

# Effects of preoperative oral carbohydrate electrolyte drinks on preoperative hypokalemia incidence in patients scheduled for laparoscopic colorectal resection: a randomized clinical trial

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## Research article

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# Abstract

**Background:**In our previous study, hypokalemia incidence was high in patients scheduled for laparoscopic colorectal resection. The present trial was conducted to verify the effects of preoperative carbohydrate drinks containing potassium in these patients. **Methods:** Patients were randomly assigned to control, placebo, and case groups. In control group, patients were fasted from midnight. In placebo group, patients were fasted from midnight and received carbohydrate drinks 2–3 h before surgery. In case group, patients were fasted from midnight and received carbohydrate drinks containing potassium supplementation 2–3 h before surgery. The primary outcome was the incidence and severity of preoperative hypokalemia. The other outcomes included postoperative gastrointestinal function, including the time to postoperative first flatus (FFL) and first feces (FFE) and other complications. **Results:** The final analysis included 122 participants. The incidence of preoperative hypokalemia in case group was significantly lower than that in control and placebo groups (50% vs. 88.1% vs. 77.5%,  $p < 0.001$ ). The severity of hypokalemia in control and placebo groups was greater than that in case group. No regurgitation or aspiration occurred in the three groups. No significant differences were observed among the three groups regarding time to FFL and FFE. **Conclusions:** Preoperative carbohydrate drinks containing potassium may have significantly reduced the incidence of preoperative hypokalemia and improved preoperative thirst and hunger, but did not improve postoperative well-being. However, as part of the enhanced recovery after surgery protocol, preoperative carbohydrate drinks containing potassium should be recommended, as early as first admittance to hospital.

## Background

Compared with traditional management, enhanced recovery after surgery (ERAS) has been recommended in recent years. Following the ERAS protocol in elective colorectal surgery could improve the prognosis.<sup>[1]</sup> Preoperative fasting time and carbohydrate treatment are crucial parts of the ERAS protocol. Intake of clear fluids until 2 h before anesthesia is not associated with increased complications such as regurgitation and aspiration.<sup>[2, 3]</sup> Administration of oral carbohydrates 2–3 h before anesthesia induction provides beneficial effects such as improved insulin resistance.<sup>[4, 5]</sup> However, preoperative carbohydrates might not speed up surgical recovery or improve postoperative well-being.<sup>[6]</sup>

Similar to fasting and preoperative fluids, bowel preparation is another focus of ERAS. Bowel preparation is recommended for rectal surgery and remains controversial in colonic surgery.<sup>[1, 7]</sup> Hypokalemia is associated with various symptoms, including gastrointestinal disorders, arrhythmia, and muscle weakness. Therefore, the importance of normal perioperative potassium levels might be underestimated. Nevertheless, no study has been conducted on preoperative potassium management in patients scheduled for laparoscopic colorectal resection, whose preoperative hypokalemia incidence was found to be high in our previous study.<sup>[8]</sup> Although oral administration is commonly recommended for prophylactic potassium supplement, a previous study demonstrated that use of the oral route is extremely rare.<sup>[9]</sup> Therefore, adding potassium to preoperative fluids might be a useful choice.

The present randomized clinical trial was conducted to verify the effects of preoperative carbohydrate drinks containing potassium in patients scheduled for elective laparoscopic colorectal resection.

## Methods

This randomized prospective parallel study was performed in accordance with the Declaration of Helsinki. It was approved by the Institutional Review Board of the third affiliated hospital of Sun Yat-sen University (approval number: [2016]2-184) and registered with the Chinese Clinical Trial Registry at [www.chictr.org](http://www.chictr.org) on February 7, 2017 (registration number: ChiCTR-IOR-17010561). This manuscript adhered to the applicable CONSORT 2010 checklist.

All patients who were scheduled for elective laparoscopic colorectal resection from March 1, 2017 to February 29, 2018 were considered for inclusion. The inclusion criteria were as follows: (i) age 18–80 years, (ii) American Society of Anesthesiologists Physical Status I to III, (iii) provided informed written consent. Patients who met any of the following criteria were excluded: (i) comorbid intestinal obstruction and gastric emptying disorder; (ii) diabetes; (iii) body mass index  $\geq 30$  kg/m<sup>2</sup>; (iv) severe renal insufficiency or long-term use of potassium-sparing diuretics; (v) history of neurological or mental illness; (vi) patients with hyperkalemia or hypokalemia. Patients who were transferred to open surgery or underwent colostomy during the operation were excluded from the final analysis.

Patients were randomly assigned to control, placebo, and case groups according to computer-generated random numbers. In the control group, patients were fasted from midnight; in the placebo group, patients were fasted from midnight and received carbohydrate drinks (5–6 mL/kg containing 14.2% carbohydrates) 2–3 h before surgery; and in the case group, patients were fasted from midnight and received carbohydrate drinks containing potassium supplementation (5–6 mL/kg containing 14.2% carbohydrates and 1 g of potassium) 2–3 h before surgery. All the drinks were prepared in bottles prepared by the hospital pharmacy with the same appearance and were distributed by the same trial assistant who was not involved in the follow-up or assessment. The random number was sealed in an envelope until the morning of surgery. All patients were fasted from solid food from midnight before surgery. To maintain blinding, the anesthetist was not involved in the follow-up or assessment. Patients received standardized care during the perioperative period.

## Sample size

This study was a randomized clinical trial with three parallel groups. The main outcomes were the incidence rates of preoperative hypokalemia. The following formula was used to calculate the sample sizes: (see Formula 1 in the Supplementary Files)

According to our pilot trial, which resulted in

$p_A = 0.88$ ,  $p_B = 0.77$ , and  $p_C = 0.41$ , 40 participants were required in each group for a power of 80% and a two-tailed p-value of 0.05 was considered as statistically significant. A final sample size of  $n = 44$  was

determined based on an assumed dropout rate of approximately 10%; therefore, 44 patients were enrolled in each group, and the total number of patients was 132.

## Procedures

Anesthesia was induced with intravenous midazolam (0.03 mg/kg), fentanyl (3–5 µg/kg), propofol (1.5–2.5 mg/kg), and cisatracurium (0.2 mg/kg) and maintained with sevoflurane (0.7–1.2 minimum alveolar concentration), remifentanyl (0.05–0.15 µg · kg · min), and cisatracurium (0.1 mg · kg · h). Ventilation was controlled with a tidal volume of 8–10 mL/kg with end tidal CO<sub>2</sub> of 35–45 mmHg. The volume was admitted according to central venous pressure (maintained at 5–12 cmH<sub>2</sub>O).

Potassium was measured by obtaining venous blood before anesthesia induction. If the blood potassium was less than 2.8 mmol/L, potassium would be supplemented intravenously before induction of anesthesia.

Standardized analgesic strategy was used for all patients. Fifteen minutes before the end of surgery, patients were intravenously infused with flurbiprofen axetil (1 mg/kg) as an analgesic and tropisetron (5 mg) to prevent vomiting. Postoperatively, patient-controlled intravenous analgesia devices containing sufentanil (2 µg/kg) and tropisetron (10 mg) were applied to all patients for 2 days.

## Outcomes

The primary outcome was the incidence and severity of preoperative hypokalemia.

Normal potassium levels were defined as blood potassium levels between 3.5 and 5.5 mmol/L. Potassium levels between 3.0 and 3.5 mmol/L, more than 2.5 and less than 3.0 mmol/L, and less than 2.5 mmol/L were considered as slight, moderate, and severe hypokalemia, respectively.<sup>[8]</sup>

Pre-anesthesia thirst (0, no thirst; 10, unbearable thirst), hunger (0, no hunger; 10, unbearable hunger), flavor (0, unbearable flavor; 10, tasty flavor), and anxiety scores (0, no anxiety; 10, high anxiety) were assessed using a visual analog score based on that of a previous study.<sup>[10]</sup>

The other outcomes included postoperative gastrointestinal function, the time to postoperative first flatus (FFL) and first feces (FFE) and other complications. Postoperative hospitalization stays and hospitalization costs were also recorded.

## Statistical analysis

The Statistical Package for the Social Sciences 21.0 (IBM Corporation, Armonk, NY, USA) was used to perform statistical analyses. Quantitative data were expressed as the mean ± standard deviation, and qualitative data and ordinal data were expressed as absolute frequencies. The one-sample Kolmogorov–Smirnov test was used to test the normality of the quantitative data. According to the distribution of quantitative data, a one-way analysis of variance or non-parametric test was used. The least significant difference method was used for further comparison among the groups. The Kruskal–Wallis test was

used to compare quantitative data which was not normal distribution. For qualitative data, the chi-square test or Fisher's exact probability test was used to compare differences. Differences were considered significant when two-tailed p-values were  $< 0.05$ . A justified p-value was used for multiple comparisons (the significance of p value should be less than  $0.05/n$ , n means comparison frequency).

## Results

A total of 181 patients were considered for inclusion. After the exclusion of those who met the exclusion criteria, 132 patients were included and randomly assigned to three groups. Ten patients were excluded from the final analysis, including nine who transferred to open surgery and one who dropped out. The procedure of inclusion is shown in flow diagram. The final analysis included 122 participants. Demographics including age and sex distribution and some surgical aspects showed no significant differences among the three groups (Table 1).

Table 1  
Demographics and surgical characteristics

Patient Characteristic	Controls (n = 42)	Placebos (n = 40)	Cases (n = 40)	P
Age (year)	55.81 ± 13.83.	55.25 ± 13.45	56.55 ± 12.43	0.908
Gender (F)	21(50.0%)	14(35.0%)	22(55.0%)	0.175
BMI (kg/m <sup>2</sup> )	21.69 ± 3.33	23.12 ± 3.35	22.24 ± 2.62	0.122
ASA				0.377
Ⅰ	11(26.2%)	8(20.0%)	10(25.0%)	
Ⅱ	30(71.4%)	31(77.5%)	28(70.0%)	
Ⅲ	1(2.4%)	1(2.5%)	2(5.0%)	
Hypertension	8(19.0%)	8(20.0%)	6(15.0%)	0.874
Surgery type				0.992
Colectomy	30(71.4%)	29(72.5%)	29(72.5%)	
Rectal resection	12(28.6%)	11(27.5%)	11(27.5%)	
Duration of operation (min)	195.76 ± 47.31	197.93 ± 49.26	204.88 ± 63.64	0.728
Duration of pneumoperitoneum (min)	123.63 ± 50.48	128.21 ± 55.38	133.84 ± 58.65	0.711
Fluid input (ml)	1779.27 ± 426.76	1943.13 ± 575.38	1848.68 ± 632.51	0.407
Crystalloid solution (ml)	1175.61 ± 369.99	1295.63 ± 506.75	1180.26 ± 422.60	0.383
Colloidal solution (ml)	603.66 ± 259.90	647.50 ± 302.12	642.11 ± 270.77	0.742
Blood transfusion	1(2.4%)	1(2.5%)	1(2.5%)	1.000
Urine volume (ml)	534.10 ± 299.98	611.67 ± 437.67	545.14 ± 299.86	0.594

The incidence of preoperative hypokalemia in the case group was significantly lower than that in the control and placebo groups (50% vs. 88.1% vs. 77.5%,  $p < 0.001$ , Table 2). The severity of hypokalemia in the control and placebo groups was greater than that in the case group (Table 2).

Table 2  
Outcomes and complications.

Patient Characteristic	Controls (n = 42)	Placebos (n = 40)	Cases (n = 40)	P
Preoperative hypokalemia	37 (88.1%)	31 (77.5%)	20 (50.0%)	∞0.001
Severity of hypokalemia				0.001
Normal	5 (11.9%)	9 (22.5%)	20 (50%)	
Slight	21 (50.0%)	19 (47.5%)	18 (45%)	
Moderate	15 (35.7%%)	12 (30%)	2 (5%)	
Severe	1 (2.72.4%%)	0 (0%)	0(0%)	
Pre-anesthetic thirst scores	4.00 ± 3.24	1.16 ± 1.46	2.18 ± 2.37	∞0.001
Pre-anesthetic hunger scores	4.54 ± 3.52	1.29 ± 2.08	1.50 ± 2.05	∞0.001
Pre-anesthetic anxiety scores	3.43 ± 2.12	2.71 ± 2.27	3.74 ± 2.68	0.166
Flavor scores	/	7.60 ± 1.75	6.94 ± 1.83	0.130
Regurgitation and aspiration	0	0	0	/

Regarding the flavor of the fluid, no significant differences were observed between the placebo and case groups ( $7.60 \pm 1.75$  vs.  $6.94 \pm 1.83$ ,  $p = 0.130$ , Table 2).

Pre-anesthesia thirst was more severe in the control group than in the placebo and case groups ( $4.00 \pm 3.24$  vs.  $1.16 \pm 1.46$  vs.  $2.18 \pm 2.37$ ,  $p < 0.001$ , Table 2), without significant differences between the placebo and case groups ( $1.16 \pm 1.46$  vs.  $2.18 \pm 2.37$ ,  $p = 0.063$ , Table 2). Pre-anesthesia hunger was also more severe in the control group than in the placebo and case groups, without significant differences between the placebo and case groups (Table 2). No regurgitation or aspiration occurred in any of the three groups (Table 2).

No significant differences were observed among the three groups regarding time to FFL and FFE and hospital stays (Table 3). No significant differences were observed among the three groups considering hypokalemia on Postoperative Day 1 and no patient had hypokalemia on Postoperative Day 2 (Table 3).

Table 3  
Postoperative complications

Patient Characteristic	Controls (n = 42)	Placebos (n = 40)	Cases (n = 40)	P
Time to first flatus (h)	46.56 ± 24.25	45.50 ± 20.60	49.78 ± 24.67	0.696
Time to first feces (h)	78.62 ± 44.12	83.74 ± 40.11	73.13 ± 33.03	0.499
Time to first meal (h)	71.10 ± 35.49	81.60 ± 39.54	70.56 ± 34.90	0.322
Time to off-bed activity (h)	35.06 ± 18.39	35.18 ± 12.70	31.64 ± 13.29	0.490
Postoperative hospitalization stays (day)	8.75 ± 4.45	8.44 ± 3.14	8.00 ± 2.56	0.633
Hospitalization expense (ten thousand yuan)	6.50 ± 1.35	6.71 ± 0.84	6.32 ± 0.95	0.303
Postoperative hypokalemia (2 h post-operation)	7(16.7%)	7(17.5%)	6(15.0%)	0.953
Postoperative hyperkalemia (day 1)	0	0	0	/
POD1 NRS pain scores	3.20 ± 1.16	3.68 ± 1.51	3.46 ± 1.17	0.249
POD2 NRS pain scores	1.46 ± 1.16	1.60 ± 1.22	1.71 ± 1.06	0.634
Postoperative nausea	12(28.6%)	8(20.0%)	11(27.5%)	0.655
Postoperative vomiting	6(14.3%)	3(7.5%)	7(17.5%)	0.444
Postoperative abdominal distention	7(16.7%)	7(17.5%)	9(22.5%)	0.737
Postoperative arrhythmia	1(2.4%)	0	1(2.5%)	1.000
Postoperative cardiac failure	0	0	0	/
Postoperative fever	0	0	2(5.0%)	0.211
Ileus	1(2.4%)	1(2.5%)	0	1.000
Anastomotic fistula	1(2.4%)	1(2.5%)	0	1.000
Anastomotic hemorrhage	1(2.4%)	1(2.5%)	0	1.000

## Discussion

Although preoperative carbohydrate drinks and prophylactic potassium are recommended for patients, the prevalence of perioperative hypokalemia remains high. In the present study, preoperative

carbohydrate drinks containing potassium significantly reduced the incidence of preoperative hypokalemia. However, the postoperative well-being and complications showed no significant differences among patients with and without preoperative carbohydrate drinks with and without potassium.

A previous study demonstrated that fluid and electrolyte management with oral rehydration therapy before surgery is superior to intravenous therapy.<sup>[11]</sup> Patients with normal fluid and electrolyte balance are likely to experience stable induction of anesthesia.<sup>[12, 13]</sup> Preoperative oral carbohydrate intake also improves patient-reported outcomes such as hunger before the induction of anesthesia.<sup>[14, 15]</sup> In line with previous studies, the present study also showed that patients treated with preoperative oral carbohydrates had lower thirst and hunger scores. However, carbohydrates with potassium were not superior to carbohydrates without potassium in terms of prognosis, although they significantly reduced the incidence of preoperative hypokalemia without changing the flavor of the fluid.

Hypokalemia is common in hospitalized patients; approximately 20% of inpatients experience hypokalemia<sup>[16]</sup> Perioperative hypokalemia is even higher in patients scheduled for laparoscopic colorectal resection.<sup>[8]</sup> Bowel preparation combined with systemic antibiotics is effective in reducing the incidence of surgical site infection in colorectal surgery.<sup>[17]</sup> Therefore, bowel preparation is recommended in the ERAS protocol for patients scheduled for rectal resection.<sup>[1]</sup> For colonic surgery, bowel preparation is not recommended for routine use and remains controversial<sup>[1, 18]</sup> In the present study, all patients received bowel preparation with polyethylene glycol electrolyte. Although bowel preparations based on polyethylene glycol minimize the loss of potassium, the incidence of hypokalemia increases five- to nine-fold after bowel preparation even for patients without underlying diseases.<sup>[7]</sup> In our previous study, the hypokalemia incidence was as high as 70%.<sup>[8]</sup>

The clinical symptoms depend on the severity of hypokalemia. Severe hypokalemia would lead to disorders of various systems including lethal heart arrhythmias, respiratory failure, constipation or intestinal paralysis<sup>[19]</sup>. Slight or mild hypokalemia typically presents with no clinical symptoms. Hypokalemia remains a risk factor for postoperative complications and delayed recovery.<sup>[20]</sup> A previous study recommended prophylactic potassium administration for patients scheduled for gastrointestinal surgery.<sup>[21]</sup> Potassium can be administered intravenously or orally. Intravenous potassium is suitable for severe hypokalemia and must be monitored under electrocardiography. The injection of potassium is also a high-alert medication requiring careful monitoring. Furthermore, the injection of potassium can cause vascular irritation and discomfort. Oral potassium supplements are recommended for patients with mild to moderate hypokalemia and those receiving prophylactic potassium. However, the administration of potassium by the oral route is extremely rare and research on the reason for this is scarce.<sup>[9]</sup> Several factors might contribute to this situation; for example, the flavor of potassium is not well tolerated and the importance of oral potassium might not be well known. Adding potassium to preoperative fluids might be a useful option. In the present study, preoperative carbohydrate drinks containing potassium were well tolerated and the flavor did not differ from that of carbohydrates. Most importantly, oral carbohydrate drinks containing 1 g of potassium administered 2 h before anesthesia significantly

reduced the incidence of preoperative hypokalemia in patients scheduled for colorectal resection compared with those who drank only carbohydrate fluids.

Although preoperative oral carbohydrate drinks and prophylactic potassium have been recommended, their effects on postoperative outcomes remain controversial. Our retrospective study demonstrated that preoperative hypokalemia prolonged postoperative time to FFE but not the time to FFL.<sup>[8]</sup> Several randomized controlled clinical trials have demonstrated that preoperative oral carbohydrates and oral rehydration solutions do not improve the quality of recovery in either minimally invasive body surface surgery or major abdominal surgery<sup>[22–24]</sup> The present study showed that oral carbohydrate drinks with and without 1 g of potassium administered 2–3 h before anesthesia induction did not improve the postoperative outcomes. Several factors might account for it. First, most of the hypokalemia caused by fasting or bowel preparations was mild to moderate.<sup>[7]</sup> Second, optimal preoperative carbohydrate drinks and prophylactic potassium administration are only a part of the ERAS protocol. Third, all the patients with hypokalemia were treated intraoperatively or postoperatively in the present study. No patients suffered hypokalemia on Postoperative Day 1.

In addition, several limitations of the study should be disclosed. First, only 1 g of potassium was administered 2–3 h before surgery, which resulted in half of patients still having hypokalemia. All patients were fasted overnight which was also a limitation. Second, bias may have been present in the patients' reporting of some of the parameters used in the present study. Unlike scintigraphy, some of the parameters, including the time to postoperative FFL and the time to FFE used to determine the gastrointestinal motility, are not gold standards. Third, short hospitalization is one of the endpoints of the ERAS protocol; some patients are reluctant to accept short hospitalization because of limited education level or other unclear reasons.<sup>[25]</sup> The hospitalization stay in the present study was long despite our best efforts to provide consulting services about the beneficial effects of ERAS. Therefore, the effect of hypokalemia on postoperative well-being should be explored in the near future. Finally, this was a single center study the results of which must be confirmed in a future multi-center study with a large population.

## Conclusions

In summary, preoperative carbohydrate drinks containing potassium significantly reduced the incidence of preoperative hypokalemia and improved preoperative thirst and hunger, but did not improve postoperative outcomes. However, as part of the ERAS protocol, preoperative carbohydrate drinks containing potassium should be recommended, as early as first admittance to hospital.

## List Of Abbreviations

ERAS, enhanced recovery after surgery;

FFL, first flatus;

FFE, first feces;

## Declarations

**Ethics approval and consent to participate:** The study was performed in accordance with the Declaration of Helsinki. It was approved by the Institutional Review Board of the third affiliated hospital of Sun Yat-sen University (approval number: [2016]2-184). Informed written consent was obtained from all individual participants included in the study.

**Consent for publication:** Not applicable.

**Availability of data and materials:** All data generated or analysed during this study are included in this published article.

**Competing interests:** The authors have no conflicts of interest.

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## Supplementary Files

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