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Randomized Control Trials

A randomized controlled study of preoperative oral carbohydrate loading versus fasting in patients undergoing elective craniotomy☆

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SUMMARY

Object: The aim of this study was to evaluate the effect of preoperative oral carbohydrate loading versus fasting on the outcomes of patients undergoing elective craniotomy.
Methods: In a single-center randomized controlled study, 120 neurosurgical patients who were admitted for elective craniotomy were included and randomized into 2 groups: 58 patients received 400 mL of oral carbohydrate loading 2 h before surgery (intervention group), and 62 patients were fasting for 8 h prior to surgery as routine management (control group). The primary end point was glucose homeostasis. Secondary outcomes included handgrip strength, pulmonary function and postoperative complications.
Results: Better glucose homeostasis (5.6 ± 1.0 mmol/L vs. 6.3 ± 1.2 mmol/L, P = 0.001) was achieved in patients who received preoperative oral carbohydrate loading compared to fasting. Furthermore, patients in the intervention group had better handgrip strength (25.3 ± 7.1 kg vs. 19.9 ± 7.5 kg, P < 0.0001) and pulmonary function (in terms of peak expiratory flow rate) (315.8 ± 91.5 L/min vs. 270.0 ± 102.7 L/min, P = 0.036) compared to the controls postoperatively. The rates of postoperative surgical and non-surgical complications did not differ between the groups. Both postoperative and total hospital length of stay (LOS) reduced significantly in the intervention group (-3d, P < 0.0001 and P = 0.004).
Conclusions: Oral carbohydrate loading given 2 h before surgery in patients undergoing elective craniotomy seems to improve glucose homeostasis, handgrip strength and pulmonary function as well as decrease LOS without increasing the risk of postoperative complications. Routine use of preoperative oral carbohydrate loading could be suggested in clinical settings, though further evaluation of its safety and efficacy is warranted.

1. Introduction

Previous studies had proven the benefits of preoperative oral carbohydrate supplements given up to 2 h before induction of anesthesia in enhancing recovery and thus were recommended for patients undergoing elective surgery in modern guidelines [1,7,16]. Systematic reviews have provided evidence on the efficacy of preoperative carbohydrate as part of fast-track surgical or enhanced recovery after surgery (ERAS) protocols in reducing hospital stay, possibly mediated partially by decreased postoperative insulin resistance and faster return of intestinal function in patients undergoing elective surgery [4,11,14]. Recent randomized controlled trials continued to support its effectiveness with improved biochemical and functional outcomes concerning glucose metabolism, pulmonary function, handgrip strength, and perioperative thirst, hunger, anxiety and fatigue [12,18]. The safety

☆ This study has been registered in the Chinese Clinical Trial Registry (http://www.chictr.org.cn/showproj.aspx?proj=16480) with registration number ChiCTR-INR-16009662.

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of preoperative carbohydrate was also suggested by evidence of non-increased risk of postoperative complications [12,14,18]. However, all current available evidence involved patients undergoing elective abdominal surgery, orthopedic surgery, cardiac surgery, thyroidectomy, etc., whilst there has been no reported literature on preoperative oral carbohydrate loading concerning patients undergoing elective craniotomy. Whether the recommendations for general elective surgery patients may apply to elective craniotomy patients remains unknown.

Because of the paucity of studies on the preoperative fasting and carbohydrate loading in patients who received elective craniotomy, we have analyzed the associated metabolic changes and clinical outcomes in a prospective randomized study to compare the efficacy and safety of preoperative oral carbohydrate loading versus fasting in clinical application.

2. Methods

2.1. Patient population

Patients admitted for elective craniotomy at the Department of Neurosurgery of Tangdu Hospital (Xi'an, People's Republic of China) between October 2016 and July 2017 were included in our study if they were aged between 18 and 65 years-old, had a single intracranial lesion, and if they or their legally authorized representative gave informed consent. We excluded patients with intracranial trauma, pathology requiring emergent surgery, preoperative disturbance of consciousness, significant cognitive impairment who were unable to cooperate, and presence of a confounding condition (e.g., pregnancy) or disease that could potentially impact postoperative recovery (e.g., paralysis, spinal deformity, autoimmune diseases, myocardial infarction, severe infection, liver and renal malfunction, or severe psychological or mental illness), and those with diabetes or with a preoperative fasting glucose of greater than 7 mmol/L, those who were using steroids or immunosuppressants, those with history of abnormal gastric emptying or intestinal obstruction.

2.2. Evaluation and therapy

Patients who met the inclusion criteria were randomly assigned, in a 1:1 ration, into 2 groups using a computer-generated randomization codes which were held in sealed opaque envelopes. The intervention group received 400 mL of oral carbohydrate loading (i.e. Maltodextrin Fructose Solution, SuQian®, Xi'an, China; 12.5% carbohydrate, 0.5 kcal/ml, 260 mOsm/kg, pH 4.9) 2 h before surgery. The control group was fasting for 8 h prior to surgery as routine management.

All patients received general anesthesia, which was induced with propofol sufentanil and rocuronium, and maintained with propofol, fentanyl and sevoflurane. Intravenous glucose and exogenous insulin were not allowed during surgery as well as the preoperative period. Other aspects of perioperative patient care were standardized according to a predefined ERAS protocol for elective craniotomy patients [20]. Briefly, preoperative baseline evaluation was done to assess the physical, mental, and nutritional status of patients. Preoperative counseling was given to educate the patients and family to follow the instructions including smoking and alcohol abstinence, antithrombotic prophylaxis, intestinal preparation and fasting. Intraoperatively, goal-directed fluid restriction strategy and hypothermia avoidance were followed as an established practice for craniotomy. Local anesthesia at scalp incision and absorbable skin suture were incorporated in the ERAS protocol. Oral free fluids were permitted 6 h after surgery, while a light diet was allowed 8–12 h after surgery as tolerated by the patient. Intravenous fluids other than treatment medications (such as anticonvulsants) were not routinely encouraged after the first postoperative day unless the patients could not maintain a urine output or blood pressure by oral intake. Visual analogue scales (VAS) were used to assess the severity of postoperative nausea and vomiting (PONV). Tropisetron was given when PNOV VAS $\geq$5; droperidol and promethazine were given in addition to tropisetron in severe cases. Nonopioid analgesia was used for postoperative pain management with intravenous acetaminophen or nonsteroidal antiinflammatory drugs (NSAIDs). Early removal of urinary catheter, in-bed limb exercises started 6 hours after awakening from anesthesia, and early ambulation within 24 h after surgery were encouraged.

Clinical characteristics including age, sex, primary diagnosis of intracranial diseases, preoperative co-morbidity status (ASA grades) and patient comorbidities (smoking, diabetes, hypertension, hypercholesterolemia, etc.) were recorded. Preoperative baseline metabolic characteristics were also measured, which included age, height, weight, recent weight loss, body mass index, muscle mass, fat mass, handgrip strength, fasting glucose, and fasting insulin.

The primary end point was glucose homeostasis presented as fasting glucose and insulin levels. Fasting peripheral venous blood samples were collected at bedside and sent for the measurement of glucose and insulin levels in the Clinical Lab Department. The baseline glucose and insulin levels were obtained 4 h before surgery (i.e. 2 h before preoperative carbohydrate loading). Blood samples were also drawn at the time when patients entered operating room, and on the morning of postoperative day (POD) 1–3 for repeated measurement of glucose and insulin concentrations.

Secondary outcomes including handgrip strength and pulmonary function were repeatedly measured and documented on POD 1–3 daily. For the evaluation of pulmonary function, peak expiratory flow rate (PEFR) was measured with a peak flow meter. Additional tests were performed as clinically indicated until discharge. Surgical complications (e.g. surgical site infection, intracranial infection, epilepsy, and hemorrhage) and non-surgical complications (e.g. respiratory complications, cardiovascular complications, gastrointestinal complications, urinary tract complications and venous thromboembolism) were recorded as well. The medications, clinical presentations, and results of repeated neuroimaging and laboratory tests were documented. The postoperative length of stay (LOS), total hospital LOS, 30-day reoperation/readmission rates and mortality were also recorded.

Local institutional review board approval was obtained to perform this study and to use archived material for research purposes. The registration number of this study is ChiCTR-INR-16009662, registered at the Chinese clinical trial registry (http://www.chictr.org.cn/showproj.aspx?proj=16480). The protocol adheres to the principles set forth in the US Code of Federal Regulations, Title 45, Part 46, Protection of Human Subjects, revised June 23, 2005, and the World Medical Association Declaration of Helsinki.

2.3. Statistical analysis

Based on the hypothesis that preoperative carbohydrate loading was expected to improve postoperative glucose homeostasis by at least 25% (expected postoperative fasting glucose was estimated to be approximately 6.0 mmol/L for most elective craniotomy patients), a sample size of at least 58 patients per arm was calculated to have a power of 80% and a significance of 5%. Interim analysis was planned when the minimal number of the predefined sample size was met. To test whether variables differed across groups, the chi-square test or Fisher exact test was used according to the testing condition. Comparisons between continuous data were done using ANOVA or Mann–Whitney U test according to the testing

condition. Statistical significance was defined as $p < 0.05$. All of the tests were 2-sided. Statistical analysis was performed using SPSS software (version 16.0, SPSS, Inc.).

3. Results

3.1. Baseline characteristics

A total of 197 patients were screened for eligibility, of whom 57 were excluded (not meeting inclusion criteria, n = 44; declined to participate, n = 10, refused to consent for surgery, n = 3). Of the remaining 140 patients, 20 (12 in the intervention group and 8 in the control group) who completed the study had diabetes and thus were exclude from the data analysis. Our results are therefore based on 120 patients (Fig. 1). Demographic and clinical features were not significantly different between the intervention and control groups (Table 1).

3.2. Fluid balance

Other than the oral consumption of 400 mL carbohydrates 2 h before surgery in the intervention group, there was no significant difference of perioperative fluid balance between the two groups. During intraoperative fluid management, a goal-directed fluid restriction strategy was followed for all patients. The median volume of neither the crystalloids nor the colloids differed between the two groups (crystalloids: 2000 mL vs. 1850 mL, P = 0.396; colloids: 600 mL vs. 500 mL, P = 0.163, Table 1). Intravenous glucose was not allowed during the preoperative and intraoperative period. Postoperatively, patients were instructed to early oral refeeding and rapid de-escalation of intravenous fluids. Patients received a median of 1500 mL (half of which was glucose-containing) intravenous fluids on POD 1 similarly in both groups. Maintenance intravenous fluids were discontinued by POD 3 in most patients in the intervention group while continued for a median of 5 days in the control group (P < 0.0001).

3.3. Glucose homeostasis

There was no significant difference of the glucose levels at baseline preoperatively (5.3 ± 0.9 mmol/L in the intervention group vs. 5.6 ± 0.9 mmol/L in the control group, P = 0.112). Glucose levels were increased significantly in the intervention group (6.3 ± 1.6 mmol/L) when patient entered the operating room because of their oral carbohydrate loading 2 h prior to surgery (vs. 5.6 ± 1.0 mmol/L in the control group, P = 0.020). There was a trend towards a decrease of fasting glucose though not statistically significant in the intervention group compared to the control group on POD 1 (5.5 ± 1.3 mmol/L vs. 5.8 ± 1.1 mmol/L, P = 0.174) and POD 2 (5.7 ± 1.1 mmol/L vs. 6.0 ± 1.1 mmol/L, P = 0.138); whilst a significantly lower fasting glucose was observed on POD 3 (5.6 ± 1.0 mmol/L vs. 6.3 ± 1.2 mmol/L, P = 0.001) (Fig. 2A). The overall pattern of insulin levels were similar in both groups, which increased on POD 1 and then decreased over the next couple of days (Fig. 2B). The changes of insulin levels were well correlated with the glucose levels, with patients in the intervention group demonstrating significantly lower fasting insulin on POD 3 (8.1 ± 3.7 μunits/mL vs. 9.9 ± 4.5 μunits/mL, P = 0.019) (Fig. 2B).

3.4. Handgrip strength, pulmonary function and other secondary outcomes

There was no baseline difference of handgrip strength (28.1 ± 11.1 kg in the intervention group vs. 29.8 ± 10.1 kg in the control group, P = 0.583) and pulmonary function (as represented by PEFR, 343.5 ± 108.9 L/min in the intervention group vs. 362.1 ± 87.7 L/min in the control group, P = 0.307) preoperatively between the two groups. As expected, both handgrip strength and PEFR declined in both groups postoperatively and were lowest on POD 1. There was a trend of improvement of handgrip strength in both groups later during POD 2–3. The performance of patients in the intervention group was significantly better than that in the control group, though neither group returned to baseline levels upon POD 3 (25.3 ± 7.1 kg vs. 19.9 ± 7.5 kg, P < 0.0001, Fig. 2C).

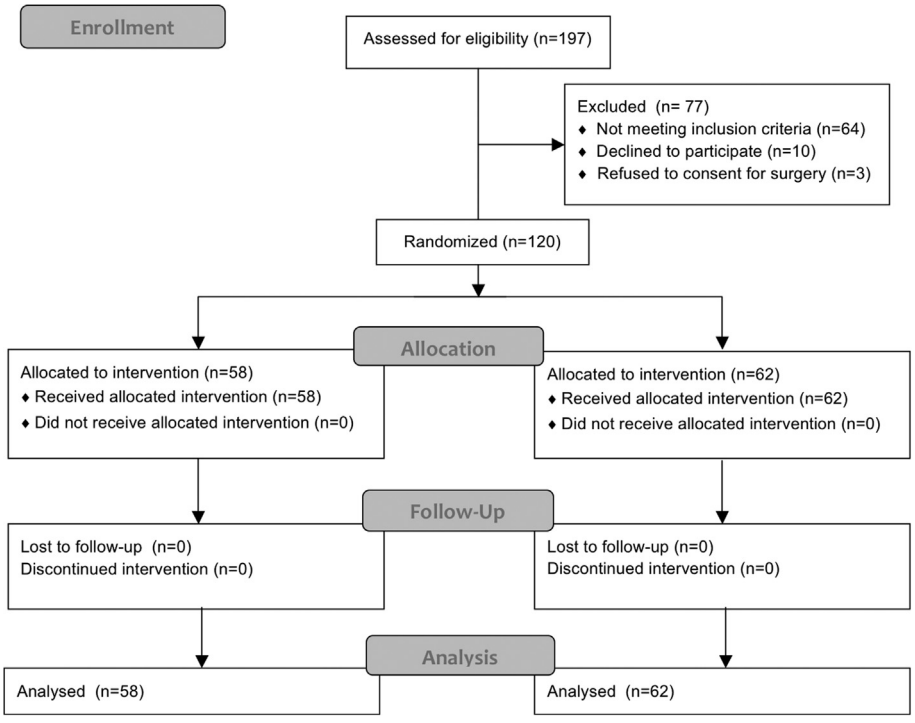

Fig. 1. CONSORT flow diagram.

Table 1
Baseline patient demographics and clinical characteristics.

Parameter	Intervention group	Control group	p Value
	No. of patients (%)		
No. of patients	58	62	
Age (years)			0.676
<40	34 (58.6)	34 (54.8)	
40-65	24 (41.4)	28 (45.2)	
Sex			0.471
male	17 (29.3)	22 (35.5)	
female	41 (70.7)	40 (64.5)	
BMI			0.253
<18.5	2 (3.4)	0 (0)	
18.5–23.9	47 (81.0)	55 (88.7)	
>24	9 (15.5)	7 (11.3)	
ASA grades			0.301
Grade I	8 (13.8)	13 (21.0)	
Grade II	50 (86.2)	49 (79.0)	
Concomitant diseases			
CHD/Hypertension	12 (20.7)	10 (16.1)	0.519
Smoker	5 (8.6)	9 (14.5)	0.315
Liver/Gall bladder	7 (12.1)	4 (6.5)	0.287
Lung	5 (8.6)	7 (11.3)	0.626
Miscellaneous	3 (5.2)	4 (6.5)	0.765
Intracranial lesions			0.882
Meningioma	30 (51.7)	27 (43.5)	
Vestibular Schwanoma	6 (10.3)	9 (14.5)	
CPA epidermoid cyst	5 (8.6)	5 (8.1)	
Glioma	11 (19.0)	16 (25.8)	
Trigeminal neuralgia	3 (5.2)	3 (4.8)	
Cavernous malformation	3 (5.2)	2 (3.2)	
Lesion location			0.660
Supratentorial superficial	20 (34.5)	20 (32.3)	
Supratentorial deep	20 (34.5)	18 (29.0)	
Infratentorial	18 (31.0)	24 (38.7)	
	Median (range)		
Anesthetic time (min)	260 (90–690)	280 (140–730)	0.178
Surgical time (min)	220 (60–650)	240 (120–690)	0.254
Intraoperative blood loss (ml)	300 (10–1500)	300 (50–2600)	0.868
Intraoperative fluid (ml)			
Crystalloid	2000 (1000–6500)	1850 (1000–4500)	0.396
Colloid	600 (0–1500)	500 (500–1500)	0.163
Blood transfusion (ml)			
RBC	0 (0–800)	0 (0–1600)	0.477
Plasma	0 (0–400)	0 (0–800)	0.477

BMI = body mass index, ASA = American Society of Anesthesiologists', CHD = chronic heart disease, CPA = cerebellopontine angle.

Similarly, PEFR was improved in both groups, and patients in the intervention group did better than those in the control group (315.8 ± 91.5 L/min vs. 270.0 ± 102.7 L/min, P = 0.036, Fig. 2D).

The occurrence of surgical complications, which include surgical site infection, intracranial infection, seizure, intracranial hemorrhage and other complications (e.g. stroke, facial paralysis after acoustic neuroma, tinnitus, etc.), as well as non-surgical complications, which include respiratory, cardiovascular, digestive, urinary and venous thromboembolism, did not differ between the two groups (Table 2). There was no PONV VAS difference between the intervention and control group, with similar portion of patients having mild intensity of PONV (score 1–4) postoperatively (84.5% vs. 71.0%, P = 0.200). Accordingly, the use of tropisetron, which was prescribed when PNOV VAS ≥5, did not differ between the two groups. Droperidol and promethazine were given in addition to tropisetron in severe cases with PNOV VAS 7–10. Three patients in the intervention group and five patients in the control group received these, which had no significant difference (P = 0.788).

Both median postoperative LOS and total hospital LOS reduced significantly in the intervention group compared with the control group (postoperative LOS: 4 d vs. 7 d, P < 0.0001; total hospital stay: 10 d vs. 13 d, P = 0.004, Table 2). There was no perioperative mortality in both groups. No 30-day readmission and reoperation occurred in both group either.

4. Discussion

It has been a while since the change of concept that preoperative clear fluids given up to 2 h prior to surgery is preferred than traditional prolonged fasting. Previous studies have shown that preoperative carbohydrate-rich loading may revamp metabolic stableness in terms of less insulin resistance, lower total ketone bodies, and improve clinical outcomes in terms of better pulmonary function, handgrip strength, as well as less perioperative thirst, hunger, anxiety and fatigue compared to traditional prolonged fasting [4,11–14,18,21]. In addition, preoperative oral carbohydrate loading was shown to be associated with decreased incidences of postoperative clinical complications and no increased risk of PONV [8,12]. In accordance with these findings involving patients undergoing elective abdominal surgery, orthopedic surgery, cardiac surgery, thyroidectomy, etc., results of the current study showed evidence of improved glucose homeostasis, handgrip strength and pulmonary function without increasing the risk of postoperative complications, which for the first time confirmed the safety and efficacy of preoperative carbohydrate loading 2 h prior to surgery in patients undergoing elective craniotomy.

Transient insulin resistance serves as an indicator for metabolic stress in response to surgery. It can last for a period of about 2–3 weeks and is marked by hyperglycemia [17]. The resultant

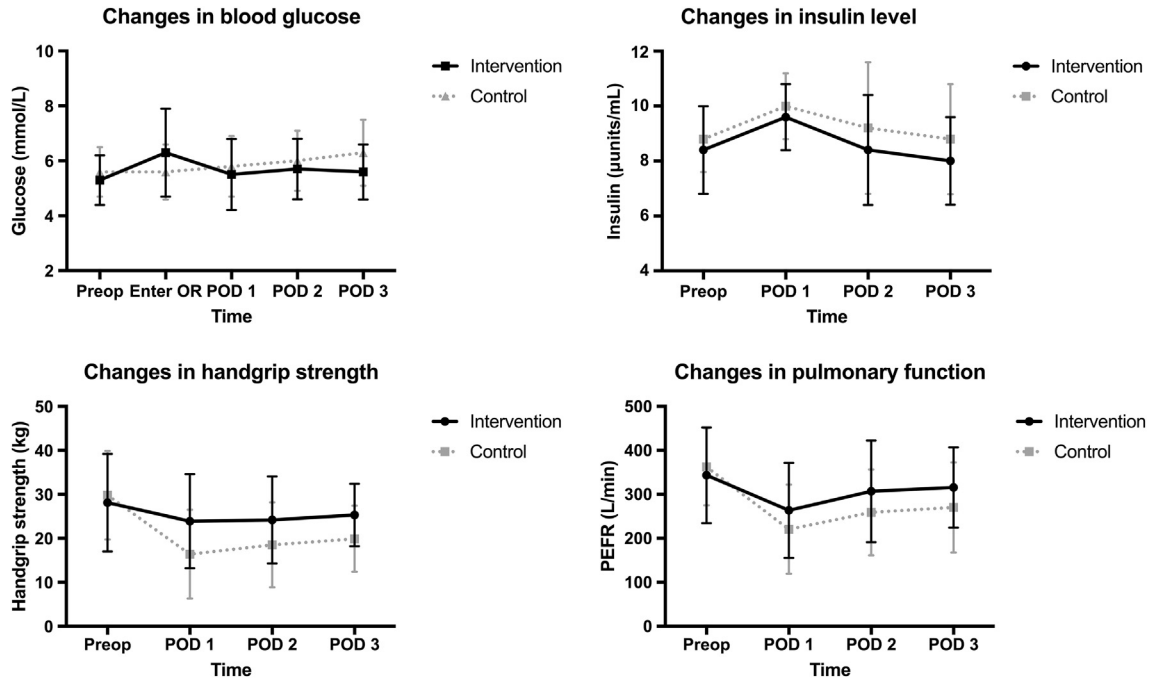

Fig. 2. Changes in primary and secondary endpoints measured from preoperative baseline to postoperative days (POD) 1–3. (A) Changes in blood glucose. (B) Changes in insulin level. (C) Changes in handgrip strength. (D) Changes in pulmonary function.

hyperglycemia is associated with increased risks of postoperative morbidity [15,17]. In accordance with observations from previous studies [5,12,19,21], patients in our study who had elective craniotomies (prolonged major surgical procedures) were amongst the group of relatively severe responders to surgical stress and were benefited with oral carbohydrate loading 2 h prior to surgery, as indicated by better glucose homeostasis and lower insulin levels postoperatively.

It is notable that better glucose homeostasis after surgery was only achieved on POD 3 in the intervention group, with statistical significance as compared with the control group. Though a seeming benefit was also observed on the preceding two PODs, the effect was not as profound. The similar changes of pattern were also observed regarding insulin levels. Since stress response can last for 2–3 weeks [17] it is possible for the patients take a while to recover from the surgical stress, while preoperative oral carbohydrate loading may speed up this process.

Provision of a carbohydrate drink prior to surgery may attenuate loss of muscle mass after surgery [22]. Accordingly, studies had proven that a shortened fasting using carbohydrates preoperatively was beneficial to muscle strength in terms of improved handgrip strength perioperatively in patients receiving colorectal surgery [12] and laparotomy cholecystectomy [6,23]. In addition, abbreviated fasting also has a beneficial effect on pulmonary function as reflected by better respiratory dynamics in such patients [12,23], probably as a result of maintenance of muscular strength. Results of the current study on elective craniotomy patients are consistent with these findings. For patients underwent major surgical procedures, a better-preserved muscle function plays a key role in reducing postoperative complications and enhancing recovery,

Table 2
Postoperative complications and length of hospital stay.

Parameter	Intervention group	Control group	p Value
	No. of patients (%)		
Mortality	0	0	–
Surgical complications			
Surgical site infection/subcutaneous effusion	1 (1.7)	2 (3.2)	>0.999
Intracranial infection	3 (5.2)	5 (8.1)	0.718
Epilepsy	3 (5.2)	2 (3.2)	0.672
Hemorrhage[a]	2 (3.4)	3 (4.8)	>0.999
Others[b]	3 (5.2)	2 (3.2)	0.672
Non-surgical complications			
Respiratory	2 (3.4)	5 (8.1)	0.441
Cardiovascular	0	0	–
Gastrointestinal	0	0	–
Urinary tract	0	1 (1.6)	>0.999
DVT	0	2 (3.2)	0.496
	Median (range)		
Postoperative LOS	4 (1–13)	7 (3–28)	<0.0001
Total hospital LOS	10 (4–29)	13 (5–34)	0.004

DVT = Deep vein thrombosis, LOS = length of stay.
[a] Hemorrhage refers to small amount of epidural hematoma or surgical area hemorrhage, not including intracranial hemorrhage which needs re-operation.
[b] Including cerebral infarction, facial paralysis after resection of vestibular Schwanoma (House-Brackmann score ≥ 3), tinnitus, etc.

which may also contribute to a shortened hospital stay as shown by previous [2] and the current study.

Current available evidence on the benefits of preoperative carbohydrate loading is mostly based on small studies and seems not appealing with respect to clinical outcomes [4,14]. Results of the most recent systematic review stated a modest reduction in total hospital LOS (−0.30 d, 95% CI -0.56 to −0.04 d) associated with preoperative oral carbohydrate loading compared to prolonged fasting or placebo [14]. Apart from the overall moderate methodological quality of the included studies and evidence of publication bias, significant heterogeneity amongst studies may account for this. Minor surgery subgroup with expected LOS of no longer than 24 h was mixed with major surgery subgroup having a longer LOS. Indeed a larger absolute decrease in LOS was seen in the latter group (−1.66 d, 95% CI -2.97 to −0.34 d), which was also shown in the current study with significant reduction of both median postoperative LOS (−3 d) and total hospital LOS (−3 d). However, what should be born in mind is that these beneficial effects on LOS were gained in trials incorporating fast-track surgical or ERAS protocols. It may be difficult to demonstrate absolute benefit from a single intervention within an ERAS protocol where multi-disciplinary and multi-module management interventions together may reduce the overall 'stress response' and improve the outcome.

The current study was not powered to evaluate the effect of preoperative carbohydrate loading on postoperative complications because the occurrence of such complications is already relatively low in craniotomy patients. These elements were incorporated secondary to potential safety concerns. Our results supported the safety of preoperative carbohydrate loading by showing no difference of surgical and non-surgical complications rates between the groups (Table 2). This should be interpreted with caution due to the unpowered sample size for these outcomes. One exception to this issue is the PONV VAS, which is statistically powered and associated with no increased scores in the intervention group. Unchanged or even decreased risks of PONV were also found in patients ingesting carbohydrate-rich drinks compared to fasting or placebo in previous randomized clinical trials [9,10,12].

The key limitation to the current study is the lack of a placebo and control for fluid balance preoperatively, which raises concerns about the interference of fluids management with the outcomes. Another design flaw that comes with the lack of placebo control is non-blinding, which allowed for the possibility that the groups were not randomly treated with respect to their overall care. In addition, the primary endpoint of glucose homeostasis in this study was assessed with blood glucose and insulin levels but not insulin sensitivity (the reciprocal of insulin resistance), which can be measured with short insulin tolerance tests (ITT) that is not interfered by the physiological fluctuation of serum insulin/glucose and thus more reproducible and reliable [3,12]. Lastly, subjective perioperative well-being of patients (such as perioperative thirst, hunger, anxiety and fatigue) was not included as end points of this study. These outcomes may provide with more evidence to justify the application of preoperative oral carbohydrate loading in craniotomy patients and should be further evaluated in future studies.

5. Conclusions

Oral carbohydrate loading given 2 h prior to surgery in patients undergoing elective craniotomy seems to be effective and safe in improving glucose homeostasis, handgrip strength and pulmonary function as well as reducing LOS without increasing the risk of postoperative complications, compared with prolonged preoperative fasting. Routine use of preoperative oral carbohydrate loading could be encouraged in craniotomy patients, though more powered and well-designed studies are warranted to justify its clinical role.

Conflict of interest

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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