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Hyperbaric-Oxygen Therapy Improves Survival and Functional Outcome of Acute Severe Intracerebral Hemorrhage

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Background. Prognosis of spontaneous intracerebral hemorrhage (ICH) remains poor worldwide.

Aims of the study. To investigate the effect and optimal protocol for hyperbaric-oxygen therapy (HBOT), and reduce incidence of upper gastrointestinal bleeding (UGIB) in ICH.

Methods. This prospective, randomized, controlled trial included 565 patients with acute severe ICH. Participants were randomly assigned to a sham-control group (Group A) and four intervention groups: Groups B and C with 2.0 atmospheres absolute (ATA) pressure and HBOT exposure for 60 or 90 sessions, respectively; and Groups D and E with 1.5 ATA for 60 or 90 sessions, respectively. All patients received emergency craniotomy with hematoma evacuation. Outcome measures were modified Barthel Index (MBI) and modified Rankin Scale (mRS) scores, mortality rates at follow-up six months. UGIB rates were assessed as potential side effect.

Results. In four intervention groups, MBI and mRS scores were all significantly improved, and mortality rates were all significantly decreased compared with Group A (all $p < 0.005$). UGIB rates were 39.25, 60.00, 64.49, 36.79, and 34.26% in Groups A, B, C, D, and E, respectively. UGIB rates in Groups B and C were significantly increased compared with Groups A, D and E (all $p < 0.005$). None of UGIB were clinically significant.

Conclusions. HBOT significantly improves survival and functional outcomes of ICH. HBOT at 1.5 and 2.0 ATA had the same beneficial effect. A pressure of 1.5 ATA and 60 HBOT exposures represents an optimal protocol for HBOT. Further studies are needed to optimize the protocol per specific patient.

Key Words: Acute severe hypertensive intracerebral hemorrhage, Basal ganglia area, Craniotomy or decompressive craniectomy, Evacuation of hematoma, Hyperbaric-oxygen therapy, Upper gastrointestinal bleeding.

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Introduction

Spontaneous, nontraumatic acute intracerebral hemorrhage (ICH) is the most devastating, most lethal and most disabling type of stroke. This crucially important neurological and neurosurgical emergency affects several million people worldwide each year (1). Less than half (46%) of patients with ICH survive 1 year and less than a third (29%) survive 5 years (2).

Hyperbaric-oxygen therapy (HBOT) has been of increasing scientific interest. The primary focus of HBOT research fields has been stroke (3). For ICH, there have been fewer studies on HBOT. Several years ago, we initiated research on the use of HBOT for postoperative ICH patients. We found that HBOT was beneficial to the functional outcome, but the incidence of upper gastrointestinal bleeding (UGIB) or ''stress ulcer bleeding'' (SUB) was increased (4). In order to provide an adjunctive therapeutic method to effectively reduce the rates of disability and mortality of ICH patients, we conducted a prospective trial from January 2005−February 2015. In this trial, we investigated the effectiveness, appropriate length of therapy and appropriate pressure of HBOT in ICH patients, and how to reduce the incidence of UGIB.

Materials and Methods

Study Participants and Location

The data were obtained for patients admitted to the Department of Neurosurgery, Harrison International Peace Hospital (a third grade, first-class general hospital), which is affiliated to Hebei Medical University in Hengshui City, Hebei Province, People's Republic of China.

The study included 565 consecutive patients with acute severe hypertensive basal ganglia hemorrhage who received emergency craniotomy or decompressive craniectomy with simultaneous evacuation of hematoma immediately after admission. Participants were patients with a first stroke. The study protocol was approved by the Academic Committee and Ethics Committee of the Harrison International Peace Hospital. Written informed consent was provided by each participant or their legal surrogate prior to inclusion in the study, and this study was performed in accordance with the ethical standards adopted in the 1964 Declaration of Helsinki and its later amendments. Eligible participants attended clinic visits or were followed-up at the time of randomization (baseline) and at 2 month intervals for 6 months.

Inclusion Criteria

The inclusion criteria were as follows: (1) eligible patients were at least 18 years of age; (2) diagnosis was consistent with the diagnostic criteria for hypertensive intracerebral hemorrhage revised by the Fourth National Cerebrovascular Disease Conference (China) (5); (3) diagnosis was supported by computed tomography (CT) scan or magnetic resonance imaging (MRI), with location of hematoma in the basal ganglia area and hematoma volumes at least 50 cm^3 (a ''poor-outcome threshold'') (6) on admission; (4) patients with intracerebral hematoma occurring in only one location, namely the hemorrhage located on only one side of the basal ganglia region; (5) hospital admission within 6 h of symptom onset; (6) patients had a previous history of hypertension and systolic blood pressure (SBP) on admission was not higher than 220 mmHg; (7) vital signs were stable.

Exclusion Criteria

The first priority was to exclude absolute contraindications and relative contraindications for HBOT: (1) tension pneumothorax without treatment, bullous lung disease; (2) external ventricular drainage; (3) obstructive airway or restrictive airway disease, such as asthma, or emphysema with carbon dioxide retention; (4) heart rate below 50 beats per min, or electrocardiogram showed II degree and greater atrioventricular block; (5) high myopia, or any optic nerve or retinal disorder; (6) unstable seizure disorders; (7) Graves's disease or any thyroid disorder being treated with thyroid hormone and increased the metabolic rate; and (8) high fever (body temperature $\geq$39°C).

In addition, patients with the following conditions were excluded from the trial: (1) multiple localized ICH; (2) secondary ICH (for example, secondary to arteriovenous malformation, intracranial aneurysm, or tumor); (3) respiratory and circulatory failure; (4) severe heart, lung, liver, kidney and other major organ dysfunction; (5) medical history of nervous system diseases with neurological dysfunction sequelae; (6) significant mental retardation, psychoses, or other diseases affecting the patient's mental state; (7) recent history of trauma (especially fracture of the skull base with cerebrospinal fluid leakage) within three months; (8) cancer, autoimmune disorder, hemorrhagic disease, or tendency to bleed; (9) history of peptic ulcer; (10) pregnancy; and (11) membership in a transient population.

Trial Design

The study was a prospective single-center, double-blind, parallel-group-design, randomized sham-controlled trial.

Sample Size, Patient Randomization and Blinding

The following formula was used to determine the total sample size: $n = (t^2PQ)/d^2$. With an admissible error of 10%, n equals 400 (Q/P). According to prior research, because the incidence of UGIB (P) was 46.114% (89 of 193 patients) (4), n equaled 468 for this trial. Given an anticipated dropout rate of 10−20%, approximately 562 patients were required to be enrolled in the trial. Taking into account the

equal proportion grouping, a total sample size of approximately 565 patients was necessary. The patients were randomly assigned to one of the five parallel and equally-sized groups (in 1:1:1:1:1 ratio). There were 113 cases in each of the five groups: Groups A, B, C, D and E. Recruitment of this number of patients required a 10 year study period.

Consecutive patients enrolled in the study were numbered according to their order of admission. To randomize the 565 ICH patients into 5 parallel-groups, their serial numbers were entered into the Statistical Product and Service Solutions (SPSS) statistical package by an investigator with no clinical involvement in the trial and a randomization sequence was created. The patients were then randomly assigned to five parallel groups. The time of enrollment and randomization was the admission time. The allocation sequence was concealed from the researcher enrolling and assessing participants in sequentially numbered, opaque, sealed, stapled envelopes. According to admission order number, the corresponding envelopes were opened only after the enrolled participants had undergone all baseline assessments and it was time to allocate the intervention. Only hyperbaric chamber operators and the technologists who manipulated each patient's breathing mixture were aware of the allocated treatment arm. Participants and their family members, physicians, nurse practitioners and those assessing the outcomes of the trial, such as outpatient doctors or community doctors and data analysts, were kept blind to the treatment allocation.

General Management of Spontaneous ICH

Following hospital admission, maintained airway patency, stabilize respiration and circulation immediately, using mechanical ventilation if necessary. Confirm the diagnoses of ICH by emergent CT scan or MRI. Follow emergent neurosurgical consultation with rapid admission to a specialized neurosurgical intensive care unit (NSICU).

Control blood pressure to achieve SBP of 140 mmHg within 1 hour of randomization (reduce and maintain SBP in the range of 110–140 mmHg) (7–9). If the patient was using antiplatelet and antithrombotic agents these were discontinued and the effects were promptly reversed with appropriate platelet transfusion (10) and appropriate drugs. Institute active control intracranial hypertension, administer proton pump inhibitors (omeprazole) for stress-ulcer prophylaxis (all patients), prevention of venous thromboembolism, and supportive general management.

In view of the fact that most of the patients were at risk for cerebral herniation, all of them received immediate emergency craniotomy (or decompressive craniectomy) with simultaneous evacuation of hematoma completely through a trans-sylvian, transinsular approach. A drainage catheter was placed in the residual cavity. If there was postoperative re-bleeding, a re-craniotomy for hematoma evacuation was performed for patients with a re-bleeding volume exceeding 50 cm^3. Patients with a small amount of postoperative re-bleeding were treated by infusion of urokinase (fibrinolytic agent) (11,12) into the hematoma residual cavity through the drainage catheter to dissolve and remove the blood clots. A standardized three-stage rehabilitation program was begun as early as possible (13).

We generally initiated HBOT on the eighth day of ICH onset, namely the seventh day after surgery (HBOT was started at week 2 post-stroke).

Intervention Protocols and Operating Procedures of HBOT

HBOT was administered in an air-filled, multiperson medical hyperbaric chamber. Group A was the sham-control group and other four groups were intervention groups. Treatment pressure of HBOT and the exposure numbers were as follows: Group B 2.0 atmospheres absolute (ATA), 60 pressure exposures (2 cycles of HBOT); Group C 2.0 ATA, 90 pressure exposures (3 cycles of HBOT); Group D 1.5 ATA, 60 pressure exposures; Group E 1.5 ATA, 90 pressure exposures. For detailed procedures, see as follows.

Group A: Exposures had 15 min of uniform compression followed by 70 min of room air inhalation. For patient blinding purposes, patients underwent a brief compression to reach a pressure of 1.34 ATA (5 pounds per square inch, gauge, [psig]) at the initiation of each exposure session. The chamber was then slowly uniformly decompressed from 1.34–1.0 ATA (normal room pressure) within 15 min. Room air (21% oxygen) was breathed in via a tight-fitting face mask, hood, or endotracheal tube with a simulated 10 min air break at 30 min intervals. Patients left the chamber after another 15 min under normal pressure (1.0 ATA), equivalent to the decompression time of the intervention groups. Multiperson chambers were pressurized and decompressed with room air. The period (length of stay) in the chamber at each exposure was 100 min for all patients in the five study groups. A complete intervention cycle comprised 30 exposures: once daily for 5 consecutive days per week (week days only) for a total of 6 consecutive weeks. The cycle was repeated for an intermission of one week (7d). A total of 90 exposures, namely three cycles. The treatment cycle programs were identical for the 5 groups.

Group B: Exposures had 15 min of slow uniform compression after which the chamber was pressurized to reach the desired pressure of 2.0 ATA (treatment pressure) and constant pressure was maintained for 70 min. Pure oxygen (100% oxygen) was breathed in via a tight-fitting face mask, hood, or endotracheal tube twice for 30 min each, and the air in the chamber was breathed in for 10 min in between to reduce oxygen toxicity. Patients were taken out of the chamber after 15 min of slow uniform

decompression to reach 1.0 ATA. That is, the total oxygen breathing time in each pressure exposure was 60 min with a 10 min air break at 30 min intervals. There were 60 pressure exposures with hyperbaric-oxygen (two cycles). Other procedures and the third cycle procedure was the same as that in Group A.

Group C: The HBOT procedure was almost the same as that in Group B, but there were 90 pressure exposures with hyperbaric-oxygen (three cycles).

Group D: The HBOT procedure was almost the same as that in Group B, but the treatment pressure was 1.5 ATA. Altogether there were 60 pressure exposures at 1.5 ATA (two cycles).

Group E: The HBOT procedure was almost the same as that in Group C, but the treatment pressure was 1.5 ATA. Altogether there were 90 pressure exposures at 1.5 ATA (three cycles).

HBOT was suspended if there UGIB (or ''SUB'') occurred. Three different kinds of stress-related mucosal bleeding (namely UGIB) might occur in patients with ICH: occult gastrointestinal bleeding (GIB), overt GIB and clinically important GIB (14−17). For management and controlled (or stopped) criterion of UGIB, see below. UGIB in most of the patients were controlled for 3 or 4 d and the longest controlled time was 5 d, and the HBOT could be continued. Thus, the schemes of HBOT were completed in accordance with the randomly-assigned intervention program.

Outcome Measures

Outcome measures were mortality rates in four time periods, and overall mortality rates, the modified Barthel Index (MBI) score and the modified Rankin Scale (mRS) score at the six month follow-up after randomization of each group. As potential side effect of HBOT, UGIB rates in four time periods and overall UGIB rates at the six month follow-up of each group were assessed. The four time periods were as follows: the first phase (within 7 d onset of ICH); the second phase (weeks 2−8, the first cycle period of HBOT); the third phase (9−15 weeks, the second cycle); the fourth phase (16−21 weeks, the third cycle). The volumes of parenchymal hematoma were estimated using a computerized planimetric method and a simplified formula (Coniglobus formula) for the volume of an ellipsoid: ABC/2.

The predicted primary outcome was that the MBI scores and the mRS scores in the four intervention groups would be different (significantly improved) compared to Group A. The predicted secondary outcome was that the mortality rates in the four intervention groups would all be different (significantly decreased) compared to Group A. We expected that the UGIB rates of patients who received HBOT at the pressure of 2.0 ATA (Groups B and C) would be different (significantly increased) compared to the sham-control group (Group A) and that the UGIB rates of patients who received HBOT at the pressure of 1.5 ATA (Groups D and E) would be similar to Group A. Thus, we could reduce the treatment pressure and shorten the length of HBOT without increasing the rates of UGIB, promote the postoperative functional recovery of ICH patients through HBOT, and also reduce the side effects and risks of higher pressure.

Management and Controlled Criterion for UGIB

Early and sufficient fluid administration, blood transfusion when really required; adequate therapy to inhibit acid secretion (proton pump inhibitors-omeprazole, all patients). Endoscopic or surgical hemostasis was undertaken, if necessary.

Occult blood test was negative in fasting gastric juice from nasogastric tube or stool for 3 consecutive days.

Statistical Analysis

Statistical analysis and comparisons were performed using the SPSS 18.0 statistical package (IBM). The MBI scores, mRS scores, number of deaths, and numbers of UGIB case in the 5 groups were analyzed and compared through analysis of variance (ANOVA), the least-significant difference (LSD) *t*-test, the χ^2 test, and the rank-sum test. Multiple pairwise comparisons increased the chance of a Type I error, namely an increase in the rate of false-positive results. Thus, the level of the tests was adjusted such that $\alpha' = \alpha$/the number of comparisons, and because there were 10 pairwise comparisons in the trial, $p < 0.005$ indicated statistical significance and $p < 0.001$ indicated a highly significant difference.

Results

Study Participants

The Patient Flow Chart is shown in (Figure 1). A total of 719 patients were screened from January 2005−February 2015, of whom 132 cases ineligible and 16 cases met the inclusion criteria but declined to be enrolled. The remaining 571 patients were eligible and consented to enter the trial, but 6 cases refused surgery. At the end of the pre-planned 10 year period, we reached the goal sample size and 565 eligible patients were successfully registered in the trial.

During the study, HBOT was discontinued in a total of 32 cases in the 5 groups due to noncompliance (intolerance) with trial protocols, or changes in the patient's condition (such as worsening of neurological status). Thus, the numbers of patients unsuitable to continue HBOT and terminated were: 6, 8, 6, 7 and 5 patients, respectively, from Groups A, B, C, D and E. By further excluding deaths, the total number of patients who completed the full course of HBOT according to the prearranged protocol was 445 of the initial 565 cases: 71, 90, 90, 97 and 97 in Groups A, B, C, D and E, respectively. We followed all surviving

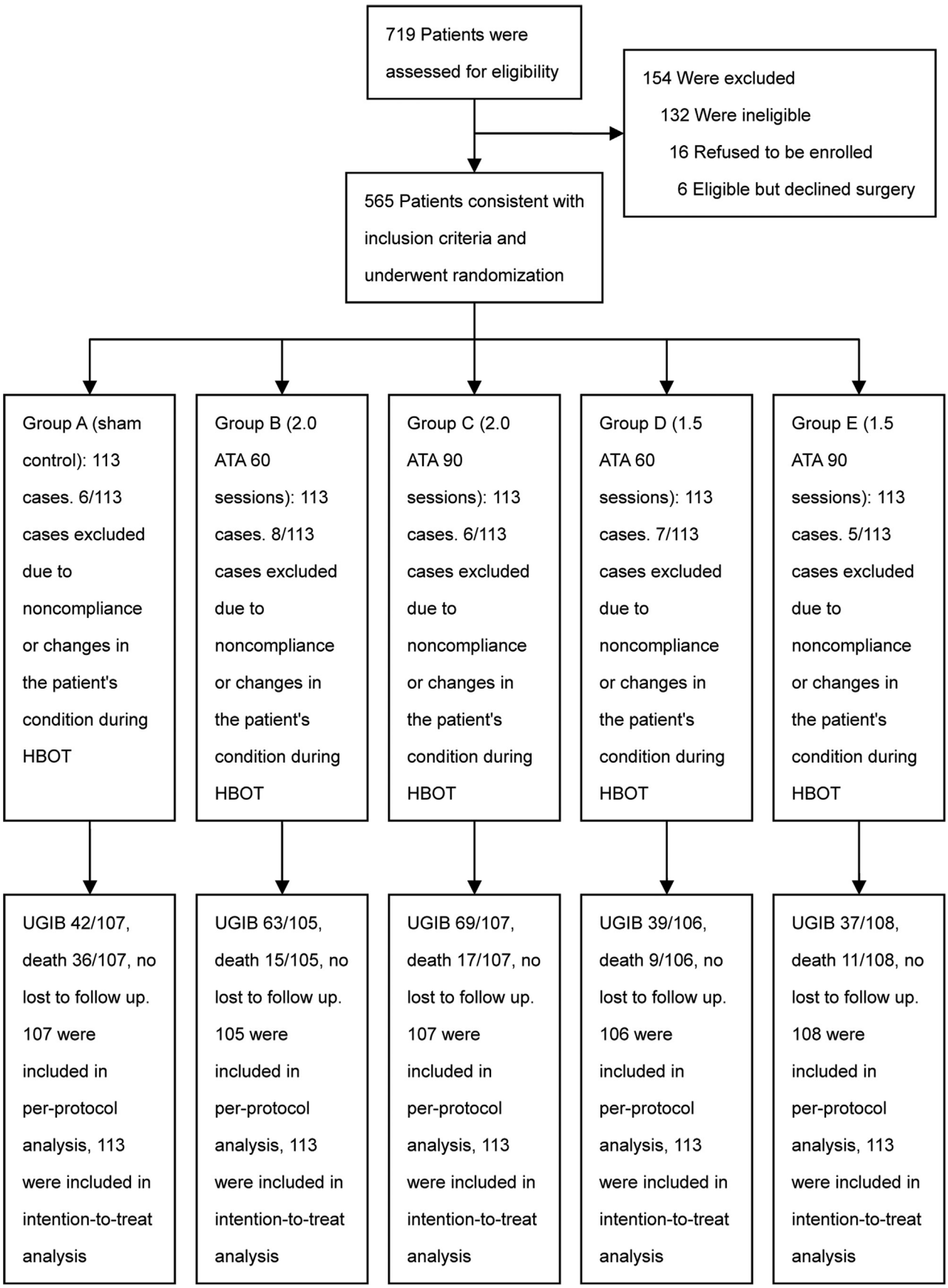

Figure 1. Patient Flow Chart. ATA, atmospheres absolute; HBOT, hyperbaric-oxygen therapy; UGIB, upper gastrointestinal bleeding.

patients for 6 months as planned, and no further cases were lost.

Among the 250 patients with UGIB there was only one bleeding episode. No patients experienced repeated bleeding. In addition, during the period after the end of three cycles of HBOT to 6 months postoperatively when the overall outcome was evaluated, there were no UGIB cases and death cases in the 5 groups.

The baseline data for each group are shown in (Table 1). The baseline characteristics were balanced between the 5 groups.

Per-Protocol Analysis

The per-protocol analysis included 533 patients: Group A, 107; Group B, 105; Group C, 107; Group D, 106; and Group E, 108. The number of cases of UGIB and deaths in the four time periods in each group are shown in detail in (Table 2). UGIB occurred in a total of 250 of 533 (46.904%) patients. Death occurred in 88 (16.510%) of 533 patients. The MBI and the mRS scores in each group are shown in (Table 2 and Figure 2). The detailed results of the statistical analysis and multiple comparisons of UGIB incidence, mortality rates, and the two kinds of scores are shown in (Tables 2 and 3). There were significant differences among the 5 groups in the UGIB rates and mortality rates within the second phase (the first cycle period of HBOT), as well as the total UGIB rates, total mortality rates, MBI scores, and mRS scores (Tables 2 and 3) detailly. The total mortality rates in the 5 groups are presented in (Figure 3).

Intention-To-Treat Analysis

The intention-to-treat analysis included all 565 patients enrolled in the trial, 113 patients in each of the five groups. UGIB was considered to have occurred in the cases of the HBOT termination in which noncompliance (intolerance) or changes in the patient's condition made it unsuitable to continue HBOT, and the time of exclusion was considered to be the time at which UGIB occurred. MBI and mRS scores at the time of exclusion were used for statistical analysis. In Group A there were 6 of 113 cases; 2 of these patients survived and 4 died. In Group B, there were 8 of 113 cases; 5 survived and 3 died. In Group C, there were 6 of 113 cases; 3 survived and 3 died. In Group D, there were 7 of 113 cases; 4 survived and 3 died. Finally, in Group E, there were 5 of 113 cases; 2 survived and 3 died.

There were a total of 282 UGIB cases (49.912%) in the 565 patients. The total number of deaths in the 5 groups was 104 (18.407%) of 565 patients. The numbers of cases of UGIB and deaths in the four time periods in each group, and total cases of UGIB and deaths are shown in detail in (Table 4). The MBI and the mRS scores in each group are shown in (Table 4 and Figure 2). The detailed results of statistical analysis and multiple comparisons of UGIB incidence, mortality rates, MBI and mRS scores are shown in (Tables 4 and 5). There were significant differences among the 5 groups in the UGIB and mortality rates within the second phase (the first cycle period of HBOT), as well as the total UGIB rates, total mortality rates, MBI scores, and mRS scores. For details, (Tables 4 and 5). The total mortality rates in the 5 groups are shown in (Figure 3).

Outcomes

The primary outcome was the MBI and mRS scores obtained at the 6 month postoperative follow-up in Groups B, C, D and E were significantly improved compared with Group A; about 13−19 points higher in MBI scores, and about 0.8−1.2 points lower in mRS scores. There were no significant between-group differences in Groups B, C, D and E. For the MBI and mRS scores, Groups B and C had the superior trend compared with Groups D and E. Compared to Group B, Group C had the superior trend, and compared to Group D, Group E had the superior trend.

The secondary outcome was the mortality rates within Phase 2 and the total mortality rates at the 6 month postoperative follow-up. Rates in Groups B, C, D and E were all significantly decreased compared with Group A. A decrease approximately 17−25% in the total mortality rates. There were no significant between-group differences among Groups B, C, D and E in the mortality rates within Phase 2 and the total mortality rates. Within the Phase 1, Phase 3 and Phase 4, all mortality rates were not significantly different among the five groups.

As potential side effect of HBOT, the UGIB rates within the second phase and the total UGIB rates in Groups B and C were significantly increased compared to those in Groups A, D and E, an increase of approximately 20% in the total UGIB rates. There were no significant between-group differences in Groups B and C, and among Groups A, D and E. Within the first phase, the third and fourth phase, UGIB rates were not significantly different among the five groups. Clinically important GIB resulting in hemodynamic instability never occurred during HBOT.

Adverse Effects and Risk of HBOT

Common side effects and risks of HBOT mainly include barotrauma, central nervous system- and pulmonary oxygen toxicity, claustrophobia, anxiety and visual disturbances (18); in addition, decompression illness, pneumothorax, and bradycardia and so on. None of these events occurred during HBOT in the current trial.

Two patients experienced grand mal epileptic seizures before entering the hyperbaric chamber, and HBOT was terminated before completing the intervention protocol. These events were considered to be related to emotion and the brain damage resulting from ICH rather than HBOT-related oxygen toxicity. Five female patients occasionally sweated more during exposures, but there was no

Table 1. Baseline characteristics of study participants

Characteristic	Group A (N = 113)	Group B (N = 113)	Group C (N = 113)	Group D (N = 113)	Group E (N = 113)	Values of statistics	p
Time from onset of ICH to randomization (hours)[a]						0.363	0.835
Median (IQR; range)	4.00 (3.00−5.00; 1−6)	4.00 (3.00−5.00; 1−6)	4.00 (3.00−5.00; 1−6)	4.00 (3.00−5.00; 1−6)	4.00 (3.00−5.00; 1−6)		
Age (years)[a]						0.489	0.744
Median (IQR; range)	58.00 (52.50−65.00; 23−92)	58.00 (50.00−66.00; 28−91)	59.00 (52.00−67.00; 38−91)	60.00 (50.50−66.00; 35−95)	59.00 (53.00−66.00; 28−83)		
Male sex (N, %)[b]	63 (55.75)	66 (58.41)	73 (64.60)	68 (60.18)	70 (61.95)	1.796	0.773
SBP (mmHg)[a]						0.465	0.761
Median (IQR; range)	176.00 (162.00−198.00; 140−220)	180.00 (163.00−200.00; 141−220)	178.00 (161.00−203.00; 142−220)	176.00 (158.00−199.50; 141−220)	175.00 (161.00−194.00; 140−220)		
DBP (mmHg)[a]						0.300	0.878
Median (IQR; range)	108.00 (101.00−124.50; 90−149)	110.00 (102.50−122.00; 91−150)	108.00 (101.50−120.50; 91−148)	108.00 (98.00−121.00; 90−149)	108.00 (100.50−121.00; 90−150)		
GCS scores[a]						0.458	0.766
Median (IQR; range)	9.00 (5.00−12.00; 3−15)	9.00 (5.00−12.00; 3−15)	9.00 (5.50−12.00; 3−15)	9.00 (6.00−12.00; 3−15)	8.00 (6.00−11.00; 3−15)		
NIHSS score[a]						0.581	0.676
Median (IQR; range)	11.00 (6.50−14.50; 0−42)	10.00 (5.50−14.00; 0−41)	10.00 (5.00−14.50; 0−42)	10.00 (4.00−14.00; 0−42)	9.00 (4.00−14.00; 0−42)		
History of hypertension (years)[a]						0.378	0.824
Median (IQR; range)	8.00 (3.50−13.00; 1−24)	8.00 (4.00−14.50; 1−24)	9.00 (4.00−15.00; 1−25)	9.00 (4.00−14.00; 1−24)	9.00 (4.00−13.50; 1−25)		
Diabetes mellitus (N, %)[b]	35 (30.97)	37 (32.74)	33 (29.20)	39 (34.51)	31 (27.43)	1.653	0.799
Hematoma volume (cm^3)[a]						0.548	0.701
Median (IQR; range)	83.00 (66.00−95.00; 50−140)	81.00 (66.00−94.50; 50−139)	78.00 (65.00−95.50; 50−138)	76.00 (63.50−94.50; 50−140)	76.00 (65.50−98.50; 50−138)		
Intraventricular extension (N, %)[b]	54 (47.79)	56 (49.56)	58 (51.33)	48 (42.48)	51 (45.13)	2.240	0.692
Left side of hematoma[b]	57 (50.44)	62 (54.87)	55 (48.67)	59 (52.21)	52 (46.02)	2.050	0.727

DBP, diastolic blood pressure; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; IQR, interquartile range; N, number patients; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure.

For continuous variables, data were median (IQR; range); for categorical variables, data were number (%).

[a]Analysis of variance (ANOVA), Statistic is F.

[b]Rank-sum test (Kruskal-Wallis test), Statistic is H.

Table 2. Primary and secondary outcomes and preliminary statistical analysis (Per-Protocol analysis)

Characteristic	Group A ($N = 107$)	Group B ($N = 105$)	Group C ($N = 107$)	Group D ($N = 106$)	Group E ($N = 108$)	Values of statistics	p
The first week (N)[a]							
UGIB	11	10	9	12	9	0.795	0.939
Death	5	4	4	2	3	1.494	0.828
Weeks 2−8 (N)[a]							
UGIB	14	31	34	10	13	31.662	0.000
Death	23	6	8	5	4	30.096	0.000
Weeks 9−15 (N)[a]							
UGIB	9	12	14	11	8	2.382	0.666
Death	4	3	4	1	2	3.366	0.499
Weeks 16−21 (N)[a]							
UGIB	8	10	12	6	7	3.754	0.440
Death	4	2	1	1	2	4.588	0.332
6 months (total N, %)[a]							
UGIB	42/107 (39.25)	63/105 (60.00)	69/107 (64.49)	39/106 (36.79)	37/108 (34.26)	34.314	0.000
Death	36/107 (33.64)	15/105 (14.29)	17/107 (15.89)	9/106 (8.49)	11/108 (10.19)	31.277	0.000
MBI scores[b]						6.183	0.000
Mean ± SD (95% CI)	38.27 ± 24.598 (32.45, 44.09)	55.48 ± 28.096 (49.59, 61.36)	57.50 ± 27.813 (51.67, 63.33)	51.79 ± 25.913 (46.57, 57.02)	53.23 ± 25.532 (48.08, 58.37)		
Median (IQR; range)	34.00 (20.00−52.00; 1−96)	54.00 (34.00−80.25; 2−100)	54.00 (34.00−86.50; 3−100)	52.00 (34.00−73.50; 2−100)	52.00 (34.00−75.00; 2−100)		
mRS scores[b]						9.774	0.000
Mean ± SD (95% CI)	4.47 ± 1.449 (4.19, 4.75)	3.38 ± 1.717 (3.05, 3.71)	3.24 ± 1.747 (2.91, 3.58)	3.58 ± 1.498 (3.30, 3.87)	3.45 ± 1.608 (3.15, 3.76)		
Median (IQR; range)	5.00 (4.00−6.00; 1−6)	3.00 (2.00−5.00; 0−6)	3.00 (2.00−4.00; 0−6)	4.00 (3.00−5.00; 0−6)	4.00 (2.00−5.00; 0−6)		

CI, confidence intervals; IQR, interquartile range; MBI, modified Barthel Index; mRS, modified Rankin Scale; N, number patients; SD, standard deviation; UGIB, upper gastrointestinal bleeding.
[a]χ^2 Tests, Statistic is χ^2.
[b]Analysis of variance (ANOVA), Statistic is F.

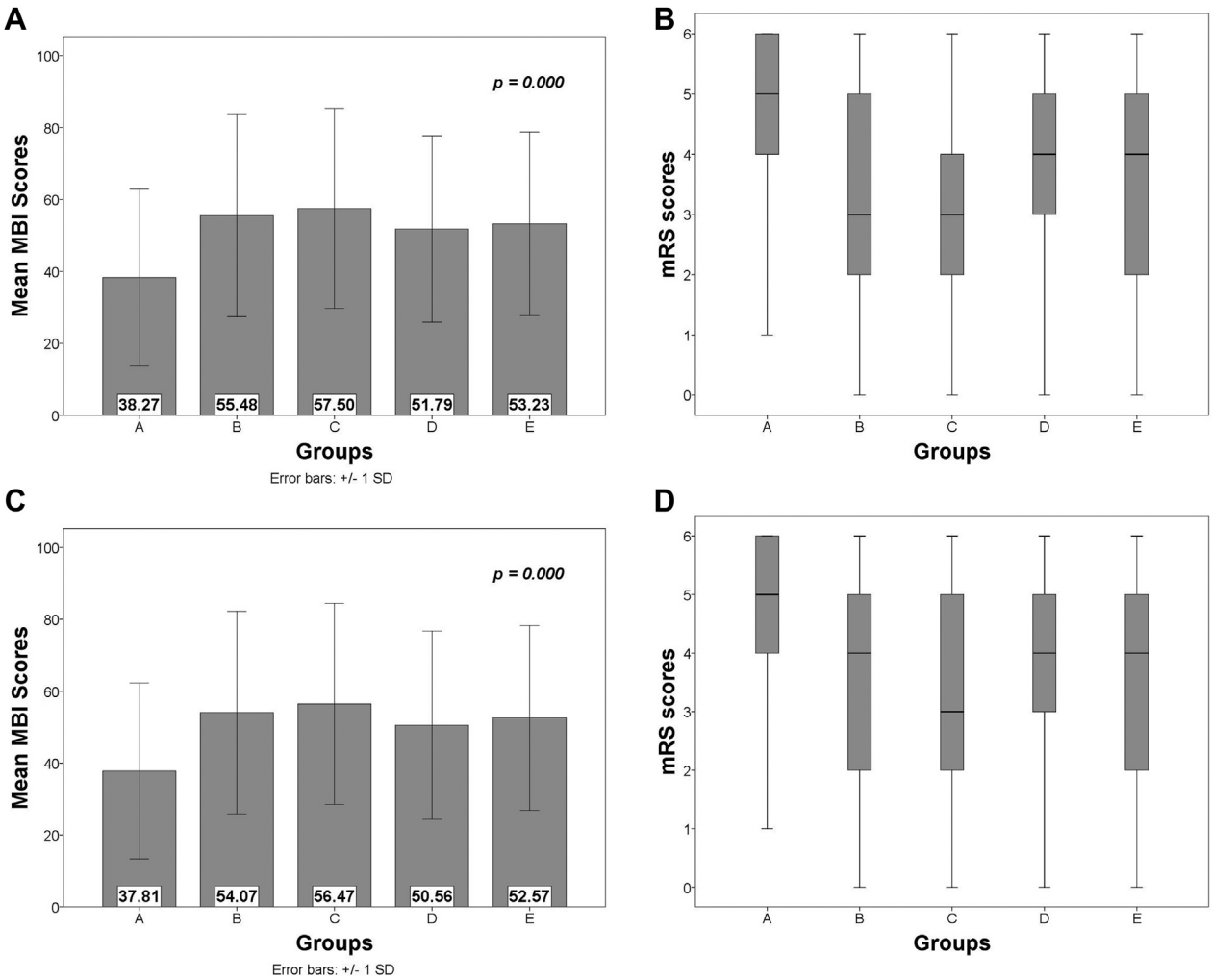

Figure 2. MBI scores and mRS scores at the 6 month follow-up after randomization. Simple bar charts (Mean with SD) show centralization trend and dispersion degree of data, box-and-whisker plots show data distributions: (A and B) per-protocol analysis; (C and D) intention-to-treat analysis. The *p* values indicated that there were significant differences among the population means of 5 groups. MBI, modified Barthel Index; mRS, modified Rankin Scale; SD, standard deviation.

Table 3. Further statistical analysis in pairwise comparisons (Per-Protocol analysis)

	Intergroup comparison									
Characteristic	**A & B**	**A & C**	**A & D**	**A & E**	**B & C**	**B & D**	**B & E**	**C & D**	**C & E**	**D & E**
Weeks 2−8 UGIB rate[a]										
χ^2	8.468	10.628	0.845	0.082	0.126	14.227	10.277	16.921	12.651	0.408
p (two-sided)	0.004	0.002	0.392	0.838	0.765	0.000	0.002	0.000	0.000	0.659
Weeks 2−8 mortality rate[a]										
χ^2	11.432	8.725	13.801	16.019	0.266	0.130	0.506	0.770	1.498	0.126
p (two-sided)	0.001	0.003	0.000	0.000	0.783	0.767	0.532	0.407	0.249	0.748
Total UGIB rate[a]										
χ^2	9.126	13.645	0.137	0.577	0.454	11.377	14.163	16.339	19.647	0.150
p (two-sided)	0.004	0.000	0.778	0.481	0.571	0.001	0.000	0.000	0.000	0.775
Total mortality rate[a]										
χ^2	10.871	9.054	20.220	17.317	0.106	1.757	0.835	2.719	1.543	0.181
p (two-sided)	0.001	0.004	0.000	0.000	0.848	0.201	0.407	0.142	0.231	0.815
MBI scores[b]										
LSD-*t*	−17.210	−19.232	−13.526	−14.959	−2.022	3.684	2.251	5.706	4.273	−1.433
p	0.000	0.000	0.000	0.000	0.609	0.342	0.562	0.142	0.271	0.706
mRS scores[b]										
LSD-*t*	1.086	1.224	0.882	1.014	0.138	−0.204	−0.073	−0.342	−0.211	0.131
p	0.000	0.000	0.000	0.000	0.533	0.357	0.741	0.121	0.337	0.551

LSD, least-significant difference; MBI, modified Barthel Index; mRS, modified Rankin Scale; UGIB, upper gastrointestinal bleeding.
[a]χ^2 Tests.
[b]Analysis of variance (ANOVA).

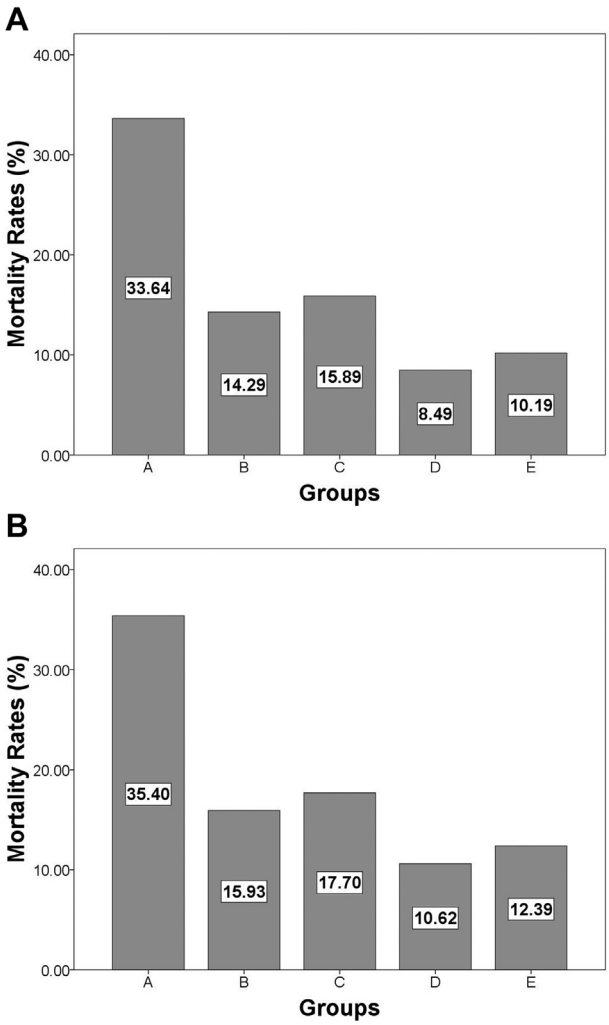

Figure 3. Mortality rates in five groups at the 6 month follow-up after randomization. (A) per-protocol analysis; (B) intention-to-treat analysis.

significant effect on HBOT. Some patients who had undergone decompressive craniectomy had bone-window depression or swelling, but there was no obvious adverse reaction.

Discussion

ICH remains a significant cause of disability and mortality throughout the world. Despite considerable research effort, progress has been slow in finding a safe and widely available acute treatment for ICH that reduces stroke-related disability (19) and treatment at present remains mainly supportive (20). ICH accounted for a larger proportion of strokes in Chinese than whites (33 vs. 12%) (21). The incidence rate of ICH in China is much higher than the worldwide incidence (66.2 vs. 24.6 per 100 000 person-years) (22,23). Therefore, ICH is an important disease endangering the health of individuals worldwide, especially the Chinese. Thus, further research on therapeutic measures poses a challenging clinical and public health problem for neurosurgeons and neurologists.

The essential base of the recovery after acute brain injury was stunned brain regions that are dysfunctional but sublethal in the vicinity of ICH. These non-active (dormant) regions may remain dysfunctional for 6−9 months postictus, or even longer (24). Repair/regeneration mechanisms are all energy/oxygen dependent. HBOT enables the necessary metabolic changes by supplying the missing energy/oxygen needed for regeneration (25).

HBOT can significantly increase the oxygen partial pressure of brain tissue, improve oxygen supply and tissue oxygenation (26−28). However, the effects of hyperbaric-oxygenation cannot be explained simply as a compensation of the oxygen deficit. Hyperbaric-oxygen has a variety of other, much broader and more complex mechanisms of action. The clinical efficacy of hyperbaric-oxygen derives from modulation of intracellular transduction cascades, alteration of protein expression, and modulation of signaling pathways that affect vascular structure and function, lead to synthesis of growth factors, promote wound healing and ameliorate post-ischemic and post-inflammatory injuries (29,30).

HBOT has obvious curative effect on all of the multiple steps along the brain injury path caused by ICH, such as reduce microglia activation (31); inhibit excessive release of excitatory amino acid (32); improve mitochondrial function (in both neurons and glial cells) and cellular metabolism, reduce neuronal apoptosis, alleviate oxidative stress, promote blood-brain barrier integrity, relieve cerebral edema and decrease intracranial pressure (33,34); attenuated neuroinflammatory processes (35,36); maintain the balance between oxidative and antioxidant systems in brain tissue (37).

It is worth emphasizing that HBOT also has a even further neuroprotective effect. Including effectively operate and activate neural plasticity (reactivations of neuronal activity in the stunned areas; inhibition of Nogo-A, an endogenous growth-inhibitory factor; creation of new synapses and new axonal connections, and so on); lead to neovascularization, induce cerebral angiogenesis and improve both white and gray microstructures indicating regeneration of nerve fibers (25,29,33,38,39). Neuroplasticity was thought to be a substrate for recovery after brain damage (40). HBOT can promote neurogenesis of the endogenous neural stem cells (in the mature human brain, the presence of stem cells has been found and neuropoiesis is an established phenomenon) (34,41,42); promote more stem/progenitor cells production and mobilization from the bone marrow of humans into the systemic circulation, and home to injuries and accelerate healing (peripheral stem cells were known to cross the blood-brain barrier into the brain and formed new neurons, astrocytes, and microglia); stimulate neurogenesis, orchestrated gliosis and trophic factor production (35,43−46); and so on.

Table 4. Primary and secondary outcomes and preliminary statistical analysis (Intention-to-Treat analysis)

Characteristic	Group A ($N = 113$)	Group B ($N = 113$)	Group C ($N = 113$)	Group D ($N = 113$)	Group E ($N = 113$)	Values of statistics	p
The first week (N)[a]							
UGIB	11	10	9	12	9	0.733	0.947
Death	5	4	4	2	3	1.492	0.828
Weeks 2−8 (N)[a]							
UGIB	16	35	37	13	15	30.742	0.000
Death	25	7	9	5	6	30.094	0.000
Weeks 9−15 (N)[a]							
UGIB	12	15	16	13	10	2.221	0.695
Death	5	4	6	3	3	2.456	0.653
Weeks 16−21 (N)[a]							
UGIB	9	11	13	8	8	2.812	0.590
Death	5	3	1	2	2	5.432	0.246
6 months (total N, %)[a]							
UGIB	48/113 (42.48)	71/113 (62.83)	75/113 (66.37)	46/113 (40.71)	42/113 (37.17)	33.459	0.000
Death	40/113 (35.40)	18/113 (15.93)	20/113 (17.70)	12/113 (10.62)	14/113 (12.39)	29.509	0.000
MBI scores[b]						5.870	0.000
Mean ± SD	37.81 ± 24.473	54.07 ± 28.179	56.47 ± 27.983	50.56 ± 26.195	52.57 ± 25.719		
(95% CI)	(32.10, 43.52)	(48.33, 59.81)	(50.71, 62.24)	(45.39, 55.74)	(47.44, 57.70)		
Median (IQR; range)	32.00 (19.50−51.50; 1−96)	53.00 (33.00−78.00; 2−100)	54.00 (34.00−86.00; 3−100)	51.00 (33.00−69.50; 2−100)	52.00 (34.00−74.00; 2−100)		
mRS scores[b]						9.395	0.000
Mean ± SD	4.52 ± 1.440	3.49 ± 1.722	3.35 ± 1.767	3.68 ± 1.513	3.54 ± 1.631		
(95% CI)	(4.25, 4.79)	(3.17, 3.81)	(3.02, 3.67)	(3.40, 3.96)	(3.24, 3.84)		
Median (IQR; range)	5.00 (4.00−6.00; 1−6)	4.00 (2.00−5.00; 0−6)	3.00 (2.00−5.00; 0−6)	4.00 (3.00−5.00; 0−6)	4.00 (2.00−5.00; 0−6)		

CI, confidence intervals; IQR, interquartile range; MBI, modified Barthel Index; mRS, modified Rankin Scale; N, number patients; SD, standard deviation; UGIB, upper gastrointestinal bleeding.
[a] χ^2 Tests, Statistic is χ^2.
[b] Analysis of variance (ANOVA), Statistic is F.

Table 5. Further statistical analysis in pairwise comparisons (Intention-to-Treat analysis)

Characteristic	Intergroup comparison									
	A & B	A & C	A & D	A & E	B & C	B & D	B & E	C & D	C & E	D & E
Weeks 2−8 UGIB rate[a]										
χ^2	9.026	10.755	0.459	0.062	0.083	13.415	10.605	15.480	12.471	0.185
p (two-sided)	0.004	0.001	0.553	0.848	0.886	0.000	0.001	0.000	0.000	0.691
Weeks 2−8 mortality rate[a]										
χ^2	12.072	9.104	16.094	13.986	0.270	0.392	0.092	1.300	0.674	0.105
p (two-sided)	0.001	0.003	0.000	0.000	0.796	0.567	0.784	0.282	0.437	0.768
Total UGIB rate[a]										
χ^2	9.389	13.004	0.073	0.665	0.310	11.076	14.885	14.960	19.299	0.298
p (two-sided)	0.003	0.000	0.893	0.497	0.677	0.001	0.000	0.000	0.000	0.682
Total mortality rate[a]										
χ^2	11.226	9.076	19.583	16.449	0.127	1.384	0.582	2.330	1.246	0.174
p (two-sided)	0.001	0.004	0.000	0.000	0.859	0.327	0.568	0.181	0.352	0.835
MBI scores[b]										
LSD-*t*	−16.265	−18.665	−12.756	−14.757	−2.399	3.509	1.508	5.909	3.907	−2.001
p	0.000	0.000	0.002	0.000	0.537	0.357	0.693	0.123	0.310	0.595
mRS scores[b]										
LSD-*t*	1.035	1.177	0.841	0.982	0.142	−0.195	−0.053	−0.336	−0.195	0.142
p	0.000	0.000	0.000	0.000	0.511	0.367	0.805	0.119	0.367	0.511

LSD, least-significant difference; MBI, modified Barthel Index; mRS, modified Rankin Scale; UGIB, upper gastrointestinal bleeding.
[a]χ^2 Tests.
[b]Analysis of variance (ANOVA).

The landmark investigation of Holbach KH et al. established the ideal HBOT pressure at 1.5 ATA (47). Breathing 100% oxygen at excess pressure (such as 2.4 ATA) should generate very high oxygen levels in tissues, which can cause an inhibitory effect or even focal toxicity (33). Therefore, we only carried out our trial with two pressures (1.5 ATA and 2.0 ATA).

The minimal pressure for the patients to sense a pressure increase was 1.3 atmospheres (33,48). Experienced divers cannot discriminate chamber pressures of 1.2 and 1.5 ATA nor if they are breathing air or oxygen (49). In our study design, patients in the sham-control group underwent a brief compression to reach a pressure of 1.34 ATA and then slowly decompressed to normal pressure. This not only ensured the implementation of blinding, but also reduced the impact of increased pressure on the results of the study as far as possible.

Further Explanation of Principal Findings

a) HBOT increases parasympathetic (vagal) activity in a dose-dependent manner (50,51). This induces gastric hypercontractility, which might result in excessive mechanical rubbing of gastric mucosa (52) and effectively reduce or stop gastric mucosal blood flow by mechanical compression, causing mechanical breaks at fold points in the gastric epithelium (53,54) as well as gastric hypersecretion of acid and pepsin. This might promote the occurrence of UGIB. During Phase 2, combined with the patients were in high stress states, thus, an increase in the rate of UGIB was inevitable. After the pressure was reduced, the degree of gastric hypersecretion and gastric hypermotility due to HBOT was reduced accordingly. This might be the reason why there was no increase in the rate of UGIB in the 1.5 ATA groups during Phase 2.
b) With the prolongation of time, after the stress states had gradually relieved, namely during the second and the third cycle period of HBOT, the UGIB rates in the intervention groups were not increased. It could be explained that the gastric acid hypersecretion and gastric hypermotility due to the single HBOT were not enough to cause UGIB, the stimulation intensity of the vagus nerve by HBOT was limited. This further illustrates that UGIB as a potential side effect of HBOT is of minor.
c) There was a lower risk of clinically important GIB caused by HBOT, but this possibility could not be completely ruled out. Therefore, for patients with severe ICH, the application of a pressure of 2.0 ATA or higher should be avoided as far as possible during HBOT. Especially during Phase 2, treatment pressure should be appropriately reduced.
d) HBOT could significantly improve survival and functional outcomes in ICH patients after open cranial surgery. The improvement of neurological function scores was not significantly different between 1.5 ATA and 2.0 ATA groups, but the outcome at the pressure of 2.0 ATA showed a superior trend compared with 1.5 ATA. These were consistent with the report of Eschenfelder CC et al. that the neuroprotective effect of hyperbaric-oxygenation was dose dependent

(55). It also suggested that the efficacy of HBOT should be achieved through repeated and relatively long-term treatment. There were no significant difference between 60 and 90 pressure exposures at pressures of 1.5 ATA and 2.0 ATA. Therefore the pressure of 1.5 ATA and 60 pressure exposures can be used as one of the optimal protocols for HBOT.

Although the current trial focused on postoperative ICH patients, our findings bear the promise that HBOT may serve as a valuable adjuvant therapeutic practice in ischemic stroke and traumatic brain injury and other neurological disorders. However, further study is necessary.

About the UGIB

HBOT plays a dual role in the occurrence of UGIB. On the one hand, HBOT increases vagal activity (50,51). This induces gastric hypersecretion and gastric hypercontractility, which might promote the occurrence of UGIB. On the other hand, HBOT could increase tissue oxygen delivery, increase gastric juice prostaglandin E levels close to normal values (56), and reduce sympathetic activity (57). These effects reduce splanchnic vasoconstriction, improve the gastrointestinal mucosal ischemia, hypoxia and protective defenses. Therefore, HBOT could also protect the gastrointestinal mucosa and promote ulcer healing. In the current study cohort which is at increased risk for UGIB there an increase rate of UGIB in the groups that received 2.0 ATA, but this increase was mild and none of the hemorrhage were serious.

Study Limitations

First, clinical trials in human are not the same as animal studies. In the clinical setting, HBOT is almost never given soon after ictus. The delay in the implementation of HBOT may alter the therapeutic effect of HBOT. Second, the sham-control design presents difficulties. For example, the true sham-control should be that the patients are placed in the hyperbaric chamber, the chamber is not compressed, but patients cannot detect pressure fluctuations at normal pressure setting, the blinding purpose for patients could not be implemented. Some studies have simulated the effects at normal pressure by breathing air with lower than a normal oxygen level at higher pressure (58). This involved ethical issues and the effects of pressure. Thus, the control design of the current trial was a more reasonable scheme.

However, further research is necessary and the efficacy at a pressure between 1.5–2.0 ATA, such as 1.8 ATA or 1.75 ATA and other pressures should also be studied. A stepwise pressure treatment protocol could also be carried out, such as 1.5 ATA during the first treatment cycle and 2.0 ATA during the second cycle.

Conclusions

HBOT could significantly improve survival and functional outcome (prognosis) of patients with acute severe hypertensive basal ganglia hemorrhage after surgery. HBOT is safe and can be used for ICH during the acute/sub-acute phase. The clinical benefit of 1.5 ATA was the same as 2.0 ATA. The pressure of 1.5 ATA and 60 pressure exposures can be used as one of the optimal protocols of HBOT. Further studies are needed to optimize the protocol per specific patient.

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