ELSEVIER

Urologic Oncology: Seminars and Original Investigations ▮ (2017) ▮▮▮–▮▮▮

UROLOGIC ONCOLOGY

Original article

Renal outcome after radical cystectomy and urinary diversion performed with restrictive hydration and vasopressor administration in the frame of an enhanced recovery program: A follow-up study of a randomized clinical trial

Fiona Mei Wen Wu, M.B.B.S., M.R.C.S., M.Med.[a], Fiona Burkhard, M.D.[a], Filippo Turri, M.D.[a], Marc Furrer, M.D.[a], Lukas Loeffel, M.D.[b], George Thalmann, M.D.[a], Patrick Wuethrich, M.D.[b,*]

[a] *Department of Urology, Inselspital, Bern University Hospital, Bern, Switzerland*
[b] *Department of Anaesthesiology and Pain Medicine, Inselspital, Bern University Hospital, Bern, Switzerland*

Received 22 February 2017; received in revised form 9 May 2017; accepted 29 May 2017

Abstract

Objective: To determine whether a restrictive perioperative fluid management in the context of an enhanced recovery after surgery program for radical cystectomy and urinary diversion affects renal function, as fluid restriction and the use of vasopressors have been linked to impaired tissue perfusion, potentially resulting in renal dysfunction.

Methods: We followed 166 patients initially included in a randomized clinical trial and equally allocated to receive a continuous norepinephrine administration combined with 1 ml/kg/h initially, and after cystectomy 3 ml/kg/h crystalloid infusion (intervention group, $n = 83$), or a standard crystalloid infusion of 6 ml/kg/h throughout surgery (control group, $n = 83$). All patients followed our institutional enhanced recovery after surgery program. We prospectively assessed renal function (plasma creatinine values and estimated glomerular filtration rate Chronic Kidney Disease Epidemiology Collaboration equation) postoperatively. Decreased renal function was defined as a decrease in glomerular filtration rate is greater than 20% compared to preoperative values.

Results: There was no significant difference in renal function between the groups postoperatively at any time point after discharge: diabetes mellitus (HR = 2.81 [95% CI: 1.48–5.36]; $P = 0.002$), preoperative estimated glomerular filtration rate (HR = 1.02 [95% CI: 1.00–1.03]; $P = 0.007$), and age (OR = 1.03 [95% CI: 11.00–1.06]; $P = 0.038$) were negative predictors for renal deterioration.

Conclusion: Postoperative renal function evolution was similar in patients receiving restrictive hydration with norepinephrine administration when compared to liberal hydration intraoperatively, suggesting that there is no influence of fluid management and administration of vasopressors on mid-term renal function.

Keywords: Cystectomy; Hydration; Norepinephrine; Renal function

1. Introduction

Increasing focus is being placed on enhanced recovery after surgery (ERAS) programs for various major surgical procedures aiming to reduce complications and length of hospital stay [1,2]. One of the cornerstones of ERAS protocols is the perioperative avoidance of salt and water overload [2]. In a previous randomized clinical trial (RCT), we showed that a zero postoperative fluid balance significantly reduces blood

This study was supported by internal institutional research funds of the Department of Anesthesiology and Pain Medicine and of the Department of Urology, University Hospital Bern, Bern, Switzerland. The funding sources had no role in the design and conduct of the study; the collection, management, analysis, or interpretation of the data; or in the preparation, review, or approval of the manuscript.

* Corresponding author. Tel.: +41-316-322725; fax: +41-316-320554.
E-mail address: patrick.wuethrich@insel.ch (P. Wuethrich).

http://dx.doi.org/10.1016/j.urolonc.2017.05.024
1078-1439/

loss, overall major complications, and gastrointestinal complications in patients undergoing pelvic lymph node dissection (PLND), open radical cystectomy (RC), and urinary diversion (UD) [3,4]. These observations have been confirmed for major abdominal surgery by several meta-analyses showing that restrictive hydration was associated with lower morbidity and mortality [5,6].

However, concerns have been raised that a restrictive perioperative hydration and the use of vasopressors can cause hypovolemia, and thus renal dysfunction [7]. These concerns are based on the fact that perioperative urinary output is still widely considered a surrogate of renal function, and thus additional fluid boluses are recommended to reverse oliguria despite lack of evidence [8–10]. In addition, based on the specific metabolic implications of bowel in the urinary tract, a more liberal fluid administration has generally been applied.

We hypothesize that a restrictive perioperative hydration and the administration of vasopressors will not affect mid-term renal function. Therefore, patients, included in a precedent RCT assessing the in-hospital complication rate and allocated to either a restrictive intraoperative hydration combined with pre-emptive administration of norepinephrine or a liberal hydration scheme in the context of an ERAS protocol, were evaluated.

2. Patients and methods

This follow-up study and the original RCT were approved by the local ethics committee (KEKBE 2016-00660 and 154/08). The original RCT included 166 patients scheduled for PLND, RC, and UD [4]. In this follow-up analysis, we included patients with complete 3-, 6-, and 12-month postoperative follow-up data (Fig. 1).

2.1. Perioperative management

The protocol of the original RCT has been described previously [4]. Briefly, patients were equally allocated to the intervention group or to the control group. In the intervention group, a norepinephrine infusion was started after anesthesia induction at 2 μg/kg/h, and 1 ml/kg/h of a balanced crystalloid solution (Ringerfundin) was administrated until the bladder had been removed, followed by 3 ml/kg/h of crystalloid until the end of surgery. In the control group, a bolus of 6 ml/kg crystalloid was administrated during induction of anesthesia, followed by 6 ml/kg/h of crystalloid intraoperatively.

Blood loss exceeding 500 ml was compensated with an equal amount of Ringerfundin. Packed blood cells were transfused if hemoglobin values decreased to <80 g/l (<100 g/l in patients with coronary artery disease). If hypotension persisted or if severe metabolic acidosis expected to be caused by hypovolemia, occurred, rescue treatment consisted of additional boluses of Ringerfundin. Urinary output was not assessed intraoperatively.

The surgical technique for PLND, RC, and UD (ileal orthotopic bladder substitution or ileal conduit) has been described previously and was identical in all patients [11,12].

A standardized care pathway was used to enhance recovery after surgery in all patients. Postoperatively, patients received 1,000 ml of Ringerfundin and 500 ml 5% glucose per day until oral substitution was adequate in both groups. Patients were allowed to drink clear fluids immediately after surgery, encouraged to chew gum, and started on an oral liquid diet on postoperative day 1 according to our ERAS program.

2.2. Data collection and outcome measures

All patients were scheduled for 3-, 6-, and 12-month follow-up visits that included oncological surveillance and laboratory analysis (plasma creatinine values). At each visit, the blood pressure, plasma creatinine, plasma glucose, urine culture, and residual urine volume of each patient were determined, and renal ultrasonography was performed. All patients with confirmed mechanical obstruction (ureteroileal, stomal obstruction, or bladder outlet obstruction) were reoperated, and the obstruction resolved.

Estimated glomerular filtration rate (eGFR) was calculated based on the Chronic Kidney Disease Epidemiology Collaboration equation, as this equation was developed to create a more precise formula to eGFR from plasma creatinine values, especially when the actual GFR is >60 ml/min/1.73 m^2, and thus performs better than the Modification of Diet in Renal Disease Study (MDRD) equation at higher GFR, with less bias and greater accuracy [13–15].

We defined a clinically relevant renal deterioration as a 20% decrease in eGFR compared to baseline value before surgery. This threshold was chosen because it can demand dosage adjustment for most renal-excreted drugs [16]. Chronic kidney disease (CKD) stages were also used to classify renal function.

The objectives were to compare the postoperative eGFR between the 2 groups (1) at 3, 6, and 12 months postoperatively, (2) among patients with baseline renal dysfunction (defined as <90 ml/min/1.73 m^2) at 12 months postoperatively, and (3) in looking for independent risk factors for decreased renal function at 6 months postoperatively.

2.3. Statistical analysis

Data are expressed in medians with ranges for continuous variables and frequencies for categorical ones. We performed exploratory analyses using the Fisher's exact or the chi-square test and continuous data with the Mann-Whitney U test.

Renal function deterioration–free survival was estimated for the time from surgery to event (20% decrease in eGFR compared to baseline value) with the Kaplan-Meier method