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Intraoperative Goal-directed Fluid Management and Postoperative Brain Edema in Patients having High-Grade Gliomas Resections: a Randomized Trial

Xiaoyuan Liu[1*§], M.D., Ph.D.; Xingyue Zhang[1,2*], M.D.; Yifang Fan[1], M.D.; Bo Wang[1], M.D.; Jie Wang[1], M.D., Ph.D.; Min Zeng[1], M.D., Ph.D.; Shu Li[1], M.D., Ph.D.; Mi Shen[3], M.D., Ph.D.; Wei Zhang[4], M.D., Ph.D.; Daniel I. Sessler[5], M.D.; Yuming Peng[1,6], M.D., Ph.D.

[1]Department of Anesthesiology, Beijing Tiantan Hospital, Capital Medical University, Beijing, PR China.

[2]Department of Anesthesiology, Xuanwu Hospital, Capital Medical University, Beijing, PR China.

[3]Department of Radiology, Beijing Tiantan Hospital, Capital Medical University, Beijing, PR China.

[4]Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, PR China

[5]Department of **O**UTCOME **R**ESEARCH, Cleveland Clinic, Cleveland, Ohio, USA

[6]**O**UTCOME **R**ESEARCH **C**onsortium, Cleveland, Ohio, USA

*Xiaoyuan Liu and Xingyue Zhang contributed equally.

§Corresponding authors and requests for reprints: Xiaoyuan Liu, M.D., Ph.D.

Department of Anesthesiology, Beijing Tiantan Hospital, Capital Medical University, PR China.

Mailing address: No.119, Nansihuan Xilu, Fengtai District, Beijing, PR China 100160.

Phone: 8610-59976658

Email: lxy13621278793@163.com

Email addresses:

Xiaoyuan Liu: lxy13621278793@163.com

Xingyue Zhang: zhangxingyue@xwhosp.org

Yifang Fan: fanyifangxwz@163.com

Bo Wang: wawb330@163.com

Jie Wang: wangjietth@ccmu.edu.cn

Min Zeng: fly800727@163.com

Shu Li: lishu@bjtth.org

Mi Shen: shenmi_07@aliyun.com

Wei Zhang: zhangwei_vincent@126.com

Daniel I. Sessler: DS@CCF.org

Yuming Peng: pengyuming@bjtth.org

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Highlights

Fluid management directed by stroke volume variation is suitable for patients undergoing supratentorial high-grade glioma resections.

Goal-directed fluid management does not reduce brain edema after major neurosurgery.

Goal-directed volume management may promote brain relaxation.

Data statement

The authors confirm that the data that support the results of the study are available in the article. Raw data supporting the results of this study are available from the corresponding author upon reasonable request.

Abstract

Introduction: Patients with high-grade gliomas often have severe brain edema. Goal-directed fluid management protects neurological function, but whether reduces postoperative brain edema remains unknown.

Methods: Patients having elective resection of supratentorial malignant gliomas were randomly assigned to goal-directed versus routine fluid management. Patients assigned to goal-directed management group were given 3 mL kg^{-1} hydroxyethyl starch solution when stroke volume variation exceeded 15% for 5 minutes. Fluid was managed per routine by attending anesthesiologists in reference patients. The primary outcome was cerebral edema volume after surgery as assessed by computerized tomography.

Results: A total of 480 eligible patients were randomly assigned to the goal-directed (n = 240) or the routine fluid management group (n = 240). The amounts of crystalloid (5.4 vs. 7.0

ml kg^{-1} $hour^{-1}$, $P < 0.001$), colloid (1.1 vs. 1.7 ml kg^{-1} $hour^{-1}$, $P < 0.001$), and overall fluid balance (0.3 vs. 1.9 ml kg^{-1} $hour^{-1}$, $P < 0.001$) were significantly lower in goal-directed fluid management. There was no significant difference in postoperative brain edema volume between groups (36.0 cm^3 vs. 38.9 cm^3, mean difference: 0.18cm^3, 95% CI: -5.7 to 5.9). Goal-directed patients had lower intraoperative dural tension (risk ratio: 0.63, 95% CI: 0.50 to 0.80, $P < 0.001$). There was no significant difference in Karnofsky Performance Status between the two groups at 30 days after surgery.

Conclusions: Goal-directed fluid therapy substantially reduced intravenous fluid volumes, but did not reduce postoperative brain edema in patients having brain tumor resections.

Key words: Anesthesia, postoperative brain edema, goal-directed fluid treatment, high-grade glioma

Introduction

Postoperative brain edema increases intracranial pressure (ICP), worsens neural function, and increases morbidity and mortality in patients having brain tumor resections.[1] Development of postoperative brain edema is a complex process that depends of various factors including blood-brain barrier disruption,[2] tumor characteristics,[3] and systemic hypervolemia.

Excessive intraoperative fluid administration reduces oncotic pressure and aggravates tissue and cerebral edema.[4] Goal-directed individualized fluid management seeks to avoid excessive volume administration while maintaining optimal individualized hemodynamics and organ perfusion.[5] A meta-analysis of 23 studies (3205 patients) reported that goal-directed fluid management reduces postoperative pulmonary edema in surgical patients.[6] Trials also report that goal-directed fluid management reduces postoperative neurological events after neurosurgery.[7, 8] However, the effect of goal-directed fluid management on postoperative brain edema in neurosurgical patients remains unclear.

We therefore tested the primary hypothesis that goal-directed fluid management reduced postoperative cerebral edema volume in patients with malignant supratentorial gliomas. Secondary outcomes included intraoperative brain relaxation, dural tension grade, postoperative complications and 30-day Karnofsky Performance Status.

Methods

The Ethics Committee approved this study and the trial was registered on the clinicaltrials.gov. The protocol for our trial was published.[9] Written informed consents were obtained from all participants. This research paper is being reported in line with Consolidated Standards of Reporting Trials (CONSORT, Supplemental Digital Content 1, http://links.lww.com/JS9/D137) guidelines.[10]

Subjects

We enrolled adults 18-65 years old scheduled for elective supratentorial high-grade glioma resection at hospital who were designated American Society of Anesthesiologists (ASA) physical status 1-3. We excluded patients who had recurrent cancer, tumor within brain ventricles, New York Heart Association Functional Classification functional class of II-IV, cardiac ejection fraction <20%, chronic obstructive pulmonary disease, renal insufficiency (creatinine clearance rate < 30 ml kg^{-1}). We excluded patients who had extensive peripheral arterial occlusive disease, coagulopathy, surgery in the prone position, body mass index <18.5 kg m^{-2} or >30 kg m^{-2}, or were scheduled for awake craniotomy.

Anesthetic management

Midazolam 0.02-0.05 mg kg^{-1} was injected intravenously preoperatively. Total intravenous anesthesia was induced with sufentanil, rocuronium or cisatracurium, propofol or etomidate, and maintained with propofol and remifentanil. The dose of propofol was adjusted to maintain Bispectral Index between 40 and 60. Sufentanil analgesia was given during skull fixation, scalp incision, and dura suturing. Additionally, the remifentanil infusion rate was adjusted according to the intensity of the painful stimulus.

After tracheal intubation, lungs were mechanically ventilated in volume-controlled mode with tidal volume 8-10 mL kg^{-1}, respiratory rate 10-15 breaths min^{-1}, $P_{ET}CO_2$ 30-35 mm Hg, fraction of inspired oxygen 0.4-0.6, fresh gas flow 1-2 L min^{-1}, and positive end-expiratory pressure 0-5 cm H_2O. Two hundreds and fifty milliliter of 20% mannitol was infused within 20 minutes after skin incision, but no other dehydrating drugs such as hypertonic saline were given during surgery. Mean arterial pressure was maintained within ±20% of baseline to the extent practical, and heart rate was kept between 50-100 beats min^{-1}. Red blood cells were transfused as needed to maintain hemoglobin concentration ≥ 7 g dL^{-1}. The body temperature was maintained at about 36 - 37℃, blood glucose kept normal level range (3.9-6.7mmol/L)[11].

Blinding and grouping

Patients were randomly assigned to goal-directed or routine fluid management at the ratio of 1:1 with block sizes of 6. One day before surgery, an independent research assistant distributed a sealed, opaque envelope containing treatment assignments to the responsible anesthesiologist. The randomization envelope was opened on the day of surgery and allocations were thus concealed as long as practical. Patients and follow-up assessors were unaware of the treatment and assignment.

The fluid management protocol was only implemented during surgery. The fluid management protocol in the routine group was according to the following principles: first, the 4:2:1 rule was applied to supply the preoperative and the intraoperative physiological requirements. Besides, the infusion speed was adjusted to keep the blood pressure, heart rate, urine volume and supply blood loss. Second, the type of fluid was mainly crystalloid solution, and the amount of colloid solution was 500ml. Last, about 300ml crystalloid was infused regularly before induction, consistent with the goal-directed fluid management group.

In those assigned to goal-directed fluid management, when stroke volume variation (EV1000, Edwards Lifesciences Corporation, Irvine, CA, USA, hemodynamic data were measured every 20 seconds) exceeded 15% for a cumulative 5 minutes during a 15-minute period, a bolus of 3-ml kg^{-1} of hydroxyethyl starch was infused within the subsequent 15 minutes. Up to 5 hydroxyethyl starch boluses were permitted, with subsequent boluses of acetate Ringer's solution. When stroke volume variation was <15% and mean arterial pressure was <80% of baseline, norepinephrine or phenylephrine was infused to increase blood pressure when cardiac index ≥ 2.0 L min^{-1} m^{-2}. Dopamine was substituted when cardiac index was < 2.0 L min^{-1} m^{-2}. If estimated blood loss exceeded 3 ml kg^{-1} min^{-1} over 20 minutes or exceeded 20% of the estimated total blood volume, an additional fluid bolus could be given independent of stroke volume variation, or allogeneic red blood cells and plasma could be transfused per transfusion guidelines.[12] Postoperative fluid management from the end of the

surgery to the CT scan was based on routine practice for all of the patients. Postoperative hourly fluid administration was calculated as the fluid volume infused during the period divided by the duration from the departure from the operating room to the CT scan. Colloid solution was not routinely used in patients after surgery.

Primary outcome

Our primary outcome was brain edema within 24 hours postoperatively, as assessed by computed tomography (CT), which can provide accurate and reliable edema volume assessements comparable to magnetic resonance imagining.[13] Two independent neuroradiologists, blinded to the group allocation, were trained to evaluate cerebral edema from CT scans.

CT scans without contrast were performed with a 16-row multi-detector scanner (Discovery CT 750HD, GE Healthcare, Milwaukee, USA), a 64-row multi-detector scanner (LightSpeed VCT, GE Healthcare, Milwaukee, USA) and a 256-row multi-detector scanner (Revolution CT, GE Healthcare, Milwaukee, USA). The scan settings were: tube voltage 120 kV; tube current 300 mA; field of view 23cm×23 cm; and matrix 512×512 pixals. Images were handled by a picture archiving and communication system (NEUSOFT PACS/RIS v2.1, Shenyang, China). Maximum tumor diameters were measured on axial, coronal, and sagittal images and defined as x, y, and z. The volume was calculated as the following formula: $V = \frac{4}{3}\pi \times \frac{x}{2} \times \frac{y}{2} \times \frac{z}{2}$.[14]

Postoperative brain edema surrounding the surgical resection cavity was defined by low density on CT images. Image evaluators manually delineated a region of interest and the operative cavity on each slice. The area ($S_{edema+cavity}$ and S_{cavity}) were calculated automatically by the PACS (picture archiving and communication system, NEUSOFT PACS/RIS v2.1, Shenyang, China). Total volume was acquired by multiplying the area and slice thickness. We obtained the total volume of the abnormal density or signal ($V_{edema+cavity}$) and the volume of

the cavity (V_{cavity}). The volume of edema (V_{edema}) was calculated by the following formula: $V_{edema} = V_{edema+cavity} - V_{cavity}$.[13]

Secondary outcomes

Brain relaxation was dichotomized as satisfactory (scores 1 and 2, representing complete and adequate relaxation) or unsatisfactory (scores 3 and 4, representing a firm and bulging brain).[15] Dural tension was classified into three ordinal grades: hard, tight, and loose.[16] Both indicators were judged by the attending neurosurgeons. Other outcomes included a brain composite outcome including cerebral hemorrhage, stroke and brain re-operation, and a composite outcome that included all complications, hospital length of stay, intensive care unit admission, hospital cost and Karnofsky Performance Status on the 30th postoperative day[17]. Safety outcomes included postoperative renal function (urine volume, creatinine, estimated glomerular filtration rate), coagulation function (prothrombin time, international normalized ratio, activated partial thromboplastin time, fibrinogen), and 30-day postoperative complications.

Statistical plan and sample size calculation

The statistical analysis plan was developed before data were accessed. Post hoc analyses was specified. Descriptive statistics are reported as means and standard deviations or medians with inter-quartile range (IQR) as appropriate and counts (percentage) for categorical data. Normally distributed continuous variables were compared with Student's t-tests, while skewed variables were compared with Mann-Whitney U tests. Categorical variables were compared with χ^2 or Fisher's exact tests. The primary outcome, brain edema volume, was compared with the Student's t-test. Secondary outcomes were analyzed via appropriate statistical methods per data type. Baseline characteristics in each group are presented as numbers and percentages along with absolute standardized differences, defined as absolute differences in means, mean ranks, or proportions divided by the pooled standard deviation.

We preplanned sub-groups including ASA physical status, Karnofsky Performance Status score, pathology classification, Steinhoff grade and midline shift. Missing data was imputed using inverse probability weighting and worst-case imputation scenarios. SPSS 16.0 for Windows was used for all statistical analyses. For each hypothesis, a two-sided $P < 0.05$ was considered statistically significant.

We used the PASS 2011 software (NCSS LLC, USA) for Windows to calculate the sample size. Our estimation was based on a pilot study enrolling 20 patients who had about 50 cm^3 brain edema after brain tumor resections under routine fluid management [12]. With alpha set at a two-sided 0.05 and power at 80%, we estimated that 450 would allow to identify differences in postoperative brain edema volume of 4 cm^3 with a standard deviation of 18 and 16 in the two groups. Expecting 5% of patients to drop out, we planned to enroll 480 patients.

Results

Between November 2018 and September 2022, we screened 781 patients, and 480 were enrolled and randomized. We were unable to obtain a postoperative CT scan in one patient. Consequently, 99.8% of the postoperative brain edema assessments were made as planned (Figure 1). The time interval between the end of surgery and CT examination was 4.2 (2.8-5.6) hours in the goal-directed group and 4.3 (3.3-5-5) hours in the routine fluid management group ($P = 0.335$). Typical MRI images of enrolled patients are presented in eFigure 1A-C, Supplemental Digital Content 2, http://links.lww.com/JS9/D138, and a schematic of the methods used to assess cerebral edema is shown in eFigure 1D, Supplemental Digital Content 2, http://links.lww.com/JS9/D138.

Demographic and baseline variables were well balanced in patients assigned to routine and guided fluid management (Table 1). Patients assigned to goal-directed fluid management were given significantly less intraoperative total fluid volume (6.7 mL kg^{-1} $hour^{-1}$ vs. 8.8 mL

kg $^{-1}$ hour^{-1}, $P < 0.001$), less crystalloid (5.4 mL kg $^{-1}$ hour^{-1} vs. 7.0 mL kg $^{-1}$ hour^{-1}, $P < 0.001$), and less colloid (1.1 mL kg $^{-1}$ hour^{-1} vs. 1.7 mL kg $^{-1}$ hour^{-1}, $P < 0.001$) than the routine treatment group. Consequently, intraoperative fluid balance, intravenous fluid volume minus urine output and blood loss, was less in goal-directed therapy group than the routine group (0.3 mL kg $^{-1}$ hour^{-1} vs. 1.9 mL kg $^{-1}$ hour^{-1}, $P < 0.001$). The rate of fluid input including crystalloid given from the end of surgery to CT examination was comparable between groups ($P > 0.05$). Between the two groups, there was no difference in the number of cases with postoperative colloid use ($P > 0.05$). No significant differences was found in the use of mannitol or steroids during surgery or after surgery.

More patients in the directed fluid management group received vasoactive drugs than the routine group: 42% vs. 27%, $P < 0.001$. Trends in stroke volume variation and cardiac index in the goal-directed fluid-management group are shown in Figure 2. The measured values of the above-mentioned parameters basically met the requirements of the goal-directed fluid management program. Moreover, we recorded the number of cases with colloid intervention in the goal-directed fluid management group, and the proportion was as high as 92.9%. Cumulative duration of MAP < 80% baseline was approximately same in the two groups: 93 min vs. 93 min, $P = 0.761$. Serum lactate concentrations at the end of surgery were similar: 0.9 mmol L^{-1} vs. 1.0 mmol L^{-1}, $P = 0.102$. $PaCO_2$ was lower in the goal-directed fluid treatment group at the end of surgery (35 mm Hg vs. 36 mm Hg, $P = 0.003$), although not by a clinically meaningful amount (Table 2).

Primary Outcome

Brain edema volumes were not statistically different in patients assigned to goal-directed and routine fluid management: 36.0 cm^3 vs. 38.9 cm^3, mean difference: 0.18cm^3, 95% CI: -5.7 to 5.9, $P = 0.938$. No significant interactions were identified for pre-defined or *post hoc* subgroups (Figure 3). The sensitivity analysis also yielded similar results.

Secondary outcomes

Excessive intraoperative dural tension was less common in patients assigned to guide fluid management: 169/240 (70%) vs. 128/240 (53%), risk ratio: 0.63, 95% CI: 0.50 to 0.80, $P < 0.001$, Table 3. Surgeons' satisfaction with brain relaxation was 83% under directed fluid management and 77% under routine management, with a difference not significantly: risk ratio 0.73, 95% CI: 0.51 to 1.05, $P = 0.088$, Table 3.

Neither the incidence of postoperative composite complications (21.7% vs. 21.7%, risk ratio: 1.00, 95% CI: 0.65 to 1.54, P = 1.000) nor cerebral composite complications (8.3% vs. 5.0, risk ratio: 1.73, 95% CI: 0.83 to 3.62, P = 0.143) differed significantly between two groups. There was no significant difference in Karnofsky Performance Status between the two groups at 30 days after surgery, the length of hospital stay, cost, or ICU admission between the two groups (Table 3). There were no significant differences in renal function within 30 days postoperatively.

Discussion

Postoperative brain edema is influenced by the amount of damage to brain tissue, vascular injury, and inflammation — all of which are hard to quantify. Fluid management is therefore just one of many factors influencing brain edema, and probably not the most important.[18] It was nonetheless well worth considering since, unlike most factors promoting brain edema during neurosurgery, fluid management is modifiable. However, goal-directed fluid management targeting stroke volume variation < 15% did not reduce the volume of postoperative brain edema in patients with high-grade gliomas.

The amount of fluid given to patients with goal-directed systems depends on the variable assessed, the intervention threshold, and the bolus volume when thresholds are exceeded. Our protocol specified administering a 3-ml/kg bolus of hydroxyethyl starch when stroke volume

variation exceeded 15% for a cumulative 5 minutes. Other studies have used different approaches, although there is currently no evidence to indicate that any particular one is preferable. For example, Wu showed that maintenance of stroke volume variation < 10% during neurosurgery shortened ICU duration, improved postoperative neurological markers, and reduced neurological events.[8] In Wu's trial, when stroke volume variation threshold was 10%, the intraoperative fluid balance was +3.4 mL kg^{-1} $hour^{-1}$; whereas, when the stroke volume variation threshold was 18%, the balance was only +2.3 mL kg^{-1} $hour^{-1}$. However, for patients undergoing spinal surgery, < 14% was set as the target, and the balance of fluid management was 4.9 mL kg^{-1} $hour^{-1}$.[19] Because the choice of target and threshold greatly affects the absolute value of fluid balance, it is difficult to compare the results of different studies.

The type of fluid used presumably also influences outcomes. Colloids have the advantage of maintaining intravascular oncotic pressure and hemodynamic endpoints longer with lower total fluid volumes.[20] Although even the use of starch was not available in Europe, it was recommended in the Chinese consensus on fluid therapy for surgical patients.[21] A concern in our patients is that brain tumors cause varying degrees of blood-brain barrier destruction, potentially resulting colloid leakage into brain tissue and subsequent swelling. Nonetheless, moderate amounts of colloid such as in the current trial can help avoid brain edema by maintaining adequate colloid oncotic pressure.[22] In addition, we used acetate ringer's solution, not lactate ringer's solution, as crystal fluid with the osmolarity of 308 mosm/kg, which is near to normal physical osmolarity and can avoid the low-osmolarity edema.

For patients underwent neurosurgery, especially those with severe brain edema, too much fluid volume could worsen brain edema, nevertheless, too strict fluid volume could increase the risk of hypoperfusion. Therefore, the fluid selected as the bolus should rapidly correct hypervolume with a small volume. In previous studies, both crystalloids and colloid had been used as response bolus. However, more fluid volume was infused when crystalloid used for

increase stroke volume variation, comparing with colloid.[20, 23] Colloid had been used as bolus to increase stroke volume variation in several neurosurgical studies[7, 8, 23] which indicated that colloid effectively increased stroke volume variation and was suitable for craniotomy, restoring the volume condition to the expected status with a relatively small amount of volume.

According to the stroke volume variation cut-offs of the grey-zone,[24] the median cut-off was 13% with the 95% confidence interval between 9% and 17%. The cut-off value of stroke volume variation is generally set at 9–15%.[25] Xia's[23] research showed that maintaining stroke volume variation <13% led to normal cerebral metabolism and oxygenation. Wu et al.[8] found maintaining stroke volume variation <18% increased ICU stay and the incidence of postoperative neurological events compared with < 10%. Luo et al.[7] found maintaining <15% ensured stable circulation and adequate tissue perfusion with the limited amount of fluid input. We set the target of <15%, as the previous study,[7] and showed that the goal-directed therapy with <15% provided better intraoperative brain condition compared with the routine therapy.

A limitation of the reference group is that the routine therapy varies across institutions, and even among providers within an institution. Our center generally takes a relatively restrictive approach to fluid management in neurosurgery. Consequently, total fluid volume differed by about 24%. Brain edema volume was similar with and without guided management in our patients but might differ in other institutions with more fluid routinely. Our primary outcome was brain edema as determined by CT examination within 24 hours postoperatively. The second limitation is that the interventional fluid management was restricted to the intraoperative period. The difference in the fluid volumes and balances during surgery between groups would be diluted by the postoperative fluid volume before CT scan although the rate of fluid input were controled comparable. An additional consideration is

that brain edema continues and fluctuates for days after surgery. Cytotoxic edema, for example, is observed within a day whereas vasogenic edema presents after 2-4 days.[26]

A final limitation is that magnetic resonance imaging is considered more sensitive to a brain edema.[27] However, magnetic resonance imaging examination requires considerable cooperation from patients which often is not practical shortly after craniotomies. We therefore used tomography to assess the cerebral edema which was more practical, at the expense of reduced precision. Edema volumes were nonetheless similar with reasonably small confidence intervals. It thus seems unlikely that use of more precise imaging would meaningfully change our conclusions. Moreover, the proportion of the number of cases with colloid intervention in the goal-directed fluid management group was as high as 92.9%. However, the stroke volume variation values in the plot were recorded and presented every 15 minutes, not continuous data export as the raw data or the values recored in the case report form. Therefore, it must occur that some stroke volume variation more than 15% of the data appeared between the two recording points without being recorded. Finally, given the paucity of literature with cerebral edema volume as the primary outcome measure and insufficient reference data, we may have been conservative in the sample-size estimation.

In conclusion, goal-directed fluid management does not reduce brain edema after major neurosurgery. In contrast, goal-directed volume management may promote brain relaxation and maintain hemodynamics stability simultaneously

Table 1. Demographic and clinical characteristics at baseline.

ASD: absolute standardized difference; IQR: interquartile range; BMI: Body Mass Index; ASA, American society of anesthesiologists; KPS: Karnofsky Performance Status; GCS: Glasgow coma scale; PT: prothrombin time; INR: international standardized ratio; APTT: activated partial thrombin time; WHO: World Health Organization.

[a] Absolute standardized difference > 0.179 = ($1.96 * \sqrt{\frac{1}{240} + \frac{1}{240}}$) were considered imbalanced.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Antiepileptic drug: Depakine/ Levetiracetam/ Oxcarbazepine.

[d] The maximum Mini Mental State Examination, median score is 30 points. Normal values are < 24 for people with less than post-secondary education, <23 for those with less than secondary education, <20 for those with less than primary education.

[e] Others include meningioma, ependymoma, metastatic carcinoma, lymphoma, inflammatory lesion, neuroepithelial tumor, and melanoma.

[f] Others include tumors with WHO grade I-II and tumors without WHO grade.

Table 2. Intraoperative characteristics.

IQR: interquartile range; CT: computed tomography; ICU: intensive care unit.

[a] The amount of fluid balance is equal to the total input volume (crystoloid fluid, colloidal fluid, RBC, plasma) in minus the total output volume (blood loss, urine).

Table 3. Effectiveness outcomes.

CI: confidence interval; IQR: inter-quartile range; SSI: surgical site infection; DVT: deep vein thrombosis; PE: pulmonary embolism; KPS: Karnofsky Performance Status; LOS: length of hospital stay; ICU: intensive care unit; CNY: Chinese Yuan.

[a] One patient in the control group did not undergo postoperative head CT examination, and the minimum edema volume in the control group was used to impaction the missing value.

[b] Brain relaxation was dichotomized to satisfactory (scores 1 and 2, representing complete and adequate relaxation) or unsatisfactory (scores 3 and 4, representing a firm and bulging brain).

[c] The degree of PONV was scored from 0 to 10, with 0 scoring no PONV and 10 scoring severe PONV. Patients with a score greater than or equal to 4 or requiring antiemetic treatment were defined as medium/severe PONV.

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Figure 1. Flowchart.

BMI: Body Mass Index; NYHA: New York Heart Association; COPD: Chronic Obstructive Pulmonary Disease; CCr: creatinine clearance rate; GDFT: goal-directed fluid therapy.

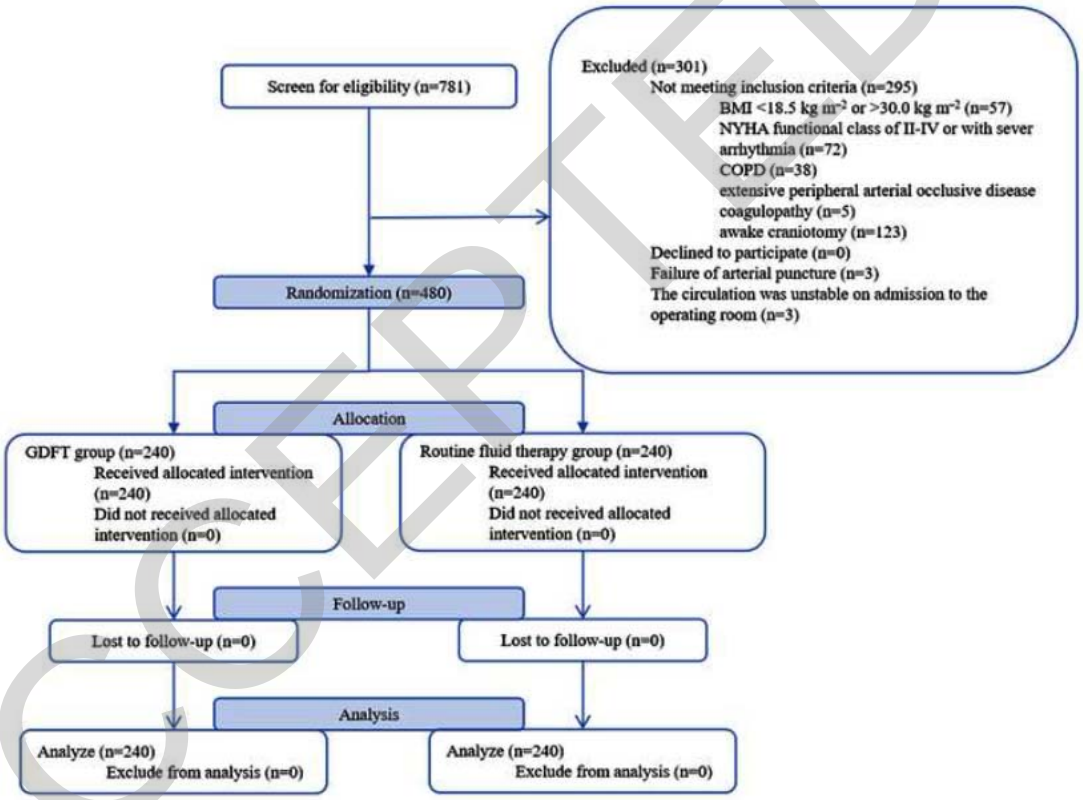

Figure 2. Stroke volume variation and cardiac index in goal-directed fluid management group.

Stroke volume variation (A) and cardiac index (B) are presented as medians and 95% confidence intervals.

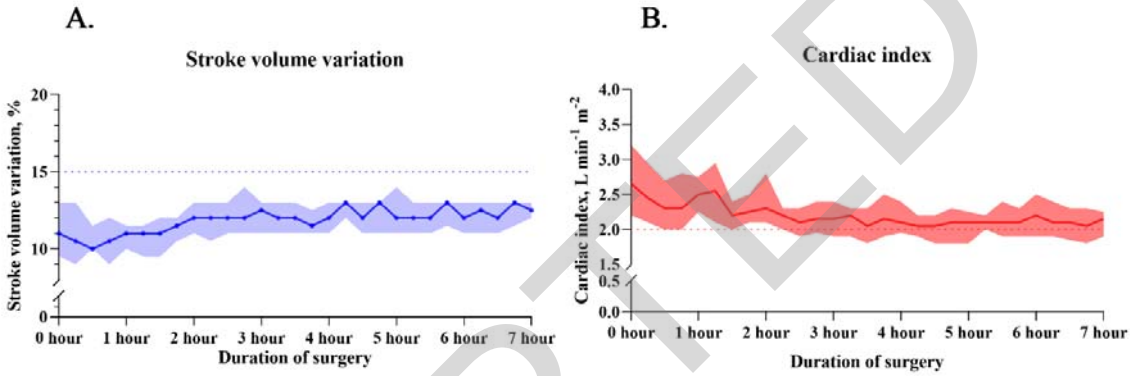

Figure 3. Forest plots for subgroup analysis for brain edema.

ASA: American Society of Anesthesiologists; WHO: World Health Organization; KPS: Karnofsky Performance Status.

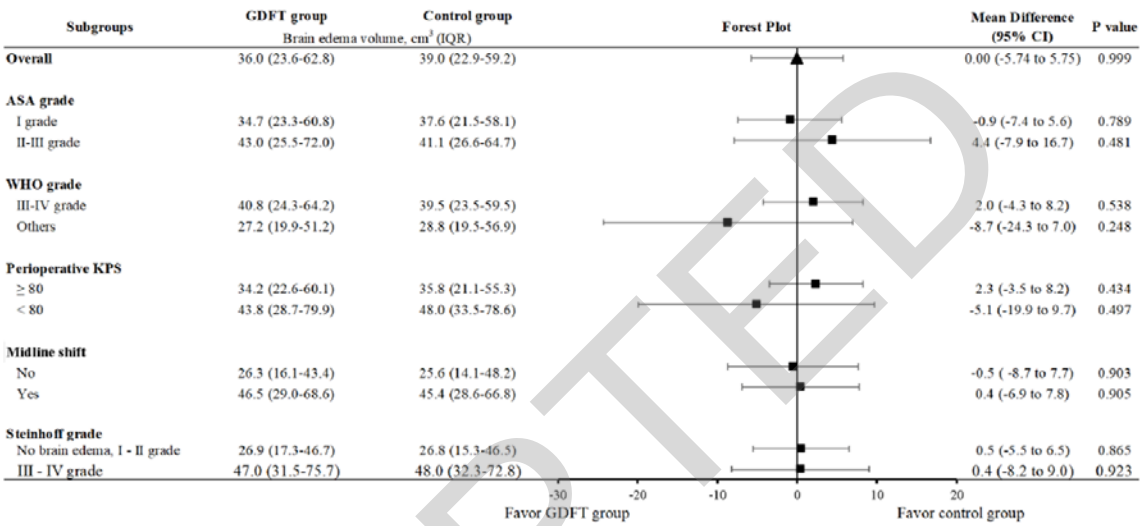

Table 1. Demographic and clinical characteristics at baseline.

	Goal-directed fluid (n=240)	Routine fluid management [a] (n=240)	ASD
Age, years, median (IQR)	48 (38-56)	49.5 (40-58)	0.128
Gender, male, no. (%)	143 (59.6)	125 (52.1)	0.151
BMI, kg m^{-2}, median (IQR) [b]	24.0 (21.9-26.0)	23.7 (21.8-26.2)	0.077
Medical history, yes, no. (%)			
Hypertension	35 (14.6)	48 (20.0)	0.144
Heart disease	1 (0.4)	3 (1.3)	0.092
Diabetes	17 (7.1)	15 (6.3)	0.033
Stroke	2 (0.8)	3 (60.0)	0.041
Pulmonary disease	6 (2.5)	5 (2.1)	0.028

Renal disease	0 (0.0)	3 (1.3)	0.159
Smoke	69 (28.7)	64 (26.7)	0.047
Preoperative epilepsy	21 (8.8)	13 (5.4)	0.130
Medication history, yes, no. (%)			
Aspirin	2 (0.8)	3 (1.3)	0.041
Antiepileptic drug [c]	28 (11.7)	27 (11.3)	0.012
Preoperative functional score			
ASA grade, no. (%)			0.111
I grade	187 (77.9)	179 (74.6)	
II grade	48 (20.0)	52 (21.7)	
III grade	5 (2.1)	9 (3.8)	
Charlson Comorbidity Index, median (IQR)	0 (0-1)	1 (0-2)	0.154
Preoperative KPS, no. (%)			0.083
≥80	189 (78.8)	181 (75.4)	
≥50	45 (18.8)	53 (22.1)	
< 50	6 (2.5)	6 (2.5)	

Preoperative GCS, median (IQR)	15 (15-15)	15 (15-15)	0.000
Tumor characteristics			
Tumor side, no. (%)			0.138
Left	115 (47.9)	128 (53.3)	
Right	115 (47.9)	99 (41.3)	
Both sides	10 (4.2)	13 (5.4)	
Tumor type, no. (%)			0.137
Glioma	227 (94.6)	224 (93.3)	
Others [d]	13 (5.4)	16 (6.7)	
WHO grade, no. (%)			
III-IV grade	201 (83.8)	209 (87.1)	
Others [e]	39 (16.3)	31 (12.9)	
Tumor volume, cm^3, median (IQR)	35.8 (17.4-63.7)	37.4 (19.1-63.5)	0.050
Midline shift, yes, no. (%)	154 (64.2)	153 (63.7)	0.009
Steinhoff grade, no. (%)			0.099
No brain edema	0 (0.0)	1 (0.4)	

I grade	17 (7.1)	16 (6.7)
II grade	96 (40.0)	93 (38.8)
III grade	88 (36.7)	92 (38.3)

ASD: absolute standardized difference; IQR: interquartile range; BMI: Body Mass Index; ASA, American society of anesthesiologists; KPS: Karnofsky Performance Status; GCS: Glasgow coma scale; PT: prothrombin time; INR: international standardized ratio; APTT: activated partial thrombin time; WHO: World Health Organization.

[a] Absolute standardized difference > 0.179 = $(1.96*\sqrt{\frac{1}{240}+\frac{1}{240}})$ were considered imbalanced.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Antiepileptic drug: Depakine, Levetiracetam, Oxcarbazepine.

[d] Others include meningioma, ependymoma, metastatic carcinoma, lymphoma, inflammatory lesion, neuroepithelial tumor, and melanoma.

[e] Others include tumors with WHO grade I-II and tumors without WHO grade.

Table 2. Intraoperative characteristics.

	Goal-directed fluid (n=240)	Routine fluid management (n=240)	*P* value
Fasting time, hour, median (IQR)	11.3 (11.0-12.1)	11.1 (10.8-12.0)	0.960
Surgery duration, hour, median (IQR)	4.5 (3.7-6.1)	4.8 (3.8-5.8)	0.773
Fluid management, median (IQR)			
Input volume	6.7 (5.4-8.5)	8.8 (7.3-10.7)	< 0.001
Crystalloid, mL kg^{-1} h^{-1}	5.4 (4.5-6.4)	7.0 (5.8-8.5)	< 0.001
Colloidal, mL kg^{-1} h^{-1}	1.1 (0.5-2.2)	1.7 (1.3-2.2)	< 0.001
Red blood cell, no. (%)	5 (2.1)	13 (5.4)	0.055
Plasma, no. (%)	7 (2.9)	12 (5.0)	0.242
Output volume, mL kg^{-1} h^{-1}	6.5 (5.0-8.2)	6.9 (5.3-8.6)	0.129
Blood loss	0.7 (0.6-1.0)	0.8 (0.6-1.0)	0.082
Urine	5.6 (4.3-7.2)	6.1 (4.4-7.6)	0.212
Fluid balance, [a] mL kg^{-1} h^{-1}	0.3 (-1.3-1.6)	1.9 (0.7-3.2)	< 0.001
Medication, no. (%)			
Positive vasoactive drug	102 (42.5)	64 (26.7)	< 0.001
Negative vasoactive drug	37 (15.4)	30 (12.5)	0.357
Mannitol	215 (89.6)	210 (87.5)	0.474
Steroid	37 (15.4)	41 (17.1)	0.621
Arterial blood gases after surgery, median (IQR)			

PaO_2, mm Hg	216 (188-251)	226 (180-265)	0.274
Glucose, mmol L^{-1}	5.1 (4.8-6.2)	5.3 (4.8-6.5)	0.073
Hemoglobin, g L^{-1}	11.6 (10.5-13.1)	11.6 (10.4-12.7)	0.302
$PaCO_2$, mm Hg	35.1 (33.1-37.4)	36.0 (33.5-39.4)	0.003
Lactic acid, mmol L^{-1}	0.9 (0.7-1.2)	1.0 (0.65-1.5)	0.102
Medications from the end of surgery to CT examination			
Total input, mL h^{-1}, median (IQR)	108 (88-131)	113 (92-133)	0.107
Crystalloid, mL h^{-1}, median (IQR)	109 (89-135)	114 (94-139)	0.095
Colloidal, no. (%)	10 (4.2)	8 (3.3)	0.631
Mannitol, no. (%)	65 (27.1)	80 (33.3)	0.136
Steroid, no. (%)	171 (71.3)	175 (72.9)	0.684
Hemodynamics			
Cumulative duration of MAP < 80% baseline, min, median (IQR)	93 (31-206)	93 (17-228)	0.761

IQR: interquartile range; CT: computed tomography; ICU: intensive care unit.

[a]. The amount of fluid balance is equal to the total input volume (crystalloid fluid, colloidal fluid, red blood cell, plasma) in minus the total output volume (blood loss, urine).

Table 3. Outcomes.

	Goal-directed fluid (n=240)	Routine fluid management (n=240)	Difference, risk ratio (95% CI)	*P* value
Primary outcome, cm^3, median (IQR)				
Brain edema volume, per protocol	36.0 (23.6-62.8)	39.0 (22.9-59.2)	0.00 (-5.74 to 5.75)	0.999
Brain edema volume, intention-to-treat [a]	36.0 (23.6-62.8)	38.9 (22.9-59.2)	0.18 (-5.56 to 5.92)	0.938
Secondary outcomes, no. (%)				
Brain relaxation [b]			0.73 (0.51 to 1.05)	0.088
Satisfactory	199 (82.9)	184 (76.7)	-	
Unsatisfactory	41 (17.1)	56 (23.3)	-	
Dural tension grade				< 0.001
Hard or tight	71 (29.6)	112 (46.7)	0.63 (0.50 to 0.80)	
Loose	169 (70.4)	128 (53.3)	-	
Medium/severe PONV [c], no. (%)	5 (2.4)	11 (5.1)	0.45 (0.16 to 1.29)	0.127
Postoperative laboratory examination, median (IQR)				
Urea, mmol L^{-1}	3.8 (3.1-4.6)	3.7 (2.8-4.5)	0.15 (-0.10 to 0.40)	0.197
Creatinine, μmol L^{-1}	61 (52-72)	60 (51-70)	1.12 (-1.58 to 3.83)	0.341
Estimate glomerular filtration rate, mL min^{-1}	117 (109-127)	115 (107-127)	1.86 (-0.96 to 4.67)	0.240

Postoperative Complications, no. (%)				
Composite complications	52 (21.7)	52 (21.7)	1.00 (0.65 to 1.54)	1.000
Cerebral complications	20 (8.3)	12 (5.0)	1.73 (0.83 to 3.62)	0.143
Cerebral hemorrhage	9 (3.8)	4 (1.7)	2.25 (0.70 to 7.21)	0.160
Stroke	11 (4.6)	6 (2.5)	1.8 (0.69 to 4.88)	0.217
Re-operation	6 (2.5)	6 (2.5)	1.00 (0.33 to 3.06)	1.000
SSI	8 (3.3)	6 (2.5)	1.33 (0.47 to 3.78)	0.587
Myocardial infarction	1 (0.4)	0 (0.0)	-	0.317
Pulmonary infection	15 (6.3)	9 (3.8)	1.67 (0.74 to 3.73)	0.209
DVT	17 (7.1)	24 (10.0)	0.71 (0.39 to 1.28)	0.253
PE	0 (0.0)	1 (0.4)	-	0.317
Postoperative KPS, no. (%)				0.213
≥ 80	178 (75.1)	167 (71.4)	1.05 (0.94 to 1.17)	
≥ 50	55 (23.2)	58 (24.8)	0.94 (0.68 to 1.29)	
< 50	4 (1.7)	9 (3.8)	0.44 (0.14 to 1.41)	
Hospitalization				
LOS, median (IQR)	10 (8-14)	11 (8-14)	0.23 (-0.89 to 1.34)	0.858
ICU admission, no. (%)	112 (46.7)	128 (53.3)	0.88 (0.73 to 1.05)	0.144
ICU duration, hr, median (IQR)	19 (16-41)	18 (17-24)	-1.62 (-17.2 to 13.9)	0.458

Mechanical ventilation, no. (%)	1 (0.4)	3 (1.3)	0.33 (0.03 to 3.18)	0.315
Cost, 1000 CNY, median (IQR)	78 (62-10)	75 (62-96)	5.96 (-5.22 to 17.14)	0.995

CI: confidence interval; IQR: inter-quartile range; SSI: surgical site infection; DVT: deep vein thrombosis; PE: pulmonary embolism; KPS: Karnofsky Performance Status; LOS: length of hospital stay; ICU: intensive care unit; CNY: Chinese Yuan.

* The valid sample size of postoperative delirium outcome was 252 cases.

[a] One patient in the control group did not undergo postoperative head CT examination, and the minimum edema volume in the control group was used to impaction the missing value.

[b] Brain relaxation was dichotomized to satisfactory (scores 1 and 2, representing complete and adequate relaxation) or unsatisfactory (scores 3 and 4, representing a firm and bulging brain).

[c] The degree of PONV was scored from 0 to 10, with 0 scoring no PONV and 10 scoring severe PONV. Patients with a score greater than or equal to 4 or requiring antiemetic treatment were defined as medium/severe PONV.