

# Restrictive Deferred Hydration Combined with Preemptive Norepinephrine Infusion during Radical Cystectomy Reduces Postoperative Complications and Hospitalization Time

## A Randomized Clinical Trial

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### ABSTRACT

**Background:** Anesthetics and neuraxial anesthesia commonly result in vasodilation/hypotension. Norepinephrine counteracts this effect and thus allows for decreased intraoperative hydration. The authors investigated whether this approach could result in reduced postoperative complication rate.

**Methods:** In this single-center, double-blind, randomized, superiority trial, 166 patients undergoing radical cystectomy and urinary diversion were equally allocated to receive  $1 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  of balanced Ringer's solution until the end of cystectomy and then  $3 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  until the end of surgery combined with preemptive norepinephrine infusion at an initial rate of  $2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  (low-volume group;  $n = 83$ ) or  $6 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  of balanced Ringer's solution throughout surgery (control group;  $n = 83$ ). Primary outcome was the in-hospital complication rate. Secondary outcomes were hospitalization time, and 90-day mortality.

**Results:** In-hospital complications occurred in 43 of 83 patients (52%) in the low-volume group and in 61 of 83 (73%) in the control group (relative risk, 0.70; 95% CI, 0.55–0.88;  $P = 0.006$ ). The rates of gastrointestinal and cardiac complications were lower in the low-volume group than in the control group (5 [6%] vs. 31 [37%]; relative risk, 0.16; 95% CI, 0.07–0.39;  $P < 0.0001$  and 17 [20%] vs. 39 [48%], relative risk, 0.43; 95% CI, 0.26–0.60;  $P = 0.0003$ , respectively). The median hospitalization time was 15 days [range, 11, 27d] in the low-volume group and 17 days [11, 95d] in the control group ( $P = 0.02$ ). The 90-day mortality was 0% in the low-volume group and 4.8% in the control group ( $P = 0.12$ ).

**Conclusion:** A restrictive-deferred hydration combined with preemptive norepinephrine infusion during radical cystectomy and urinary diversion significantly reduced the postoperative complication rate and hospitalization time. (*ANESTHESIOLOGY* 2014; 120:365–77)

It is well established that perioperative fluid management influences postoperative complication rates in major gastrointestinal surgery.<sup>1–4</sup> However, the optimal intraoperative fluid regimen is still controversial in terms of how much fluid to infuse, choice of fluids (crystalloids or colloids), use of vasopressors, or a goal-directed hemodynamic therapy (GDT).<sup>1–4</sup>

Restrictive intraoperative hydration has shown ambiguous results, some showing a reduced postoperative morbidity,<sup>1,3</sup> whereas others found no benefit in terms of reduction of complications.<sup>5–7</sup> However, the impact of intraoperative restrictive deferred crystalloid hydration combined with the administration of preemptive continuous norepinephrine infusion on the postoperative complication rate has not yet been investigated in patients undergoing major gastrointestinal surgery. Norepinephrine, which has a strong  $\alpha$ - and only a mild  $\beta$ -adrenergic effect, may counteract anesthesia-induced vasodilation and consequent hypotension and ensure sufficient organ perfusion.<sup>8</sup> This could be a valuable alternative to IV fluid boluses, as liberal hydration is known

#### What We Already Know about This Topic

- Norepinephrine counteracts the vasodilating effects of anesthesia, thus allowing blood pressure to be maintained with less fluid administration
- In a randomized trial, the investigators compared major outcomes in patients given conventional amounts of fluid with fluid sparing induced by norepinephrine administration

#### What This Article Tells Us That Is New

- The incidence of major complications was significantly reduced, with a relative risk of 0.7 (95% CI, 0.55–0.88)
- The duration of hospitalization was also significantly reduced from a median of 17 to 15 days

to cause interstitial edema and increased postoperative complications.<sup>1,3</sup>

To test this hypothesis in a major surgery model we chose open radical cystectomy combined with pelvic lymph node dissection and urinary diversion, because it is an extensive and time-consuming but standardized surgical intervention in a high case-load tertiary center. In addition, despite

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improvements in surgical technique and perioperative care, radical cystectomy is associated with early postoperative complication rates of 26–64%<sup>9–13</sup> and a 90-day mortality rate of 2–7%.<sup>12–14</sup>

The goal of this study was to compare the impact of intraoperative restrictive deferred hydration combined with preemptive infusion of norepinephrine *versus* that of a more liberal crystalloid hydration (including fluid preloading during induction and “generous” intraoperative hydration) on in-hospital complication rates, hospitalization time, 90-day postoperative complications, and mortality in patients undergoing pelvic lymph node dissection, radical cystectomy, and urinary diversion.

## Material and Methods

### Trial Design and Participants

This prospective, single-center, double-blind (patient, data assessor, and surgeon), parallel-group, randomized, controlled superiority trial was approved by the local ethics committee (Kantonale Ethikkommission Berne, KEKBE154/08) and registered at ClinicalTrials.gov (NCT01276665). After providing written informed consent, 190 consecutive patients were assessed for eligibility between November 2009 and September 2012 (fig. 1).

Patients with American Society of Anesthesiologists physical status II or III undergoing pelvic lymph node dissection and open radical cystectomy with either an ileal conduit or an ileal orthotopic bladder substitution for urinary diversion were included. Exclusion criteria were known coagulopathies, significant hepatic dysfunction (prothrombin ratio <50%), significant renal dysfunction (estimated glomerular filtration rate <60 ml/min), congestive heart failure (New York Heart Association scores ≥3), and contraindications for epidural analgesia.

### Randomization and Masking

The randomization sequence was created by computer-generated permuted block randomization with 1:1 allocation. The allocation sequence was concealed in opaque sealed envelopes that were sequentially numbered. The randomization sequence was kept concealed until after written consent had been obtained. Patients were allocated to the groups by assigning them the sequentially numbered envelope with the lowest number. Stratification was done for the type of urinary diversion (ileal conduit *vs.* ileal orthotopic bladder substitution). Patients, urologists, and data assessors were blinded to group assignment. In order to blind the surgeons, crystalloid bags and perfusion pumps were placed behind an opaque panel during surgery and were not visible to the urologists. Data were recorded prospectively in a standardized case report form. Assessors of the postoperative data had no access to the anesthesiologic patients’ data as these were kept sealed.

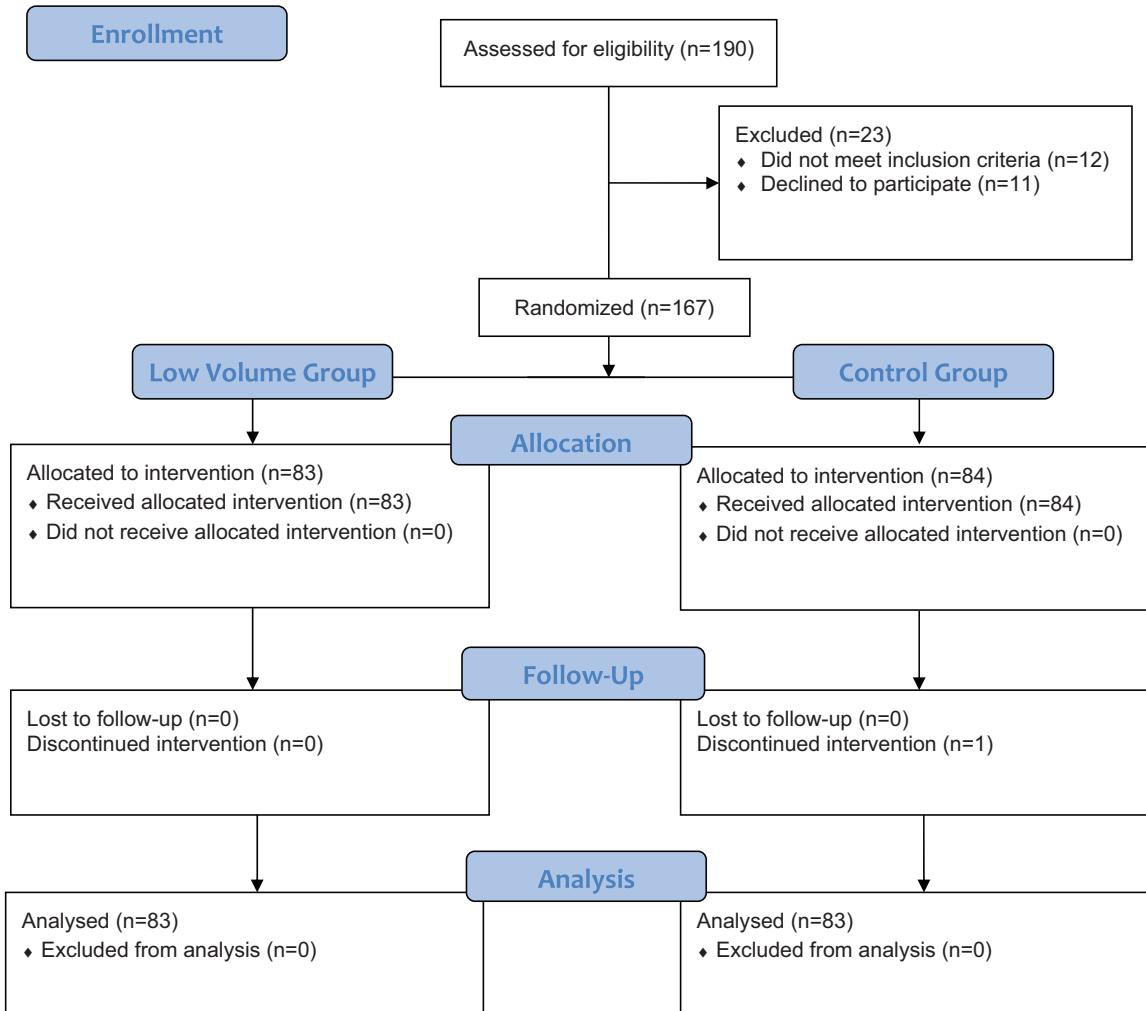
### Preoperative Care, Surgery, Anesthesia, and Monitoring

No antegrade bowel preparation was used. Patients fasted till midnight and could drink clear drinks till 2 h before surgery. All patients were premedicated with midazolam (7.5 mg) or lorazepam (1 mg) 30 min before induction of anesthesia. Surgery was standardized and performed as previously described with the patient in a 30° head-down position in the presence of one senior urologist (Drs. Burkhard, Thalmann, and Studer).<sup>15–17</sup>

Standard monitoring included continuous electrocardiographic data, heart rate, nasopharyngeal core temperature, pulse oxymetry, invasive mean arterial pressure (MAP) with a radial artery catheter and central venous pressure with a venous catheter inserted in the right jugular vein. For study purposes, an esophageal Doppler probe (Deltex Medical Ltd., Chichester, United Kingdom) was inserted immediately after induction of anesthesia and placed to obtain the best possible Doppler velocity signal from the descending aorta. Stroke volume, cardiac output, and corrected flow time were recorded. An epidural catheter was placed at the T9/T10 level: an 18-gauge epidural needle was inserted by a paramedian approach and the epidural space was identified with the loss-of-resistance technique. After a test dose of 1.5 ml lidocaine 2% with 0.005 mg/ml epinephrine to rule out subarachnoidal or intravascular placement, a 0.25% bupivacaine infusion at a rate of 8 ml/h was administrated until the end of the pelvic lymph node dissection and then stopped until closure of the abdominal wall. Anesthesia was induced with propofol (2 mg/kg), fentanyl (2 µg/kg), rocuronium (0.6 mg/kg) and maintained with isoflurane at an age-corrected minimum alveolar concentration of 0.6. Ventilation with an inspired oxygen fraction of 60% was mechanically controlled to maintain  $P_{\text{arterial}}\text{CO}_2$  between 35 and 40 mmHg, with a positive end-expiratory pressure of 5 mmHg and tidal volume of 8 ml/kg. Normothermia was maintained with a convective air warming system (Bair Hugger; 3M-Switzerland, Rüschlikon, Switzerland) and a Hotline® fluid warmer (Smith Medical International Ltd., Ashford, Kent, United Kingdom).

### Intraoperative Fluid Therapy

**Restrictive Deferred Fluid Group with Preemptive Norepinephrine Administration (“Low-volume Group”).** After induction of anesthesia, a preemptive norepinephrine infusion was started at a rate of  $2 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  until the end of surgery and a balanced Ringer’s solution (Ringerfundin®; B. Braun Medical AG, Sempach, Switzerland) was infused at a rate of  $1 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  until the bladder was removed, followed by  $3 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  of balanced Ringer’s solution until the end of surgery (deferred hydration). If hypotension was observed (MAP <60 mmHg), norepinephrine infusion rate was titrated to maximum  $8 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  after an initial bolus of 10 µg. If hypotension persisted, a bolus of 250 ml of balanced Ringer’s solution was given.



**Fig. 1.** Consolidated Standards of Reporting Trials flow diagram.

**Control Group.** A preload bolus of 6 ml/kg of balanced Ringer's solution was administrated during induction of anesthesia. After that, balanced Ringer's solution was infused at a constant rate of  $6 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  until the end of surgery. If hypotension was observed (MAP <60 mmHg) a bolus of 250 ml balanced Ringer's solution was given and in case of persistent hypotension this procedure was repeated to a maximum of 10 boluses.

In both groups, blood loss of greater than 500 ml was substituted with an equal amount of balanced Ringer's solution. Packed erythrocytes units were transfused if hemoglobin values were less than 8 g/dl (<10 g/dl in patients with coronary artery disease). Fresh frozen plasma transfusion was administrated in the presence of continuous excessive microvascular bleeding (relative indication based on the senior surgeons' observations) or if prothrombin time was greater than 1.5 times normal.<sup>18</sup> Colloid solution (Voluven balanced<sup>®</sup>; Fresenius Kabi AG, Stans, Switzerland) was only infused as a rescue medication if a MAP less than 60 mmHg persisted after the abovementioned correction with balanced Ringer's solution, and in case of severe metabolic

acidosis (base excess <-5, pH <7.25) attributable to severe hypovolemia.

#### Intra- and Postoperative Biomarkers

Serum lactate and central venous oxygen saturation ( $S_{cvO_2}$ ) were assessed after induction of anesthesia, after cystectomy, after urinary diversion, at the end of surgery, and on postoperative day (POD) 1. Hemoglobin, hematocrit, C-reactive protein, procalcitonin, albumin, and creatinine levels were assessed preoperatively, on PODs 1, 2, and 5. The cardiac biomarkers high-sensitive troponin T, brain natriuretic peptide (BNP), serum and urine osmolality, were assessed preoperatively, on PODs 1 and 2. At hospital discharge, hemoglobin, hematocrit, creatinine, and BNP serum levels were assessed.

#### Postoperative Patient Management

The epidural analgesia was reactivated during closure of the abdominal wall with a mixture composed of bupivacaine 0.1%, fentanyl 2 µg/ml, and epinephrine 2 µg/ml using a CADD-Legacy ambulatory infusion pump (model

6300; Deltec Inc., St. Paul, MN). The initial infusion rate was 8 ml/h, with a maximum infusion rate till 15 ml/h, and with additional bolus volumes of 5 ml (lockout time: 1 h). After surgery patients were admitted to the intermediate care unit. IV paracetamol and metamizol (both 1 g every 6 h) were given postoperatively. The epidural catheter was removed on POD 5.

Postoperative hydration was identical in both groups and consisted primarily of 1,000 ml of balanced Ringer's solution and 500 ml of glucose 5% per 24 h until resumption of normal food intake.<sup>19</sup> If the MAP were less than 60 mmHg, first, a bolus of 500 ml of balanced Ringer's solution was administrated, second, by persistent MAP less than 60 mmHg, norepinephrine was infused up to a rate of 200 µg/h. Packed erythrocytes units were transfused according to the American Society of Anesthesiologists guidelines,<sup>20</sup> and fresh frozen plasma transfusion was given if the prothrombin time was greater than 1.5 times the normal value. The amounts of packed erythrocytes units, fresh frozen plasma units, and fluids given postoperatively were recorded.

Postoperative patients were allowed to drink clear fluids immediately. A peroral liquid diet was started on POD 1 as well as active mobilization. To enhance recovery of bowel function, the use of chewing gum was encouraged<sup>21</sup> and subcutaneous application of neostigmine 0.05 mg was started on POD 2. Flatus and stool passage were recorded. Body weight was measured daily. Perioperative antibiotic therapy consisted of obramycin and metronidazole for 2 days and amoxicillin/clavulanic acid until removal of all stents and catheters. Low-molecular-weight heparin was started on the evening before surgery and maintained throughout hospitalization.

### Outcome Measures

The primary endpoint was the in-hospital complication rate assessed according to a modified postoperative morbidity survey and Clavien–Dindo classification for radical cystectomy<sup>3,22</sup> (appendix). Secondary endpoints were hospitalization time, the 90-day postoperative complication rate according to the Clavien–Dindo classification,<sup>10,23</sup> and 90-day mortality. Start of the hospitalization time was defined as the moment the patient was admitted into the hospital (in all cases the day before surgery). Discharge criteria were: removal of all drains and catheters, and the ability to handle the urostoma bag or empty the ileal orthotopic neobladder spontaneously and free of residual urine.

All outcome measures were registered by assessors blinded to the intraoperative fluid regimen.

### Statistics

On the basis of the assumption that the application of intraoperative restrictive deferred fluid regimen with preemptive norepinephrine infusion would reduce the complication rate

from 38<sup>11–13</sup> to 20%, a sample size of 83 patients per group was calculated for each group with a type I error of 0.05 and a power of 80%. Data were analyzed on a modified intention-to-treat basis (one patient was excluded after randomization because the initially planned surgery was cancelled). Data are expressed with 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 as appropriate. Relative risks (RRs) and 95% CIs were also calculated. The primary outcome was analyzed using Fisher exact test with RR and 95% CI. The significance level was set at 0.05.

Multiple logistic regression analyses using a full model were applied to identify independent risk factors for postoperative complications and reported as adjusted odds ratios (ORs) with 95% CIs. Confounders considered were groups (low-volume *vs.* control group), type of urinary diversion (ileal conduit *vs.* ileal orthotopic bladder substitution), age (categorized into: <65 yr, 65–74 yr, 75–84 yr, ≥85 yr), neoadjuvant chemotherapy, preoperative anemia, American Society of Anesthesiologists physical status score (II *vs.* III), Charlson Comorbidity Index age adjusted, Glasgow Prognostic Score, body mass index, and preoperative serum BNP values. Interaction terms were not included because of insufficiently large sample size. Confounders were considered as significant if their *P* values were less than 0.10. The fit and predictive capability of the model was assessed using the Hosmer–Lemeshow goodness-of-fit test and receiver operating characteristic area under the curve. The statistical softwares used were SPSS 19.0 (SPSS Inc., Chicago, IL) and Statistical Analysis System software (version 9.3; SAS Institute, Cary, NC).

### Results

Of 190 consecutive patients, 167 fulfilled the eligibility criteria and were randomized. One of these patients was excluded because the intervention was aborted, leaving 166 patients included in the final analysis (fig. 1). Complete follow-up data were available for all 166 participants. Preoperative and patient characteristics were similar for the two groups (table 1).

The total median volume of balanced Ringer's solution infused intraoperatively was 1,700 ml [range, 700, 4,000 ml] in the low-volume group *versus* 4,300 ml [2,800, 6,200 ml] in the control group; *P* < 0.0001 (table 2). The median dose of norepinephrine administered intraoperatively to the low-volume group was 3.6 µg·kg<sup>-1</sup>·h<sup>-1</sup> [2.0–8.0 µg·kg<sup>-1</sup>·h<sup>-1</sup>]. Neither group was given colloid solution. Significantly lower median cardiac output values were observed in the low-volume group than in the control group during the periods of cystectomy (3.7 l/min [2.2–8.7 l/min] *vs.* 4.8 l/min [1.7–11.9 l/min]; *P* = 0.002) and urinary diversion (4.2 l/min [2.4–7.3 l/min] *vs.* 5.5 l/min [3.5–11.0 l/min]; *P* = 0.002).

min] *vs.* 5.0 l/min [2.3–11.1 l/min];  $P = 0.003$ ) but not at the end of surgery (table 2). In both groups, cardiac output values at the end of surgery did not differ significantly from values at the beginning of surgery. On POD 1, a significantly greater increase in body weight was observed in the control group (2.0 kg [-2, +7 kg]) than in the low-volume group (0.0 kg [-3, +4 kg];  $P < 0.0001$ ; table 3).

### In-hospital Complications

In-hospital complications occurred in 43 of 83 patients (52%) in the low-volume group *versus* 61 of 83 patients (73%) in the control group (RR, 0.70; 95% CI, 0.55–0.88;  $P = 0.006$ ). The absolute reduction in the number of patients experiencing complications was 22% (95% CI, 7–36%). The total number of complications was 77 in the low-volume group *versus* 161 in the control group ( $P < 0.0001$ ; table 4). According to the Clavien–Dindo classification, the majority of complications were minor (Clavien–Dindo classification grade 1 or 2) in both groups: low-volume group (33 of 83 patients; 40%) and control group (42 of 83 patients; 51%; fig. 2).

Gastrointestinal complications occurred in 5 of 83 (6%) of the low-volume group *versus* 31 of 83 (37%) of the control group (RR, 0.16; 95% CI, 0.07–0.39;  $P < 0.0001$ ). The most common complications observed were ileus and constipation, which occurred in 0 of 83 (0%) and 2 of 83 (2%) patients of the low-volume group *versus* 8 of 83 (10%) and 18 of 83 (22%) of the control group ( $P = 0.007$  and  $P = 0.0006$ , respectively; table 4).

Cardiac events occurred in 17 of 83 patients (20%) of the low-volume group *versus* 40 of 83 patients (48%) in the control group (RR, 0.43; 95% CI, 0.26–0.69;  $P = 0.0003$ ). The majority of cardiac events were minor complications consisting of a transient increase of BNP during the two first PODs: 11 of 83 (13%) patients in the low-volume group *versus* 28 of 83 (34%) patients in the control group (RR, 0.39; 95% CI, 0.21–0.74;  $P = 0.003$ ). The incidences of the major complications such as acute myocardial infarction and congestive heart failure did not differ between the two groups, nor did the rates of renal, infectious, pulmonary, and thromboembolic complications (table 4).

Multiple logistic regression analyses identified group allocation (low-volume *vs.* control group: OR, 0.44 [95% CI, 0.21–0.92];  $P = 0.029$ ), body mass index (per increasing value: OR, 1.13 [95% CI, 1.01–1.25];  $P = 0.029$ ), BNP (per increasing value BNP: OR, 1.01 [95% CI, 1.00–1.03];  $P = 0.045$ ), preoperative anemia (no *vs.* yes: OR, 0.426 [95% CI, 0.18–1.02];  $P = 0.056$ ), and Glasgow Prognostic Score (per increasing value: 1.61 [95% CI, 0.93–2.88];  $P = 0.089$ ) as independent predictors of complications (Hosmer–Lemeshow test:  $P = 0.685$  and receiver operating characteristic area under the curve: 0.78; table 5).

### Length of Hospital Stay, 90-day Postoperative Complication Rate, and Mortality

The median length of hospital stay was 15 days [11, 27d] in the low-volume group and 17 days [10, 95d] in the control group ( $P = 0.01$ ).

The total number of patients experiencing complications within the 90th POD was lower in the low-volume group (44 of 83; [53%]) than in the control group (64 of 83 [77%];  $P = 0.0019$ ). The majority of complications in both groups were classified as minor (grade 1 or 2; table 6).

The 30-day and 90-day overall mortality rates were 0 and 2.4%, respectively. No patient in the low-volume group died, but four patients (4.8%) in the control group did ( $P = 0.12$ ). Two patients died because of rapid disease progress, one died of septic shock, and one of pneumonia. Three of these patients were older than 75 yr.

### Discussion

Intraoperative restrictive deferred hydration combined with preemptive norepinephrine infusion was associated with significantly reduced in-hospital and 90-day postoperative complication rates and a shortened hospitalization time.

Consistent with other reports<sup>10,24</sup> constipation and ileus were the most frequently observed gastrointestinal complications in our patients receiving more liberal crystalloid hydration, despite the use of the modified Clavien–Dindo classification for radical cystectomy,<sup>10</sup> which has rarely been applied in other studies. In the low-volume group, gastrointestinal complications were significantly lower with a more rapid recovery of bowel function, which is of relevance because gastrointestinal dysfunction can lead to prolonged hospitalization.<sup>22,25</sup> The postoperative body weight increase and the hypoalbuminemia observed in the control group reflect overhydration, which is known to delay recovery of bowel motility because of excess fluid in the intestinal wall.<sup>19</sup> Excess of fluid leads to shedding of the glycocalyx followed by extravasation and edema.<sup>26</sup>

The number of cardiac events was high in both groups, but significantly lower in the low-volume group; however, it has to be stated that in both groups most cardiac events were a transient increase of serum BNP. Severe cardiac complications like arrhythmia, congestive heart failure, and acute myocardial infarction did not differ between the groups. Serum BNP release is directly proportional to ventricular volume expansion, and thus the transient BNP increases observed in the control group may reflect a perioperative volume overload and correlates with Berri *et al.*'s<sup>27</sup> observations, where a postoperative serum BNP increase was associated with a positive fluid balance in patients undergoing pancreatectomy. In addition, a postoperative BNP increase has been associated with prolonged hospitalization time in patients undergoing major orthopedic surgery.<sup>28</sup> The number of arrhythmias and myocardial infarctions, complications that could be attributed to

**Table 1.** Preoperative Patient Characteristics

Characteristic	Low-volume Group (n = 83)	Control Group (n = 83)
Age (yr)		
<65	68 [38–88] 26 (31%)	69 [42–88] 31 (37%)
65–74	36 (43%)	25 (30%)
75–84	17 (21%)	22 (27%)
≥85	4 (5%)	5 (6%)
Body weight (kg)	74 [40–160]	77 [41–112]
BMI (kg/m <sup>2</sup> )	24 [18–42]	24 [20–39]
Sex (female/male)	27/56 (33%/67%)	25/58 (30%/70%)
ASA physical status score		
2	52 (63%)	46 (55%)
3	31 (37%)	37 (45%)
CCI age adjusted		
0–2	14 (17%)	23 (28%)
3–5	61 (73%)	49 (59%)
>5	8 (10%)	11 (13%)
Glasgow Prognostic Score		
0	36 (44%)	29 (35%)
1	28 (34%)	38 (46%)
2	18 (22%)	16 (19%)
NYHA functional classification		
0	62 (75%)	61 (73%)
1	6 (7%)	4 (5%)
2	15 (18%)	18 (22%)
Hypertension	41 (44%)	53 (56%)
Diabetes mellitus	10 (12%)	6 (7%)
COPD	19 (23%)	17 (21%)
Aspirin	21 (25%)	15 (18%)
Antihypertensives	36 (43%)	48 (58%)
Statin	16 (19%)	16 (19%)
β-Blocker	13 (16%)	22 (27%)
Neoadjuvant chemotherapy	11 (13%)	13 (16%)
Preoperative anemia	27 (33%)	39 (47%)
Hemoglobin (g/dl)	12.9 [8.4–15.9]	12.6 [7.3–16.7]
Hematocrit	0.38 [0.25–0.48]	0.37 [0.25–0.50]
Thrombocytes (g/l)	250 [122–211]	252 [111–770]
Glucose (mm)	6.26 [4.1–13.5]	6.30 [4.2–13.0]
C-reactive protein (mg/l)	3 [3–197]	3 [3–92]
Procalcitonin (ng/ml)	0.1 [0.0–0.5]	0.1 [0.0–0.36]
Serum creatinine (μmol)	81 [34–120]	80 [34–150]
eGFR (MDRD)/1.73 m <sup>2</sup> (ml/min)	76 [60–90]	76 [60–90]
Albumin (g/l)	35 [19–48]	34 [18–46]
Osmolality (mosmol/kg)	289 [278–300]	289 [267–298]
Brain natriuretic peptide (pg/ml)	25 [5–350]	29 [5–341]
High-sensitive troponin T (μg/l)	0.01 [0.01–0.016]	0.01 [0.01–0.015]

Data are presented as median [range] or absolute value (%). There were no significant differences between the groups. Anemia definition according to the World Health Organization: hemoglobin <13 g/dl for men and <12 g/dl for women.

ASA = American Society of Anesthesiologists; BMI = body mass index; CCI = Charlson Comorbidity Index; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; MDRD = modification of diet in renal disease; NYHA = New York Heart Association.

norepinephrine, were not different between the groups. Our results show that the use of norepinephrine combined with a low-volume fluid regimen as administered in our study was safe and not detrimental to cardiac function, as has often been postulated.

A frequently used argument against restrictive intraoperative hydration is the fear of increased infectious complications attributable to hypovolemia and the ensuing

tissue hypoperfusion.<sup>2</sup> In our low-volume group, the rate of infectious complications was not increased. On POD 1, the patients' body weight and urine osmolality, factors that mirror hydration status, were comparable with the preoperative values, indicating a zero fluid balance rather than hypovolemia. An  $S_{cv}O_2$  value less than 70% is considered an early marker for tissue hypoperfusion and is associated with increased postoperative complications.<sup>29,30</sup>  $S_{cv}O_2$  remained

**Table 2.** Intraoperative Parameters

	Low-volume Group (n = 83)	Control Group (n = 83)	P Value
Type of surgery			0.34
Ileum conduit	32 (39%)	39 (47%)	
Ileal orthotopic bladder substitution	51 (61%)	44 (53%)	
Total duration of surgery (min)	390 [240–570]	390 [210–585]	0.92
Blood loss (ml)	800 [300–1,800]	1,200 [400–3,000]	<0.0001
Volume of intraoperative fluid given			
Total volume of crystalloid (ml)	1,700 [700–4,000]	4,300 [2,800–6,200]	<0.0001
Total volume of crystalloid perfused ( $\text{ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ )	3.5 [1.3–6.0]	8.8 [5.1–16.7]	<0.0001
Fresh frozen plasma perfused (ml)	0 [0–600]	0 [0–1,200]	0.001
Allogeneic blood transfused (ml)	0 [0–600]	0 [0–2,100]	<0.0001
Total volume of fluid perfused ( $\text{ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ )	3.6 [1.3–5.2]	9.3 [5.2–16.7]	<0.0001
Mean arterial pressure (mmHg)			
During pelvic lymph nodes dissection	70 [55–100]	68 [55–90]	0.14
During cystectomy	70 [57–93]	70 [55–100]	0.38
During urinary diversion	60 [60–102]	70 [55–92]	0.17
Heart frequency (beats/min)			
During pelvic lymph node dissection	66 [45–94]	63 [45–90]	0.25
During cystectomy	69 [43–102]	63 [40–90]	0.09
During urinary diversion	76 [41–107]	74 [40–98]	0.06
Central venous pressure (mmHg)			
During pelvic lymph node dissection	12 [5–21]	15 [5–23]	<0.0001
During cystectomy	12 [2–23]	16 [3–25]	<0.0001
During urinary diversion	10 [3–22]	14 [3–29]	<0.0001
Cardiac output (l/min)			
Start of surgery	4.4 [2.3–8.8]	4.9 [2.7–10.7]	0.22
During pelvic lymph node dissection	3.7 [2.3–7.7]	4.4 [1.8–11.8]	0.11
During cystectomy	3.7 [2.2–8.7]	4.8 [1.7–11.9]	0.0019
During urinary diversion	4.2 [2.4–7.3]	5.0 [2.3–11.1]	0.0034
End of surgery	4.2 [2.4–9.6]	5.1 [2.8–13.8]	0.10
Stroke volume (ml)			
Start of surgery	70 [36–122]	77 [35–210]	0.06
During pelvic lymph node dissection	60 [37–144]	73 [34–205]	0.0126
During cystectomy	57 [30–120]	77 [32–188]	0.0007
During urinary diversion	58 [25–115]	72 [32–168]	0.0003
End of surgery	56 [26–130]	72 [37–175]	0.0121
Corrected flow time (ms)			
Start of surgery	320 [209–420]	333 [238–424]	0.0389
During pelvic lymph node dissection	300 [203–411]	329 [224–426]	0.0257
During cystectomy	291 [217–388]	328 [217–413]	0.0005
During urinary diversion	295 [182–390]	337 [213–439]	<0.0001
End of surgery	304 [211–405]	327 [306–436]	0.0067
Intraoperative $S_{\text{cv}}\text{O}_2$ (%)			
Start of surgery	85 [66–89]	86 [73–89]	0.50
End cystectomy	80 [58–89]	82 [54–89]	0.40
End surgery	82 [58–84]	83 [60–89]	0.87
Intraoperative serum lactate (mm)			
Start of surgery	1 [0.6–0.8]	0.9 [0.6–2.4]	0.15
End cystectomy	1.2 [0.6–2.0]	1.0 [0.5–3.1]	0.0008
End surgery	1.3 [0.7–4.2]	1.2 [0.6–2.6]	0.06

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

$S_{\text{cv}}\text{O}_2$  = central venous oxygen saturation.

greater than 70% in our low-volume group, indicating an adequate balance between oxygen delivery and consumption. Serum lactate is another indicator of tissue oxygenation, and a serum lactate greater than 2 mm indicates

acidosis. The low number of patients in both groups with postoperative serum lactate levels greater than 2 mm and the median serum lactate levels of less than 1.5 mm observed perioperatively are comparable with those levels in studies

**Table 3.** Postoperative Fluid Administration, Body Weight Differences, Renal, Metabolic, Inflammatory, and Cardiac Biomarkers

Characteristic	Low-volume Group (n = 83)	Control Group (n = 83)	P Value
Postoperative day 1			
Total fluid volume perfused (ml)	2,100 [800–4,000]	2,050 [1,000–4,100]	0.90
Weight difference vs. preop (kg/BW)	+0.0 [-3 to +4]	+2 [-2 to +7]	<0.0001
S <sub>cv</sub> O <sub>2</sub> (%)	80 [43–98]	80 [68–98]	0.14
Serum lactate (mm)	1.1 [0.6–2.3]	1.0 [0.5–5.1]	0.81
Number of patients with lactate level >2 mm	3 (4%)	2 (2%)	
Hemoglobin (g/dl)	8.5 [5.4–12.6]	8.2 [5.3–11.7]	0.47
Hematocrit	0.25 [0.16–0.37]	0.25 [0.16–0.34]	0.52
Serum creatinine (μM)	94 [53–269]	84 [43–200]	0.02
eGFR (MDRD)/1.73 m <sup>2</sup> (ml/min)	67 [19–90]	74 [26–90]	0.02
Serum osmolality (mosmol/kg)	288 [278–300]	289 [267–297]	0.15
Urine osmolality (mosmol/kg)	510 [216–979]	553 [244–843]	0.64
Albumin (g/l)	32 [23–48]	31 [20–54]	0.0027
Procalcitonin (ng/ml)	1.1 [0.1–25.1]	1.1 [0.1–9.2]	0.95
C-reactive protein (mg/l)	85 [42–171]	81 [3–242]	0.64
Brain natriuretic peptide (pg/ml)	50 [5–419]	72 [5–962]	0.0187
High-sensitive troponin T (μg/l)	0.01 [0.001–0.22]	0.01 [0.001–0.065]	0.46
Postoperative day 2			
Total fluid volume perfused (ml)	1,500 [400–3,200]	1,750 [1,000–3,900]	0.07
Weight difference vs. POD 1 (kg/BW)	+0.4 [-4 to +3]	-0.5 [-5 to +3]	<0.0001
Hemoglobin(g/dl)	8.4 [5.7–11.3]	8.1 [5.8–10.5]	0.33
Hematocrit	0.25 [0.17–0.34]	0.24 [0.17–0.31]	0.50
Serum creatinine (μM)	78 [45–303]	75 [39–212]	0.48
eGFR (MDRD)/1.73 m <sup>2</sup> (ml/min)	76 [27–90]	82 [26–90]	0.39
Serum osmolality (mosmol/kg)	284 [270–299]	283 [269–304]	0.13
Urine osmolality (mosmol/kg)	472 [176–808]	486 [134–834]	0.67
Albumin (g/l)	31 [25–38]	32 [20–39]	0.97
C-reactive protein (mg/l)	182 [57–331]	188 [9–398]	0.47
Procalcitonin (pg/l)	0.9 [0.2–20.4]	0.9 [0.1–8.9]	0.31
Brain natriuretic peptide (pg/ml)	87 [5–822]	102 [5–567]	0.16
High-sensitive troponin T (μg/l)	0.01 [0.001–0.137]	0.01 [0.001–0.069]	0.07
Postoperative day 3			
Total fluid volume perfused (ml)	1,500 [500–2,500]	1,500 [500–2,800]	0.13
Weight difference vs. POD 2 (kg/BW)	-0.2[-4 to +5]	0 [-3 to +4]	0.63
Serum creatinine (μM)	75 [38–339]	72 [38–191]	0.77
eGFR (MDRD)/1.73 m <sup>2</sup> (ml/min)	79 [31–90]	85 [29–90]	0.38
Albumin (g/l)	29 [23–38]	29 [19–39]	0.68
C-reactive protein (mg/l)	160 [30–320]	183 [12–480]	0.15
Procalcitonin (pg/l)	0.7 [0.1–13.1]	0.8 [0.1–13.1]	0.56
Postoperative day 4			
Total fluid volume perfused (ml)	1,000 [500–2,500]	1,000 [500–3,500]	0.17
Weight difference vs. POD 3 (kg/BW)	0 [-4.1 to +7.9]	0 [-4.2 to +5.0]	0.52
Postoperative day 5			
Total fluid volume perfused (ml)	1,000 [500–3,500]	1,000 [500–2,100]	0.30
Weight difference vs. POD 4 (kg/BW)	0 [-4 to +7]	0 [-5 to +6]	0.79
Hemoglobin (g/dl)	9.3 [6.3–13.2]	9.4 [7.0–12.1]	0.60
Hematocrit	0.28 [0.18–0.42]	0.28 [0.19–0.36]	0.79
Serum creatinine (μM)	72 [28–234]	72 [40–233]	0.39
eGFR (MDRD)/1.73 m <sup>2</sup> (ml/min)	84 [32–90]	88 [24–90]	0.33
Albumin (g/l)	27 [20–37]	27 [19–35]	0.64
C-reactive protein (mg/l)	84 [7–480]	95 [3–510]	0.48
Procalcitonin (pg/l)	0.4 [0.1–8.3]	0.4 [0.1–12.0]	0.80

(Continued)

**Table 3.** (Continued)

Characteristic	Low-volume Group (n = 83)	Control Group (n = 83)	P Value
Hospital discharge			
Weight difference vs. preoperative (kg/BW)	-1.8 [-10 to +4]	-1.0 [-12 to +4]	0.62
Hemoglobin (g/dl)	9.5 [7.4–13.2]	9.8 [7.2–13.2]	0.31
Hematocrit	0.29 [0.22–0.42]	0.30 [0.20–0.39]	0.19
Serum creatinine ( $\mu$ M)	76 [28–222]	72 [40–197]	0.23
eGFR (MDRD)/1.73 m <sup>2</sup> (ml/min)	80 [23–90]	88 [22–90]	0.58
Brain natriuretic peptide (pg/ml)	50 [10–341]	54 [17–379]	0.99

Data are presented as median [ranges] or absolute value (%).

BW = body weight; eGFR = estimated glomerular filtration rate; MDRD = modification of diet in renal disease; POD = postoperative day;  $S_{cv}O_2$  = central venous oxygen saturation.

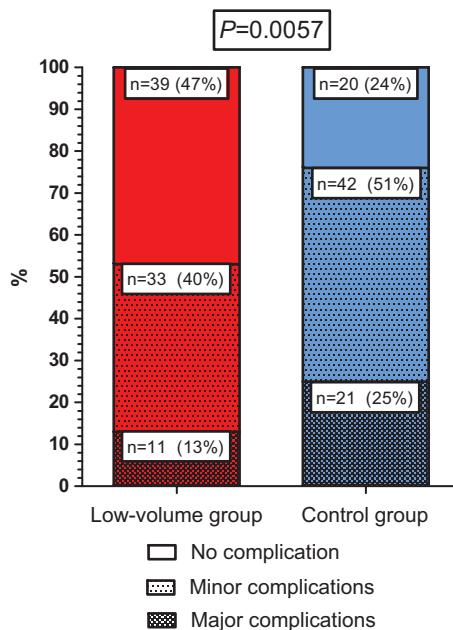
using hemodynamic optimization strategies (GDT).<sup>2,31</sup> The nonsignificant difference in infectious complications further corroborates adequate tissue perfusion and the safety of the restrictive deferred hydration combined with preemptive norepinephrine infusion. The significantly lower 90-day

complication rate in the low-volume group is particularly noteworthy in these patients who are at high risk for complications and documents the safety of the restrictive deferred hydration combined with preemptive norepinephrine infusion. The complication rate in the control group is in line

**Table 4.** In-hospital Complications

Category	Complication	Low-volume Group (n = 83)	Control Group (n = 83)	RR	95% CI	P Value
Gastrointestinal	Illeus	5 (6%)	31 (37%)	0.16	0.07–0.39	<0.001
	Constipation	0 (0%)	8 (10%)			0.001
	Gastrointestinal bleeding	2 (2%)	18 (22%)			<0.001
	Gastric ulcer	1 (1%)	2 (2%)			0.99
	Anastomotic bowel leak	2 (2%)	2 (2%)			1
		0 (0%)	1 (1%)			0.32
Infectious	Urinary tract infection	16 (19%)	20 (24%)	0.80	0.45–1.43	0.57
	Pyelonephritis	7 (8%)	7 (8%)			1
	Urosepsis	4 (5%)	3 (4%)			1
	Pneumonia	0 (0%)	1 (1%)			1
	Wound infection	2 (2%)	4 (5%)			0.41
Wound	Wound dehiscence	3 (4%)	5 (6%)			0.72
		3 (4%)	4 (5%)	0.75	0.17–3.24	1
Genitourinary	Renal failure	7 (8%)	14 (17%)	0.50	0.21–1.17	0.16
	Transient increase of creatinine	4 (5%)	3 (4%)			0.08
	Urethral anastomosis leakage	2 (2%)	6 (7%)			0.32
Cardiac	Acute myocardial infarction (all NSTEMI)	1 (1%)	6 (7%)			0.10
	Arrhythmia	3 (4%)	3 (4%)			1
	Congestive heart failure	2 (2%)	3 (4%)			0.65
	Transient BNP increase	11 (13%)	28 (34%)			<0.001
Thromboembolic	Pulmonary embolism	1 (1%)	4 (5%)	0.25	0.03–2.20	0.17
	Anemia requiring postoperative transfusion	23 (28%)	40 (48%)	0.58	0.38–0.87	0.01
Neurological	Peripheral neuropathy	2 (2%)	6 (7%)	0.33	0.07–1.61	0.28
	Delirium/agitation	1 (1%)	4 (5%)			0.37
		1 (1%)	2 (2%)	1.50	0.26–8.75	1
Miscellaneous	Peripheral neuropathy	3 (4%)	1 (1%)			0.62
	Delirium/agitation	3 (4%)	1 (1%)			1
		0 (0%)	1 (1%)			1
Total number of complications		77	161			
Total number of patients with complications		43 (52%)	61 (73%)	0.70	0.55–0.88	0.006
Number of patients with more than one complication		26 (31%)	37 (45%)	0.70	0.47–1.05	0.11

BNP = brain natriuretic peptide; NSTEMI = non-ST elevation myocardial infarction; RR = relative risk.



**Fig. 2.** In-hospital complications that patients experienced, by highest grade according to the Clavien–Dindo classification (minor complications: grade I to II; major complications: grade IIIa to V).

**Table 5.** Multiple Regression Analysis Evaluating Relevant Predictors Associated with In-hospital Complications ( $P < 0.10$  Considered as Significant)

Predictors	OR	95% CI	P Value
Group (low-volume vs. control)	0.439	0.210–0.920	0.029
BMI (per increasing value)	1.127	1.012–1.254	0.030
BNP (per increasing value)	1.013	1.000–1.026	0.045
Preoperative anemia (no vs. yes)	0.426	0.177–1.022	0.056
GPS (per increasing value)	1.606	0.929–2.777	0.089
Age (<65 yr vs. ≥85 yr)	0.860	0.067–11.055	0.993
Age (65–74 yr vs. ≥85 yr)	0.536	0.059–4.830	0.216
Age (75–84 yr vs. ≥85 yr)	1.164	0.144–9.428	0.513
Neoadjuvant chemotherapy (no vs. yes)	0.951	0.318–2.845	0.929
ASA physical status score (II vs. III)	0.998	0.390–2.550	0.996
CCI age adjusted (per increasing value)	1.210	0.772–1.895	0.405
Urinary diversion (ileal conduit vs. ileal orthotopic bladder substitution)	0.643	0.239–1.732	0.383

ASA = American Society of Anesthesiologists; BMI = body mass index; BNP = brain natriuretic peptide; CCI = Charlson Comorbidity Index; GPS = Glasgow Prognostic Score; OR = odds ratio.

**Table 6.** 90-day Postoperative Complications Experienced by Highest Grade by Patients According to the Clavien–Dindo Classification System

Complication	Low-volume Group (n = 83)	Control Group (n = 83)	RR	95% CI	P Value
Grade I	10 (12%)	9 (11%)			
Grade II	23 (28%)	33 (39%)			
Grade IIIa	5 (6%)	7 (8%)			
Grade IIIb	5 (6%)	5 (6%)			
Grade IVa	1 (1%)	5 (6%)			
Grade V	0 (0%)	4 (5%)			
Total	44 (53%)	63 (75%)	0.67	0.54–0.87	0.0019

RR = relative risk.

with the complication rates reported by other high case-load institutions, despite the fact that in this study complications were graded according to the modified Clavien–Dindo classification.<sup>10,32</sup> This is of importance because it indicates that the complication rate in the control group, although significantly higher than in the low-volume group, was not excessive when compared with rates in other centers of excellence.

Although serum creatinine values were increased in the low-volume group on POD 1 (most likely because of less serum dilution), renal function (serum creatinine values, estimated glomerular filtration rate, and urine osmolality) did not differ between the groups from POD 2 until discharge. Fluid restriction and the adjuvant use of norepinephrine did not result in more renal complications and a more liberal fluid administration did not appear to have a protective effect on renal function. On the basis of these findings, the often assumed beneficial effect of preoperative fluid boluses and liberal fluid administration to protect renal function seems questionable.<sup>33</sup> It has been shown that intraoperative urinary output is dependent not only on fluid management but also on the intraoperative release of stress hormones, osmolality, and adiuretin secretion.<sup>34</sup>

Major concern is often voiced concerning the vasoconstrictive effect of norepinephrine. Our results document, however, that the preemptive norepinephrine infusion at an initial rate of  $2 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  has no identifiable negative consequences. On the contrary, it counteracts the decreased sympathetic tone and vasodilatation induced by epidural analgesia, anesthetics, and analgesics and may be more physiological at compensating for a plegic vascular system than the liberal use of IV fluids. This is also substantiated by the overall lower complication rate in this group. In addition, although postoperative serum BNP and transient creatinine level increases were rated by us as complications, which makes difficult the comparison with other series that did not include these parameters, the incidence of overall complications, using similar Clavien-Dindo classification, in the low-volume group was still lower than that of other major urological centers.<sup>10,32</sup> Our results call into question the current policy of liberal fluid administration to replace basic fluid volume depleted by, e.g., perspiration, exudation through the surgical wound, loss into the third space, and to correct hypotension due to vasodilation.<sup>1,3,6,35</sup>

Besides the preemptive and concomitant use of norepinephrine, our low-volume group protocol differed from protocols of precedent studies because of the deferred fluid administration: less fluid was administrated during pelvic lymph node dissection and cystectomy (the main period of bleeding); thereafter during construction of the urinary diversion more fluid was administered. This may explain why blood loss was significantly reduced in the low-volume group and consequently, less packed erythrocytes units was transfused perioperatively. This again could explain the enhanced recovery in the low-volume group.<sup>36</sup>

A possible limitation of this study is that the low-volume group is not compared with a GDT protocol, a mode of fluid management that has been shown to enhance bowel recovery and shorten hospitalization time after abdominal surgery.<sup>25</sup> The GDT approach, which consists of a baseline fluid substitution with additional fluid bolus to optimize cardiac preload, is generally associated with more fluid administration (including colloids), than administered in our control group. In addition, the routine or preemptive use of norepinephrine administration was not a first-line option in GDT protocols in contrast to our protocol.<sup>2,25,37,38</sup> In a previous randomized trial comparing the effect of GDT ( $14 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ ) with that of standard intraoperative fluids administered at the discretion of the anesthesiologist ( $11 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ ) on bowel function after radical cystectomy, a significant reduction of ileus was noted in the GDT group (22 vs. 53%).<sup>38</sup> By comparison, the rates of constipation and ileus in both our groups were far lower. This could be explained not only because of the intraoperative hydration, but also by the fact that in the study by Pillai *et al.*,<sup>38</sup> not every patient had an epidural analgesia and it was instituted only for 48 h. In addition, our

finding is in line with a recent study showing that GDT and a zero fluid balance fluid regimen have similar complication rates after colorectal surgery.<sup>6</sup> Our results using intraoperative restrictive deferred hydration combined with preemptive norepinephrine infusion raise questions concerning the validity of GDT or liberal intraoperative fluid administration (as in Pillai *et al.*'s control group) during open radical cystectomy and urinary diversion.

A minor limitation of this study is the lack of continuous  $S_{cv}\text{O}_2$  monitoring. We only measured  $S_{cv}\text{O}_2$  at three time-points during surgery and thus, cannot exclude that  $S_{cv}\text{O}_2$  values less than 70% occurred intraoperatively in both groups.

A strength of this study is that because all patients were managed with the same postoperative enhanced recovery protocol, the risk of possible confounding factors caused by individualized postoperative management is limited. And because no patients were lost to postoperative follow-up, it is unlikely that any complications were missed.

In conclusion, restrictive deferred fluid management combined with preemptive norepinephrine administration in patients undergoing standardized pelvic lymph node dissection, open radical cystectomy, and urinary diversion resulting in a postoperative zero fluid balance, lower in-hospital and 90-day postoperative complication rates, and reduced hospitalization time.

## Appendix. Definitions of Postoperative Complications/Events

### Gastrointestinal Complications

Ileus: no evidence of bowel function (no flatus and no passage of stool) with abdominal distension requiring cessation of oral intake and intravenous fluid support by POD 5<sup>10</sup>

Constipation: no passage of stool without signs of ileus by POD 5<sup>10</sup>

Gastric ulcer: diagnosis made by gastroscopy

Anastomotic bowel leak: considered as a complication if requiring surgery or prolonged drainage

### Complications of Infections

Urinary tract infection: temperature  $>38^\circ\text{C}$  in the last 24 h and leukocytosis and a prompted urinary analysis that showed bacterial counts  $>100,000$  requiring antibiotics

Sepsis: bacterial infection and at least two of the following clinical signs: hypo- or hyperthermia, tachycardia, tachypnea, leukocytopenia or leukocytosis, positive blood culture<sup>3</sup>

Pneumonia: temperature  $>38^\circ\text{C}$  and leukocytosis and clinical signs of pneumonia, requiring antibiotics

Wound infection: pus can be expressed or aspirated, requiring surgical intervention

### Wound Complications

Wound dehiscence: diagnosed clinically and requiring resuturing

### Cardiac Events

Myocardial infarction: increase of the enzyme high-sensitive troponin T above the hospital laboratory's myocardial infarction threshold ( $>0.05 \mu\text{g/l}$ ), and either new Q wave changes, or persistent changes in ST-T segments

Arrhythmia: confirmed by 12-lead electrocardiography and requiring new medication or electroconversion

Congestive heart failure and pulmonary edema: shortness of breath, rales, jugular venous distension, peripheral edema, third heart sound, radiologic signs (cardiomegaly, interstitial or alveolar edema), brain natriuretic peptide value >500 pg/ml and diagnosis requiring diuretics

Transient brain natriuretic peptide increase: postoperative serum brain natriuretic peptide values between 100 and 500 pg/ml (considered as minor cardiac event)

### Thromboembolic Complications

Pulmonary embolism: evidenced by spiral computerized tomography scanning<sup>3</sup>

### Genitourinary Complications

Renal dysfunction: transient increase of creatinine: creatinine >50% upper limit of normal value<sup>3</sup>

Renal failure: severe reduction in glomerular filtration rate (15–29 ml·min<sup>-1</sup>·1.73 m<sup>-2</sup>) at discharge

Urinary leakage: radiologically diagnosed, requiring stenting

### Neurological Complications

Presence of a *de novo* focal deficit, confusion/delirium

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### Competing Interests

The authors declare no competing interests.

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