Superior Functional Outcome after Radical Cystectomy and Orthotopic Bladder Substitution with Restrictive Intraoperative Fluid Management: A Followup Study of a Randomized Clinical Trial

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Purpose: Continuous intraoperative norepinephrine infusion combined with restrictive deferred hydration improves surgical field visibility, and significantly decreases intraoperative blood loss and postoperative complications in patients undergoing radical cystectomy and urinary diversion. We determined whether the intraoperative fluid regimen would affect functional results (continence and erectile function) 1 year after orthotopic ileal bladder substitution.

Materials and Methods: We analyzed a subgroup of 93 patients who received an ileal orthotopic bladder substitute. The subgroup was part of a randomized trial in 167 patients initially allocated to continuous norepinephrine administration starting with 2 μg/kg per hour combined with 1 ml/kg per hour initially and 3 ml/kg per hour crystalloid infusion after cystectomy (norepinephrine/low volume group of 51) or a standard crystalloid infusion of 6 ml/kg per hour throughout surgery (42 controls). We prospectively assessed daytime and nighttime continence, and erectile function 1 year postoperatively in the 93-patient subgroup.

Results: Daytime continence was reported by 44 of 51 patients (86%) in the norepinephrine/low volume group and by 27 of 42 controls (64%) ($p = 0.016$), and nighttime continence was reported by 38 (75%) and 25 (60%), respectively ($p = 0.077$). Erectile function recovery was reported by 26 of 33 preoperatively potent patients (79%) in the norepinephrine/low volume group and by 11 of 29 controls (38%) ($p = 0.002$).

Conclusions: Patients who undergo radical cystectomy and orthotopic bladder substitution with continuous norepinephrine infusion and restrictive hydration during surgery have significantly better daytime continence and erectile function 1 year postoperatively.

Key Words: urinary bladder, cystectomy, norepinephrine, urinary incontinence, erectile dysfunction

Abbreviations and Acronyms

PDE-5I = phosphodiesterase-5 inhibitor

PLND = pelvic lymph node dissection

RC = radical cystectomy

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Study received local ethics committee approval.

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RADICAL cystectomy with PLND and urinary diversion is associated with a high incidence of early postoperative complications and increasing efforts are being made to improve the postoperative outcome.[1] The results of our previous prospective, randomized clinical trial showed that preemptive continuous norepinephrine infusion combined with restrictive intravenous hydration during surgery significantly decreased intraoperative blood loss (median 800 vs 1,200 ml), the perioperative blood transfusion rate (33% vs 60%), surgical field visibility and the 90-day postoperative major complication rate (13% vs 25%).[2,3]

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However, to our knowledge it is unknown whether continuous preemptive norepinephrine infusion combined with restrictive deferred hydration during surgery had a negative or positive impact on functional outcomes (daytime and nighttime continence, and erectile function) assessed 1 year postoperatively in the subgroup of patients who underwent orthopic ileal bladder substitution.

MATERIALS AND METHODS

Trial Design and Participants

The study was approved by the local ethics committee and registered at ClinicalTrials.gov (NCT01276665). All patients provided written informed consent. The original double-blind, single center, randomized study included 167 consecutive patients scheduled for PLND, RC and an ileal conduit or orthotopic bladder substitute between November 2009 and September 2012.[2] The study inclusion criterion was ASA® (American Society of Anesthesiologists) physical status 2 or 3. Exclusion criteria were coagulopathy, relevant hepatic and renal dysfunction, congestive heart failure and contraindication to thoracic epidural analgesia. Patients were prospectively and equally randomized into 2 groups, including continuous preemptive norepinephrine infusion combined with restrictive deferred hydration (norepinephrine/low volume group) and a group with more liberal hydration (controls).

In this 1-year followup analysis we included only the subgroup of patients who received an orthotopic ileal bladder substitute and had complete 12-month postoperative followup data available (fig. 1). Patients who reported stress urinary incontinence preoperatively were excluded from orthotopic bladder substitution.

Patient Treatment

The original study protocol and design were described previously.[2] Briefly, patients were randomly assigned to the norepinephrine/low volume group or to the control group.

In the norepinephrine/low volume group norepinephrine infusion was started at the time of anesthesia induction at a rate of 2 μg/kg per hour. Ringerfundin® balanced crystalloid solution (1 ml/kg per hour) was administered until the bladder was removed followed by 3 ml/kg per hour of crystalloid solution until the end of surgery. The norepinephrine infusion rate was adapted up to a maximum of 8 μg/kg per hour to maintain mean arterial blood pressure between 60 and 100 mm Hg.

In the control group a bolus of 6 ml/kg of crystalloid was administered during anesthesia induction followed by 6 ml/kg per hour of crystalloid solution intraoperatively. Hypotension (ie mean arterial blood pressure less than 60 mm Hg) was corrected by repetitive boluses of 250 ml crystalloid solution.

The surgical technique of PLND, RC and orthotopic ileal bladder substitution with an afferent tubular segment was described previously[4,5] and it was identical in all patients. At least 1 senior urologist was present during surgery.

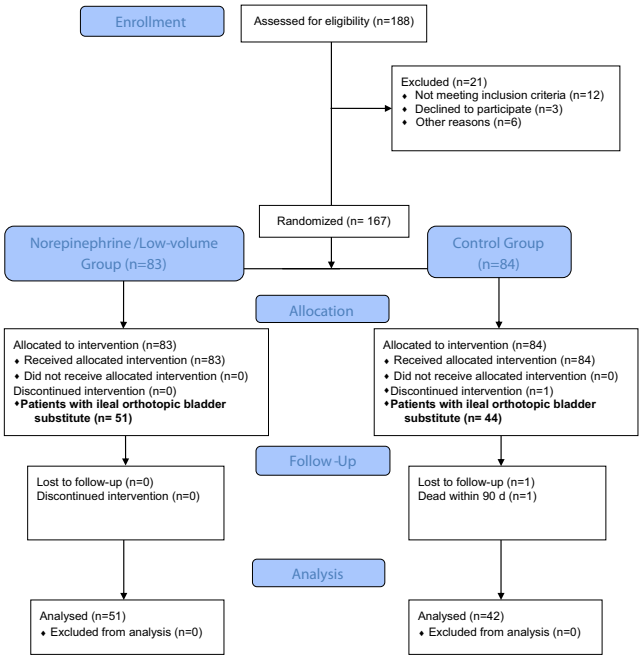

Figure 1. CONSORT diagram of original clinical trial from which patient subgroups with ileal orthotopic bladder substitute were chosen for analysis. *d,* days.

Data Collection and Outcome Measures

Data on attempted nerve sparing and followup were prospectively entered into the departmental database. Patients were routinely followed 3, 6 and 12 months postoperatively to assess oncologic and functional outcomes. At these visits a standardized, previously published questionnaire on voiding, daytime and nighttime continence, and erectile function[6] was completed by a urological nurse specialist or urology resident blinded to operative details and randomization groups at the time of questioning.[7] This questionnaire assessed the presence of and degree of daytime and nighttime urinary continence, the number of pads used, whether the pads were dry, damp or wet and the assumed quantity of urine loss. Continence was defined as complete dryness or the loss of no more than a few drops of urine once or twice per month with some patients wearing a pad as a safety measure. Continence was stratified by day, night and gender.[8] Erectile function was assessed using the IIEF (International Index of Erectile Function) questionnaire.[9] The use of PDE-5I or alprostadil was noted.

Statistical Analysis

This was a secondary exploratory study of a patient subgroup. Analysis was based on the modified intent to treat population from which 2 patients randomized to the control group were excluded due to no functional outcome data at 6 and 12 months (fig. 1). Data were analyzed using nonparametric statistical models and are shown as the median and range or number and percent. Categorical data were compared with the Fisher exact or chi-square test. The RR and 95% CI were also calculated for daytime/nighttime continence and erection rates as