Safety and efficacy of a novel neurosurgical enhanced recovery after surgery protocol for elective craniotomy: a prospective randomized controlled trial

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OBJECTIVE Although enhanced recovery after surgery (ERAS) programs have gained acceptance in various surgical specialties, no established neurosurgical ERAS protocol for patients undergoing elective craniotomy has been reported in the literature. Here, the authors describe the design, implementation, safety, and efficacy of a novel neurosurgical ERAS protocol for elective craniotomy in a tertiary care medical center located in China.

METHODS A multidisciplinary neurosurgical ERAS protocol for elective craniotomy was developed based on the best available evidence. A total of 140 patients undergoing elective craniotomy between October 2016 and May 2017 were enrolled in a randomized clinical trial comparing this novel protocol to conventional neurosurgical perioperative management. The primary endpoint of this study was the postoperative hospital length of stay (LOS). Postoperative morbidity, perioperative complications, postoperative pain scores, postoperative nausea and vomiting, duration of urinary catheterization, time to first solid meal, and patient satisfaction were secondary endpoints.

RESULTS The median postoperative hospital LOS (4 days) was significantly shorter with the incorporation of the ERAS protocol than that with conventional perioperative management (7 days, $p < 0.0001$). No 30-day readmission or reoperation occurred in either group. More patients in the ERAS group reported mild pain (visual analog scale score 1–3) on postoperative day 1 than those in the control group (79% vs. 33%, OR 7.49, 95% CI 3.51–15.99, $p < 0.0001$). Similarly, more patients in the ERAS group had a shortened duration of pain (1–2 days; 53% vs. 17%, OR 0.64, 95% CI 0.29–1.37, $p = 0.0001$). The urinary catheter was removed within 6 hours after surgery in 74% patients in the ERAS group (OR 400.1, 95% CI 23.56–6796, $p < 0.0001$). The time to first oral liquid intake was a median of 8 hours in the ERAS group compared to 11 hours in the control group ($p < 0.0001$), and solid food intake occurred at a median of 24 hours in the ERAS group compared to 72 hours in the control group ($p < 0.0001$).

CONCLUSIONS This multidisciplinary, evidence-based, neurosurgical ERAS protocol for elective craniotomy appears to have significant benefits over conventional perioperative management. Implementation of ERAS is associated with a significant reduction in the postoperative hospital stay and an acceleration in recovery, without increasing complication rates related to elective craniotomy. Further evaluation of this protocol in large multicenter studies is warranted.

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KEYWORDS enhanced recovery after surgery; ERAS; neurosurgery; elective craniotomy; postoperative length of stay; outcomes

ABBREVIATIONS ASA = American Society of Anesthesiologists; DVT = deep vein thrombosis; ERAS = enhanced recovery after surgery; KPS = Karnofsky Performance Status; LOS = length of stay; POD = postoperative day; PONV = postoperative nausea and vomiting; VAS = visual analog scale.

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CONVENTIONAL craniotomy is typically associated with significant physiological stressors and prolonged functional recovery. An excessive stress response can predispose patients to an increased risk of cardiovascular and cerebrovascular complications, nutrient malabsorption, and delayed convalescence.³³ With our increasing understanding of perioperative pathophysiology, the concept of enhanced recovery after surgery (ERAS), introduced by Kehlet in 1997, has been established in an effort to improve functional outcomes after surgery and decrease perioperative morbidity.^{17,21} Several ERAS protocols have gained acceptance in a wide variety of surgical subspecialties.^{3,24,25,35,39} To the best of our knowledge, however, ERAS protocols within neurosurgery, specifically for elective craniotomy, have not been established. Owing to the rapid worldwide development of neurosurgery in recent decades, minimally invasive craniotomy has benefited a huge number of patients with improved recovery and satisfaction.⁸ Given the core concept of evidence-based review of ERAS and ERAS protocols for abdominal and pelvic surgeries, Hagan et al. proposed a preliminary set of recommendations including seventeen ERAS items for creating a standardized protocol for craniotomy.¹² However, the safety and feasibility of implementing a detailed neurosurgical ERAS protocol for craniotomy in a clinical setting have not been described in the literature.

Here, we describe our experience with the implementation of a novel, multidisciplinary, evidence-based, neurosurgical ERAS protocol for elective craniotomy at a large tertiary care hospital in China. The aim of this study was to evaluate the safety and efficacy of this ERAS protocol and to prospectively evaluate whether it resulted in a shorter postoperative length of stay (LOS) and lower perioperative morbidity than those in patients who received the standard of care at our institution.

Methods

Patient Recruitment

All patients, ages 18–65 years (inclusive), with a single intracranial lesion, medically eligible for elective craniotomy, and admitted between October 2016 and May 2017 were eligible for inclusion in this study. However, patients with intracranial trauma, pathology requiring emergent surgery, preoperative disturbance of consciousness, and a confounding condition (e.g., pregnancy) or disease that could impact postoperative recovery (e.g., paralysis, spinal deformity, autoimmune diseases, myocardial infarction, severe infection, liver and renal malfunction, or severe psychological or mental illness) were excluded. A total of 197 patients were assessed for eligibility prior to enrollment (Fig. 1). Fifty-seven patients were excluded for not meeting the inclusion criteria, refusal to participate, or refusal to consent to surgery; therefore, a total of 140 patients were enrolled. After informed consent was obtained, patients were prospectively randomized into two groups by computerized random number generation conducted by the research coordinator: control group or ERAS group. A total of 70 patients were allocated to the control group and received conventional perioperative

care based on institutional practice patterns. Alternatively, the remaining 70 patients were allocated to the ERAS group that received care according to the novel neurosurgical ERAS protocol described in this study. Given the requirement for active patient participation, it was not possible to perform the study with blinded participants and care providers. However, those who collected data and assessed outcomes were blinded from the patients' study arm.

ERAS Protocol and Conventional Care

We were supported by the local institutional ethics committee in developing a neurosurgical ERAS protocol through a quality patient care initiative. Institutional review board approval was also obtained prior to recruiting patients for this study. In June 2016, we set up a Neurosurgical ERAS Working Group including clinicians and ancillary staff from neurosurgery, anesthesiology, inpatient and operative nursing, as well as nutrition services. This multidisciplinary working group was then used to develop and apply the neurosurgical ERAS protocol outlined in this study. The protocol was designed for patients undergoing elective craniotomy, adapted from concepts elicited from other established protocols for general surgery, and completed after an extensive review of the current evidence-based perioperative care interventions supported in the literature. However, some critical concepts for abdominal and/or pelvic surgery do not apply to neurosurgical patients and were thus excluded from our protocol. In addition, we reviewed the published literature on other successful ERAS protocols, particularly the preliminary ERAS recommendations for oncological craniotomy proposed by Hagan et al.¹² Briefly, our protocol consists of three main sections: 1) preoperative management and evaluation, which include preoperative counseling, preoperative functional status evaluation, preoperative smoking and alcohol abstinence, mental state assessment, evaluation and prophylactic antithrombotic therapy, postoperative nausea and vomiting (PONV) risk score assessment, preoperative intestinal intervention, nutritional assessment, and preoperative oral carbohydrate loading; 2) surgical and anesthetic management, which include minimally invasive surgery for craniotomy, scalp incision anesthesia, nonopioid analgesia, absorbable skin suture, hypothermia avoidance, and fluid balance; and 3) postoperative management, which includes PONV, postoperative diet, urinary drainage, early off-bed activity and ambulation, and so on (Supplementary File 1).

The working group was instructed to follow the components of the ERAS protocol in a step-by-step manner and to implement as many ERAS elements as possible. Once the patient was enrolled in this study, the Neurosurgical ERAS Record Checklist (Supplementary File 2) was attached in the patient's medical record system during his or her entire hospital stay.

The perioperative care of patients in the conventional care (i.e., control) group was performed under the individual practice patterns of the surgeons and anesthesiologists at our institution, which are based on traditional neurosurgical postoperative protocols commonly employed in this patient population.

FIG. 1. CONSORT flow diagram for the trial. Figure is available in color online only.

Compliance With Ethical Standards

Informed consent was obtained from each participant in this study. Review and analysis of patient information were approved by the Ethical Committee of Tangdu Hospital. This randomized controlled trial was registered with the Chinese Clinical Trial Registry (<http://www.chictr.org.cn/showproj.aspx?proj=16480>), and its registration no. is ChiCTR-INR-16009662.

Outcome Measurements

Patient demographic data (age, sex), preoperative nutritional information (total body weight, BMI), preoperative comorbidity status (American Society of Anesthesiologists [ASA] classification), and patient comorbidities (smoking, diabetes, hypertension, hypercholesterolemia, etc.) were assessed and recorded at admission.

The primary endpoint of this study was postoperative hospital LOS, which was defined as the number of calendar days from the operation to the date of discharge during the index hospitalization. Total hospital LOS and 30-day readmission rates were also recorded. Total hospital stay was calculated by adding the LOS during any subsequent readmissions to the index hospital LOS. Secondary endpoints included postoperative morbidity, surgical complications (e.g., surgical site infection, intracranial infection, epilepsy, and hemorrhage), nonsurgical complications (e.g., respiratory complications, cardiovascular complications,

gastrointestinal complications, urinary tract complications, and venous thromboembolism), functional recovery status (e.g., discharge and 30-day Karnofsky Performance Status [KPS] score), and patient satisfaction ratings.

Discharge Criteria

Patients in either the ERAS or the control group were discharged once they met our predefined discharge criteria, which included the following: adequate pain management with oral analgesia, adequate intake of solid food without the need for intravenous fluids, no fever, independent mobility, and safe disposition home. The decision to discharge was made via the consensus of two senior attending physicians in the Department of Neurosurgery, who were instructed to follow the discharging criteria and were independent of the researchers involved in this study.

Statistical Analysis

Data on patient characteristics, intraoperative parameters, and postoperative course were collected during the index hospitalization and at the 30-day follow-up. As the primary endpoint of this study, expected postoperative LOS was estimated to be approximately 7 days for most elective craniotomy patients in our hospital. Based on the hypothesis that our ERAS protocol was expected to reduce the postoperative LOS by at least 25%, a sample size of at least 58 patients per arm was calculated to have a power

of 80% and a significance of 5%. Considering a dropout rate maximized to 20%, we determined the final sample size to be 70 patients in each group. Interim analysis was planned when the minimal number of the predefined sample size was met. Descriptive statistics of the control and ERAS groups were used to compare all relevant patient characteristics. Continuous data with a normal distribution were statistically tested for group differences using the Student t-test. Data without normal distribution were analyzed using the Mann-Whitney U-test. Readmission, complication, and mortality rates were analyzed using the chi-square test (with/without Yates' correction) or the Fisher exact test. A p value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS (version 19, IBM Corp.).

Results

The two patient groups were similar with respect to sex, age, BMI, ASA physical status, and comorbidities (Table 1). Baseline characteristics did not significantly differ between the two groups. Comorbidities such as hypertension, diabetes, and chronic pulmonary diseases (e.g., chronic obstructive pulmonary disease, sleep apnea) were equally distributed between the two groups. In each group, the proportion of females was higher than that of males, although there was no significant sex difference between the two groups.

All patients in both groups underwent craniotomy by the same experienced surgical team, and all patients received their allocated intervention. The relevant details of surgery and operative outcomes are shown in Table 2. There was no significant difference in the primary indication for surgery. The majority of patients presented with common neurological diseases such as meningioma, vestibular schwannoma, glioma, cholesteatoma, trigeminal neuralgia, and cavernous malformation. In both groups, meningioma and glioma composed the majority of pathologies. There was no significant difference between the two groups in terms of lesion location (i.e., superficial or deep-seated supratentorial or infratentorial lesion). The median duration of surgery was similar between the ERAS and control groups at 3.71 (range 1–10.83) hours versus 4 (range 2–11.5) hours, respectively ($p = 0.254$). Blood loss was minimal in most cases and did not differ between two groups (median 300 ml, range 0–1500 ml in ERAS group vs. 300 ml, 50–2600 ml in controls; $p = 0.868$). Nine (13%) patients in the ERAS group required blood transfusions (i.e., red blood cell and blood plasma transfusions) during the operation versus 6 (9%) patients in the control group (OR 1.57, 95% CI 0.53–4.69, $p = 0.412$). The median volume of neither the crystalloid nor the colloid during intraoperative fluid management differed between the two groups ($p = 0.396$ and 0.163 , respectively; Table 2).

Key program adherence measures for our ERAS protocol are shown in Table 3. For PONV management, a higher percentage of patients in the ERAS group received preoperative PONV prophylaxis (24%, OR 46.12, 95% CI 2.71–784.8, $p < 0.0001$) based on the preoperative PONV risk score. There was no PONV visual analog scale (VAS) score difference between the ERAS and control groups (p

TABLE 1. Summary of characteristics of 140 patients who underwent craniotomy

Parameter	ERAS Group	Control Group	p Value
No. of patients	70	70	
Median age in yrs (range)	51 (19–67)	49 (18–65)	0.945
Sex			0.476
Males, no. (%)	22 (31%)	26 (37%)	
Females, no. (%)	48 (69%)	44 (63%)	
Median BMI in kg/m ² (range)	24.9 (15.9–29.6)	23.7 (19.1–28.4)	0.676
ASA classification			0.41
I, no. (%)	13 (19%)	17 (24%)	
II, no. (%)	57 (81%)	53 (76%)	
Concomitant disease			
CHD/hypertension, no. (%)	18 (26%)	15 (21%)	0.550
Smoker, no. (%)	6 (9%)	9 (13%)	0.412
Liver/gallbladder, no. (%)	7 (10%)	4 (6%)	0.346
Lung, no. (%)	5 (7%)	8 (11%)	0.382
Diabetes, no. (%)	12 (17%)	8 (11%)	0.334
Miscellaneous, no. (%)	13 (19%)	6 (9%)	0.084
Subtotal, no. (%)	61 (87%)	54 (77%)	0.122

CHD = chronic heart disease.

$= 0.115$). The percentage of patients receiving oral and nasal cavity preparation (63/70 [90%] ERAS vs. 8/70 [11%] controls; OR 69.75, 95% CI 23.84–204.1, $p < 0.0001$) and gastrointestinal intervention (8/70 [11%] ERAS vs. 0/70 [0%] controls; OR 19.18, 95% CI 1.09–339.3, $p = 0.006$) was also significantly increased in the ERAS group. Of note, reduced preoperative fasting was a key element in our ERAS protocol. A total of 45/70 (64%) patients in the ERAS group followed a fasting period of 6–8 hours for food (OR 40.20, 95% CI 11.45–141.2, $p < 0.0001$), whereas most patients (67/70 [96%]) in the control group followed the routine fasting period of 8–12 hours (OR 0.025, 95% CI 0.007–0.009, $p < 0.0001$). Several elements were exclusive to our ERAS protocol, such as oral intake of a maltodextrin fructose solution (400 ml) 2 hours before surgery (64/70 [91%], OR 1399, 95% CI 77.22–25350, $p < 0.0001$) and incisional local anesthetic with ropivacaine (0.2%) immediately before scalp incision (61/70 [87%], OR 912.8, 95% CI 52.01–16019, $p < 0.0001$). In the ERAS group, subcutaneous suturing (67/70 [96%]) and skin suturing (54/70 [77%]) with absorbable sutures were mainly used for the skin closure, as compared to a high percentage of non-absorbable sutures (and stapler use) in the control group (subcutaneous suture 70/70 [100%], OR 0.0003, 95% CI 0.00002–0.007, $p < 0.0001$; skin suture 65/70 [93%], $p < 0.0001$).

For deep vein thrombosis (DVT) evaluation and prophylaxis, patients in both groups were encouraged to perform frequent active and passive movement of their lower limbs. However, the rate of mechanical DVT prophylaxis after surgery was significantly higher in the ERAS group

TABLE 2. Details of surgery and operative outcomes

Parameter	ERAS Group	Control Group	p Value
No. of patients	70	70	
Indication for surgery			
Meningioma, no. (%)	38 (54%)	30 (43%)	0.799
Convexity	18 (26%)	13 (19%)	0.309
Parafalx	10 (14%)	7 (10%)	0.605
CPA	6 (9%)	3 (4%)	0.491
Other locations	4 (6%)	7 (10%)	0.530
Acoustic neuroma, no. (%)	7 (10%)	9 (13%)	0.595
CPA cholesteatoma, no. (%)	6 (9%)	8 (11%)	0.778
Glioma, no. (%)	13 (19%)	18 (26%)	0.309
Glioblastoma	5 (7%)	6 (9%)	
Astrocytoma	2 (3%)	3 (4%)	
Anaplastic astrocytoma	2 (3%)	2 (3%)	
Oligodendroglioma	1 (1%)	2 (3%)	
Other*	3 (4%)	5 (7%)	
Other lesions, no. (%)	6 (9%)	5 (7%)	1
Trigeminal neuralgia	3 (4%)	3 (4%)	
Cavernous malformation	3 (4%)	2 (3%)	
Lesion location			0.571
Supratentorial superficial	25 (36%)	22 (31%)	
Supratentorial deep-seated	23 (33%)	20 (29%)	
Infratentorial	22 (31%)	28 (40%)	
Median length of procedure in hrs (min, 1st Q, 3rd Q, max)	3.71 (1, 1.98, 5.62, 10.83)	4 (2, 3, 4.83, 11.5)	0.254
Median blood loss during surgery in ml (min, 1st Q, 3rd Q, max)	300 (10, 180, 500, 1500)	300 (50, 200, 400, 2600)	0.868
Median RBC transfusion during surgery in U (min, 1st Q, 3rd Q, max)	0 (0, 0, 0, 4)	0 (0, 0, 0, 8)	0.477
Median blood plasma transfusion during surgery in ml (min, 1st Q, 3rd Q, max)	0 (0, 0, 0, 400)	0 (0, 0, 0, 800)	0.477
Median intraop crystalloid in ml (min, 1st Q, 3rd Q, max)	2000 (1000, 1500, 2500, 6500)	1850 (1000, 1375, 2625, 4500)	0.396
Median intraop colloid in ml (min, 1st Q, 3rd Q, max)	600 (0, 500, 1000, 1500)	500 (500, 500, 750, 1500)	0.163

CPA = cerebellopontine angle; Q = quartile; RBC = red blood cell.

* Other = including intraventricular, olfactory groove, and prepontine cistern meningiomas.

(45/70 [64%]) according to the patients' DVT risk scores (OR 9.66, 95% CI 4.30–32.67, $p < 0.0001$).

Postoperatively, a significantly higher percentage of patients in the ERAS group had early urinary catheter removal (i.e., within 24 hours). Specifically, 52/70 (74%) patients in the ERAS group had their urinary catheter removed in less than 6 hours after surgery (OR 400.1, 95% CI 23.56–6796, $p < 0.0001$). One patient in each group required reinsertion of the urinary catheter due to urinary retention. For postoperative dietary management, patients in the ERAS group had a faster time to first water intake (median 4 hours in ERAS group vs. 8 hours in control group, $p < 0.0001$), first oral polymeric nutritional supplement drink intake (median 8 hours vs. 11 hours, $p < 0.0001$), and first oral solid food intake (median 24 hours vs. 72 hours, $p < 0.0001$). The percentage of patients ambulating on postoperative day (POD) 1 and 2 was significantly higher in the ERAS group (64% in ERAS vs. 0% in controls on POD 1, OR 251.6, 95% CI 14.93–4239, $p < 0.0001$; 27% vs. 7% on POD 2, OR 4.84, 95% CI 1.69–13.86, $p = 0.004$).

Primary outcome measures are shown in Table 4. There was a significant reduction in the median postoperative LOS (7 days in controls vs. 4 days in ERAS group, $p < 0.0001$) as well as in the total hospital LOS (13 vs. 10 days, $p = 0.004$).

Univariate analysis showed a significant association between a shorter postoperative LOS (≤ 4 days) and the following parameters in the ERAS group: blood loss no more than 300 ml during surgery, preoperative carbohydrate loading, absorbable skin suture, oral solid intake on POD 1, no postoperative wound drainage. There was also a trend toward statistical significance for an association between a shorter LOS and mechanical prophylaxis for DVT as well as PONV VAS score. A multivariate logistic regression model including variables with $p < 0.20$ in the univariate analysis were analyzed to determine independent predictors of a shorter postoperative LOS. Oral solid intake on POD 1 (OR 0.11, 95% CI 0.007–0.58, $p = 0.014$) and a mild PONV VAS score (OR 0.852, 95% CI 0.015–0.941, $p = 0.033$) were found to significantly influence postoperative LOS in the ERAS group (Supplemental Table 1).

TABLE 3. Key ERAS program measures

Parameter	ERAS Group	Control Group	p Value
No. of patients	70	70	
PONV management			
Preop PONV risk score (range)	2 (0–3)	2 (0–3)	
Preop PONV prophylaxis, no. (%)	17 (24%)	0 (0%)	<0.0001
PONV VAS score, no. (%)			0.115
Mild (1–4)	60 (86%)	50 (71%)	
Moderate (5–6)	7 (10%)	15 (21%)	
Severe (7–10)	3 (4%)	5 (7%)	
Preop intestinal intervention, no. (%)	8 (11%)	0 (0%)	0.0063
Oral & nasal cavity prep, no. (%)	63 (90%)	8 (11%)	<0.0001
Preop fasting & carb loading, no. (%)			
Fasting food for 8–12 hrs	25 (36%)	67 (96%)	<0.0001
Fasting food for 6–8 hrs	45 (64%)	3 (4%)	
2 hrs preop, oral maltodextrin fructose solution, 400 ml	64 (91%)	0 (0%)	<0.0001
Scalp incision anesthetic: ropivacaine 0.2%, no. (%)	61 (87%)	0 (0%)	<0.0001
Intravenous antibiotics given before incision, no. (%)	70 (100%)	70 (100%)	1
Surgical incision suturing, no. (%)			
Subcutaneous suture			
Nonabsorbable suture	3 (4%)	70 (100%)	<0.0001
Absorbable suture	67 (96%)	0 (0%)	
Skin suture			
Absorbable suture	54 (77%)	0 (0%)	<0.0001
Nonabsorbable suture	16 (23%)	65 (93%)	
Surgical skin stapler	0 (0%)	5 (7%)	
Evaluation & prophylactic antithrombotic therapy, no. (%)			
Lower limbs active/passive activity	52 (74%)	58 (83%)	0.217
Mechanical prophylaxis (intermittent pneumatic compression or graduated compression stockings)	45 (64%)	11 (16%)	<0.0001
Urinary drainage, no. (%)			
Removal of urinary catheter in 6 hrs	52 (74%)	0 (0%)	<0.0001
Removal of urinary catheter in 6–24 hrs	10 (14%)	7 (10%)	
Removal of urinary catheter over 24 hrs	8 (11%)	63 (90%)	
Urinary catheter re-insertion	1 (1%)	1 (1%)	1
Postop diet (min, 1st Q, 3rd Q, max)			
Time to first water intake in hrs	4 (4, 4, 6, 24)	8 (4, 6, 12, 48)	<0.0001
Time to first oral liquid intake in hrs	8 (6, 6, 12, 24)	11 (8, 9.5, 30, 48)	<0.0001
Time to first oral solid food intake in hrs	24 (24, 24, 36, 72)	72 (24, 36, 72, 96)	<0.0001
Adherence to ambulation, no. (%)			
Patients ambulating on POD 1	45 (64%)	0 (0%)	<0.0001
Patients ambulating on POD 2	19 (27%)	5 (7%)	
Patients ambulating on POD 3	3 (4%)	16 (23%)	
Patients ambulating ≥ POD 5	3 (4%)	49 (70%)	

Similarly, for predictors of postoperative LOS in the control group, multivariate analysis was performed using variables with $p < 0.20$ in the univariate analysis. Results showed that ambulation on POD 1 was the only independent predictor for a shorter postoperative LOS (OR 0.06, 95% CI 0.004–0.92, $p = 0.043$).

When combining the two groups, absorbable skin suture (OR 0.03, 95% CI 0.003–0.300, $p = 0.003$), oral solid

intake on POD 1 (OR 0.11, 95% CI 0.03–0.51, $p = 0.004$), and no postoperative wound drainage (OR 0.12, 95% CI 0.01–0.94, $p = 0.044$) were established as independent predictors for a shorter postoperative LOS in the multivariate analysis (Supplemental Table 2).

Of note, no 30-day readmission or reoperation for any indication was required in either group (Table 4). The total cost of hospitalization was significantly cheaper in the

TABLE 4. Primary outcome measures

Parameter	ERAS Group	Control Group	p Value
No. of patients	70	70	
Median total hospital LOS from admission to discharge in days (min, 1st Q, 3rd Q, max)	10 (4, 7, 14, 29)	13 (5, 10, 18, 34)	0.004
Median hospital LOS from end of procedure to discharge in days (min, 1st Q, 3rd Q, max)	4 (1, 3, 6, 13)	7 (3, 6, 11, 28)	<0.0001
30-day all-cause readmission rate, no. (%)	0 (0)	0 (0)	
Reoperation rate for any indication w/in 30 days, no. (%)	0 (0)	0 (0)	
Total cost of hospitalization in RMB (min, 1st Q, 3rd Q, max)	52930 (35697, 45579, 60184, 91493)	64316 (44973, 52603, 82417, 139153)	0.001

ERAS group (Chinese Yuan Renminbi [RMB] 52930, range 35697–91493) than in the control group (RMB 64316, range 44973–139153; $p = 0.001$).

Secondary outcome measures are shown in Table 5. Of note, these elements were incorporated given potential safety concerns regarding the ERAS protocol. Importantly, there were no perioperative deaths in either group. The occurrence of surgical complications including surgical site infection, intracranial infection, seizure, intracranial hemorrhage, and other complications (e.g., stroke, facial paralysis after vestibular schwannoma, tinnitus, etc.) was similar in the two groups. Three patients in the ERAS group and two patients in the control group had a surgical site infection but recovered after sterile dressing change and antibiotic treatment. Four patients in the ERAS group and six patients in the control group had an intracranial infection but recovered after antibiotic treatment and lumbar drainage. One patient in the control group had a postoperative cerebral infarction (i.e., stroke) and was later diagnosed with multiple end organ dysfunction requiring a

2-week stay in the intensive care unit. Two patients (3%) in the ERAS group and three patients (4%) in the control group had insignificant intracranial or epidural hemorrhage but did not require any reoperation or further medical treatment (OR 1.52, 95% CI 0.25–9.41, $p = 1$).

The occurrence of nonsurgical complications including respiratory, cardiovascular, digestive, and urinary complications and venous thromboembolism was also similar in the two groups. No patient in the ERAS group developed a DVT, although two patients in the control group had a DVT (OR 0.19, 95% CI 0.009–4.13, $p = 0.496$). Functional recovery was also similar in the two groups. The median discharging KPS score for the ERAS group was 90 (range 70–100, SD 9.165, 95% CI 90–90), whereas the median score for the control group was 80 (range 50–100, SD 14.23, 95% CI 80–90). Though a statistically significant difference in the discharging KPS score was not achieved, there was a trend toward a lower KPS score in the control group. The benefits of the ERAS protocol may account for this, but this hypothesis needs to be verified with a larger

TABLE 5. Secondary outcome measures

Parameter	ERAS Group	Control Group	p Value
No. of patients	70	70	
Surgical complication, no. (%)			
Mortality	0 (0%)	0 (0%)	
Surgical site infection/subcutaneous effusion	3 (4%)	2 (3%)	1
Intracranial infection	4 (6%)	6 (9%)	0.512
Epilepsy	3 (4%)	2 (3%)	1
Hemorrhage*	2 (3%)	3 (4%)	1
Others†	5 (7%)	3 (4%)	0.718
Nonsurgical complication, no. (%)			
Respiratory complication	2 (3%)	5 (7%)	0.441
Cardiovascular complication	1 (1%)	0 (0%)	1
Digestive complication	0 (0%)	0 (0%)	
Urinary tract complication	0 (0%)	1 (1%)	1
DVT	0 (0%)	2 (3%)	0.496
Functional recovery			
Median discharging KPS score (min, 1st Q, 3rd Q, max)	90 (70, 80, 90, 100)	80 (50, 80, 90, 100)	0.055
Median 30-day follow-up KPS score (min, 1st Q, 3rd Q, max)	100 (80, 90, 100, 100)	100 (80, 80, 100, 100)	0.673

* Hemorrhage refers to small amount of epidural hematoma or surgical area hemorrhage, not including intracranial hemorrhage that needs re-operation.

† Including cerebral infarction, facial paralysis after acoustic neuroma (House-Brackmann facial paralysis rating ≥ 3), tinnitus, etc.

TABLE 6. Postoperative wound drainage and pain management

Parameter	ERAS Group	Control Group	p Value
No. of patients	70	70	
Postop wound drainage management, no. (%)			
Postop drain placement	12 (17%)	68 (97%)	<0.0001
Postop drainage duration			0.059
<24 hrs	4 (33%)	6 (9%)	
24–48 hrs	7 (58%)	56 (82%)	
>48 hrs	1 (8%)	6 (9%)	
Postop surgical pain management, no. (%)			
POD 1 pain VAS score			<0.0001
1–3	55 (79%)	23 (33%)	
4–6	13 (19%)	42 (60%)	
7–9	2 (3%)	5 (7%)	
Postop pain duration in days, no. (%)			<0.0001
1–2	37 (53%)	12 (17%)	
2–3	18 (26%)	26 (37%)	
3–4	13 (19%)	27 (39%)	
>4	2 (3%)	5 (7%)	
Analgesic medication administration	15 (21%)	21 (30%)	0.246

sample in future studies. Of note, the patient in the control group who developed a cerebral infarction had a KPS score of 50 at the time of discharge but improved to 80 at the 30-day follow-up, indicating the patient's improved recovery. These results confirm that our discharging criteria for both groups were objective and were judiciously adhered to by the physicians. Therefore, we can confidently assume that no patient in either group was improperly discharged. We also found improved patient satisfaction at discharge in the ERAS group compared to that in controls (92.2 ± 4.3 vs. 86.8 ± 7.4 , $p = 0.0001$).

Postoperative wound drainage and pain management are summarized in Table 6. Postoperative wound drainage (epidural, surgical field, and lateral ventricle drainage) was not employed as a routine management criterion and was only used if necessary in a few cases in the ERAS group (12/70 [17%])—compare that to the relatively universal use of wound drainage in the control group (68/70 [97%], OR 0.006, 95% CI 0.001–0.003, $p < 0.0001$). Drainage duration of 24–48 hours was most frequently employed in both groups. The postoperative VAS score related to surgical site pain was assessed on POD 1 and daily thereafter until the patient had no complaint of pain or was discharged. The proportion of patients with milder pain (VAS score 1–3) was higher in the ERAS group than in controls on POD 1 (79% vs. 33%, OR 7.49, 95% CI 3.51–15.99, $p < 0.0001$). The duration of pain complaints was also shorter for patients in the ERAS group than in controls ($p < 0.0001$). However, there was no significant difference in analgesic medication administration between the two groups ($p = 0.246$).

Discussion

Design and Development of a Novel ERAS Protocol for Elective Craniotomy

Recent studies have shown that ERAS protocols have been widely utilized in the perioperative period in several surgical fields such as colorectal surgery, urological surgery, and orthopedic surgery and have resulted in significantly shorter hospital stays, improved functional recovery, and decreased morbidity.^{3,16,28,34} However, an ERAS protocol for elective craniotomy has rarely been employed in the field of neurosurgery. Hagan et al. proposed some key components of an ERAS protocol applicable to craniotomy based on available evidence from other surgical specialties.¹² Given this preliminary protocol for the perioperative care of patients undergoing elective craniotomy, our extensive review of the literature related to surgical management, and our institutional experience, we developed the novel ERAS protocol for elective craniotomy outlined in this study.

In this randomized controlled trial, we established and assessed a novel multidisciplinary, evidence-based, neurosurgical ERAS protocol for elective craniotomy patients at a major tertiary care medical center in China. Our protocol was associated with a shortened postoperative LOS and promoted rapid recovery after surgery. Importantly, the surgical and nonsurgical complications experienced by our patient population were not significantly different between the ERAS and control groups. Patients in the ERAS group also experienced earlier oral water and food intake and ambulation after surgery. Accelerated functional recovery was also achieved in measures related to prophylaxis and management of PONV, DVT, preoperative fasting, incisional local anesthetic, wound closure, urinary drainage duration, and surgical site pain, among others. To the best of our knowledge, this is the first neurosurgical ERAS protocol for elective craniotomy patients and the first randomized controlled trial to evaluate the efficacy of an ERAS protocol in neurosurgical patients admitted for elective craniotomy. Our protocol appears to be safe, effective, and feasible in this patient population.

Preoperative Management and Evaluation in the ERAS Protocol

Preoperative patient education and counseling are essential to improve patient perceptions of their surgical outcomes and thus can ensure patient compliance regarding perioperative management protocols.³⁷ A detailed step-by-step overview of our ERAS protocol was provided to all patients enrolled in this study. At our institution, preoperative evaluations were started at an outpatient center, and patients were instructed to abstain from both alcohol and smoking for at least 2 weeks prior to surgery. Preoperative nutritional, psychological (anxiety and depression evaluation), DVT, PONV, and pain evaluations were performed to anticipate the relative risks of each individual, and associated prophylaxis measures were taken based on these results. Once a patient was admitted, a preoperative evaluation that included pulmonary function exercises (chest movement, balloon blowing, and abdominal breathing exercises) and in-bed exercises of defecation and urinary

function was performed in collaboration with the nursing team. Altogether, our goal was to fully establish and evaluate the patient's baseline condition and functional status.

A poor preoperative nutritional status is associated with increased perioperative morbidity and hospital LOS.¹⁰ Every patient in this study was evaluated preoperatively, and those with a poor nutritional status were evaluated and treated by experts in our nutritional service department. According to our results, the majority of patients who underwent elective craniotomy showed a good preoperative enteral nutrition (EN) status, which was a notable difference from previous studies of ERAS protocols, especially for patients undergoing colorectal surgery.³⁴ Clearly, a patient's nutritional status is less likely to be affected by the surgical site following elective craniotomy than after colorectal surgery.

The concept of preoperative fasting and nutritional loading has changed from prolonged fasting to the allowance of clear fluids up to 2 hours before surgery and solids up to 6 hours prior to surgery, according to ASA guidelines.¹⁵ In our protocol, oral carbohydrate loading (i.e., maltodextrin fructose solution, 400 ml) was applied 2 hours prior to surgery. Previous studies have shown that preoperative oral consumption of clear carbohydrate-rich fluids may attenuate insulin resistance and improve postoperative hunger, thirst, and fatigue as compared to conventional fasting.^{27,40} Meanwhile, the risk of PONV has not been shown to increase with oral carbohydrate loading.¹² The results of this study support the efficacy and safety of a shortened fasting duration and oral carbohydrate loading 2 hours prior to surgery in patients undergoing elective craniotomy.

Surgical and Anesthetic Management in the ERAS Protocol

Considering that the current study is the first to implement an ERAS protocol for craniotomy, we limited our protocol to open surgery at this stage. Further designs and verifications of an ERAS protocol for endoscopic endonasal surgery have been planned at our center as well.

Perioperative anesthesia and optimization of pain management were key elements of our ERAS protocol. Suboptimal postoperative analgesia can cause discomfort after surgery, increase the incidence of postoperative complications, and prolong the postoperative hospital stay. However, there has been no consensus regarding an optimal analgesic regimen for postcraniotomy pain.⁵ Our protocol incorporated recent evidence and expert opinions on effective perioperative pain control. For example, prior studies have shown that scalp infiltration with ropivacaine or bupivacaine may reduce both the severity and incidence of postoperative pain,^{5,11} and local administration of ropivacaine (0.2%) prior to scalp incision was employed as one of the key elements of our protocol. In addition, studies have shown that morphine is minimally effective for pain relief in craniotomy patients.^{23,38} Therefore, postoperative morphine and equivalent opioids were not routinely prescribed in our patient population given their limited efficacy and wide range of side effects, unless a patient's pain VAS score was greater than 7. Instead, nonopioid analgesia strategies such as the administration of intravenous acetaminophen or nonsteroidal antiinflammatory drugs (NSAIDs) were

applied according to the intensity of the patient's postoperative VAS score. In our study, most patients in the ERAS group reported mild pain (VAS score 1–3) on POD 1 ($p < 0.0001$) and a shortened duration (1–2 days) of postoperative pain ($p < 0.0001$; Table 6). These results support the efficacy of our pain management strategy, which may improve patients' postoperative functional recovery.

As regards the anesthetic protocol, prior studies have found no difference between total intravenous anesthetic (TIVA) and inhalation anesthetics in the neurosurgical population.^{26,31} At our center, combined intravenous-inhalation anesthesia was adopted for craniotomy patients according to anesthesiologist preference. Atropine and dexamethasone were administered preoperatively to reduce gland secretion and minimize the stress response. Propofol, sufentanil, and rocuronium were administered to induce anesthesia, whereas propofol, fentanyl, and sevoflurane were used for anesthesia maintenance. Intraoperatively, a fluid restriction strategy was followed as an established practice for craniotomy. In order to meet the dual goals of good operative field exposure and hemodynamic stability, cardiac output–guided hemodynamic management and intraoperative goal-directed fluid restriction (GDFR) were incorporated into our ERAS protocol. Hence, the fluid administration strategy was similar in both groups in our study. Evidence has shown that the intraoperative GDFR strategy may be associated with a significant decrease in the intensive care unit LOS, costs, and postoperative complications.²²

Scalp incision closure was achieved by absorbable intradermal running suturing in our ERAS protocol. All wounds were covered with sterile adhesive strips. Previous evidence has proven that intradermal suture alone is as safe as traditional skin closure with nylon sutures, with the advantages of eliminating the need for suture removal and better cosmetic results.^{29,30}

In addition, several measures, such as the use of a heating pad and warmed liquids for intravenous infusion and surgical field washing, were applied to prevent intraoperative hypothermia in the ERAS protocol, which aided anesthesiologists in maintaining patients' body temperature during surgery. Perioperative blood glucose control was managed using intensive insulin therapy in both groups to decrease the morbidity and mortality associated with derangements in glucose metabolism due to surgery.^{2,9} Proton pump inhibitors (PPIs; omeprazole, esomeprazole) were administered intravenously for gastrointestinal tract mucosal protection and stress ulcer prophylaxis.¹

Postoperative Management in the ERAS Protocol

Postoperative nausea and vomiting are related to increased intracranial pressure and higher risks of bleeding, brain edema, and aspiration.^{13,19} We applied the PONV Simplified Risk Assessment Scale as one of the indications for PONV prophylaxis and treatment. Dexamethasone was routinely used for prophylaxis, and tropisetron, a serotonin 5-HT₃ receptor antagonist most commonly used in patients undergoing chemotherapy, was administered for intervention. Based on the PONV VAS score after surgery, prevention measures (PONV VAS score ≥ 3) and intervention measures (PONV VAS score ≥ 3) were applied

for attenuating symptoms. These strategies may have also contributed to improved postoperative pain management.

Early restoration of an oral diet and early mobilization have been encouraged in most ERAS protocols. Since the craniotomy surgical site is independent of the gastrointestinal tract, which imparts less risks for abnormal gastrointestinal function, early restoration of a normal diet was encouraged postoperatively for all patients except those who were in a prolonged comatose state following craniotomy.¹² In addition, we combined different measures of rapid de-escalation of intravenous fluids and early liquid and solid food intake in our ERAS protocol.³⁴ Time to postoperative oral diet intake was improved in the ERAS group with the majority of patients tolerating oral fluids and solid food by POD 1, and maintenance intravenous fluids were discontinued by POD 3 in most patients in the ERAS group. Under our ERAS protocol, patients were allowed to take fluids orally in the early postoperative period; thus, oral water intake was started at a median of 4 hours after surgery, and a polymeric nutritional supplement drink was given at a median of 8 hours after surgery. Nutritional supplement drinks combined with an ordinary solid diet were encouraged for patients 24 hours after surgery (median 24 hrs, range 24–72 hrs). According to our results, these measures improved the functional status of patients in the ERAS group compared to that in the control group.

Prolonged urinary catheterization is related to increased infection rates; thus, indwelling urinary catheters were encouraged to be removed by POD 1 or earlier in patients in the ERAS group.³² The restoration of spontaneous urinary function was measured in terms of duration of urinary catheterization, which was significantly shorter in the ERAS group, with 74% of urinary catheters removed within 6 hours after surgery. However, we had one case from each study group that required catheter reinsertion because of urinary retention. Both patients were elderly males who may have had impaired urinary function related to benign prostatic hypertrophy (BPH).

Early mobilization can improve postoperative cardiopulmonary function and thereby reduce the risk of pulmonary complications and DVT.^{4,42} In our protocol, in-bed limb exercises were started 6 hours after patients were awakened from anesthesia, and ambulation was started within 24 hours after surgery. Patients were instructed and monitored by a physical therapist. Early mobilization has been shown to prevent the development of DVT and muscle atrophy.^{14,21} With our analgesic and PONV prophylaxis regimens, more patients in the ERAS group (64%) were able to ambulate on POD 1 than those in the control group (0%; $p < 0.0001$).

Safety and Efficacy of Our Neurosurgical ERAS Protocol for Elective Craniotomy Patients

The primary endpoint of this study was postoperative LOS. Under the same discharge criteria, changes in postoperative LOS can function as a sensitive marker to evaluate the efficacy of an ERAS protocol. The effectiveness of our protocol was supported by significantly shorter hospital stays for patients in the ERAS group, with a reduction of at least 3 days in the postoperative LOS compared

to the LOS among patients who received the standard of care. Similar results were achieved regarding total hospital LOS. However, it is important to note that several factors can influence total hospital LOS, unlike postoperative LOS, such as patient age, sex, disease severity, and complications as well as supply factors such as clinical practice style, bed availability, satisfaction of discharge criteria, and medical insurance policies.^{6,41} Moreover, there was no readmission or reoperation case in either of the two patient groups. Therefore, we chose postoperative LOS as the more reliable indicator to assess the efficacy of our ERAS protocol.

Our results indicated that our protocol may lead to a shorter postoperative LOS without increasing the readmission or reoperation rates. These findings imply that our ERAS protocol played an important role in reducing patient stress and promoting rapid recovery. In addition, multivariate analysis revealed that oral solid food intake on POD 1 and a mild PONV VAS score were independent predictors of a shorter postoperative LOS in the ERAS group, whereas ambulation on POD 1 was the only independent predictor in the control group. These predictors can be interpreted as determinants of postoperative LOS in each group under circumstances in which most other factors do not vary significantly within each group. It is also understandable that absorbable skin suture, oral solid food intake on POD 1, and no postoperative wound drainage, which are among the key distinguishing factors between the two groups, were independent predictors for postoperative LOS in all patients.

Perioperative complications may influence recovery outcomes by increasing patient morbidity and mortality.^{7,18} Before the application of our ERAS protocol, the rates of surgical and nonsurgical complications at our center were relatively low under traditional standards of care. Therefore, we did not observe a significant difference in postoperative complications between the ERAS and control groups in this study. According to other reports on ERAS protocols, the influence of an ERAS protocol is unlikely to influence surgical complication rates.²⁸ As regards surgical complications, we believe that the results reemphasized the core role of a minimally invasive surgical strategy and manipulation during the whole perioperative period. As for nonsurgical complications, although we did not observe a difference between the two groups, we still believe that the trend in the nonsurgical complication rate decreased with the ERAS protocol application. Limited by our case number, the current results may not reflect the positive influences of the ERAS protocol in this respect. Ultimately, the postoperative morbidity rate in the ERAS group was not increased as compared to that in the control group, which confirmed the safety of the ERAS protocol.

Study Limitations

There are several limitations to this study. First, as in most of the previous randomized controlled trials investigating ERAS protocols, blinding was not used in the clinical setting in our study. However, blinding is likely not applicable because of the multitude of direct interventions under most ERAS protocols.^{20,36} Blinding of the patient study arm was employed for those who collected data

and assessed outcomes in this study. Relatedly, both the patients and medical staff must be clearly aware of what is expected in order to effectively employ the components of our ERAS protocol. Second, ours is the first neurosurgical ERAS protocol in the literature, and we intended to establish and assess our protocol by refining currently available ERAS protocols to better reflect neurosurgical conditions managed via elective craniotomy. But given the different characteristics among our patient cohort, the various operative practice patterns among surgeons at our institution, the unique safety concerns with our patients as compared to those of general surgery patients, as well as the paucity of similar studies related to craniotomy patients, several refinements to this preliminary neurosurgical ERAS protocol are likely to be required. Though our data support the efficacy and safety of this ERAS protocol at our tertiary care medical center, larger multicenter studies are needed to evaluate its generalizability to neurosurgical patients undergoing elective craniotomy. For instance, practices already utilizing most components of the protocol may not achieve substantial reductions in LOS with the introduction of the current ERAS protocol. Similarly, practice settings with a LOS < 7 days for elective tumor craniotomy may not realize large gains. The efficacy and benefits of our current neurosurgical ERAS protocol, which standardizes current best practices, needs to be confirmed in future studies performed at different medical centers with different healthcare systems and different levels of patient care. Lastly, although the application of our novel ERAS protocol in its entirety has shown promising results, little information is known regarding the individual contribution of each intervention, which should also be investigated in future studies.

Conclusions

Here, we have developed, implemented, and supported the use of our multidisciplinary, evidence-based, neurosurgical ERAS protocol for elective craniotomy, which resulted in improved outcomes and enhanced recovery after surgery. This randomized controlled trial supports the safety and efficacy of our ERAS protocol for patients undergoing elective craniotomy. Further assessment of this protocol with larger multicenter studies is warranted, and the adoption of such protocols in the care of craniotomy patients should be encouraged.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Conception and design: He, Y Wang, Liu, T Zhao, Yu, Jiang, Ye, Sun, Gao, Qu. Acquisition of data: Y Wang, Liu, B Zhao, L Zhao, Lv, Zhang, Zheng, Xue, Lei Chen, Wu, M Li, Ma, Z Li, R Li, J Li, Yan, H Zhao. Analysis and interpretation of data: Y Wang, T Zhao, B Zhao, Zhang, Yan. Drafting the article: He, Y Wang, Liu, T Zhao, Sankey. Critically revising the article: He, Y Wang, Liu, Yu, Jiang, Ye, L Zhao, Lv, Zheng, Lei Chen, Sankey, Long Chen, Wu, Ma, Gao. Reviewed submitted version of manuscript: He, T Zhao, Yu, Jiang, Ye, L Zhao, Lv, Zhang, Xue, Lei Chen, Sankey, Long Chen, Wu, M Li, Ma, Z Li, R Li, J Li, H Zhao, Sun, Gao, Qu. Approved the final version of the manuscript on behalf of all authors: He. Statistical analysis: Y Wang, Liu, B Zhao, Zhang. Administrative/technical/material support: He, Y Wang, Liu, T Zhao, B Zhao, Jiang, Ye, L Zhao, Lv, Zhang, Zheng, Xue, Lei Chen, Long Chen, Wu, M Li, Ma, Z Li, R Li, J Li, Yan, H Zhao, Sun, Gao. Study supervision: He, T Zhao, B Zhao, Yu, Jiang, Ye, M Li, Ma, R Li, Sun, Gao, Qu.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

ERAS Protocol For Elective Craniotomies (Supplementary File 1); Neurosurgical ERAS Record Checklist (Supplementary File 2); and Supplemental Tables 1 and 2. <https://thejns.org/doi/suppl/10.3171/2018.1.JNS171552>.

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