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.

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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 randomization 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 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.

### Table 1. Electrolyte Composition of the Two Different Crystalloid Solutions

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

G5K = potassium-enriched, chloride-depleted 5% glucose 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 in GI recovery, as first defecation can be defecation of a portion of normal stool (Bristol form scale 3 to 4). As first defecation is the most widely used endpoint in GI recovery, we based our power analysis on this. How- ever, 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 prepara-

tive 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. Incidence of PONV and antiemetic use were recorded.14

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, chlorine), and osmolality during the first 4 PODs. 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 hyperka-

lemia (more than 4.5 or less than 3.5 mmol/l), hyponatrae-

mia (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. Hypoglycemia 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 (β = 0.10) to detect a difference of 1 day between the groups at a two-sided significance level of 5% (α = 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. Cat-

ergorical data were compared with the Fisher exact or the chi-

squared 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 out-

come 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, 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.

Urinary sodium values were significantly lower in the G5K group 6h after surgery and on POD 4 even if a Bonferroni correction for multiple testing (6 time points) of

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**Fig. 1.** Consort flowchart diagram. G5K = potassium-enriched, chloride-depleted 5% glucose solution.
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 18.2%) group, suggesting fewer perioperative electrolyte shifts in this group. An accelerated return of normal GI function (secondary endpoint) was the 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.\textsuperscript{4,5,20} A positive salt and water balance delay return of GI function in patients undergoing colorectal surgery or cystectomy,\textsuperscript{4,6} while patients with no weight gain on POD 1 have fewer overall and GI complications.\textsuperscript{5,6} However, not only the quantity of crystalloid

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 sensorimotor 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 sensorimotor 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 crystallloid 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.

Table 2. Baseline Demographics and Surgical Patient Characteristics

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

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.
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.\textsuperscript{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.\textsuperscript{6,21–24}

After having demonstrated, in the context of an ERAS protocol,\textsuperscript{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.\textsuperscript{4} Both groups had a similar fluid balance of around 0.9% NaCl, still the most commonly used 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.\textsuperscript{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.\textsuperscript{6,21–24}

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### Table 3. Perioperative Management

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

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; GSK = potassium-enriched, chloride-depleted 5% glucose solution; OBS = orthotopic bladder substitution; POD = postoperative day.
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 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,

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.
### Table 4. Perioperative Biochemistry and Markers of Renal Function

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>6-h Postoperative</th>
<th>POD 1</th>
<th>POD 2</th>
<th>POD 3</th>
<th>POD 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serum creatinine (µmol/l)</strong></td>
<td></td>
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</tr>
<tr>
<td>G5K group</td>
<td>79 [62 to 121]</td>
<td>105 [71 to 223]</td>
<td>99 [64 to 225]</td>
<td>85 [60 to 188]</td>
<td>83 [59 to 202]</td>
<td>75 [61 to 163]</td>
</tr>
<tr>
<td>HL estimator (95% CI)</td>
<td>2 (–2 to 5)</td>
<td>4 (0 to 8)</td>
<td>4 (1 to 7)</td>
<td>2 (0 to 4)</td>
<td>3 (–1 to 6)</td>
<td>3 (0 to 7)</td>
</tr>
<tr>
<td>P value</td>
<td>0.412</td>
<td>0.095</td>
<td>0.613</td>
<td>0.425</td>
<td>0.446</td>
<td>0.518</td>
</tr>
<tr>
<td><strong>eGFR (ml/min)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G5K group</td>
<td>77 [47 to 89]</td>
<td>55 [25 to 89]</td>
<td>64 [29 to 90]</td>
<td>78 [35 to 189]</td>
<td>77 [45 to 90]</td>
<td>73 [46 to 90]</td>
</tr>
<tr>
<td>Control group</td>
<td>75 [51 to 89]</td>
<td>62 [29 to 89]</td>
<td>62 [25 to 90]</td>
<td>65 [31 to 90]</td>
<td>75 [28 to 90]</td>
<td>80 [37 to 89]</td>
</tr>
<tr>
<td>HL estimator (95% CI)</td>
<td>2.0 (–8 to 12)</td>
<td>2.0 (–10 to 15)</td>
<td>1.5 (–12 to 14)</td>
<td>5.5 (–5 to 17)</td>
<td>4.0 (–6 to 13)</td>
<td>–1.0 (–12 to 12)</td>
</tr>
<tr>
<td>P value</td>
<td>0.612</td>
<td>0.763</td>
<td>0.844</td>
<td>0.317</td>
<td>0.334</td>
<td>0.518</td>
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<tr>
<td><strong>Serum osmolality (mOsm/kg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HL estimator (95% CI)</td>
<td>2 (–2 to 5)</td>
<td>4 (0 to 8)</td>
<td>4 (1 to 7)</td>
<td>2 (0 to 4)</td>
<td>3 (–1 to 6)</td>
<td>3 (0 to 7)</td>
</tr>
<tr>
<td>P value</td>
<td>0.201</td>
<td>0.015</td>
<td>0.018</td>
<td>0.060</td>
<td>0.126</td>
<td>0.081</td>
</tr>
<tr>
<td><strong>Serum sodium (mmol/l)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G5K group</td>
<td>138 [129 to 143]</td>
<td>134 [126 to 138]</td>
<td>135 [125 to 138]</td>
<td>137 [127 to 142]</td>
<td>137 [121 to 140]</td>
<td>137 [123 to 140]</td>
</tr>
<tr>
<td>Control group</td>
<td>139 [135 to 142]</td>
<td>137 [132 to 140]</td>
<td>136 [133 to 141]</td>
<td>139 [137 to 145]</td>
<td>139 [134 to 143]</td>
<td>139 [134 to 143]</td>
</tr>
<tr>
<td>HL estimator (95% CI)</td>
<td>1 (–1 to 2)</td>
<td>2 (0 to 3)</td>
<td>1 (0 to 2)</td>
<td>2 (0 to 3)</td>
<td>2 (1 to 4)</td>
<td>3 (1 to 4)</td>
</tr>
<tr>
<td>P value</td>
<td>0.376</td>
<td>0.016</td>
<td>0.021</td>
<td>0.015</td>
<td>0.003*</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td><strong>Serum chloride (mmol/l)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G5K group</td>
<td>101 [94 to 112]</td>
<td>107 [96 to 112]</td>
<td>106 [95 to 113]</td>
<td>102 [90 to 107]</td>
<td>101 [84 to 106]</td>
<td>101 [87 to 105]</td>
</tr>
<tr>
<td>Control group</td>
<td>106 [102 to 113]</td>
<td>110 [103 to 115]</td>
<td>108 [104 to 113]</td>
<td>103 [100 to 109]</td>
<td>103 [98 to 106]</td>
<td>103 [98 to 108]</td>
</tr>
<tr>
<td>HL estimator (95% CI)</td>
<td>4 (2 to 6)</td>
<td>2 (0 to 5)</td>
<td>2 (1 to 4)</td>
<td>1 (0 to 3)</td>
<td>2 (0 to 3)</td>
<td>2 (1 to 4)</td>
</tr>
<tr>
<td>P value</td>
<td>0.001</td>
<td>0.023</td>
<td>0.009*</td>
<td>0.109</td>
<td>0.010</td>
<td>0.010</td>
</tr>
<tr>
<td><strong>Serum potassium (mmol/l)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G5K group</td>
<td>3.9 [3.2 to 4.8]</td>
<td>4.5 [3.4 to 5.3]</td>
<td>4.1 [3.5 to 4.8]</td>
<td>4.1 [3.5 to 4.7]</td>
<td>4.1 [3.5 to 4.7]</td>
<td>4.1 [3.4 to 4.7]</td>
</tr>
<tr>
<td>Control group</td>
<td>4.1 [3.7 to 4.6]</td>
<td>4.5 [4.0 to 5.8]</td>
<td>4.1 [3.9 to 4.7]</td>
<td>3.9 [3.5 to 4.4]</td>
<td>3.9 [3.4 to 4.3]</td>
<td>3.7 [3.1 to 4.4]</td>
</tr>
<tr>
<td>HL estimator (95% CI)</td>
<td>0.2 (0.0 to 0.4)</td>
<td>0.1 (–0.2 to 0.3)</td>
<td>0.0 (–0.2 to 0.2)</td>
<td>–0.2 (–0.4 to 0.0)</td>
<td>–0.3 (–0.5 to –0.1)</td>
<td>–0.3 (–0.5 to –0.1)</td>
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<tr>
<td>P value</td>
<td>0.089</td>
<td>0.646</td>
<td>0.795</td>
<td>0.102</td>
<td>0.007*</td>
<td>0.004*</td>
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<tr>
<td><strong>Serum magnesium (mmol/l)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G5K group</td>
<td>0.79 [0.68 to 0.89]</td>
<td>0.70 [0.51 to 1.05]</td>
<td>0.74 [0.59 to 0.92]</td>
<td>0.81 [0.64 to 0.95]</td>
<td>0.78 [0.57 to 1.18]</td>
<td>0.81 [0.61 to 0.92]</td>
</tr>
<tr>
<td>Control group</td>
<td>0.79 [0.66 to 0.88]</td>
<td>0.67 [0.54 to 1.01]</td>
<td>0.68 [0.57 to 0.96]</td>
<td>0.74 [0.64 to 0.88]</td>
<td>0.74 [0.59 to 0.80]</td>
<td>0.74 [0.58 to 0.84]</td>
</tr>
<tr>
<td>HL estimator (95% CI)</td>
<td>–0.01 (–0.05 to 0.03)</td>
<td>–0.04 (–0.10 to 0.02)</td>
<td>–0.06 (–0.11 to 0.00)</td>
<td>–0.07 (–0.12 to –0.01)</td>
<td>–0.09 (–0.13 to –0.03)</td>
<td>–0.08 (–0.13 to –0.04)</td>
</tr>
<tr>
<td>P value</td>
<td>0.629</td>
<td>0.151</td>
<td>0.041</td>
<td>0.013</td>
<td>&lt; 0.001*</td>
<td>0.002*</td>
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<tr>
<td><strong>Serum Glc (mmol/l)</strong></td>
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<tr>
<td>G5K group</td>
<td>6.9 [5.0 to 9.2]</td>
<td>8.5 [6.5 to 13.0]</td>
<td>7.4 [6.3 to 9.2]</td>
<td>6.8 [5.6 to 8.2]</td>
<td>6.1 [5.3 to 8.1]</td>
<td>6.0 [5.2 to 8.0]</td>
</tr>
<tr>
<td>Control group</td>
<td>6.1 [4.9 to 8.4]</td>
<td>8.9 [5.6 to 13.0]</td>
<td>7.1 [5.6 to 11.1]</td>
<td>6.3 [4.8 to 8.8]</td>
<td>6.1 [4.0 to 9.8]</td>
<td>5.7 [4.9 to 9.4]</td>
</tr>
<tr>
<td>HL estimator (95% CI)</td>
<td>–0.58 (–1.30 to 0.05)</td>
<td>–0.50 (–1.60 to 1.40)</td>
<td>–0.20 (–0.80 to 0.50)</td>
<td>–0.65 (–1.23 to 0.02)</td>
<td>–0.29 (–0.93 to 0.23)</td>
<td>–0.9 (–0.19 to 0.17)</td>
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<tr>
<td>P value</td>
<td>0.098</td>
<td>0.418</td>
<td>0.518</td>
<td>0.062</td>
<td>0.296</td>
<td>0.307</td>
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</table>

(Continued)
<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>6-h Postoperative</th>
<th>POD 1</th>
<th>POD 2</th>
<th>POD 3</th>
<th>POD 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serum phosphate (mmol/l)</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>G5K group</td>
<td>1.04 [0.68 to 1.31]</td>
<td>1.07 [0.70 to 1.75]</td>
<td>1.21 [0.56 to 1.69]</td>
<td>0.94 [0.68 to 1.24]</td>
<td>0.93 [0.35 to 1.22]</td>
<td>0.97 [0.29 to 1.40]</td>
</tr>
<tr>
<td>Control group</td>
<td>1.01 [0.53 to 1.42]</td>
<td>1.20 [0.41 to 1.76]</td>
<td>1.21 [0.56 to 1.69]</td>
<td>0.93 [0.35 to 1.22]</td>
<td>0.97 [0.29 to 1.40]</td>
<td>0.97 [0.29 to 1.40]</td>
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<tr>
<td><strong>Urine osmolality (mOsm/kg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G5K group</td>
<td>480 [114 to 1,133]</td>
<td>528 [171 to 867]</td>
<td>555 [211 to 922]</td>
<td>526 [117 to 983]</td>
<td>527 [316 to 943]</td>
<td>552 [412 to 1,173]</td>
</tr>
<tr>
<td>Control group</td>
<td>533 [130 to 1,105]</td>
<td>618 [241 to 934]</td>
<td>55 [15 to 164]</td>
<td>54 [15 to 164]</td>
<td>54 [15 to 164]</td>
<td>54 [15 to 164]</td>
</tr>
<tr>
<td><strong>Urine sodium (mmol/l)</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Urine chloride (mmol/l)</strong></td>
<td></td>
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<td></td>
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<tr>
<td><strong>Serum renin (ng/l)</strong></td>
<td></td>
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<tr>
<td>G5K group</td>
<td>20.0 [2.9 to 20.3]</td>
<td>21.7 [3.0 to 20.3]</td>
<td>21.0 [4.0 to 20.3]</td>
<td>15.6 [2.6 to 20.3]</td>
<td>15.6 [2.6 to 20.3]</td>
<td>15.6 [2.6 to 20.3]</td>
</tr>
<tr>
<td>Control group</td>
<td>19.6 [2.9 to 20.3]</td>
<td>21.7 [3.0 to 20.3]</td>
<td>21.0 [4.0 to 20.3]</td>
<td>15.6 [2.6 to 20.3]</td>
<td>15.6 [2.6 to 20.3]</td>
<td>15.6 [2.6 to 20.3]</td>
</tr>
<tr>
<td><strong>Serum aldosterone (pmol/l)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G5K group</td>
<td>214 [76 to 1,741]</td>
<td>370 [86 to 2,255]</td>
<td>375 [54 to 1,319]</td>
<td>375 [54 to 1,319]</td>
<td>375 [54 to 1,319]</td>
<td>375 [54 to 1,319]</td>
</tr>
<tr>
<td>Control group</td>
<td>214 [76 to 1,741]</td>
<td>370 [86 to 2,255]</td>
<td>375 [54 to 1,319]</td>
<td>375 [54 to 1,319]</td>
<td>375 [54 to 1,319]</td>
<td>375 [54 to 1,319]</td>
</tr>
</tbody>
</table>

Data are presented as median [range] with Hodges-Lehmann 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; G5K = potassium-enriched, chloride-depleted 5% glucose solution; Glc = glucose; POD = postoperative day.
which has been reported by some studies, is more likely
caused by the concomitant fluid overload than by the hypo-
natremia per se.

Magnesium is another factor potentially affecting recov-
ergy of GI function. As the G5K solution contains two-
fold more magnesium than the balanced Ringer's maleate
solution (Ringerfundin®) and patients in the control group
required significantly more magnesium replacement postop-
eratively, this could be another factor favoring return of GI
function in the G5K group.

Intracellular uptake of glucose (50 g/l in the G5K solu-
tion) and at the same time by uptake of water through osmo-
sis 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 intracel-
lar, 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 func-
tion and cause prolonged POI.29–31

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

### Table 5. Side Effects and In-hospital Complications

<table>
<thead>
<tr>
<th>Electrolytes/biochemistry</th>
<th>G5K Group (n = 22)</th>
<th>Control Group (n = 22)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP plasma value (&gt; 100 pg/ml)</td>
<td>8 (36.4)</td>
<td>11 (50.0)</td>
<td>0.543</td>
</tr>
<tr>
<td>Hypophosphatemia (&lt; 0.8 mmol/l)</td>
<td>6 (27.3)</td>
<td>10 (45.5)</td>
<td>0.348</td>
</tr>
<tr>
<td>Hyperchloremia (&gt; 107 mmol/l)</td>
<td>12 (54.5)</td>
<td>18 (81.8)</td>
<td>0.104</td>
</tr>
<tr>
<td>Hypokalemia (&lt; 3.5 mmol/l)</td>
<td>2 (9.1)</td>
<td>4 (18.2)</td>
<td>0.664</td>
</tr>
<tr>
<td>Hyperglycemia (&gt; 10.0 mmol/l)</td>
<td>3 (13.6)</td>
<td>6 (27.3)</td>
<td>0.457</td>
</tr>
<tr>
<td>Hypoosmolality (&lt; 280 mmol/l)</td>
<td>10 (45.5)</td>
<td>9 (40.9)</td>
<td>1.000</td>
</tr>
<tr>
<td>Hyponatremia (&lt; 135 mmol/l)</td>
<td>13 (59.1)</td>
<td>4 (18.2)</td>
<td>0.012</td>
</tr>
<tr>
<td>Mild hyponatremia (130–134 mmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6h postoperatively</td>
<td>11 (50)</td>
<td>6 (27.3)</td>
<td>0.131</td>
</tr>
<tr>
<td>POD 1</td>
<td>8 (36.4)</td>
<td>3 (13.6)</td>
<td></td>
</tr>
<tr>
<td>POD 2</td>
<td>3 (13.6)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>POD 3</td>
<td>3 (13.6)</td>
<td>1 (4.5)</td>
<td></td>
</tr>
<tr>
<td>POD 4</td>
<td>4 (18.2)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Moderate hyponatremia (&lt; 130 mmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6h postoperatively</td>
<td>1 (4.5)</td>
<td>0 (0)</td>
<td>0.010</td>
</tr>
<tr>
<td>POD 1</td>
<td>1 (4.5)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>POD 2</td>
<td>1 (4.5)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>POD 3</td>
<td>1 (4.5)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>POD 4</td>
<td>1 (4.5)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Hypomagnesemia (&lt; 0.66 mmol/l)</td>
<td>8 (36.4)</td>
<td>14 (63.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hyperaldosteronism (&gt; 340 pmol/l)</td>
<td>9 (40.9)</td>
<td>9 (40.9)</td>
<td>1.000</td>
</tr>
<tr>
<td>Increased renin plasma value</td>
<td>19 (86.4)</td>
<td>20 (90.9)</td>
<td>1.000</td>
</tr>
<tr>
<td>Electrolyte replacement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with intravenous potassium replacement</td>
<td>3 (13.6)</td>
<td>12 (54.5)</td>
<td>0.104</td>
</tr>
<tr>
<td>Patients with intravenous magnesium replacement</td>
<td>4 (18.2)</td>
<td>17 (77.3)</td>
<td>0.457</td>
</tr>
<tr>
<td>Patients with subcutaneous insulin injection</td>
<td>3 (13.6)</td>
<td>6 (27.3)</td>
<td>0.457</td>
</tr>
<tr>
<td>Total amount of insulin injected (IU)</td>
<td>12</td>
<td>24</td>
<td>0.457</td>
</tr>
<tr>
<td>Patients with sodium replacement (oral)</td>
<td>2 (9.1)</td>
<td>0</td>
<td>0.988</td>
</tr>
<tr>
<td>Criteria for kidney injury</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient AKIN (stage1/2) POD 1–2</td>
<td>1/1 (9.1)</td>
<td>0 (0)</td>
<td>0.488</td>
</tr>
<tr>
<td>RIFLE at discharge (class R “risk”)</td>
<td>2 (9.1)</td>
<td>1 (4.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Number of patients developing at least one complication (n)</td>
<td>13 (59.1)</td>
<td>9 (40.9)</td>
<td>1.000</td>
</tr>
<tr>
<td>Cardiovascular complications (n)</td>
<td>5 (22.7)</td>
<td>2 (9.1)</td>
<td>0.457</td>
</tr>
<tr>
<td>Pulmonary complications (n)</td>
<td>3 (13.6)</td>
<td>3 (13.6)</td>
<td>0.457</td>
</tr>
<tr>
<td>Infectious complications (n)</td>
<td>2 (9.1)</td>
<td>5 (22.7)</td>
<td>0.457</td>
</tr>
<tr>
<td>Surgical complications (n)</td>
<td>1 (4.5)</td>
<td>7 (31.8)</td>
<td>0.457</td>
</tr>
<tr>
<td>Neurologic complications (n)</td>
<td>4 (18.2)</td>
<td>2 (9.1)</td>
<td>0.457</td>
</tr>
<tr>
<td>Length of hospital stay (d)</td>
<td>14.5 (10–23)</td>
<td>15.5 (11–26)</td>
<td>0.233</td>
</tr>
</tbody>
</table>

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.

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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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References

3. Wuethrich PY, Burkhard FC: Improved perioperative outcome with norepinephrine and a restrictive fluid administration during open radical cystectomy and urinary diversion. Urol Oncol 2015; 33:66.e21–4