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Intraoperative Continuous Norepinephrine Infusion Combined with Restrictive Deferred Hydration Significantly Reduces the Need for Blood Transfusion in Patients Undergoing Open Radical Cystectomy: Results of a Prospective Randomised Trial

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Abstract

Background: Open radical cystectomy (ORC) is associated with substantial blood loss and a high incidence of perioperative blood transfusions. Strategies to reduce blood loss and blood transfusion are warranted.
Objective: To determine whether continuous norepinephrine administration combined with intraoperative restrictive hydration with Ringer's maleate solution can reduce blood loss and the need for blood transfusion.
Design, setting, and participants: This was a double-blind, randomised, parallel-group, single-centre trial including 166 consecutive patients undergoing ORC with urinary diversion (UD). Exclusion criteria were severe hepatic or renal dysfunction, congestive heart failure, and contraindications to epidural analgesia.
Intervention: Patients were randomly allocated to continuous norepinephrine administration starting with 2 μg/kg per hour combined with 1 ml/kg per hour until the bladder was removed, then to 3 ml/kg per hour of Ringer's maleate solution (norepinephrine/low-volume group) or 6 ml/kg per hour of Ringer's maleate solution throughout surgery (control group).
Outcome measurements and statistical analysis: Intraoperative blood loss and the percentage of patients requiring blood transfusions perioperatively were assessed. Data were analysed using nonparametric statistical models.
Results and limitations: Total median blood loss was 800 ml (range: 300–1700) in the norepinephrine/low-volume group versus 1200 ml (range: 400–2800) in the control group ($p < 0.0001$). In the norepinephrine/low-volume group, 27 of 83 patients (33%) required an average of 1.8 U (±0.8) of packed red blood cells (PRBCs). In the control group, 50 of 83 patients (60%) required an average of 2.9 U (±2.1) of PRBCs during hospitalisation (relative risk: 0.54; 95% confidence interval [CI], 0.38–0.77; $p = 0.0006$). The absolute reduction in transfusion rate throughout hospitalisation was 28% (95% CI, 12–45). In this study, surgery was performed by three high-volume surgeons using a standardised technique, so whether these significant results are reproducible in other centres needs to be shown.
Conclusions: Continuous norepinephrine administration combined with restrictive hydration significantly reduces intraoperative blood loss, the rate of blood transfusions, and the number of PRBC units required per patient undergoing ORC with UD.

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1. Introduction

Open radical cystectomy (ORC) combined with extended pelvic lymph node dissection (PLND) and urinary diversion (UD) is associated with substantial intraoperative blood loss and a high packed red blood cells (PRBCs) transfusion rate [1,2]. PRBC transfusions have rare but serious adverse effects and may be associated with increased cancer recurrence after ORC [3–6]. Consequently, establishing strategies to reduce intraoperative blood loss and the need for PRBC transfusion could benefit surgical outcomes.

Several factors may influence blood loss, including surgical technique, tumour characteristics, and knowledge of local anatomy. In addition, intraoperative fluid management may have an impact on blood loss, as suggested in a retrospective study of radical prostatectomy patients [7]. Anaesthetic agents and analgesia-induced vasodilation increase the risk of capillary and venous bleeding and thus may render surgery more hazardous. Moreover, vasodilation inevitably causes hypotension, which is usually compensated for with generous intravenous (IV) fluid administration. Alternatively, a low-dose infusion of norepinephrine could be used. Norepinephrine for treatment of perioperative hypotension has been shown in animals to have no negative side effects on oxygen tissue tension in the intestinal tract [8].

In the present analysis of a prospective, randomised clinical trial, we evaluate the impact of continuous norepinephrine administration combined with restrictive deferred intraoperative hydration on intraoperative blood loss and the need for PRBC transfusion in patients undergoing PLND, ORC, and UD.

2. Patients and methods

2.1. Patients

This study was approved by the local ethics committee, and all patients gave written informed consent. The study consisted of 190 consecutive patients who underwent combined ORC, PLND, and UD between November 2009 and September 2012. Inclusion criteria were an American Society of Anesthesiologists (ASA) physical status score of 2 or 3. Exclusion criteria were coagulopathies, significant hepatic dysfunction (prothrombin ratio <50%), significant renal dysfunction (chronic kidney disease stage ≥3), congestive heart failure (CHF; New York Heart Association class ≥3), and contraindication for thoracic epidural analgesia. Patients were prospectively randomised into two groups by a concealed allocation sequence (computer-generated codes): one group receiving a continuous norepinephrine administration combined with a restrictive deferred Ringer's maleate hydration (norepinephrine/low-volume group) and the second receiving a more standard liberal hydration (control group; Fig. 1). All patients were evaluated for possible differences in intraoperative blood loss, the dryness of the surgical field (as assessed by the senior surgeon), and intraoperative and postoperative need for PRBC transfusions.

2.2. Patient management

Low-molecular-weight heparin was started on the evening before surgery and maintained throughout hospitalisation in all patients. The PLND, ORC, and UD techniques were standardised and performed or supervised by at least one senior urologist (G.N.T., U.E.S. or F.C.B.) [9–11].

In the norepinephrine/low-volume group, continuous norepinephrine administration was started at 2 μg/kg per hour after induction of anaesthesia, and 1 ml/kg per hour of Ringer's maleate solution (Ringerfundin, B. Braun Medical, Sempach, Switzerland) was given until the bladder had been removed, followed by 3 ml/kg per hour until the end of surgery. In the control group, a 6 ml/kg bolus of Ringer's maleate solution was administered during induction of anaesthesia, followed by infusion at a constant rate of 6 ml/kg per hour intraoperatively (Fig. 1). In both groups, blood loss exceeding 500 ml was compensated for with an equal amount of Ringer's maleate solution (Fig. 1). Intraoperatively, PRBCs were transfused to maintain a haemoglobin >8 g/dl in all patients during surgery [12]. In the recovery room, PRBC transfusions were administered according to the following guidelines: A haemoglobin level between 7.0 and 10 g/dl combined with relevant anaemia symptoms (electrocardiographic signs of ischaemia, tachycardia not attributable to other factors such as pain or hypovolaemia) or relevant risk factors such as cardiac disease or cerebral ischaemia [12]. All patients received PRBC units at this time if their haemoglobin level was <7.0 g/dl [13]. Postoperative fluid management was similar in both groups and consisted primarily of 1000 ml of Ringer's maleate solution and 500 ml of glucose 5% per 24 h.

2.3. Data collection and outcome measures

Surgeons, patients, and data assessors were blinded to the two groups and remained blinded until the patient was discharged. To blind the urologists, crystalloid bags and perfusion pumps were placed behind a sterile opaque panel during surgery.

Prior to surgery, data were recorded on each patient's age, gender, body mass index (BMI), ASA score, Charlson Comorbidity Index age adjusted (CCIaa) score, neoadjuvant chemotherapy, preoperative anaemia (according to the World Health Organisation: haemoglobin <13 g/dl for men and <12 g/dl for women), hypoalbuminaemia (<35 g/l), and elevated C-reactive protein (CRP) values (>3 mg/l).

Blood loss was assessed by accounting for the aspirated blood and the weight difference of the gauzes before and after surgery. Blood loss was assessed separately for each of the three procedures (PLND, ORC, and UD). The number of patients receiving PRBC transfusion and the total number of PRBC units transfused were documented intraoperatively and postoperatively by the study nurse. Urine was continuously derived, first using a transurethral catheter and later by ureteral stents to avoid urine in the aspiration and gauzes.

The dryness of the surgical field during PLND, ORC, and UD was rated by the senior surgeon using a bleeding score [14,15]: Grade 1 was marked by minimal bleeding not interfering with surgery, grade 2 by mild bleeding not compromising dissection, grade 3 by moderate bleeding slightly compromising dissection, and grade 4 by severe bleeding significantly compromising dissection. During surgery, invasive mean arterial blood pressure, heart rate, and central venous pressure (CVP) were continuously monitored.

2.4. Statistical analysis

The power analysis for the initial study [16] was based on the assumption that the application of intraoperative restrictive deferred hydration would reduce the Clavien-Dindo grade 3–5 complication rate from 38% to 20% [17–19]. For this purpose, a sample size of 83 patients per group was calculated, with a type I error of 0.05 and a power of 80%. Data were analysed using nonparametric statistical models. Data are described by medians with ranges for numerical variables or frequencies or proportions for categoric variables (percentages). Categoric data were compared with Fisher exact test or chi-square test, when appropriate. Continuous data