Impact of a Potassium-enriched, Chloride-depleted 5% Glucose Solution on Gastrointestinal Function after Major Abdominopelvic Surgery

Results of a Randomized Controlled Trial

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ABSTRACT

Background: Gastrointestinal (GI) complications often delay recovery after radical cystectomy with urinary diversion. The authors investigated if perioperative administration of a potassium-enriched, chloride-depleted 5% glucose solution (G5K) accelerates recovery of GI function.

Methods: This randomized, parallel-group, single-center double-blind trial included 44 consecutive patients undergoing radical cystectomy and pelvic lymph node dissection with urinary diversion. Patients were randomized to receive either a G5K (G5K group) solution or a Ringer's maleate solution (control group). Fluid management aimed for a zero fluid balance. Primary endpoint was time to first defecation. Secondary endpoints were time to normal GI function, need for electrolyte substitution, and renal dysfunction.

Results: Time to first defecation was not significantly different between groups (G5K group, 93 h [19 to 168 h] and control group, 120 h [43 to 241 h]); estimator of the group difference, −16 (95% CI, −38 to 6); $P = 0.173$. Return of normal GI function occurred faster in the G5K group than in the control group (median, 138 h [range, 54 to 262 h] *vs.* 169 h [108 to 318 h]); estimator of the group difference, −38 (95% CI, −74 to −12); $P = 0.004$. Potassium and magnesium were less frequently substituted in the G5K group (13.6 *vs.* 54.5% [$P = 0.010$] and 18.2 *vs.* 77.3% [$P < 0.001$]), respectively. The incidence of renal dysfunction (Risk, Injury, Failure, Loss and End-stage kidney disease stage "risk") at discharge was 9.1% in the G5K group and 4.5% in the control group; $P = 1.000$.

Conclusions: Perioperative administration of a G5K did not enhance first defecation, but may accelerate recovery of normal GI function, and reduces potassium and magnesium substitution after radical cystectomy and urinary diversion. **(Anesthesiology 2016; XXX:00-00)**

INCREASING focus is being placed on enhanced recovery after surgery (ERAS) protocols for various major surgical procedures aiming to speed up recovery and reduce the length of hospital stay (LOS).[1,2] One of the cornerstones of ERAS protocols is perioperative fluid management with avoidance of salt and water overload.[2] In a previous randomized trial, we have shown that a simple hydration protocol focusing on a zero postoperative fluid balance significantly reduces overall major complications and gastrointestinal (GI) complications by more than 50%.[3,4]

GI recovery is a critical factor determining postoperative recovery and consequently LOS. Electrolyte disturbances can negatively impact GI function, especially low potassium and magnesium levels. A relevant number of patients receiving a balanced physiologic crystalloid solution (Ringer's maleate) perioperatively experience serum electrolyte disturbances in the early postoperative period after cystectomy and urinary diversion and need substitution. Excessive administration of normal saline (NaCl, 0.9%) is associated with higher GI and renal complication rates compared to balanced solutions.[4–6] Thus, optimization of perioperatively administered crystalloid solutions is required.

What We Already Know about This Topic

- Delayed return of gastrointestinal function often complicates radical cystectomy
- A potassium-enriched, chloride-depleted 5% glucose solution may accelerate recovery of gastrointestinal function
- The authors randomized 44 patients to the chloride-depleted solution or Ringer's maleate solution

What This Article Tells Us That Is New

- The primary outcome, time to first defecation, did not differ significantly

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Open radical cystectomy combined with pelvic lymph node dissection and urinary diversion was chosen as a major surgery model for this study because it is an extensive and time-consuming, but standardized, surgical intervention in a high-caseload tertiary center. In addition, despite improvements in surgical technique and perioperative care, radical cystectomy is associated with early postoperative complication rates of more than 50% and a 90-day mortality rate of 2 to 7%.[3,7]

We hypothesized that the perioperative administration of a novel potassium-enriched, chloride-depleted 5% glucose solution (G5K) improves GI recovery while reducing electrolyte disturbances when compared to a balanced Ringer's maleate solution.

Material and Methods

Ethics

The study was approved by the local ethics committee (Kantonale Ethikkommission Bern, Bern, Switzerland; KEKBE 151/13) and by the Swiss Agency for Therapeutic Products, Bern, Switzerland (2014DR4097). It was prospectively registered at http://www.controlled-trials.com (ISRCTN32976792; principal investigator: Dr. Wuethrich; date of registration: October 30, 2013) and conducted in compliance with the Declaration of Helsinki and Good Clinical Practice. All patients gave previous written informed consent.

Study Design and Patients

This is a prospective, randomized, parallel-group, assessor- and patient-blinded, high-caseload, single-center interventional superiority trial conducted at the Department of Urology, University Hospital Bern, Bern, Switzerland.

Consecutive patients presenting for open radical cystectomy, pelvic lymph node dissection, and urinary diversion (ileal conduit, orthotopic bladder substitute, continent catheterizable ileal reservoir) were screened for eligibility and recruited from July 2014 to May 2015. Inclusion criteria were age more than or equal to 18yr and American Society of Anesthesiologists' physical status II or III. Exclusion criteria were pregnancy, congestive heart failure (New York Heart Association classification more than or equal to 3), severe hepatic disease, and estimated glomerular filtration rate less than 45 ml/min.

Patients were prospectively randomized 1:1 by a computer-generated list with 11 blocks of 4 patients. The random allocation sequence was implemented by a study coordinator blinded to the study codes and was generated by the hospital pharmacy. Patients were enrolled by the research coordinator or the senior surgeon. Patients were included in strict numerical order and assigned to the group mentioned in the sealed, nontransparent envelope with the corresponding number. The similar-looking infusion bags were specially prepared and provided by the hospital pharmacy in accordance with good manufacturing practice. The investigators who assessed the return of GI function and performed the statistical analysis were blinded to the randomization.

Perioperative Management

Preoperatively, no antegrade bowel preparation was administered, but two high enemas were given the evening before surgery. Patients had oral intake till midnight before surgery and were encouraged to drink clear fluid till 2 h before anesthesia induction.

Surgery was performed in a standardized fashion as previously described with the patient in a 30° head-down position and with one of three senior urologists present.[8–10] A gastrostomy tube was placed intraoperatively, and the orogastric tube was removed at the end of the procedure. The ureteral stents were exteriorized.

In the intervention group (G5K group), patients received a potassium-enriched, chloride-depleted 5% glucose crystalloid solution (G5K solution, Bichsel, Switzerland) and in the control group, a balanced Ringer's maleate solution (Ringerfundin®, B. Braun, Switzerland) as a baseline infusion during the entire period requiring intravenous fluid administration. The main differences in electrolyte concentrations between the two solutions (G5K *vs.* Ringerfundin®) were as follows: chloride (65.0 *vs.* 127.0 mmol/l), sodium (50.0 *vs.* 145.0 mmol/l), potassium (30.0 *vs.* 4.0 mmol/l), and magnesium (2.0 *vs.* 1.0 mmol/l) concentrations. The G5K solution contained in addition 50 g/l glucose (277.4 mmol/l), lactate 18.0 mmol/l, and phosphate 8.0 mmol/l (table 1).

Intraoperatively, the assigned solution was administered at a rate of 1 ml kg^{-1} h^{-1} until the bladder was removed, followed by 3 ml kg^{-1} h^{-1} until the end of surgery. Norepinephrine was titrated as needed from 2 to 8 µg kg^{-1} h^{-1} to maintain a mean arterial pressure of 60 to 100 mmHg. If this was not sufficient to correct hypotension less than

Table 1. Electrolyte Composition of the Two Different Crystalloid Solutions

	G5K Group (G5K Solution)	Control Group (Ringerfundin®)
Sodium (mmol/l)	50.0	145.0
Potassium (mmol/l)	30.0	4.0
Magnesium (mmol/l)	2.0	1.0
Calcium (mmol/l)	0	2.5
Hydrogen (from hydrochloric acid) (mmol/l)	15.0	0
Chloride (mmol/l)	50.0	127.0
Chloride (from hydrochloric acid) (mmol/l)	15.0	0
Acetate (mmol/l)	0	24.0
Maleate (mmol/l)	0	5.0
Lactate (mmol/l)	18.0	0
Hydrogen phosphate (mmol/l)	8.0	0
Glucose (g/l)	50 (*i.e.*, 277.4 mmol/l)	0
Osmolality (mOsm/kg)	454	309

G5K = potassium-enriched, chloride-depleted 5% glucose solution.

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60 mmHg, boluses of 250 ml of Ringer's maleate solution were infused in both groups. Blood loss exceeding 500 ml was compensated with an equal amount of Ringer's maleate solution. Packed erythrocytes were transfused if hemoglobin values dropped less than 80 g/l (less than 100 g/l in patients with coronary artery disease). If hypotension persisted or if severe metabolic acidosis (base excess less than −5, pH less than 7.25) caused by hypovolemia occurred, additional boluses of Ringer's maleate solution were given in both groups. Patients with one to two risk factors for postoperative nausea and vomiting (PONV) were prophylactically treated with antiemetics (ondansetron).

Postoperatively, patients received 1,500 ml of the crystalloid solution allocated by randomization per day until oral substitution was adequate. The crystalloid solutions were administered using a pump with limited volume per time because of the relatively high potassium concentration in the G5K solution. Patient management adhered to our standardized care pathway.[11] Patients were allowed to drink clear fluids immediately after surgery, were encouraged to chew gum, and were started on an oral liquid diet on postoperative day (POD) 1. Subcutaneous 0.5 mg neostigmine daily was administered from POD 2 on under cardiac monitoring. A gastrostomy tube was initially left on drainage at bed level, closed if patients were without nausea and vomiting for more than 24 h, and removed once patients passed stool. Antiemetic therapy (intravenous ondansetron and/or droperidol) was initiated if patients experienced PONV.

Electrolyte substitution was performed according to our internal guideline in case of hypokalemia (K^+ less than 3.5 mmol/l), hypomagnesemia (Mg^{++} less than 0.66 mmol/l; both with intravenous substitution), and moderate hyponatremia (Na^+ less than 130 mmol/l; oral substitution). In case of hyperglycemia (more than 10 mmol/l), patients were treated with subcutaneous insulin injection (4 IU).

Bedside mobilization was encouraged as soon as possible, ideally the evening after surgery, or not later than the next morning. Active ambulation, including exercising in bed, sitting out of bed, and standing and walking in the room was started on POD 1, and prolonged mobilization as well as sitting in a chair were started on POD 2. Epidural analgesia remained until POD 5 combined with an opioid-free systemic analgesia (paracetamol and metamizol).

Endpoints

Primary endpoint was the time from end of surgery until first defecation (first portion of feces). Secondary endpoints were time to first flatus and normal GI function defined as defecation of a portion of normal stool (Bristol form scale 3 to 4).[12]As first defecation is the most widely used endpoint in GI recovery, we based our power analysis on this. However, we additionally considered the defecation of a normal portion of stool as a relevant secondary endpoint (*i.e.*, return of normal GI function), as first defecation can be defecation of residual stool (*i.e.*, rectal emptying in case of no preoperative bowel preparation) due to stimulation or paradoxical diarrhea.[13] This endpoint was added after registration but before recruitment of the first patient.

Patients were instructed to report the occurrence of flatus and defecation, which was recorded twice daily by the study nurse. Stool consistency and odor were also assessed by the ward nurse and documented by a study nurse. Bodyweight was measured every morning at the same time. Postoperative ileus (POI) was defined as no return of bowel function after POD 6 requiring cessation of oral intake, intravenous support, or nasogastric tube placement.[14] Incidence of PONV and antiemetic use were recorded.[15]

In addition, postoperative fluid balance (*i.e.*, difference in bodyweight) and event of renal dysfunction according to the Acute Kidney Injury Network and Risk, Injury, Failure, Loss and End-stage kidney disease classifications were assessed.[16–18]

Safety endpoints included measurement of biochemical parameters (sodium, potassium, chloride, magnesium, hydrogen phosphate, osmolality, brain natriuretic peptide, renin, and aldosterone), urine electrolytes (sodium, chloride), and osmolality during the first 4 PODs.[19] Plasma and urine samples were collected every morning at the same time (5:00 AM). Dyselectrolytemia was defined as hyperchloremia (plasma value more than 107 mmol/l), hypo- or hyperkalemia (more than 4.5 or less than 3.5 mmol/l), hyponatremia (less than 135 mmol/l), or hypomagnesemia (less than 0.66 mmol/l). Perioperative normoglycemia was defined as glucose plasma levels between 4.5 and 10.0 mmol/l. Hypoosmolality was defined as lower than 280 mOsm/kg.

Statistical Analysis

Based on internal retrospective data in a similar surgical population (time until first defecation, 4.82 days; SD, of 0.82 day), we calculated that a sample size of 18 patients per arm randomized 1:1 would have a 90% power ($\beta = 0.10$) to detect a difference of 1 day between the groups at a two-sided significance level of 5% ($\alpha = 0.05$) assuming a SD of 1 day. Presuming a drop-out rate of 20%, 22 patients per group were recruited.

Statistical analyses were conducted on an intention-to-treat basis. Data are expressed in medians with ranges for continuous variables or frequencies for categorical ones. Categorical data were compared with the Fisher exact or the chi-square test and continuous data with the Mann–Whitney U test for comparison of the two independent groups because of small sample sizes. Group differences in the primary outcome were evaluated using the Mann–Whitney U test for two independent groups. Nonparametric 95% CIs with Hodges–Lehmann (HL) estimator were used for differences of the two group medians.

A two-sided $P < 0.05$ was considered significant. Statistical analysis was performed by the Institute of Mathematical Statistics and Actuarial Science, University of Bern (Bern,

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Switzerland) using the Statistical Analysis System software (version 9.3; SAS Institute, USA).

Results

Demographics

Of 53 consecutive patients, 44 fulfilled the eligibility criteria, were randomized, and had complete follow-up data for the final analysis (fig. 1). Baseline demographic characteristics did not differ significantly between the groups (table 2).

Intraoperative and Postoperative Procedures

There was no statistically significant difference between groups regarding surgical characteristics, LOS, intraoperative parameters, and fluid administration (G5K group: 750 ml [range, 500 to 1,700 ml] *vs.* control group 975 ml [400 to 1,600 ml]; $P = 0.185$). The amount of fluid administered postoperatively (G5K group: 4,750 ml [4,000 to 6,000 ml] *vs.* control group 5,250 ml [4,000 to 6,000 ml], $P = 0.941$) and fluid balance did not differ significantly between the groups during the first 4 PODs. There was a significant difference in the salt load administered between the two groups (table 3).

Bowel Function

Time to first flatus did not differ significantly between groups: G5K group (44 h [13 to 118 h]) and control group (50 h [22 to 114 h]); HL estimator of the group difference, −2.5 (95% CI, −22 to 13); $P = 0.716$. Time to first defecation did not differ significantly between groups: G5K group (93 h [19 to 168 h]) and control group (120 h [43 to 241 h]); HL estimator of the group difference, −16 (95% CI, −38 to 6); $P = 0.173$. Time to return of normal GI function was significantly shorter in the G5K group (138 h [54 to 262 h]) than in the control group (169 h [108 to 318 h]); HL estimator of the group difference, −38 (95% CI, −74 to −12); $P = 0.004$ (fig. 2).

There was no significant difference in the incidence and duration of POI between groups: G5K 4.5% (1/22 patients), 3 days, and control 9.1% (2/22 patients), 3 and 4 days; $P = 1.000$. The incidence of at least one episode of PONV during PODs 1 to 4 was 22.7% (5/22 patients) in the G5K group and 45.5% (10/22) in the control group; $P = 0.203$. All patients with episodes of PONV received antiemetics (intravenous ondansetron and droperidol).

Estimated Renal function, Dyselectrolytemia, and Glycemia

There was no significant difference in median plasma creatinine values and estimated glomerular filtration rate between the groups postoperatively. Median potassium and magnesium plasma values were significantly lower in the control group on PODs 3 and 4 even if a Bonferroni correction for multiple testing (6 time points) of these components is applied. Median sodium plasma values were significantly lower in the G5K group on PODs 3 and 4, and median sodium urine value was significantly lower on POD 4 even if a Bonferroni correction for multiple testing (6 time points) of this component is applied. Median chloride plasma values were significantly lower in the G5K group.

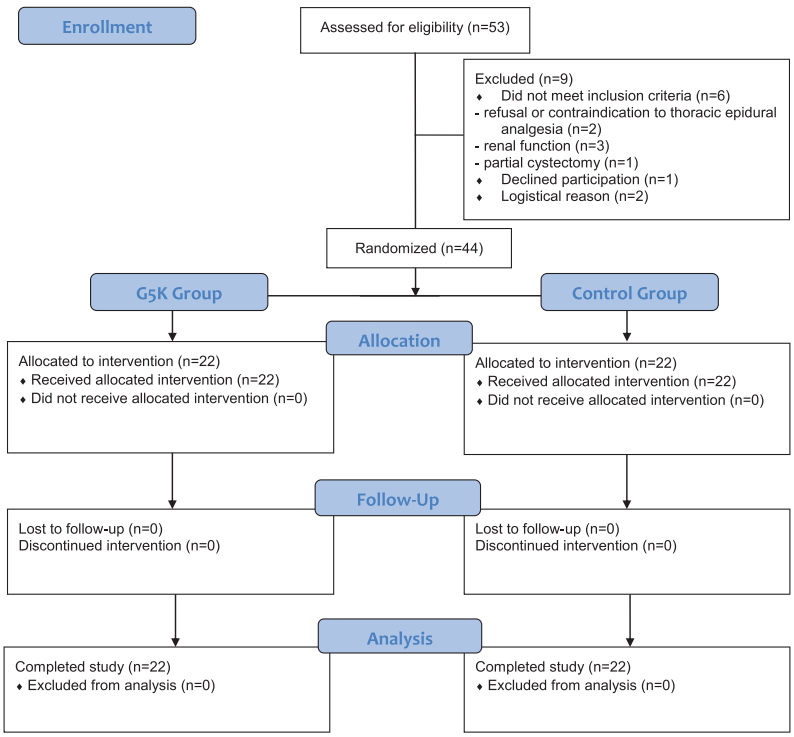

Fig. 1. Consort flowchart diagram. G5K = potassium-enriched, chloride-depleted 5% glucose solution.

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Table 2. Baseline Demographics and Surgical Patient Characteristics

Characteristics	G5K Group (n = 22)	Control Group (n = 22)
Age (yr)	71.5 (33.0–82.0)	63.5 (47.0–77.0)
Body weight (kg)	72.3 (42.0–90.0)	76.1 (52.0–173.0)
Height (cm)	170 (153–181)	172 (156–194)
BMI (kg/m^2)	24.7 (17.9–31.1)	25.8 (17.9–45.9)
Gender (female/male)	6/16 (27/73)	8/14 (36/64)
ASA physical status score		
II	13 (59)	15 (68)
III	9 (41)	7 (32)
Glasgow Prognostic Score		
0	8 (36)	10 (46)
1 or 2	14 (64)	12 (55)
Ischemic heart disease	3 (14)	4 (18)
Hypertension	11 (50)	9 (41)
Diabetes mellitus type II	0 (0)	2 (9)
COPD	6 (27)	2 (9)
CKD		
CKD grade 1	5 (23)	6 (27)
CKD grade 2 (mild)	17 (77)	12 (55)
CKD grade 3 (moderate)	0 (0)	4 (18)
Aspirin	2 (9)	4 (18)
Antihypertensives	9 (41)	8 (36)
Statins	4 (18)	4 (18)
β-Blocking agents	3 (14)	1 (5)
Neoadjuvant chemotherapy	6 (27)	6 (27)
Type of cancer		
Urothelial carcinoma	19 (86)	18 (82)
Leiomyosarcoma	1 (5)	1 (5)
Squamous cell carcinoma	2 (9)	3 (14)
Tumor stage (pT)		
Tis/CIS	1 (5)	1 (5)
Ta	4 (18)	5 (22)
T1	1 (5)	1 (5)
T2	2 (9)	7 (32)
T3	10 (46)	6 (27)
T4	4 (18)	2 (9)
Nodal involvement stage		
pN 0	16 (73)	17 (77)
pN +	6 (27)	5 (23)
Metastasis		
M0	21 (96)	21 (96)
M1	0 (0)	1 (5)
M2	1 (5)	0 (0)

Data are presented as median (range) or absolute value (%).

ASA = American Society of Anesthesiologists; BMI = body mass index; CIS = carcinoma in situ; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; G5K = potassium-enriched, chloride-depleted 5% glucose solution; Tis = tumor in situ.

Urinary sodium values were significantly lower in the G5K group 6 h after surgery and on POD 4 even if a Bonferroni correction for multiple testing (6 time points) of these components is applied. Urine chloride values were only significantly lower in the G5K group 6 h after surgery. Urine osmolality did not differ significantly between groups (table 4).

The rates of potassium and magnesium intravenous substitution were significantly higher in the control (54.5 and 77.3%) than in the G5K (13.6 and 18.2%) group, $P = 0.010$ and $P < 0.001$, respectively. There was no difference between groups for any of the renal dysfunction classifications (table 5).

At least 1 episode of mild hyponatremia was present in 13 of 22 patients (59.1%) in the G5K group and in 4 of 22 patients (18.2%) in the control group; $P = 0.012$ (table 5). However, overall only five patients in the G5K and one in the control group had a sodium plasma value under 134 mmol/l from POD 1 to 4.

Plasma glucose values were similar between the two groups (table 4). Episodes of hyperglycemia were present in 3 of 22 patients (13.6%) in the G5K group (measured 6 h after surgery, treated with a single subcutaneous injection of 4 IU insulin per patient) and in 6 of 22 patients (27.3%) in the control group (measured 6 h after surgery [4 IU insulin per patient] and on POD 1 [4 IU insulin per patient]).

Complications

The in-hospital complication rate did not differ between groups with the exception of a higher rate of surgical complications in the control group (31.8%: 2 lymphoceles, 4 wound dehiscences, and 1 ureteral anastomotic leak) compared to the G5K group (4.5%: 1 lymphocele); $P = 0.046$ (table 5).

In addition, we found four patients (18.2%) with neurologic complications in the G5K group (one transient ischemic attack on POD 2 due to a preoperatively not diagnosed internal carotid artery stenosis and three transient sensomotoric dysfunctions of the obturator nerve after surgical lymph node dissection). In the control group, we found two patients (9.1%) with neurologic complications (one transient confusion on POD 1 [with normal plasma sodium level at this time point] and one sensomotoric lesion of the femoral nerve due to positioning).

Discussion

We were unable to detect a statistically significant difference in the time from end of surgery until first defecation (first portion of feces), our primary endpoint. However, a relevant finding of this prospective randomized study is that the return of normal GI function (secondary endpoint) was accelerated by perioperative administration of a potassium-enriched, chloride-depleted 5% glucose crystalloid as a perioperative maintenance solution when compared to the usually used balanced crystalloids. In addition, the need for postoperative intravenous potassium and magnesium substitution was reduced in the G5K group, suggesting fewer perioperative electrolyte shifts in this group.

There is some evidence that the quantity of crystalloid solution administered perioperatively influences postoperative rehabilitation and morbidity as well as having an impact on postoperative recovery.[4,5,20] A positive salt and water balance delay return of GI function in patients undergoing

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Table 3. Perioperative Management

Characteristics	G5K Group (n = 22)	Control Group (n = 22)	*P* Value	Estimator of Group Differences	95% CI
Type of urinary derivation					
Ileal OBS	10 (46)	13 (59)	0.667		
Ileal conduit	11 (50)	7 (32)			
Continent ileal reservoir	1 (5)	2 (9)			
Surgery duration (min)	373 (210 to 540)	397 (230 to 480)	0.731	10.0	–30 to 58
Blood loss (ml)	880 (200 to 1,800)	1,200 (200 to 2,200)	0.135	200.0	–90 to 600
Intraoperative fluid and salt administered					
Crystalloid according to randomization (ml)	750 (500 to 1,700)	975 (400 to 1,600)	0.185	100.0	–50 to 300
Total intravenous sodium (mmol)	161 (25 to 274)	283 (102 to 471)	< 0.001	134.0	74.8 to 199.8
Total intravenous chloride (mmol)	108 (65 to 191)	248 (89 to 413)	0.002	99.5	43.4 to 189.8
Total intravenous potassium (mmol)	26 (15 to 56)	8 (3 to 13)	< 0.001	–18.3	–22.6 to –15.2
Total intravenous magnesium (mmol)	3 (1 to 5)	2 (1 to 3)	0.09	–0.4	–0.9 to 0.05
Additional Ringerfundin® (ml)	850 (0 to 1,500)	1,000 (0 to 2,250)	0.135	250.0	0 to 700
Packed erythrocytes (n)	3 (14)	3 (14)	1.000		
FFP (n)	2 (9)	1 (5)	1.000		
Fluid balance on POD 1	0.20 (–1.50 to 2.20)	0.75 (–1.60 to 2.70)	0.137	0.6	–0.2 to 1.4
Postoperative fluid administered					
Crystalloid according to randomization (ml)	4,750 (4,000 to 6,000)	5,250 (4,000 to 6,000)	0.941	0.0	0 to 0
Packed erythrocytes (ml)	0 (0 to 500)	0 (0 to 500)	0.755	1.0	0 to 0
Number of patients with packed erythrocytes (n)	7 (32)	9 (41)	0.754		
Packed erythrocytes administered (n)	14 (64)	16 (73)			
Fluid balance on POD 1	0.20 (–1.50 to 2.20)	0.75 (–1.60 to 2.70)	0.137	0.6	–0.2 to 1.4
Fluid balance on POD 2	0.05 (–1.10 to 2.00)	–0.05 (–2.90 to 1.50)	0.326	–0.1	–0.7 to 0.5
Fluid balance on POD 3	0.20 (–1.00 to 1.80)	–0.20 (–2.20 to 1.90)	0.342	–0.2	–0.7 to 0.3
Fluid balance on POD 4	–0.40 (–2.50 to 2.00)	–0.50 (–2.50 to 2.00)	0.589	0.6	–0.1 to 1.2
Total intravenous sodium (mmol)	238 (200 to 300)	761 (580 to 870)	< 0.001	512.5	380 to 570
Total intravenous chloride (mmol)	309 (260 to 390)	667 (508 to 762)	< 0.001	357.3	248 to 372
Total intravenous potassium (mmol)	143 (120 to 180)	21 (16 to 24)	< 0.001	–122.5	–156 to –104
Total intravenous magnesium (mmol)	10 (8 to 12)	5 (4 to 6)	< 0.001	–4.3	–6 to –4

Data are presented as median (range) or absolute value (%). Estimator of the group differences: Hodges–Lehmann estimator of the differences of the group medians, with corresponding 95% CI.

FFP = fresh frozen plasma; G5K = potassium-enriched, chloride-depleted 5% glucose solution; OBS = orthotopic bladder substitution; POD = postoperative day.

colorectal surgery or cystectomy,[4–6] while patients with no weight gain on POD 1 have fewer overall and GI complications.[5,6] However, not only the quantity of crystalloid solution but also the type of electrolytes in the crystalloid solution infused is of relevance. Normal saline solution (*i.e.*, 0.9% NaCl), still the most commonly used crystalloid solution worldwide, contains excessive amounts of chloride and sodium. Administration of large amounts of saline solution has been associated with increased postoperative morbidity compared to more physiologic balanced crystalloids.[21] Saline solution overload results in metabolic acidosis, with decreased renal blood flow, renal dysfunction, prolonged GI recovery time, and increased infectious complication rates compared to balanced crystalloid solutions.[6,21–24]

After having demonstrated, in the context of an ERAS protocol,[2] that a fluid management scheme based on a zero postoperative weight gain dramatically reduces complications and LOS, we now compared a balanced Ringer's maleate solution to a novel potassium-enriched (30 mmol/l) and chloride-depleted (65 mmol/l) 5% glucose–based crystalloid solution.[4] Both groups had a similar fluid balance of around zero (*i.e.*, no weight gain postoperatively) as a prerequisite according to our previously published protocol.[4] Using the novel solution, return of GI function was significantly reduced by more than 1 day; this is relevant and comparable to the published outcomes in other studies, which focused on optimizing postoperative GI function.[25] The substantially higher sodium and chloride load in the control group but similar urinary sodium and chloride concentrations postoperatively when compared to the G5K group suggest a relevant sodium and chloride retention in the control group. This is possibly explained by the kidneys' limited ability to excrete water and electrolytes perioperatively as a response to surgical trauma and postoperative stress reaction.[24] The observed difference in perioperative electrolyte load could be an explanation for the delayed return of GI function and the nonsignificant trend toward a longer time to first flatus and defecation in the control group. Both hypokalemia, which occurred in the control group, and hyponatremia caused by fluid overload have been reported to be risk factors for delayed return of normal GI function and POI[26,27] by impairing intrinsic small bowel myogenic and neurogenic

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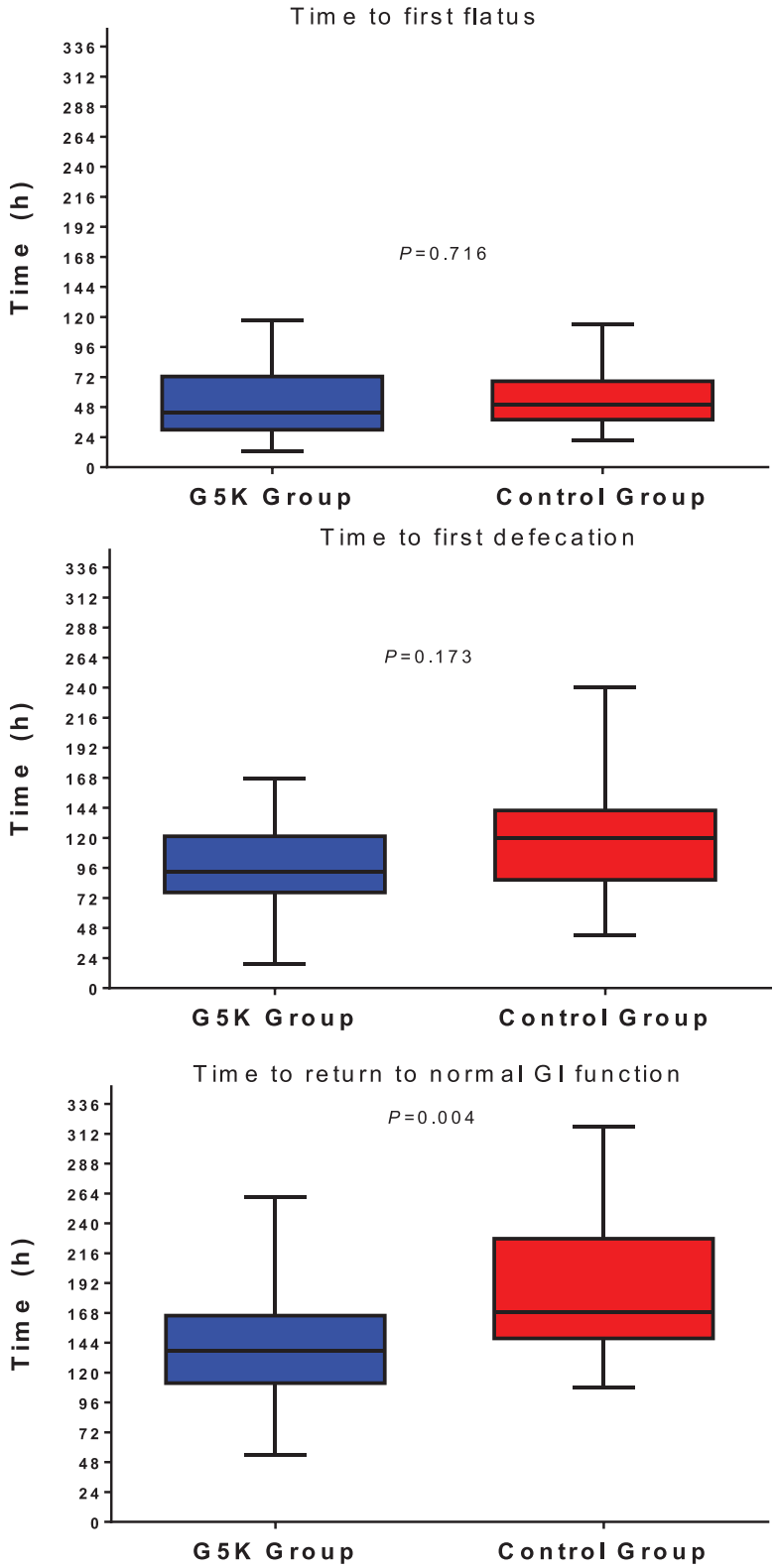

Fig. 2. Return of gastrointestinal (GI) function. Data are presented as *box plots* with *whiskers* as minimum and maximum values and interquartile range (*box*). G5K = potassium-enriched, chloride-depleted 5% glucose solution.

activity. Although patients in the G5K group had lower sodium plasma values and a higher incidence of mild hyponatremia, osmolality and fluid balance did not differ from the control group. This suggests a compensated fluid load and possibly explains why mild hyponatremia did not affect GI recovery. The higher incidence of mild hyponatremia in

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Table 4. Perioperative Biochemistry and Markers of Renal Function

	Preoperative	6-h Postoperative	POD 1	POD 2	POD 3	POD 4
Serum creatinine (μmol/l)						
G5K group	79 [62 to 121]	105 [71 to 223]	99 [64 to 225]	85 [60 to 188]	83 [59 to 202]	75 [61 to 163]
Control group	78 [54 to 108]	98 [66 to 206]	94 [56 to 220]	81 [45 to 135]	76 [39 to 107]	76 [36 to 106]
HL estimator (95% CI)	2 (–2 to 5)	4 (0 to 8)	4 (1 to 7)	2 (0 to 4)	3 (–1 to 6)	3 (0 to 7)
P value	0.412	0.995	0.613	0.425	0.446	0.518
eGFR (ml/min)						
G5K group	77 [47 to 89]	55 [25 to 89]	64 [29 to 90]	78 [35 to 189]	77 [45 to 90]	73 [46 to 90]
Control group	75 [51 to 89]	62 [29 to 89]	62 [25 to 90]	65 [31 to 90]	75 [28 to 90]	80 [37 to 89]
HL estimator (95% CI)	2.0 (–8 to 12)	2.0 (–10 to 15)	1.5 (–12 to 14)	5.5 (–5 to 17)	4.0 (–6 to 13)	–1.0 (–12 to 12)
P value	0.612	0.763	0.844	0.317	0.334	0.518
Serum osmolality (mOsm/kg)						
G5K group	285 [265 to 293]	285 [264 to 295]	283 [264 to 292]	282 [259 to 289]	282 [250 to 289]	282 [255 to 293]
Control group	286 [280 to 296]	289 [281 to 298]	287 [282 to 295]	284 [279 to 292]	284 [269 to 293]	285 [277 to 295]
HL estimator (95% CI)	2 (–2 to 5)	4 (0 to 8)	4 (1 to 7)	2 (0 to 4)	3 (–1 to 6)	3 (0 to 7)
P value	0.201	0.015	0.018	0.060	0.126	0.081
Serum sodium (mmol/l)						
G5K group	138 [129 to 143]	134 [126 to 138]	135 [125 to 138]	137 [127 to 142]	137 [121 to 140]	137 [123 to 140]
Control group	139 [135 to 142]	137 [132 to 140]	136 [133 to 141]	139 [137 to 145]	139 [134 to 143]	139 [134 to 143]
HL estimator (95% CI)	1 (–1 to 2)	2 (0 to 3)	1 (0 to 2)	2 (0 to 3)	2 (1 to 4)	3 (1 to 4)
P value	0.376	0.016	0.021	0.015	0.003*	< 0.001*
Serum chloride (mmol/l)						
G5K group	101 [94 to 112]	107 [96 to 112]	106 [95 to 113]	102 [90 to 107]	101 [84 to 106]	101 [87 to 105]
Control group	106 [102 to 113]	110 [103 to 115]	108 [104 to 113]	103 [100 to 109]	103 [98 to 106]	103 [98 to 108]
HL estimator (95% CI)	4 (2 to 6)	2 (0 to 5)	2 (1 to 4)	1 (0 to 3)	2 (0 to 3)	2 (1 to 4)
P value	0.001	0.023	0.009*	0.109	0.010	0.010
Serum potassium (mmol/l)						
G5K group	3.9 [3.2 to 4.8]	4.5 [3.4 to 5.3]	4.1 [3.5 to 4.8]	4.1 [3.5 to 4.7]	4.1 [3.5 to 4.7]	4.1 [3.4 to 4.7]
Control group	4.1 [3.7 to 4.6]	4.5 [4.0 to 5.8]	4.1 [3.9 to 4.7]	3.9 [3.5 to 4.4]	3.9 [3.4 to 4.3]	3.7 [3.1 to 4.4]
HL estimator (95% CI)	0.2 (0.0 to 0.4)	0.1 (–0.2 to 0.3)	0.0 (–0.2 to 0.2)	–0.2 (–0.4 to 0.0)	–0.3 (–0.5 to –0.1)	–0.3 (–0.5 to –0.1)
P value	0.089	0.646	0.795	0.102	0.007*	0.004*
Serum magnesium (mmol/l)						
G5K group	0.79 [0.68 to 0.89]	0.70 [0.51 to 1.05]	0.74 [0.59 to 0.92]	0.81 [0.64 to 0.95]	0.78 [0.57 to 1.18]	0.81 [0.61 to 0.92]
Control group	0.79 [0.66 to 0.88]	0.67 [0.54 to 1.01]	0.68 [0.57 to 0.96]	0.74 [0.64 to 0.88]	0.74 [0.59 to 0.80]	0.74 [0.58 to 0.84]
HL estimator (95% CI)	–0.01 (–0.05 to 0.03)	–0.04 (–0.10 to 0.02)	–0.06 (–0.11 to 0.00)	–0.07 (–0.12 to –0.01)	–0.09 (–0.13 to –0.03)	–0.08 (–0.13 to –0.04)
P value	0.629	0.151	0.041	0.013	< 0.001*	0.002*
Serum Glc (mmol/l)						
G5K group	6.9 [5.0 to 9.2]	8.5 [6.5 to 13.0]	7.4 [6.3 to 9.2]	6.8 [5.6 to 8.2]	6.1 [5.3 to 8.1]	6.0 [5.2 to 8.0]
Control group	6.1 [4.9 to 8.4]	8.9 [5.6 to 13.0]	7.1 [5.6 to 11.1]	6.3 [4.0 to 8.8]	6.1 [4.0 to 9.8]	5.7 [4.9 to 9.4]
HL estimator (95% CI)	–0.58 (–1.30 to 0.05)	0.50 (–0.60 to 1.40)	–0.20 (–0.80 to 0.50)	–0.65 (–1.23 to 0.02)	–0.29 (–0.93 to 0.23)	–0.9 (–0.19 to 0.17)
P value	0.098	0.418	0.518	0.062	0.296	0.307

(Continued)

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Table 4. (Continued)

	Preoperative	6-h Postoperative	POD 1	POD 2	POD 3	POD 4
Serum phosphate (mmol/l)						
G5K group	1.04 [0.68 to 1.31]	1.05 [0.71 to 1.66]	1.07 [0.70 to 1.75]	0.92 [0.68 to 1.24]	0.94 [0.66 to 1.14]	0.97 [0.80 to 1.28]
Control group	1.01 [0.53–1.42]	1.20 [0.48 to 1.76]	1.21 [0.56 to 1.69]	0.93 [0.35 to 1.32]	0.87 [0.31 to 1.40]	0.97 [0.29 to 1.40]
HL estimator (95% CI)	0.04 (–0.09 to 0.17)	0.20 (0.02 to 0.34)	0.10 (–0.09 to 0.23)	–0.01 (–0.17 to 0.12)	–0.08 (–0.20 to 0.04)	–0.07 (–0.26 to 0.04)
P value	0.549	0.026	0.246	0.821	0.177	0.231
Urine osmolality (mOsm/kg)						
G5K group	480 [114 to 1,133]	582 [215 to 735]	528 [171 to 667]	520 [312 to 732]	582 [133 to 882]	433 [120 to 828]
Control group	533 [130 to 1,105]	618 [243 to 934]	553 [211 to 922]	526 [167 to 832]	715 [317 to 943]	537 [178 to 993]
HL estimator (95% CI)	7 (–125 to162)	54 (–17 to 159)	51 (–54 to 167)	54 (–45 to 152)	97 (–26 to 213)	52 (–115 to 173)
P value	0.862	0.102	0.333	0.367	0.142	0.467
Urine sodium (mmol/l)						
G5K group	102 [19 to 144]	36 [11 to 93]	43 [11 to 172]	64 [18 to 226]	89 [10 to 290]	65 [10 to 143]
Control group	88 [15 to 150]	56 [24 to 183]	76 [15 to 164]	88 [56 to 217]	108 [21 to 210]	111 [33 to 211]
HL estimator (95% CI)	–4 (–28 to 21)	24 (8 to 49)	22 (–1 to 51)	26 (–1 to 51)	20 (–15 to 51)	41 (13 to 61)
P value	0.760	0.009*	0.057	0.060	0.255	0.004*
Urine chloride (mmol/l)						
G5K group	81 [21 to 142]	62 [14 to 145]	79 [11 to 195]	64 [15 to 191]	83 [11 to 209]	61 [15 to 153]
Control group	68 [20 to 160]	95 [26 to 241]	77 [27 to 224]	83 [26 to 189]	86 [18 to 192]	77 [18 to 195]
HL estimator (95% CI)	–8 (–33 to 21)	31 (5 to 59)	22 (–11 to 46)	20 (–8 to 42)	15 (–18 to 46)	17 (–7 to 41)
P value	0.387	0.031	0.209	0.142	0.467	0.095
Serum renin (ng/l)						
G5K group	20.0 [2.9 to 20.3]	31.6 [3.2 to 243.0]	21.7 [3.0 to 140.6]	15.6 [2.6 to 82.2]	16.4 [2.4 to 105.0]	18.3 [2.3 to 87.3]
Control group	19.6 [2.2 to 114.0]	38.0 [6.6 to 315.5]	21.0 [4.0 to 269.0]	9.4 [2.2 to 59.4]	6.9 [1.6 to 410.0]	9.8 [2.0 to 123.0]
HL estimator (95% CI)	2.9 (–15.5 to 12.6)	3.1 (–22.6 to 23.8)	–1.5 (–17.3 to 11.1)	–3.9 (–11.8 to 2.2)	–7.6 (–18.5 to –1.5)	–7.2 (–15.8 to 0.0)
P value	0.689	0.656	0.830	0.189	0.013	0.050
Serum aldosterone (pmol/l)						
G5K group	214 [76 to 1,741]	370 [86 to 2,255]	161 [74 to 1,142]	69 [69 to 725]	78 [69 to 524]	69 [28 to 321]
Control group	172 [69 to 464]	325 [54 to 1,319]	376 [122 to 772]	69 [69 to 340]	69 [69 to 311]	69 [69 to 214]
HL estimator (95% CI)	–34 (–128 to 22)	–40 (–255 to 122)	–2 (–65 to 53)	0 (–12 to 0)	0 (–29 to 0)	0 (–49 to 0)
P value	0.442	0.784	0.075	0.233	0.089	0.101

Data are presented as median [range] with Hodges–Lehmann (HL) estimator of the differences of the group medians (95% CI).

*The values represent significance if we would apply a Bonferroni correction for multiple testing (6 time points).

eGFR = estimated glomerular filtration rate; Glc = glucose; G5K = potassium-enriched, chloride-depleted 5% glucose solution; POD = postoperative day.

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Table 5. Side Effects and In-hospital Complications

	G5K Group (n = 22)	Control Group (n = 22)	*P* Value
Electrolytes/biochemistry			
BNP plasma value (> 100 pg/ml)	8 (36.4)	11 (50.0)	0.543
Hypophosphatemia (< 0.8 mmol/l)	6 (27.3)	10 (45.5)	0.348
Hyperchloremia (> 107 mmol/l)	12 (54.5)	18 (81.8)	0.104
Hypokalemia (< 3.5 mmol/l)	2 (9.1)	4 (18.2)	0.664
Hyperglycemia (> 10.0 mmol/l)	3 (13.6)	6 (27.3)	0.457
Hypoosmolality (< 280 mmol/l)	10 (45.5)	9 (40.9)	1.000
Hyponatremia (< 135 mmol/l)	13 (59.1)	4 (18.2)	0.012
Mild hyponatremia (130–134 mmol/l)			
6 h postoperatively	11 (50)	6 (27.3)	
POD 1	8 (36.4)	3 (13.6)	
POD 2	3 (13.6)	0 (0)	
POD 3	3 (13.6)	1 (4.5)	
POD 4	4 (18.2)	0 (0)	
Moderate hyponatremia (< 130 mmol/l)			
6 h postoperatively	1 (4.5)	0 (0)	
POD 1	1 (4.5)	0 (0)	
POD 2	1 (4.5)	0 (0)	
POD 3	1 (4.5)	0 (0)	
POD 4	1 (4.5)	0 (0)	
Hypomagnesemia (< 0.66 mmol/l)	8 (36.4)	14 (63.6)	0.131
Hyperaldosteronism (> 340 pmol/l)	9 (40.9)	9 (40.9)	1.000
Increased renin plasma value	19 (86.4)	20 (90.9)	1.000
Electrolyte replacement			
Patients with intravenous potassium replacement	3 (13.6)	12 (54.5)	0.010
Patients with intravenous magnesium replacement	4 (18.2)	17 (77.3)	< 0.001
Patients with subcutaneous insulin injection	3 (13.6)	6 (27.3)	0.457
Total amount of insulin injected (IU)	12	24	
Patients with sodium replacement (oral)	2 (9.1)	0	0.488
Criteria for kidney injury			
Transient AKIN (stage1/2) POD 1–2	1/1 (9.1)	0 (0)	0.488
RIFLE at discharge (class R "risk")	2 (9.1)	1 (4.5)	1.000
Number of patients developing at least one complication (n)	13 (59.1)	9 (40.9)	0.366
Cardiovascular complications (n)	5 (22.7)	2 (9.1)	0.412
Pulmonary complications (n)	3 (13.6)	3 (13.6)	1.000
Infectious complications (n)	2 (9.1)	5 (22.7)	0.412
Surgical complications (n)	1 (4.5)	7 (31.8)	0.046
Neurologic complications (n)	4 (18.2)	2 (9.1)	0.664
Length of hospital stay (d)	14.5 (10–23)	15.5 (11–26)	0.233

Data are presented as n (%) or as median (range).

AKIN = Acute Kidney Injury Network; BNP = brain natriuretic peptide; G5K = potassium-enriched, chloride-depleted 5% glucose solution; POD = postoperative day; RIFLE = Risk, Injury, Failure, Loss and End-stage kidney disease.

the G5K group had no apparent adverse effect, and it was not associated with fluid retention. It is likely that impaired GI function recovery as a consequence of hyponatremia, which has been reported by some studies, is more likely caused by the concomitant fluid overload than by the hyponatremia *per se*.

Magnesium is another factor potentially affecting recovery of GI function.[28] As the G5K solution contains twofold more magnesium than the balanced Ringer's maleate solution (Ringerfundin®) and patients in the control group required significantly more magnesium replacement postoperatively, this could be another factor favoring return of GI function in the G5K group.

Intracellular uptake of glucose (50 g/l in the G5K solution) and at the same time by uptake of water through osmosis probably results in a less pronounced interstitial edema in the GI tract. Due to the 5% glucose content and low sodium and chloride concentration, the G5K solution is more likely to shift water from intravascular to interstitial to intracellular, than a similar quantity of balanced Ringer's maleate solution would (*i.e.*, intravascular to interstitial). Interstitial edema, due to fluid overload or inadequate crystalloid choice (saline solution), is another factor known to affect GI function and cause prolonged POI.[29–31]

The goal of an intravenous maintenance solution is to substitute the daily needs for water and electrolytes and

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to reduce ketosis starvation by giving 50 to 100 g glucose, 1 mmol kg^{-1} d^{-1} potassium, and 1 mmol kg^{-1} d^{-1} sodium.[32] These requirements are better met by the G5K crystalloid solution than the balanced Ringer's maleate solution, a solution containing no glucose and substantially less potassium. Therefore, it is not surprising that patients in the control group needed significantly more potassium substitution and had statistically but not clinically relevant higher chloride and sodium plasma values. This is an important finding, as hypokalemia is another factor known to impair GI recovery.[33]

Established postoperative strategies to accelerate return of GI function and reduce POI have already been established in patients undergoing radical cystectomy with urinary diversion: use of epidural analgesia to avoid opioid use, alvimopan administration, chewing gum, and early oral intake are examples.[15,25] The amount of perioperative fluid and the electrolytes substituted is considered another key element, albeit still controversial. This study suggests that the electrolyte composition of a balanced crystalloid solutions influences the return of normal GI function. This is a more objective parameter than the commonly used first defecation, as the latter may be influenced by neostigmine, suppositories, or enemas or only reflect rectal emptying.

This study has some limitations. Many factors impact GI function such as the surgery (open *vs.* minimally invasive, type of urinary derivation, extent of pelvic lymph node dissection, bowel segment selected, blood loss, duration of surgery), anesthesiologic factors (opioids, fluid overload), and individual risks (gender, age, comorbidities, Glasgow prognostic score).[34] However, surgical and anesthesiologic bias was limited in our study, as perioperative management adhered to the same center-specific pathways in all patients. In addition, this study was performed in a high–caseload center; thus, it remains unclear if these findings can be extrapolated to other centers and larger patient populations. Finally, this study was not powered to confidently assess safety. However, we could not detect a difference in in-hospital complications including neurologic disturbances associated with dyselectrolytemia (*i.e.*, acute changes in sodium plasma level and its correction). It has to be emphasized that the G5K solution, mainly because of its relatively high potassium concentration, should only be administered as a maintenance fluid using a volumetric pump.

Conclusion

The administration of a potassium-enriched, chloride-depleted 5% glucose crystalloid as a perioperative maintenance solution in conjunction with a zero perioperative fluid balance did not significantly affect the time to first defecation (primary endpoint), but accelerated the return of normal GI function (secondary endpoint) after open radical cystectomy and urinary diversion. It reduced the postoperative need for potassium and magnesium substitution. However, this potassium-enriched, chloride-depleted 5% glucose crystalloid solution resulted in substantial postoperative mild hyponatremia mandating close monitoring of plasma sodium.

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Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available from Dr. Wuethrich: patrick.wuethrich@insel.ch. Raw data available from Dr. Wuethrich: patrick.wuethrich@insel.ch.

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