistransfusion, have long been of concern.12,19 During the COVID-19 pandemic, allogeneic blood transfusion has also carried a theoretic risk of transmission of coronaviruses.8

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**Table 1. Comparison of Demographic and Preoperative Data**

|                      | ANH (n = 20) | Non-ANH (n = 42) | \(P\) Value |
|----------------------|-------------|-----------------|------------|
| Age (years)          | 54.1 ± 11.2 | 56.5 ± 7.4      | 0.392      |
| Male                 | 11 (55)     | 15 (35.7)       | 0.150      |
| Body mass index (kg/m²) | 23.2 ± 2.0  | 22.4 ± 3.2      | 0.427      |
| Smoking history      | 5 (25)      | 11 (26.2)       | 0.920      |
| Hypertension         | 9 (45)      | 20 (47.6)       | 0.847      |
| American Society of Anesthesiologists classification | | | 0.528 |
| 1                    | 1 (5)       | 2 (4.8)         |            |
| 2                    | 14 (70)     | 34 (81.0)       |            |
| 3                    | 5 (25)      | 6 (14.3)        |            |
| World Federation of Neurosurgical Societies grade I/II | 9 (45) | 18 (42.9) | 0.874 |
| Fisher grade I/II    | 10 (50)     | 18 (42.9)       | 0.597      |
| Aneurysm characteristics |           |                 |            |
| Aneurysm size (mm)   | 5.8 ± 2.3   | 5.9 ± 2.7       | 0.887      |
| Multiple aneurysms   | 2 (10)      | 6 (14.3)        | 0.948      |
| Preoperative laboratory studies |       |                 |            |
| Hemoglobin level (g/dL) | 13.0 ± 1.8 | 12.9 ± 1.3     | 0.665      |
| Platelet count (K/µL)     | 247.0 ± 101.8  | 227.1 ± 67.1  | 0.393      |
| International normalized ratio | 1.0 ± 0.06 | 1.0 ± 0.07     | 0.886      |
| Prothrombin time (seconds) | 12.2 ± 1.0 | 12.1 ± 0.9     | 0.829      |
| Activated partial thromboplastin time (seconds) | 30.9 ± 5.8 | 28.7 ± 5.4     | 0.166      |
| Blood urea nitrogen level (mmol/L) | 4.8 ± 1.3 | 4.9 ± 1.5    | 0.819      |
| Bilirubin level (mg/dL) | 8.3 ± 3.5  | 9.5 ± 4.4      | 0.332      |
| Potassium level (mmol/L) | 3.7 ± 0.7 | 3.8 ± 0.4     | 0.604      |
| Calcium level (mmol/L)  | 2.1 ± 0.3   | 2.2 ± 0.2       | 0.188      |

Data are mean ± standard deviation or n (%). \(P\) values were calculated by Student t test, Mann-Whitney U test, \(\chi^2\) test, or Fisher exact test, as appropriate.

ANH, acute normovolemic hemodilution.
Table 2. Comparison of Operative and Perioperative Results

|                                   | ANH (n = 20) | Non-ANH (n = 42) | P Value |
|-----------------------------------|--------------|------------------|---------|
| Length of surgery (minutes)       | 209.8 ± 88.1 | 180.4 ± 58.7     | 0.187   |
| Mean MAP during surgery (mm Hg)   | 79.5 ± 8.0   | 80.3 ± 7.6       | 0.732   |
| Occurrence of MAP <60 mm Hg       | 6 (30.0)     | 11 (26.2)        | 0.753   |
| Intraoperative hemoglobin (g/dL)  | 11.9 ± 1.7   | 12.4 ± 1.6       | 0.271   |
| Intraoperative aneurysm rupture   | 4 (20)       | 8 (19.0)         | 0.929   |
| Estimated blood loss (mL)         | 545.0 ± 611.5| 380.5 ± 357.3    | 0.187   |
| Intraoperative fluid given        |              |                  |         |
| Total (mL)                        | 2728.6 ± 1596.6| 2491.1 ± 946.1  | 0.466   |
| Crystalloid (mL)                  | 1518.8 ± 750.3| 1544.1 ± 618.2  | 0.889   |
| Colloid (mL)                      | 1020.0 ± 593.5| 904.8 ± 431.1   | 0.389   |
| Intraoperative urine output (mL)  | 702.5 ± 474.8| 838.1 ± 531.1   | 0.335   |
| Allogeneic red blood cell transfusion |            |                  |         |
| Patients                          | 3 (15)       | 5 (11.9)         |         |
| Units                             | 8            | 18               |         |
| Fresh frozen plasma transfusion   |              |                  | 0.953   |
| Patients                          | 2 (10)       | 4 (9.5)          |         |
| Volume (mL)                       | 650          | 1500             |         |
| Intraoperative autologous blood salvage |          |                  | 0.645   |
| Patients                          | 4 (20)       | 5 (11.9)         |         |
| Volume (mL)                       | 1946         | 1568             |         |
| Postoperative laboratory studies (day 1) |        |                  |         |
| Hemoglobin level (g/dL)           | 11.5 ± 2.5   | 10.3 ± 2.0       | 0.045   |
| Platelet count (K/µL)             | 225.9 ± 87.6 | 207.1 ± 68.4     | 0.361   |
| International normalized ratio    | 1.0 ± 0.1    | 1.0 ± 0.09       | 0.897   |
| Prothrombin time (seconds)        | 12.0 ± 1.3   | 12.0 ± 1.0       | 0.830   |
| Activated partial thromboplastin time (seconds) | 25.6 ± 5.1 | 24.0 ± 3.9       | 0.148   |
| Blood urea nitrogen level (mmol/L) | 4.4 ± 0.6   | 4.5 ± 1.6        | 0.782   |
| Bilirubin level (mg/dL)           | 7.2 ± 3.3    | 7.5 ± 3.8        | 0.840   |
| Potassium level (mmol/L)          | 3.8 ± 0.6    | 3.9 ± 0.5        | 0.426   |
| Calcium level (mmol/L)            | 1.9 ± 0.3    | 2.0 ± 0.2        | 0.123   |
| Postoperative laboratory studies (day 3) |        |                  |         |
| Hemoglobin level (g/dL)           | 12.1 ± 2.0   | 10.7 ± 1.3       | 0.002   |
| Complication                      |              |                  |         |
| Vasospasm                         | 5 (25)       | 19 (45.2)        | 0.126   |
| Cerebral infarction               | 3 (15)       | 11 (26.2)        | 0.325   |
| Intracranial infection            | 2 (10)       | 2 (4.8)          | 0.433   |

Data are mean ± standard deviation or n (%). P values were calculated by Student t test, Mann-Whitney U test, χ² test, or Fisher exact test, as appropriate. ANH, acute normovolemic hemodilution; MAP, mean atrial pressure.
Moreover, an allogeneic blood transfusion may increase the risk of vasospasm and poor outcome in patients with aSAH.4,6 Although COVID-19 was suggested to make patients reluctant to seek hospital treatment,20 the number of patients with aSAH admitted to our hospital during COVID-19 did not decrease compared with the previous report.17 Therefore, all the factors discussed earlier led us to use ANH in clipping surgery for patients with aSAH. In this cohort, mild ANH was administered, because the estimated blood loss in our previous experience was about 460 mL in clipping surgery, and more importantly, severe ANH was suggested to be associated with potential brain injury.21

There were 3 reports regarding the use of ANH in surgery for patients with aSAH.22-24 The first article22 indicated that ANH can reduce homologous blood transfusion and improve functional outcomes in patients with aSAH. However, this article was published 22 years ago and only 10% of patients in the group received clipping surgery within 1 week from initial bleeding.22 This situation is different from the present guidelines, which

### Table 2. Continued

|                      | ANH (n = 28) | Non-ANH (n = 42) | P Value |
|----------------------|-------------|-----------------|--------|
| Pulmonary infection  | 4 (20)      | 8 (19.0)        | 0.929  |
| Hydrocephalus        | 1 (5)       | 3 (7.1)         | 0.748  |
| Hospital length of stay (days) | 15.3 ± 13.0 | 12.5 ± 5.4 | 0.367  |
| Clinical outcome at 1 month |            |                 |        |
| Unfavorable outcome (modified Rankin Scale score 3—6) | 4 (20) | 12 (28.6) | 0.471  |

Data are mean ± standard deviation or n (%). P values were calculated by Student t test, Mann-Whitney U test, χ2 test, or Fisher exact test, as appropriate. ANH, acute normovolemic hemodilution; MAP, mean atrial pressure.

### Table 3. Risks Associated with Allogeneic Red Cell Transfusion Rate

|                      | Univariate Analysis | Multivariable Analysis* |
|----------------------|---------------------|-------------------------|
|                      | Allogeneic Red Blood Cell Transfusion (n = 8) | None (n = 54) | P Value | Odds Ratio (95% Confidence Interval) | P Value |
| Age (years)          | 59.0 ± 8.6          | 55.2 ± 8.8             | 0.264  | —                          | —        |
| Male                 | 2 (25)              | 24 (44.4)              | 0.512  | —                          | —        |
| Body mass index (kg/m²) | 22.6 ± 1.9         | 22.8 ± 3.0             | 0.859  | —                          | —        |
| Hypertension         | 4 (50)              | 25 (46.3)              | 0.845  | —                          | —        |
| World Federation of Neurosurgical Societies grade I/II | 2 (25) | 25 (46.3) | 0.452 | — | — |
| Fisher grade I/II    | 2 (25)              | 26 (48.1)              | 0.397  | —                          | —        |
| Aneurysm characteristics |                    |                        |        |                            |          |
| Aneurysm size (mm)   | 5.6 ± 2.3           | 5.9 ± 2.6              | 0.759  | —                          | —        |
| Multiple aneurysms   | 1 (12.5)            | 7 (13.0)               | 0.971  | —                          | —        |
| Preoperative laboratory studies |         |                        |        |                            |          |
| Hemoglobin (g/dL)    | 12.4 ± 9.8          | 13.0 ± 1.5             | 0.333  | —                          | —        |
| Platelet count (K/µL) | 229.0 ± 29.2       | 233.9 ± 84.0           | 0.671  | —                          | —        |
| International normalized ratio | 1.0 ± 0.08   | 1.0 ± 0.06             | 0.660  | —                          | —        |
| Prothrombin time (seconds) | 11.9 ± 0.9   | 12.2 ± 0.9             | 0.382  | —                          | —        |
| Activated partial thromboplastin time (seconds) | 27.9 ± 4.1 | 29.6 ± 5.8 | 0.428 | — | — |
| Intraoperative rupture | 7 (87.5)    | 5 (9.3)                | <0.001 | 0.024 (0.002, 0.272) | 0.003 |
| Length of surgery (minutes) | 277.3 ± 88.0 | 176.9 ± 57.6          | 0.014  | 1.016 (0.998, 1.034) | 0.079 |

Data are mean ± standard deviation or n (%). P values were calculated by Student t test, Mann-Whitney U test, χ2 test, or Fisher exact test, as appropriate. *Multivariable logistic regression analysis included all variables significant at P < 0.10 in univariate analysis for the risk factors associated with allogeneic blood transfusion.
recommend early aneurysm within 3 days from initial hemorrhage, and in our study, 86.1% of patients received early aneurysm repair, which was consistent with the previous reports. The second research indicated that ANH was safe in neurosurgery. However, that study did not investigate the efficacy of ANH in the clipping surgery for patients with aSAH and it also included brain tumors. The third article was a case report that suggested the safety and efficacy of ANH in clipping surgery for a patient with atypical antibodies. However, its power of external validity is limited.

Our results indicated that ANH did not reduce the need for perioperative allogeneic blood transfusion. Intraoperative aneurysm rupture was the only independent predictor for blood transfusion. Because ANH did not affect the risk of intraoperative

Figure 2. Relationship of perioperative hemoglobin levels and functional outcome in patients with aneurysmal subarachnoid hemorrhage. (A) Student t test indicated that serum hemoglobin levels were significantly higher in acute normovolemic hemodilution (ANH) group than in non-ANH group on postoperative (Postop.) day 1 and day 3 (11.5 ± 2.5 g/dL vs. 10.3 ± 2.0 g/dL, \( P = 0.045 \); 12.1 ± 2.0 g/dL vs. 10.7 ± 1.3 g/dL, \( P = 0.002 \), respectively), and the preoperative (Preop) and intraoperative (Intraop) hemoglobin levels were likewise not different. (B) Only postoperative day 1 hemoglobin level was significantly associated with unfavorable outcome (11.4 ± 1.9 g/dL vs. 8.8 ± 2.0 g/dL, \( P < 0.001 \)), and hemoglobin levels tested at other indicated time points had no impact on functional outcomes.

mRS, modified Rankin Scale. (C) The areas under the curve of World Federation of Neurosurgical Societies (WFNS) grade and postoperative day 1 hemoglobin (Hb) level were 0.861 (95% confidence interval, 0.749–0.973) and 0.838 (95% confidence interval, 0.719–0.956), respectively, and their predictive powers of unfavorable outcome were not significantly different (Z = 0.275; \( P > 0.05 \)).

Table 4. Risks Associated with Unfavorable Outcomes

|                        | Univariate Analysis | Multivariable Analysis* |
|------------------------|---------------------|-------------------------|
|                        | Unfavorable (n = 16) | Favorable (n = 46) | \( P \) Value | Odds Ratio (95% Confidence Interval) | \( P \) Value |
| Age (years)            | 57.7 ± 9.9          | 55.0 ± 8.4             | 0.305 | — | — |
| Male                   | 7 (43.8)            | 19 (41.3)              | 0.864 | — | — |
| World Federation of Neurosurgical Societies grade I/II | 1 (6.25) | 26 (56.5) | <0.001 | 36.442 (2.175–610.481) | 0.012 |
| Fisher grade I/II      | 1 (6.25)            | 27 (58.7)              | <0.001 | 1.095 (0.236–5.075) | 0.908 |
| Estimated blood loss (mL) | 733.1 ± 731.4     | 350.0 ± 230.5          | 0.056 | 1.002 (0.998–1.006) | 0.388 |
| Preoperative hemoglobin level (g/dL) | 12.6 ± 1.3          | 13.0 ± 1.5             | 0.406 | — | — |
| Intraoperative hemoglobin level (g/dL) | 11.7 ± 1.3          | 12.4 ± 1.7             | 0.156 | — | — |
| Postoperative day 1 hemoglobin level (g/dL) | 8.8 ± 2.0           | 11.4 ± 1.9             | <0.001 | 0.895 (0.822–0.973) | 0.010 |
| Postoperative day 3 hemoglobin level (g/dL) | 10.8 ± 2.3          | 11.3 ± 1.5             | 0.405 | — | — |

Data are mean ± standard deviation or n (%). \( P \) values were calculated by Student t test, Mann-Whitney U test, \( \chi^2 \) test, or Fisher exact test, as appropriate.

*Multivariable logistic regression analysis included all variables significant at \( P < 0.10 \) in univariate analysis for predictors associated with unfavorable outcome.
aneurysm rupture, ANH did not increase the need for allogeneic blood transfusion. The return of autologous blood from ANH may be beneficial for maintaining hemodynamics, but it cannot help to stop the severe arterial bleeding. In contrast, ANH may facilitate hemostasis in major cancer resection because of preservation of coagulation factors.15-26 This factor may explain why ANH did not reduce the blood transfusion rate in aneurysm clipping surgery. Therefore, during the COVID-19 pandemic, coiling surgery should be considered as a preference to reduce allogeneic blood transfusion. If clipping surgery is unavoidable, clipping surgery should be performed by experienced neurosurgeons with a meticulous procedure to avoid intraoperative aneurysm rupture.

Our results also provided the first evidence that ANH significantly increased postoperative serum hemoglobin levels. Consistent with the previous report,27 serum hemoglobin levels on postoperative day 1 and day 3 were both significantly higher in the ANH group than in the non-ANH group. The increased hemoglobin levels may be caused by 1) withdrawing 400 mL of blood accompanying the intraoperative blood loss–stimulated erythropoiesis or 2) the return of 400 mL autologous blood in all patients in the ANH group significantly increased the serum hemoglobin level. However, there may be some other underlying mechanisms that warrant further investigation. Higher hemoglobin levels were reported to be associated with improved outcomes in patients with aSAH,27 and a mean hemoglobin level <11.1 g/dL during the hospital stay was suggested as a predictor for unfavorable outcome after acute SAH.28 However, we did not find a direct association between ANH and functional outcomes of patients with aSAH. This finding may be because the included number of 20 patients in the ANH group was too small to identify the patients who may benefit from ANH. To determine the potential indirect benefit of ANH in clipping surgery, we analyzed the association between postoperative hemoglobin levels and the clinical outcomes in the entire cohort. The results showed that serum hemoglobin level on postoperative day 1 was an independent risk factor for unfavorable outcome in patients with aSAH, and WFNS grade was the other independent risk factor. This finding was consistent with the previous report, which indicated that postoperative hemoglobin levels <10 g/dL were independently associated with poor outcomes in patients with early aneurysm repair.29 However, serum hemoglobin level on postoperative day 3 was not correlated with functional outcome in this cohort. This finding may be associated with a high blood transfusion rate on postoperative days 1–3, which undoubtedly increased the hemoglobin levels on postoperative day 3. WFNS grade was considered as the most powerful predictor for unfavorable outcomes.30 The predictive power of serum hemoglobin levels on postoperative day 1 was not different compared with that of WFNS grade by ROC curve analysis. ANH may indirectly improve functional outcomes through increase of postoperative serum hemoglobin levels in patients with aSAH who underwent early clipping surgery. A further prospective large-cohort study is warranted to confirm these findings.

Regarding the safety of ANH, there was no significant difference in both the frequency and spectrum of postoperative complications in the 2 groups. The complication rate in both the ANH group and the non-ANH group was consistent with the previous report.27 The proportion of patients with intracranial infection was higher in the ANH group than in the non-ANH group. However, the difference was not significant between the 2 groups, and the intracranial infection rate (10%) in the ANH group was not significantly different from that in the previous report (9.6%).31 The length of surgery and hospital length of stay were not significantly different between the 2 groups.

Limitations
First, the acute blood loss induced by ANH and surgical procedure may cause brain damage. However, the use of a mild volume of 400 mL ANH principally does not affect the hemodynamics, and patients with preoperative hemoglobin levels <10.0 g/dL were excluded in this study, which made ANH more secure. Second, the number of included patients was insufficient to identify small differences in functional outcomes. Third, although the transfusion protocol was established according to the guidelines,” a hemoglobin level cutoff of <8 g/dL for postoperative transfusion can be recommended.

CONCLUSIONS
ANH is safe but not effective in reducing perioperative allogeneic blood transfusion in clipping surgery for patients with aSAH. However, ANH may hold the potential to improve patients’ outcomes by increasing postoperative hemoglobin levels. Routine use of ANH should be considered in aneurysm clipping surgery.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT
Ping Chen: Conceptualization, Methodology, Formal analysis, Writing - original draft. Ying Wang: Data curation, Formal analysis, Writing - original draft. Xin-Huang Zhang: Data curation, Visualization, Investigation. De-Zhi Kang: Supervision, Validation. Xian-Zhong Lin: Project administration, Validation. Qing-Song Lin: Conceptualization, Writing - review & editing, Validation.

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