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Original Contribution

Enhanced recovery after elective craniotomy: A randomized controlled trial

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ABSTRACT

Study objectives: Enhanced recovery after surgery (ERAS) protocols have been proven to improve outcomes but have not been widely used in neurosurgery. The purpose of this study was to design a multidisciplinary enhanced recovery after elective craniotomy protocol and to evaluate its clinical efficacy and safety after implementation.
Design: A prospective randomized controlled trial.
Setting: The setting is at an operating room, a post-anesthesia care unit, and a hospital ward.
Patients: This randomized controlled trial (RCT) prospectively analyzed 151 patients who underwent elective craniotomy between January 2019 and June 2020.
Interventions: The neurosurgical ERAS group was cared for with evidence-based systematic optimization approaches, while the control group received routine care.
Measurements: The primary outcomes were the postoperative length of stay (LOS) and hospitalization costs. The secondary outcomes included 30-day readmission rates, postoperative complications, postoperative pain scores, length of intensive care unit (ICU) stay, duration of the drainage tube, time to oral intake, time to ambulation, and postoperative functional recovery status.
Main results: After ERAS protocol implementation, the median postoperative LOS (4 days to 3 days, difference [95% confidence interval, CI], 2 [1 to 2], $P < 0.0001$) and hospitalization costs (6266 USD to 5880 USD, difference [95% CI], 427.0 [234.8 to 633.6], $P < 0.0001$) decreased. Compared to routine perioperative care, the ERAS protocol reduced the incidence of postoperative nausea and vomiting (PONV) (28.0% to 9.2%, adjusted odds ratio [OR] 0.3, 95% CI 0.1–0.7, $P = 0.003$), shortened urinary catheter removal time by 24 h (64.0% to 83.0%, adjusted OR 2.9, 95% CI 1.3–6.5, $P = 0.031$), improved ambulation on postoperative day 1 (POD 1) (30.7% to 75.0%, adjusted OR 7.5, 95% CI 3.6–15.8, $P < 0.0001$), shortened the time to oral intake (15 h to 13 h, difference [95% CI], 3 [1 to 4], $P < 0.001$), and improved perioperative pain management.
Conclusions: Implementation of an enhanced recovery after elective craniotomy protocol had significant benefits over conventional perioperative management. It was associated with a significant reduction in postoperative length of stay, medical cost, and postoperative complications.

1. Introduction

Over the past few decades, the incidence and complexity of neurosurgical diseases have been rising worldwide [1,2]. Conventional neurosurgery has a high incidence of postoperative complications and is associated with major psychological and physiological stress [3]. The concept of enhanced recovery after surgery (ERAS), which was originally proposed by Kehlet et al. [4] in 1997, has emerged to substantially minimize the stress response and improve postoperative outcomes [5–7].

ERAS protocols have been widely applied in diverse surgical subspecialties [8,9]; however, there is a paucity of studies on the

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application of comprehensive ERAS protocols in neurosurgery. The continuous development of imaging technology, intraoperative navigation, and neuroelectrophysiological monitoring technology, along with the wide application of ultrashort-acting anesthetic drugs, have made minimally invasive neurosurgery possible with improved postoperative recovery and satisfaction [10,11]. Despite decades of research into individual elements of perioperative care [12,13], there is sparse evidence on ERAS protocols in neurosurgical anesthesia. Wang et al. [14] confirmed the feasibility of ERAS in neurosurgery. However, there have been few studies of anesthesia-specific elements in ERAS protocols.

Therefore, given these knowledge gaps, we designed and implemented this prospective randomized controlled trial (RCT) to evaluate the clinical effectiveness and safety of evidence-based enhanced recovery after elective craniotomy. The hypothesis is that the application of an ERAS protocol in patients undergoing elective craniotomy can reduce the length of stay (LOS), cost, and incidence of postoperative complications when compared to conventional perioperative care.

2. Materials and methods

This prospective RCT was conducted at Xiangya Hospital, Central South University, China. The trial protocols were approved by the institutional ethics committee of Xiangya Hospital of Central South University (approval number: 2018121104) and registered at the Chinese Clinical Trial Registry (ChiCTR1900020997, principal investigator: Dr. Wangyuan Zou, date of registration: January 24, 2019) before implementation. Written informed consent for participation was obtained from all enrolled patients.

2.1. Sample size calculation

The sample size was calculated by Statistics Analysis System 9.4 (SAS Institute Inc., Cary, NC, USA). We chose two-sample *t*-tests assuming equal variance to calculate the sample size and used the following settings: $\alpha = 0.05$, a power of 80%, standard deviation (SD) = 1.5, two-sided, and group allocation = 1:1. Based on the results of preliminary experiments and the hypothesis that the enhanced recovery after elective craniotomy protocol would reduce the postoperative LOS by 1 day, we calculated that 63 patients were needed for each of the two groups. Considering a 20% dropout rate, we needed to enroll 75 patients in each group in the final sample.

2.2. Participants and recruitment

All patients were evaluated for eligibility at the beginning of their admission to the hospital. The inclusion criteria were age 18 to 70 years, American Society of Anesthesiologists (ASA) class I or II, a single intracranial lesion, and elective craniotomy. Patients were excluded if they had a history of preoperative change in consciousness, had a disease history that could affect postoperative functional recovery (e.g., paralysis, autoimmune disease, acute or decompensated heart failure or acute coronary syndrome, or severe liver or renal malfunction), were unwilling to participate in the study for any reason, or had participated in another study within the 3 months before enrollment.

2.3. Randomization

Before enrollment, 207 patients undergoing elective craniotomy were evaluated for eligibility. Fifty-six patients were excluded from the trial after the initial assessment for not meeting the inclusion criteria, refusing surgery, or refusing to participate. Finally, 151 patients were enrolled. Subject numbers were entered into SPSS 25.0 (SPSS Inc., Chicago, IL, USA) to generate a randomization scheme. Eligible patients were prospectively randomized into either the ERAS group or the control group. Seventy-five patients were allocated to the control group receiving conventional perioperative care, whereas 76 patients were allocated to the ERAS group receiving protocolized ERAS perioperative care. Each enrolled patient was followed up by a study coordinator to ensure strict compliance with the trial protocol.

2.4. Enhanced recovery pathway

After a literature search on established ERAS protocols and considering the neurosurgical patients' conditions and surgical characteristics, we formulated a multidisciplinary enhanced recovery after neurosurgery protocol. Our protocol complies with the ERAS society research reporting guidelines [15]. Our protocol consisted of three major parts: pre, intra, and postoperative care. The study was carried out in a large tertiary hospital in China. Detailed information on the ERAS protocol for neurosurgery is summarized in Table 1.

2.5. Preoperative elements of the ERAS protocol

Before admission, all patients received education about the benefits and methods of abstinence from both smoking and alcohol before surgery. Patients in the ERAS group received a comprehensive explanation of ERAS protocols and perioperative care. Each patient's cardiopulmonary function, nutritional status, underlying disease, Karnofsky Performance Status (KPS) score [16], risk for postoperative nausea and vomiting (PONV) and mental state were evaluated and optimized before the operation. If necessary, relevant departments were counseled to assist in the diagnosis and treatment to ensure that the psychological and physical conditions of the patients were optimized as soon as possible. The Caprini Risk Assessment Scale was used to assess the risk of venous thromboembolism (VTE) for all enrolled patients after admission [17]. For high-risk VTE patients in the ERAS group, intermittent pneumatic compression and compression stockings during the perioperative period was considered the safest and most economical way to balance the risk of VTE and bleeding after neurosurgery. Neither preoperative sedative drugs nor preoperative mechanical bowel preparation was administered. According to the ASA guidelines, the fasting time in the ERAS group was reduced to 6 h before surgery for solids and 2 h before surgery for clear liquids [18]. Furthermore, the ERAS group was administered oral carbohydrate loading (12.5% carbohydrate solution, 250 ml) up to 2 h before surgery. A lung function evaluation and respiratory function exercises (including abdominal breathing exercises and balloon blowing) were routinely performed before the operation.

2.6. Intraoperative elements of the ERAS protocol

Antibiotic prophylaxis was given within 60 min before skin incision. All enrolled patients received midazolam, sufentanil, cisatracurium, and etomidate for anesthesia induction. Based on previous research [19,20] and our institution's practice of using combined intravenous and inhalational anesthesia for maintenance during elective craniotomy, combined intravenous and inhalational anesthesia was applied in this study. Target controlled infusions of propofol and remifentanil, as well as a continuous infusion of dexmedetomidine and inhaled sevoflurane, were used during the maintenance of anesthesia. Dexmedetomidine was stopped 30 min before the end of the operation. Cisatracurium was administered intermittently. Scalp block was performed for patients in the ERAS group by an anesthesiologist who was skilled in this technique; blocked nerves included the supraorbital, supratrochlear, auriculotemporal, zygomaticotemporal, greater occipital, and lesser occipital nerves. Three to four milliliters of 0.5% ropivacaine was injected into each blocked site. Parecoxib sodium was administered within 30 min before skin incision. An additional 10 to 15 ml of 0.5% ropivacaine was administered by the surgeon along the incision line before incision and during closure. Body temperature was monitored throughout the surgery, and necessary measures (e.g., fluid warmer and heating blanket) were taken to prevent hypothermia. A bispectral index (BIS) monitor (Aspect Medical Systems, Inc., Norwood, MA, USA) was used

Table 1
Comparison of major perioperative management between the ERAS protocol (ERAS group) and the conventional protocol (control group).

	ERAS protocol	Conventional protocol
Preoperative bundle		
Preoperative counseling and education	Detailed patient education (e.g., goals for postoperative pain management, lung function exercise, oral intake, and ambulation), comprehensive preoperative evaluation, and counseling conducted by trained staff	Routine counseling and education provided by the neurosurgery team
Preoperative fasting and carbohydrate loading	Shortened preoperative fasting time (solid food permissible up to 6 h and clear fluids up to 2 h before surgery); oral carbohydrate loading 2 h before anesthesia	Preoperative fasting per institutional routine (10 to 12 h for solids and 6 to 8 h for liquids); no preoperative oral carbohydrates
Lung function exercise	Preoperative routine lung function exercise, including abdominal breathing exercises and balloon blowing	No lung function exercise
Intraoperative bundle		
Scalp blocks and infiltration	Bilateral scalp blocks with 0.5% ropivacaine; ropivacaine infiltration along the incision line	No scalp blocks or infiltration
Fluid management	Individualized goal-directed fluid therapy to optimize SVV guided by the Vigileo/FloTrac system [43]	Adjusted intravenous fluid regimen according to hemodynamic and urine output but no formal goal-directed fluid management technique applied
Intraoperative monitoring	Basic monitoring (e.g., invasive blood pressure, electrocardiogram, blood oxygen saturation); BIS monitoring; ETAC monitoring; SVV monitoring	Basic monitoring
Temperature management	Continuous body temperature monitoring during the surgery; necessary measures to keep the temperature above 36 °C, such as fluid warmer and heating blanket	No specific temperature monitoring
Protective lung ventilation strategy	Low tidal volume (6–8 ml/kg) (ideal body weight), low PEEP (5 mmHg), FiO2 ≤ 60%, and lung recruitment	No protective lung ventilation strategy
Postoperative bundle		
Preoperative pain management	Multimodal analgesia [infiltration and scalp blocks, dexmedetomidine, selective COX-2 inhibitor (IV parecoxib,40 mg)]	Routine (per the individual practice of the anesthesiologist, usually selective COX-2 inhibitor)
Optimal management of PONV	1) Identify patients who are high risk for PONV: the application of the Apfel simplified risk score [21] before the surgery; 2) Reduce risk for PONV: minimization of perioperative opioids, preoperative carbohydrate loading, and shortened fasting time; 3) Routine use of antiemetic combination therapy: dexamethasone and 5-HT_3 receptor antagonist (ondansetron) during the operation	Routine (per the individual practice of the anesthesiologist, usually 5-HT_3 receptor antagonist)
Early oral nutrition and gastrointestinal protection	Oral liquids initiated within 4 h of extubation and a full diet at 12–24 h; intravenous infusion of PPIs (omeprazole) before and after surgery	Oral liquids at least 6 h after surgery, and a full diet at least 24 h after surgery; PPIs were not routinely applied
Catheter management	Early urethral catheter removal within 24 h or as soon as possible	Routine (the time with indwelling catheter was usually more than 24 h)
Early mobilization	Encourage patient to ambulate; set a daily activity goal; properly mobilize in bed 6 h after surgery and out of bed 24 h after surgery (or as soon as possible)	Routine (usually mobilization at least POD 2)

Abbreviations: 5-HT_3: 5-hydroxytryptamine 3; BIS, bispectral index; COX, cyclooxygenase; ETAC, end-tidal anesthetic-agent concentration; IV, intravenous; PEEP, positive end-expiratory pressure; POD, postoperative day; PONV, postoperative nausea and vomiting; PPIs: proton pump inhibitors; SVV, stroke volume variation.

throughout surgery to maintain the appropriate depth of anesthesia (a BIS score of 40 to 60). After cleaning the skin on the patient's forehead, anesthesiologists attached the sensor electrode to the forehead on the opposite side of the surgical site to ensure that surgical disinfectant and intraoperative body position changes would not interfere with BIS monitoring. In addition, patients in the ERAS group adopted a lung protective ventilation strategy, including low tidal volume, low positive end-expiratory pressure (PEEP) ventilation, and lung recruitment. Goal-directed fluid therapy (GDFT) was applied to optimize stroke volume variation (SVV), which was guided by the Vigileo/FloTrac system (Edwards Lifesciences, Irvine, Ca, USA), to meet the dual goals of surgical condition satisfaction and hemodynamic stability. Ephedrine was given when the patient's mean arterial pressure (MAP) was <60 mmHg or reduction in MAP was more than 20% from baseline. Atropine was given when the heart rate was <45 bpm to avoid severe bradycardia.

2.7. Postoperative elements of the ERAS protocol

After the operation, the patient returned to the postanesthesia care unit (PACU) intubated, and extubation was performed when criterias are met. The criteria for extubation included eye opening, purposeful movement, following instructions, return of the gag reflex, spontaneous respiration with tidal volume greater than 6 ml/kg of ideal body weight, and $SpO_2 > 95\%$. All patients were cared for by the same anesthesiologists and nurse anesthetists in the PACU, who were all blinded to the group assignment or randomization. Perioperative pain management adopted a multimodal analgesic scheme (i.e., the combination of scalp nerve block, scalp infiltration, and selective cyclooxygenase [COX]-2 inhibitor [parecoxib]) to ensure effective analgesia and reduce the adverse effects of opioids. Dexamethasone and a 5-hydroxytryptamine 3 (5-HT_3) receptor antagonist (ondansetron) were administered to prevent PONV. Patients in the ERAS group were given intravenous proton pump inhibitors (PPIs) before and after surgery to protect the gastrointestinal mucosa and prevent stress ulcers. A liquid diet was initiated 4 h after recovery from anesthesia, and a regular diet commenced gradually on POD 1. The intravenous infusion was stopped on POD 3. Wound drainage catheters were not employed routinely in the ERAS group. The urinary catheter was removed as early as possible on POD 1 in the ERAS group. Patients in the ERAS group were encouraged to set a daily activity

goal and ambulate as quickly as possible in the postoperative period. They were properly mobilized in bed 6 h after surgery and started to ambulate 24 h after surgery.

The perioperative management of the control group was based on the conventional perioperative neurosurgery care protocols of the Department of Anesthesiology, Neurosurgery, and Nursing at our institution, which are commonly applied in patients undergoing craniotomy in most large hospitals of China. Some of these elements that have been routinely applied in clinical practice (e.g., preoperative antibiotic therapy, smoking cessation education, etc.) were also applied in the control group. We did not change the perioperative management in the control group. Briefly, the conventional protocols included routine preoperative counseling and education, preoperative fasting per institutional routine (10 to 12 h for solids and 6 to 8 h for liquids), no preoperative oral carbohydrates, routine intraoperative fluid management regimen based on urine output and hemodynamics, basic monitoring, no routine temperature monitoring, conventional postoperative analgesia (usually selective COX-2 inhibitor) and PONV prophylaxis (usually a single antiemetic), and long-term bed rest.

2.8. Discharge criteria

Patients were discharged when they met all discharge criteria. The discharge criteria included full consciousness, adequate pain control with oral analgesics, body temperature within a normal range, ability to take adequate food without the need for intravenous nutrition, ability to move independently, effective wound healing, and major laboratory tests within normal limits. The assessments for discharge were conducted by an independent senior attending surgeon on the ward who was instructed to follow the discharge criteria and was blinded to the group assignments. Telephone follow-ups were conducted 1, 3, and 6 months after discharge. The content of the follow-up was the occurrence of adverse events and the KPS score, which was developed to objectively assess functional status and survivability [16,21].

2.9. Outcome measurements

Data on patient characteristics, perioperative variables, and postoperative situations were recorded during hospitalization and at the 6-month follow-up. The primary outcomes were postoperative LOS and total hospitalization costs. Postoperative LOS was defined as the number of calendar days from the completion of craniotomy to readiness for hospital discharge. The secondary outcomes were 30-day readmission rates, postoperative complications, postoperative pain scores, perioperative opioid consumption, length of ICU stay, duration of the drainage tube, time to first oral intake, and postoperative functional recovery status. Intraoperative variables, such as blood pressure and heart rate, were recorded. All patients were followed up at 1, 3, and 6 months after discharge. Perioperative pain was evaluated by a numeric rating scale (NRS) with a range of 0 to 10, where 0 means no pain and 10 means the worst possible pain. The patients in both groups were followed up at 2 h, 8 h, 24 h, 36 h, 48 h, and 72 h after surgery.

2.10. Statistical analysis

The mean ± SD (age, body mass index [BMI], NRS score, MAP, heart rate, and laboratory tests) or median (interquartile range) (postoperative LOS, costs, and KPS score) were used to describe continuous variables. Numbers (percentages) were used to describe categorical data (such as gender). The Kolmogorov-Smirnov test was used to determine the normal distribution of continuous variables. Student's *t*-test was used to statistically evaluate group differences in continuous data with a normal distribution. The Mann-Whitney *U* test was used to compare continuous variables without a normal distribution between the ERAS and control groups. For categorical data with small cell counts, we calculated the theoretical frequency. When the theoretical frequency was ≥5, we used the $\chi 2$ test without Yates' correction. When the theoretical frequency was <1, we used Fisher's exact test. If the theoretical frequency was between the two values, we used the $\chi 2$ test with Yates' correction. For repeated-measures data, analysis of variance (ANOVA) was used to compare each time point within the group, and the least significance difference (LSD) multiple comparison test was used for the pairwise comparison of time points within the group. Adjusted logistic regression analysis was used for the comparison of categorical data and is presented as odds ratios (ORs) with 95% confidence intervals (CIs). Adjustments were performed for demographic characteristics (including gender, age, and BMI). For measurement data (regardless of whether they were normally distributed), we calculated the 95% CI around the difference to clarify confidence about the inferred effect size in the population. For non-normally distributed measurement data (such as postoperative LOS), we used the Hodges–Lehmann estimate to calculate the difference (95% CI). All hypothesis tests were 2-sided, and a *P* value <0.05 was considered statistically significant. All statistical analyses were performed by SPSS 25.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism 8 (GraphPad Software, San Diego, CA, USA).

3. Results

3.1. Patients and surgery characteristics

During the study period from January 2019 to June 2020, 207 patients were screened for eligibility, and 151 patients were recruited and randomized (Fig. 1).

The two groups were well balanced for baseline demographic characteristics (Table 2). All enrolled patients underwent elective craniotomy by the same experienced surgical team, and all patients received the assigned interventions. No significant differences among surgical characteristics were found between the two groups (Table 2, Supplemental Table 1). Blood loss in the two groups was minimal, and the difference was not statistically significant. There were no patients requiring allogeneic blood transfusion in either group (Supplemental Table 1).

3.2. Primary outcomes

The postoperative LOS in the ERAS group was significantly shorter than that in the control group (3 days vs. 4 days, difference [95% CI], 2 [1 to 2], $P < 0.0001$) (Table 3). Similarly, the total hospitalization costs of the ERAS group (5880 USD) were significantly lower than those of the control group (6266 USD, difference [95% CI], 427.0 [234.8 to 633.6], $P < 0.0001$). The primary outcomes were further subdivided to explore the influence of supratentorial and infratentorial lesions on the results. Both types of lesions tended to decrease the postoperative LOS and costs in the ERAS group.

3.3. Secondary outcomes

Table 3 also summarizes the secondary outcomes between the two groups. There was no mortality in either group. Two patients developed incisional infections (one in the ERAS group and one in the control group), and one patient in the control group developed an intracranial infection. However, all of these patients recovered after antibiotic treatment, sterile dressing replacement or lumbar drainage. Two patients in the control group developed intracranial hypertension after the operation and improved after fluid restriction. One patient in the control group suffered cerebrospinal fluid leakage postoperatively but did not require reoperation. The Apfel simplified risk score [22] was used before the surgery to assess the risk of PONV in the two groups. The percentage of patients with high risk was similar between groups (52.6% in the ERAS group vs. 57.3% in the control group, $P = 0.625$). In the ERAS group, receiving optimal management of PONV, the incidence of PONV was significantly lower than that of the control group (OR 0.3, 95% CI

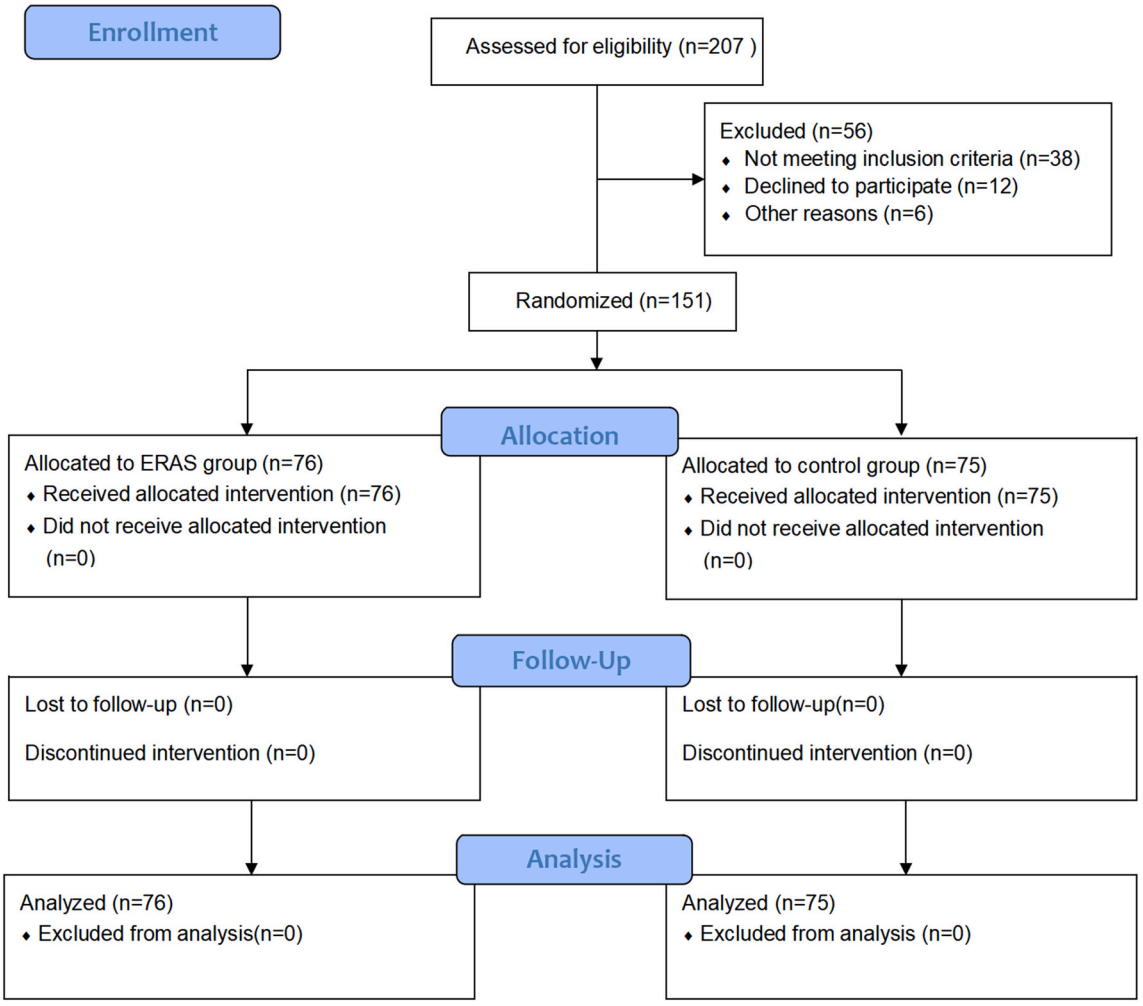

Fig. 1. CONSORT flow diagram of patients' distribution.
ERAS: enhanced recovery after recovery. A total of 207 patients who underwent craniotomy were evaluated for eligibility before enrollment. Fifty-six patients were excluded from this study after the initial assessment for not meeting the inclusion criteria, refusing to consent to surgery, or refusing to participate. Hence, 151 patients were enrolled. After informed consent was obtained, eligible patients were prospectively randomized into either the ERAS group or the control group.

0.1–0.7, $P = 0.003$).

Other nonsurgical complications were similar between the two groups. Of note, no patient required 30-day reoperation or readmission after surgery in either group. Patients receiving the ERAS protocol had a median first oral intake time of 13 h after surgery compared with 15 h in the control group (difference [95% CI], 3 [1 to 4], $P < 0.001$). For postoperative urinary catheter removal, 83.0% of patients in the ERAS group and 64.0% of patients in the control group had urinary catheter removal less than 24 h after the operation (OR 2.9, 95% CI 1.3–6.5, $P = 0.008$). For delayed removal, 4 patients in the ERAS group and 9 patients in the control group had catheter removal more than 48 h after surgery. Postoperatively, a slightly higher percentage of patients in the control group had wound drainage placement, but the difference was not statistically significant. For postoperative ambulation, patients in the ERAS group had a higher rate of ambulation on POD 1 (75.0% vs. 30.7%, OR 7.5, 95% CI 3.6–15.8, $P < 0.0001$).

There was no significant difference in KPS scores between the two groups before surgery. During the follow-up, we observed that the median KPS score of patients in the ERAS group was higher than that in the control group at the time of discharge (90 vs. 80) and 30 days after discharge (100 vs. 90), and the differences were statistically significant (difference [95% CI], −10 [−10 to −10], $P < 0.0001$). Seven patients in the ERAS group had a KPS score of <100 at the 90-day follow-up, which was significantly fewer than in the control group (20 patients, OR 3.6, 95% CI 1.4–9.1, $P = 0.006$). At the 180-day follow-up, the difference in KPS scores between the two groups was no longer statistically significant. Therefore, we believe that the ERAS protocol can effectively improve the short-term prognosis of patients undergoing craniotomy, and whether it can improve the long-term prognosis still needs further study.

Table 4 summarizes perioperative pain management. The difference in preoperative NRS scores between the two groups was not statistically significant. Intraoperatively, the ERAS group had a lower median dose of remifentanil (0.7 mg) than the control group (0.9 mg, difference [95% CI], 0.2 [0.1 to 0.3], $P < 0.0001$). Compared to the control group, patients receiving scalp block and infiltration had fewer hemodynamic fluctuations at the beginning of the operation (compared to T1) (Supplemental Table 2). When we compared the postoperative pain scores between the two groups, we found that at each follow-up time point, the NRS scores of the ERAS group were lower than those of the control group. When we performed multiple comparisons within the group, we found that the ERAS group had a statistically significant decrease in the NRS score at 8 h postoperatively (compared with 2 h after surgery), while the control group did not appear to have a statistically significant decrease until 36 h postoperatively. Opioids were not given routinely after surgery unless the patient's NRS score was greater than 6. Ten patients in the ERAS group and 32 patients in the control group experienced moderate to severe pain, which required additional tramadol

Table 2
The patient characteristics and details of surgery between the 2 groups.

Characteristics	ERAS Group ($n = 76$)	Control Group ($n = 75$)	*P* value
Age, yrs	52.9 ± 10.5	50.6 ± 9.7	0.169
Male	30 (39.5%)	32(42.7%)	0.742
BMI, kg/m^2	23.7 ± 3.0	23.8 ± 2.8	0.806
ASA classification			0.608
I	52 (68.4%)	48 (64.0%)	
II	24 (31.6%)	27 (36.0%)	
Apfel-score			0.625
<3	36 (47.4%)	32 (42.7%)	
≥3	40 (52.6%)	43 (57.3%)	
Preexisting conditions			
Chronic cardiovascular disease	16 (21.1%)	19 (25.3%)	0.568
Chronic pulmonary disease	1 (1.3%)	3 (4.0%)	0.367
Diabetes	5 (6.6%)	4 (5.3%)	>0.999
Hyperthyroidism	3 (3.9%)	1 (1.3%)	0.620
History of smoking	16 (21.3%)	14 (18.7%)	0.841
Laboratory tests[a]			
Hemoglobin, g/dL	13.5 ± 1.3	13.2 ± 1.5	0.144
WBC, 10^9/L	5.5 ± 1.5	5.4 ± 1.7	0.618
Blood platelet, 10^9/L	200.4 ± 49.5	185.4 ± 57.2	0.087
Blood glucose, mmol/L	5.1 ± 0.5	5.0 ± 0.7	0.123
Albumin, g/L	42.8 ± 4.3	41.5 ± 5.0	0.090
Indication for surgery			0.998
Trigeminal neuralgia	26 (34.2%)	24 (32.0%)	
Hemifacial spasm	25 (32.8%)	27 (36.0%)	
Meningioma	9 (11.8%)	8 (10.7%)	
Glioma	7 (9.2%)	8 (10.7%)	
Cholesteatoma	3 (4.0%)	2 (2.6%)	
Hemangioma	3 (4.0%)	3 (4.0%)	
Acoustic neuroma	3 (4.0%)	3 (4.0%)	
Lesion location			0.832
Supratentorial superficial	1 (1.3%)	2 (2.7%)	
Supratentorial deep-seated	16 (21.1%)	15 (20.0%)	
Infratentorial	59 (77.6%)	58 (77.3%)	
Duration of surgery, min[b]	142.5 (120.0, 193.8)	160.0 (120.0, 220)	0.368
Duration of ICU stay, min	0	0	
Duration of postoperative mechanical ventilation, min	35 (20, 45)	35 (20, 45)	0.470

Data are presented as the mean ± standard deviation (SD), count (percentage), or median (IQR).
Abbreviations: ERAS, enhanced recovery after surgery; CI: confidence interval; BMI, body mass index; ASA, American Society of Anesthesiologists; WBC, white blood cell; cm: centimeter; ICU, intensive care unit.
[a] Preoperative.
[b] Duration of surgery is the time between skin incision and closure of the incision.

(OR 0.2, 95% 0.1–0.5, $P < 0.0001$). The postoperative pain duration in the ERAS group was shorter than that in the control group (2 days vs. 3 days, difference [95% CI], 1 [1 to 2], $P < 0.0001$).

4. Discussion

In this study, patients assigned to the ERAS group had a significantly shorter LOS and lower hospitalization costs than the control group. Additionally, the neurosurgical ERAS protocol produced better clinical outcomes in terms of reduced postoperative complications (e.g., PONV), higher quality of early recovery, lower postoperative pain scores, and less perioperative opioid consumption.

Traditionally, most patients undergoing craniotomy have average postoperative hospital stays ranging from 4 to 6 days for safety reasons, even in the absence of perioperative complications [23,24]. However, prolonged LOS undoubtedly leads to an increase in the financial burden of patients and a decrease in patient satisfaction. A report by Neville et al. showed that early discharge after brain tumor surgery is less costly and does not increase postoperative complication rates or 30-day readmission rates [25]. Therefore, the primary hypothesis of our

Table 3
Primary outcomes and Secondary outcomes between the ERAS and control groups.

	ERAS Group (n = 76)	Control Group (n = 75)	Difference 95% CI	*P* value
Primary outcomes				
Postoperative LOS, days	3 (2, 4)	4 (4, 6)	2 (1–2)	< 0.0001
Supratentorial	5 (4, 5)	6 (5, 7)	1 (1–2)	0.009
Infratentorial	3 (2,3)	4 (4, 5)	2 (1–2)	< 0.0001
Total cost of hospitalization, USD	5880 (5603, 7024)	6266 (6031, 8961)	427.0 (234.8–633.6)	< 0.0001
Supratentorial	8154 (7145, 9983)	10,389 (9596, 11,271)	1972.5 (807.8–2908.0)	0.004
Infratentorial	5833 (5543, 6012)	6121 (5994, 6328)	367.1 (239.4–500.0)	< 0.0001
Secondary outcomes				
Surgical complications				
Mortality	0 (0)	0 (0)		
Infection [a]	1 (1.3%)	2 (2.7%)		0.620
Epilepsy	0 (0)	0 (0)		
Hemorrhage	0 (0)	0 (0)		
Intracranial hypertension	0 (0)	2 (2.7%)		0.245
Cerebrospinal fluid leakage	0 (0)	1 (1.3%)		1
Nonsurgical complications				
PONV	7 (9.2%)	21 (28.0%)		0.003
Postoperative delirium	1 (1.3%)	3 (4.0%)		0.367
Respiratory depression	0 (0)	5 (6.7%)		0.282
Cardiovascular complication	0 (0)	0 (0)		
Respiratory complication	1 (1.3%)	1 (1.3%)		> 0.999
Digestive complication	0 (0)	0 (0)		
Urinary system complication	0 (0)	0 (0)		
VTE	0 (0)	0 (0)		
30-day reoperation rate for any indication	0 (0)	0 (0)		
30-day readmission	0 (0)	0 (0)		
Time to first oral intake, h	13 (10,15)	15 (13,20)	3 (1–4)	< 0.0001
Time to urinary catheter removal				0.031
< 24 h	63 (83.0%)	48 (64.0%)		
24–48 h	9 (11.8%)	18 (24.0%)		
≥48 h	4 (5.2%)	9 (12.0%)		
Wound drainage management				
Patients	5 (6.6%)	9 (11.8%)		0.277
Time to wound drainage removal				0.377
< 24 h	1 (20.0%)	0 (0)		
24–48 h	3 (60.0%)	7 (77.8%)		
≥48 h	1 (20.0%)	2 (22.2%)		
Time to ambulation, no. (%)				< 0.0001
POD 1	57 (75.0%)	23 (30.7%)		
POD 2	11 (14.5%)	32 (42.7%)		
POD 3	6 (7.9%)	12 (16.0%)		
>POD 3	2 (2.6%)	8 (10.6%)		

(*continued on next page*)

Table 3 (*continued*)

	ERAS Group (n = 76)	Control Group (n = 75)	Difference 95% CI	*P* value
Functional recovery				
Discharge KPS score	90 (90, 100)	80 (80, 90)	−10 (−10−−10)	< 0.0001
30-day follow-up KPS score	100 (90, 100)	90 (80, 90)	-10 (−10−−10)	< 0.0001
90-day follow-up KPS score[b] (KPS = 100/KPS ⟨100)	69/7	55/20		0.006
180-day follow-up KPS score[b] (KPS = 100/KPS < 100)	76/0	71/4		0.058

Data are presented as the count (percentage) or median (IQR).
Abbreviations: OR: odds ratio, CI: confidence interval, LOS: length of stay, USD: United States dollars; PONV, postoperative nausea and vomiting; VTE, venous thromboembolism; POD: postoperative day; KPS: the Karnofsky Performance Status.

[a] There was 1 incision infection in the ERAS group, 1 incision infection and 1 intracranial infection in the control group.

[b] The KPS scores are mostly 100 at 90- and 180-day follow-up, therefore, these follow-up data are presented as categorical data (KPS =100/KPS ⟨100).

Table 4
Perioperative pain management.

	ERAS Group (n = 76)	Control Group (n = 75)	Difference (95% CI)	*P* value
Preoperative NRS score	0.4 ± 0.7	0.3 ± 0.8	−0.1 (−0.3–0.2)	0.401
Remifentanil [a], mg	0.7 (0.6, 1.0)	0.9 (0.7, 1.4)	0.2 (0.1–0.3)	< 0.0001
Postoperative NRS score				
NRS (2 h)	2.5 ± 0.8	2.9 ± 0.8	0.4 (0.2–0.7)	< 0.005
NRS (8 h)	2.0 ± 1.0**	2.9 ± 1.2	0.9 (0.5–1.2)	< 0.0001
NRS (24 h)	1.5 ± 1.2****	2.6 ± 1.3	1.1 (0.7–1.5)	< 0.0001
NRS (36 h)	0.9 ± 1.0****	2.2 ± 1.1****	1.3 (1.0–1.6)	< 0.0001
NRS (48 h)	0.7 ± 0.8****	1.7 ± 0.9****	1.0 (0.7–1.3)	< 0.0001
NRS (72 h)	0.4 ± 0.7****	1.7 ± 1.5****	1.3 (0.9–1.6)	< 0.0001
NRS ≥ 4/NRS < 4[b]	10/66	32/43		< 0.0001
Postoperative pain duration, days	2 (1,3)	3 (2, 4)	1 (1–2)	< 0.0001

Data are presented as the mean ± standard deviation (SD), or median (IQR).
Abbreviations: OR: odds ratio, CI: confidence interval, NRS, numeric rating scale.
*indicates the comparison of NRS scores within the group (compared with 2 h after operation) , *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001.

[a] Intraoperative maintenance anesthetic analgesia.

[b] The number of patients who suffer from moderate to severe pain; [c] Postoperative salvage analgesia.

research is that the ERAS protocol can reduce the postoperative LOS, which also indicates the effectiveness of the novel ERAS protocol. The data we obtained are consistent with the primary outcomes from other subspecialty ERAS studies [26]. The ERAS group had lower costs during hospitalization than the control group. Enhanced recovery after elective craniotomy might improve clinical outcomes and effectively reduce medical costs at the same time.

Conventional craniotomy is typically associated with significant psychological and physiological stress, whereas excessive stress can increase the risk of secondary cardiovascular and cerebrovascular events, malabsorption of nutrients, and delayed recovery [27,28]. Previous studies have shown that the successful implementation of certain elements of the evidence-based ERAS approach throughout the perioperative period can improve postoperative functional recovery and reduce the incidence of postoperative complications [29]. Given the importance of functional recovery in neurosurgery, our research focuses more on whether our neuroanesthesia protocols can promote the early functional recovery of patients after craniotomy.

Despite early calls for the application of an ERAS protocol in neurosurgery, few studies have been performed [30]. A systematic review published by Kapoor et al. suggested that the application of an ERAS protocol is not superior to conventional perioperative management in patients undergoing craniotomy. However, this may be because the finding was based on the limited number of low-quality RCTs [31]. This article also reflects that there is a paucity of research on enhanced recovery after neurosurgery. One recent study applied an ERAS pathway in elective craniotomy, and the results confirmed its safety and effectiveness [14]. However, detailed descriptions of anesthesia-specific care are lacking. Insufficient analgesia after craniotomy causes 80% of patients to experience moderate to severe pain [32]. Therefore, we selected postoperative pain and perioperative opioid use as our secondary outcomes. Perioperative pain management is an important part of the ERAS protocol, and proper analgesia can effectively reduce perioperative stress and improve patient comfort and rehabilitation. Opioids have many associated adverse reactions, such as respiratory depression, oversedation, and confusion, which may affect the assessment of recovery and mask early intracranial adverse events [33]. Therefore, the goal of our analgesic protocol was to reduce the consumption of opioids [34]. Dexmedetomidine is a relatively selective alpha2-adrenergic agonist that can reduce postoperative discomfort and agitation in neurosurgical patients and has a significant analgesic effect [35]. Scalp block and infiltration are safe techniques and have been studied as methods for decreasing intraoperative and postoperative pain in neurosurgery [36,37]. Selective COX-2 inhibitors (e.g., parecoxib) can effectively control neurosurgical pain without increasing the risk of postoperative bleeding [38]. Our trial indicated that patients who underwent a multimodal analgesia scheme had better perioperative pain control, decreased opioid consumption, and improved intraoperative hemodynamic control.

The incidence of PONV is as high as 43% to 70% in the craniotomy population [39], which may lead to an increased risk of aspiration pneumonia, elevated intracranial pressure, brain edema, intracranial hemorrhage, or even brain herniation. The recent guidelines recommend identifying patients' risk for PONV before surgery, adequate hydration on the day of surgery (e.g., shortening the preoperative fasting time and oral carbohydrate loading), and the combination of two or more antiemetics [40]. After the implementation of the optimal management of PONV in our ERAS protocol, we observed a significant reduction in the incidence of PONV.

The effectiveness of the ERAS protocol has been attributed to the efficient cooperation of various departments and the improvement in health care organizations and services [41,42]. A multidisciplinary ERAS protocol, such as ours, could be a safe and effective approach to improving postoperative outcomes after neurosurgery.

The application of ERAS protocols in neurosurgical anesthesia is still in the initial stage of exploration. At present, most of the related published literature is systematic reviews, and there is a lack of research on key issues in anesthesia (such as optimal management of PONV and perioperative pain management). Based on these knowledge gaps, we designed this research and confirmed the effectiveness and safety of the enhanced recovery after neurosurgery protocol, but there are still several limitations that need to be considered in our study. First, patients >70 years old and < 18 years old with critical physical conditions or complex comorbidities and those who were ASA class III or higher were excluded because of safety considerations. Second, similar to previous RCTs investigating ERAS protocols, complete blinding was likely not possible; however, the researchers who collected the data, PACU and

ICU physicians and nurses, surgeons who evaluated the discharge, and statisticians were unaware of the group assignment. Third, due to differences in medical equipment costs, healthcare provider salaries and payment systems among various countries, our result in hospitalization costs may not translate into the same benefits in other countries. Finally, whether and how to adapt the ERAS protocol to all subtypes of neurosurgical anesthesia (e.g., traumatic brain injury) needs to be further studied.

5. Conclusion

In conclusion, we found the implementation of this multidisciplinary enhanced recovery after elective craniotomy protocol had significant benefits over conventional perioperative management. The ERAS protocol was associated with a significant reduction in LOS, medical costs, and postoperative complications for patients undergoing craniotomy. However, further evaluation of the protocol in larger multicenter studies is warranted to verify our findings.

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Authors contributions

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Statistical analysis and interpretation of data: Lei Wang, Hongwei Cai, Wangyuan Zou; Drafting the article: Lei Wang, Wangyuan Zou;

Critical revision of the article: Wangyuan Zou, Jiapeng Huang, Qulian Guo;

All authors read and approved the final manuscript.

Disclosures

The authors declare no conflicts of interest.

Author statement

Our paper complies with the ERAS society research reporting guidelines.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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