Effect of Intraoperative Goal-directed Fluid Therapy on the Postoperative Brain Edema in Patients undergoing High-Grade Gliomas Resections: a study protocol of randomized control trial

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Abstract

Introduction Brain edema is the most frequent postoperative complication after brain tumor resection, especially in patients with high-grade glioma. However, the effect of SVV-based goal-directed fluid therapy (GDTFT) on postoperative brain edema and the prognosis remain unclear.

Methods and analysis This is a prospective, randomized, double-blinded, parallel-controlled trial aiming to observe whether stroke volume variation (SVV)-based GDTFT could improve the postoperative brain edema in patients undergoing supratentorial high-grade gliomas compared with traditional fluid therapy. The patient will be given 3mL/kg hydroxyethyl starch solution when the SVV is greater than 15% continually for more than 5 minutes intraoperatively. The primary outcome will be postoperative cerebral edema volume on brain CT within 24 hours.

Ethics and dissemination This trial has been registered at ClinicalTrial.gov (NCT03323580) and approved by the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University (reference number: KY2017-067-02). The findings will be disseminated in peer-reviewed journals and presented at national or international conferences relevant to subject fields.

Trial registration number NCT03323580.

Strengths And Limitations Of This Study

- This is a randomised, parallel-group, control trial to evaluate whether stroke volume variation (SVV)-guided GDTFT could improve the postoperative brain edema in neurosurgical patients with supratentorial malignant gliomas.
- This study adopts SVV-based GDTFT, with standardized randomization, endpoint assessment blinding, and experienced investigators in each key procedure of intervention and follow-up.
- One limitation of the study is it is a single-centre trial. A future multi-centre trial is needed to evaluate the effect of GDTFT on the postoperative brain edema in patients under supratentorial malignant gliomas resections.
- Certain patients with known high risks for early postoperative complications are excluded for the safety concerns.

Background

Postoperative brain edema induces increased intracranial pressure (ICP), worsened neural function, increased morbidity and mortality in patients undergoing brain tumor resections \[^1\], which is related to various factors including blood-brain barrier disruption \[^2\], tumor characteristics \[^3\], and systemic hypervolemia.
Intraoperative fluid load is regarded as one of the factors that improve cerebral edema\(^4\) for patients with supratentorial high-grade gliomas. Previous studies revealed sufficient perioperative fluid volume ensures stable circulation and maintains adequate cerebral perfusion pressure. Though strict control of fluid input provides intraoperative brain relaxation it is also associated with insufficient organ perfusion and other related complications\(^7\), including a risk of decreased cerebral perfusion pressure\(^6\), leading to aggravating cerebral edema and further lead to long-term brain injury.\(^5,6\) Therefore, how to optimize intraoperative fluid treatment is controversial. Individualized volume monitoring and fluid therapy may be required for patients with different volume status.

Goal-directed fluid treatment (GDT) was proposed by River in 2001\(^8\) for patients with severe sepsis and septic shock. GDT provides patients with individualized fluid therapy so as to achieve optimal individual cardiac function and sufficient tissue perfusion. Previous studies showed that intraoperative GDT remarkably improved prognosis\(^9–11\), shortens the length of hospital stay, and reduces the medical cost\(^12\). However, there's no research focus on the impact of intraoperative fluid treatment on postoperative brain edema, especially in patients with high-grade gliomas.

Stroke volume variation (SVV) is a new way to evaluate the perfusion intraoperatively. It was measured by the pulse contour method and predicts the response to fluid administration instantly and continuously. It has been commonly used in various settings. GDT was applied in thoroesophagectomy guided by SVV of less than 8% and was demonstrated to reduce the major morbidity and mortality compared with the control group, in which systolic blood pressure was maintained greater than 90mmHg\(^13\). A meta-analysis of 14 studies indicated that GDT reduced postoperative morbidity and length of stay in the ICU\(^14\). Recently, SVV had been reported to be sensitive in predicting fluid responsiveness in neurosurgery. Xia et al.\(^11\) studied the effects of different kinds of fluids applied by GDT in patients undergoing supratentorial tumor resection and found satisfactory brain relaxation was both achieved, whereas no difference of cerebral ischemia, lactic acid production, or increased glucose intake between groups was found. Luo et al. involved patients undergoing brain tumor surgery and found that intraoperative use of GDT reduced the length of stay in ICU of high-risk neurosurgical patients\(^15\). However, the researchers did not set a specific fluid regimen for the control group but based on the experience of the anesthesiologist. Besides, the study population included patients mostly with brain vascular diseases, resulting in a relatively insufficient sample size of brain tumors.

The cut-off value of SVV is generally set at 9%-15%\(^16,17\). Wu et al.\(^18\) investigated the effects of GDT with different SVV target values (SVV≤10% or SVV≤18%) in patients undergoing supratentorial cranial tumor surgery, and found the incidence of postoperative neurological events was lower in patients with SVV≤10% group. Luo et al. found\(^15\) maintaining SVV<15% not only ensured stable circulation and adequate tissue perfusion but also limited the amount of fluid input on the basis of satisfying tissue perfusion. However, there's still no study focusing on the effects of SVV-guiding GDT on postoperative brain edema in neurosurgical patients.
Therefore the purpose of the study is primarily to explore whether SVV-guiding GDFT optimizes intraoperative fluid treatment concerning reducing postoperative cerebral edema volume in patients with malignant supratentorial gliomas. We will conduct a randomized controlled trial to test the hypothesis that SVV-guiding GDFT could reduce postoperative cerebral edema volume compared with traditional fluid treatment.

**Methods**

**Study design**

This is a prospective, randomized, endpoint assessor blinded, parallel-controlled trial. Supratentorial malignant tumor patients will be recruited from Beijing Tiantan Hospital, Capital Medical University from 2017 to 2022. This trial was approved by the Medical Ethics Committee of Beijing Tiantan Hospital, Capital Medical University (reference number: KY2017-067-02) on 27\(^{th}\) NOV 2017, and registered in www.clinicaltrials.gov (NCT03323580). Preoperative interviews will be conducted by specially trained research assistants who inform patients of the study objectives, risks, benefits, and obtain written informed consent from his/her legal representatives. Figure 1. shows the flow chart of the study.

**Subjects**

**Inclusion criteria**

Patients scheduled to undergo elective supratentorial tumour resection with preoperative brain image indicating high-grade glioma (HGG) will be recruited for screening eligibility one day before surgery. The inclusion criteria include age between 18 and 65 years, and American Society of Anaesthesiologists (ASA) physical status I to III. HGG will be verified by postoperative histology of the World Health Organization (WHO) as grade III or IV tumors. \[^{19}\] Informed consent will be signed by the patient or his/her legal representative.

**Exclusion criteria**

Patients will be excluded from the study if the patients with recurrent carcinoma, tumor in the brain ventricular, New York Heart Association Functional Classification (NYHA) functional class of II-IV or if their cardiac ejection fraction is < 20%, chronic obstructive pulmonary disease, renal insufficiency, or creatinine clearance rate < 30 ml/kg, extensive peripheral arterial occlusive disease, coagulopathy, surgery in the prone position, Body Mass Index <18.5 kg·m\(^{-2}\) or >30.0 kg·m\(^{-2}\), and awake craniotomy.

**Randomization and Blinding**

Block randomization (block size of 6) will be applied via a computer-produced randomized table. Patients will be randomized within 24 hours before surgery. An independent research assistant will pack the allocation sequence with opaque, sealed, and stapled envelopes and distribute it to the responsible anesthesiologist.
The endpoint assessors (neuroradiologists who will analyze the postoperative CT scan and calculate the brain edema volume) will be all blinded to the grouping until the completion of the study analysis unless specific circumstances, including the occurrence of a serious adverse event. The enrolled patients and the legal representatives will also be blinded to the interventional treatment.

**Intervention**

Patients will be randomly assigned into the GDFT group and the traditional treatment group. In the GDFT group, the A-line will be connected to the EV1000A (Edwards Lifesciences, Irvine, CA, USA) to obtain the SVV, stroke volume index (SVI), and cardiac index (CI). The Vigileo/Flotrac system will analyze the pressure waveform 100 times per second over 20s, capturing 2000 data points for analysis and performing calculations by using data obtained in the most recent 20s. Each parameter will be recorded as a number once a minute. After levering, flushing, and baseline calculation, the fluid infusion will be performed according to the following protocol until the end of the surgery.

Two periphery intravenous access will be established to ensure fluid administration. The attending anesthesiologist will evaluate the parameters every 15 minutes. If SVV $\geq 15\%$ continued for at least 5 numbers during 15 minutes, a 3-ml/kg bolus of hydroxyethyl starch will be infused within the next 15 minutes through one intravenous access. When the number of the bolus is up to 5, hydroxyethyl starch will be replaced by Acetate Ringer’s Solution for further bolus infusion. If SVV is less than 15% and the MAP is lowered more than 20% of the baseline value, norepinephrine or phenylephrine will be used to raise blood pressure if CI (Cardiac output index) $\geq 2.0 \text{ L/min/m}^2$ in GDFT group. If CI $\geq 2.0 \text{ L/min/m}^2$, dopamine will be given. In traditional fluid therapy group, norepinephrine, phenylephrine or dopamine will be given by experience. When MAP increases by more than 20% from the baseline value, urapidil or nicardipine will be administered. When HR is less than 50 bpm, atropine 0.2 to 0.5mg will be given, and when HR is higher than 100bpm, esmolol will be infused 10 to 20mg in bolus or continuously (see Figure 2). Acetate Ringer’s solution will be infused at a fixed rate of 3 ml/kg·h for basic fluid maintenance through another periphery intravenous access during the whole process.

In the traditional fluid therapy group, the fluid volume is given according to the experience of the anesthesiologist. The intraoperative target value of MAP and HR maintained and the protocol of cardiovascular agents administration is as same as the GDFT group.

If bleeding in the GDF group exceeds 3ml/kg/min for more than 20 minutes, or estimated blood loss exceeds 20% of total blood volume and circulation is difficult to maintain according to the GDFT protocol, the attending anesthesiologist will decide whether violate the GDFT protocol and take emergent measures for safety.

**Anaesthesia induction and management**

Routine monitoring will include non-invasive blood pressure (NBP), electrocardiography (ECG), pulse oxygen saturation (SPO$_2$), end-tidal carbon dioxide partial pressure (EtCO$_2$), bispectral index(BIS), body
temperature, and urine output. The radial artery is punctured to monitor SVV, CI, SVI, and other parameters. After the two intravenous accesses are established using 18-G catheters, the participants will get about 300ml of Acetate Ringer's Solution before induction. A 22-G arterial line (A-line) will be inserted at the radial artery immediately after induction. Preoperative midazolam (0.02-0.05 mg/kg) and penehyclidine hydrochloride (0.5-1 mg) will be given intravenously. Anesthesia will be induced with sufentanil, rocuronium or cisatracurium, and propofol or etomidate, and maintained with total intravenous anesthesia by propofol and remifentanil. The dose of propofol will be adjusted to maintain BIS within 40 to 60. Analgesia will be supplemented with sufentanil to attenuate the potential pain stimuli, including skull pin fixation, scalp incision, and dura suture. In addition, the infusion rate of remifentanil will also be adjusted according to the strength of the pain stimulus. Intravenous rocuronium or cisatracurium will be administered as needed.

After tracheal intubation, mechanical ventilation will be performed with the following parameters: tidal volume of 6 to 8 mL·kg⁻¹, respiratory rate of 10 to 15/min to maintain normocapnia, 40-60% inspired oxygen fraction, and fresh gas at a flow rate of 1 to 2 L/min with positive end-expiratory pressure as 0 to 5 cmH₂O. Before incision, additional scalp local infiltration with 0.5% ropivacaine will be given. All patients will receive 250 mL of 20% mannitol infusion for 20 minutes at the start of the scalp incision. For all of the participants, the MAP will be maintained higher than 80% of the baseline value and HR will be maintained within 50 to 100 bpm throughout the surgery. Hemoglobin level will be maintained at more than 7 g/dl.

Data collection and measurement

All patients will receive MRI to assess the tumour size, location, vascularization, and brain edema before surgery. The degree of preoperative brain edema will be assessed according to the Steinhoff classification: 0, no signs of edema; I, mild edema, limited to 2 cm; II, moderate edema, > 2 cm but limited to the ipsilateral hemisphere; and III, severe edema, extending to the contralateral hemisphere[21]. Demographic information and past history of patients were recorded during preoperative screening. Comorbidity was ranked according to the Charlson Comorbidity Index that categorises comorbidity based on International Classification of Diseases diagnosis codes. The functional status will be assessed using Karnofsky Performance Status (KPS) at admission and 30 days after surgery. The physiological parameters, the total doses of anaesthetics will be recorded by anaesthesiologists through a designed data collection table.

All patients will receive plain CT scan within 24 hours, postoperatively. Plain CT will be performed with a 16-row multidetector scanner (Discovery CT 750HD, GE Healthcare, Milwaukee, USA), a 64-row multidetector scanner (LightSpeed VCT, GE Healthcare, Milwaukee, USA) and a 256-row multidetector scanner (Revolution CT, GE Healthcare, Milwaukee, USA). The scanning parameters will be as follows: tube voltage, 120kV; tube current, 300mA; field of view, 23cm×23cm and matrix, 512×512. Imaging data will be measured by using a picture archiving and communication system (NEUSOFT PACS/RIS v2.1, Shenyang, China). The maximum diameters of the tumor will be measured on axial, coronal, and sagittal
images and defined as x, y, and z. The volume will be calculated as the following formula: \( V = \frac{4}{3}\pi \times \frac{x}{2} \times \frac{y}{2} \times \frac{z}{2} \) \cite{20}.

Postoperative complications (defined in supplementary figure 3) and all-cause mortality will also be recorded. Long-term follow-up will be performed through telephone or a remote video interview to collect information.

**Outcomes**

This study aims to demonstrate whether SVV-guiding GDFT could reduce the postoperative brain edema volume in patients with high-grade supratentorial gliomas compared with traditional fluid therapy. The assessment of primary and secondary outcomes will be performed by a neuroradiologist and trained researchers blinded to the group allocation. Figure 3 shows data collection at each time point.

**Primary outcome**

The primary outcome is brain edema volume within 24 hours postoperatively by CT examination. Image evaluation and analysis will be performed by two independent neuroradiologists. They are specifically trained to detect cerebral edema on CT based on the following methods for 3 months before evaluation. Both of them will be blinded to the clinical data.

Postoperative brain edema is defined as edema surrounding the surgical resection cavity that has a low density on CT images. Image evaluators manually delineate a region of interest (ROI) and the operative cavity on each slice. The area \( S_{\text{edema+cavity}} \) and \( S_{\text{cavity}} \) will be calculated automatically by the PACS (picture archiving and communication system, NEUSOFT PACS/RIS v2.1, Shenyang, China). The total volume will be acquired by multiplying the area and slice thickness. We will obtain the total volume of the abnormal density or signal \( (V_{\text{edema+cavity}}) \) and the volume of the cavity \( (V_{\text{cavity}}) \). The volume of edema \( (V_{\text{edema}}) \) will be calculated by the following formula: \( V_{\text{edema}} = V_{\text{edema+cavity}} - V_{\text{cavity}} \).

**Secondary outcomes**

1. Brain relaxation will be evaluated upon opening the dura by neurosurgeons. Brain relaxation is divided into four grades: completely relaxed, satisfactorily relaxed, firm brain, bulging brain\cite{22, 23}.

2. The blood gas, electrolytes, hematocrit, lactic acid, and glucose at the beginning of fluid management and the closure of the skin incisions.

3. The renal function (urea, creatinine, estimated glomerular filtration rate) and coagulation function (fibrinogen degradation products, D dimer, prothrombin time, international normalized ratio, activated partial thromboplastin time, fibrinogen) on postoperatively-1 day.

4. Recovery quality will be evaluated by the quality of recovery-15 score (QoR-15) in five aspects (physical comfort, physical independence, psychological support, emotion, and pain) after patients recover from
general anesthesia within the first 24 hour.

5. Incidence of severe pain (numerical rating scale ≥ 5) within 24 hours and at the 1, 3, 5, 7 days after surgery will be assessed.

6. Length of ICU and hospital stay and total hospitalization cost will be recorded.

**Data Monitoring Committee**

The project will be monitored by the Data Monitoring Committee (DMC) composed of specialists in anesthesiology, neurosurgery, ethics, neuroradiologist, statistics, and methodology. The DMC will conduct audits through regular interviews or telephone. The DMC is responsible for terminating the research in case of a severe adverse event.

**Sample size calculation and Statistical plan**

We used the PASS 2011 software (NCSS LLC, USA) for Windows to calculate the sample size. According to the pilot study we conducted, the sample size of 450 will find the difference in postoperative brain edema volume of 4 cm$^3$ with a standard deviation of 18 and 16 in two groups. Considering the drop-out rate of 5%, we calculated the sample size of 480. In addition, we also estimated the sample size based on previous studies reporting the incidence of brain edema varying from 6.8% to 50% after malignant brain tumor resection. The sample size of 480 patients (240 for each group) will be sufficient to detect the difference of 13% at a two-tailed significant level of 0.05 and a power of 80% using the Student's t-test, with a drop-out rate of 5%.

Descriptive statistics will be reported as means with standard deviation and medians with inter-quartile range (IQR) for normally distributed data and skewed continuous data, respectively, and counts (percentage) for categorical data. Normally distributed continuous variables will be compared with Student's t-test, while skewed variables will be compared using the Mann-Whitney U test. The categorical variables will be compared with X$^2$ analysis or Fisher's exact test. The repeated measurement data will be analysed by repeated measurements of variance analysis with Bonferroni correction. The primary outcome, brain edema volume will be compared between groups using the Student’s t-test on intention to treat and per protocol, and the conclusion will be drawn according to the intention-to-treat analysis.

The intention-to-treat analysis will depend on the allocated population while the per-protocol analysis will depend on the actual fluid therapy the population receives. Furthermore, subgroup analysis is required in this study, and patients will be analyzed according to preoperative ASA physical status, KPS score, and WHO classification given by postoperative pathology. In addition, missing data will be imputed using inverse probability weighting and the worst-case imputation scenarios for sensitivity analysis will be performed for missing values of primary outcomes. SPSS 16.0 for windows will be used for all statistical analyses. The statistical significance will be declared at a type I error of 0.05.

**Reporting Adverse Events**
Adverse events include intraoperative sudden cough and body movement, postoperative renal failure, respiratory and circulatory arrest, acute myocardial infarction, acute pulmonary embolism, arrhythmia, and massive cerebrovascular infarction. All adverse events associated with the trial will be recorded and closely monitored until it has been proved that intraoperative fluid therapy is not the cause of the event. The principal investigator is responsible for reporting all adverse events. Once an adverse event occurs, it should be immediately reported to the research department and informed to the principal investigator to determine the severity of adverse events. All adverse events associated with this study will be recorded and reported to the Ethics Committee within 24 hours.

Discussion

This is a prospective, randomized, double-blind, parallel-controlled clinical trial aiming to observe the effects of intraoperative GDFT on the postoperative brain edema volume in neurosurgical patients with high-grade supratentorial gliomas.

In this study, we choose Acetate Ringer's Solution as a crystalloid fluid to supplement the preoperative fluid loss and intraoperative physiological requirements. Acetate Ringer's Solution has the advantage of being close to human physiology in composition and osmotic pressure, which will avoid perchloric acidosis caused by a large amount of normal saline input, the low osmotic pressure, and subsequent cerebral edema if sodium lactate Ringer's solution\textsuperscript{[24]} is administered. Moreover, we uniformly give about 300ml of crystalloid solution before induction of anesthesia to supply part of the preoperative loss. Combined with previous related studies, the basic intraoperative infusion rate will be mostly maintained at 1-4 ml/kg/h\textsuperscript{[11,15,18]}.

Hydroxyethyl starch is currently the colloid most commonly used\textsuperscript{[25]}. Although studies\textsuperscript{[26]} had pointed out that within the clinically recommended dose range (<33ml/kg)\textsuperscript{[27]}, the coagulation function is not affected\textsuperscript{[26]}, but for patients undergoing brain surgery, intraoperative hemostasis is based on electrocoagulation, which is different from the normal coagulation in the surgical field. Considering the potential impact of a large amount of hydroxyethyl starch on the coagulation function, we have set the upper limit colloid dose close to the clinically commonly used dose of 15ml/kg, which is the amount of 5 boluses for prudential reasons. Further, if the conditions are met and bolus shock therapy is needed, 3ml/kg crystalloid solution is used instead of hydroxyethyl starch.

Cerebral edema is the primary outcome of this study. Plain CT is not the optimal image examination in evaluating cerebral edema after craniocerebral surgery, compared to MR. However, considering that the degree of early postoperative cerebral edema is more closely related to intraoperative fluid management, the study stipulates that imaging examinations should be performed as soon as possible within 24 hours after surgery to evaluate cerebral edema. MRI examination takes a long time and the image effect requires cooperation of patients. Whereas patients with high-grade gliomas often present poor consciousness and low cooperation in the early postoperative period. In addition, it is often difficult for patients to enter the MRI machine due to the head dressings and tumor cavity drainage devices. Early
MRI examination within 24 hours after surgery is not clinically feasible. In neurosurgery, CT examination is usually performed 6 hours postoperatively. CT has the advantages of short examination time, low requirements for patient cooperation, and lower price, so it's more suitable for post-cranial surgery examinations. Therefore, we choose to use CT to measure postoperative cerebral edema.

**Summary**

In summary, we need to carry out a randomized controlled trial to determine the effect of intraoperative GDFT on postoperative brain edema. If intraoperative GDFT improves postoperative brain edema and reduces the incidence of perioperative complications in patients with malignant supratentorial glioma in neurosurgery, SVV-guiding GDFT will be popularized to improve postoperative outcomes for brain tumor patients.

**Ethics and dissemination**

Ethical approval has been granted by the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University on 27th NOV 2017 (reference number: KY2017-067-02, version: 1.4). The study recruited the first patient on 26th Nov, in 2018 and the study is estimated to be completed on 30th November, in 2022. The results of the study will be disseminated through presentations at scientific conferences and publications in scientific journals.

**Protocol amendment**

The principal investigator will be responsible for any decision to amend the protocol that may influence the potential safety or conduct of the study. Modification to the protocol will be made by the principal investigator and approved by the Ethics Committee, Beijing Tiantan Hospital, Capital Medical University, before implementation.

**Patient and public involvement**

Patients and the public were not directly consulted in the development of the research question or outcome measures. Patients were not involved in the design, recruitment, and conduct of the study. At the completion of this trial, a manuscript will be prepared to present the trial results. Results of the final study will be disseminated to all study participants through their preferred method of communication indicated at the time of enrolment. The burden of intervention will not be taken by participants themselves.

**Declarations**

**Availability of data and materials:**

Following publication of research results, a completely anonymous set of data can be made available upon reasonable scientific request and with ethical approval. Appropriate credit or co-authorship must be
awarded to the author of the study, depending on the extent of data use and planned research. The CRF samples used in this study are available upon reasonable scientific request.

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**Contributors:**

XYL, XYZ, SL, YFF, YMP: conceived the study, contributed to the study design and analytical plans. XYL, XYZ: drafted the protocol. All authors read and approved the final protocol.

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**Competing interests:**

None declared.

**Data sharing statement**

This manuscript is a protocol for a randomized controlled trial, which does not include data.

** Trails status:**

Protocol version: 1.4

Study start: November 26, 2018

Primary completion: October 2022

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Figures
Figure 1

Flow chart of the study.

HGG: high-grade glioma; ASA: American Society of Anaesthesiologists; WHO: World Health Organization; NYHA: New York Heart Association Functional Classification; COPD: chronic obstructive pulmonary disease; CCr: creatinine clearance rate; BMI: Body Mass Index; GDFT: goal-directed fluid therapy.
Figure 2

GDFD protocol.

SVV: stroke volume variation; MAP: mean arterial pressure; HR: heart rate; Hb: hemoglobin. GDFD: goal-directed fluid therapy.
Figure 3

Data collection at each time point.

Pre-op: preoperative; Op: operative; GDFT: goal-directed fluid therapy; SDT: standard treat; MRI: Magnetic Resonance Imaging; CT: computerized tomography; NRS: Numeric Rating Scale.

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- SPIRITchecklist0130.docx
- supplementarytable1.docx