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ARAŞTIRMA / RESEARCH

Evaluation of perioperative parameters in patients undergoing radical cystectomy urinary diversion surgery for bladder cancer

Mesane kanserinde radikal sistektomi üriner diversiyon operasyonu yapılan hastalarda perioperatif parametrelerin değerlendirilmesi

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Abstract

Purpose: The aim of this study was to evaluate the effect of red blood cell transfusion and/or inotropic/vasopressor agent infusion during intraoperative and postoperative first 24-hour period on 30-day and one-year survival.

Materials and Methods: In the final analysis, 133 patients who underwent radical cystectomy and urinary diversion surgery between November 2011 and January 2019 were included in this study. Perioperative anesthesia management early postoperative intensive care patient follow-ups were based on.

Results: A statistically significant relationship was found between intraoperative red blood cell transfusion and one-year mortality rates. A statistically significant relationship was found between red blood cell transfusion in the intensive care unit and postoperative 30-day mortality rates. The relationship between vasopressor/inotrope agent infusion in intensive care unit and postoperative 30-day mortality was statistically significant.

Conclusion: In radical cystectomy and urinary diversion, intraoperative red blood cell and/or inotrope/vasopressor drug administration, and red blood cell transfusion within first 24 postoperative hours in intensive care unit are associated with lower survival rates in both early and late periods. Future studies should focus on developing and implementing different strategies for perioperative blood management and maintenance of patient hemodynamics that may affect early and late outcomes.

Keywords: Inotrope/vasopressor infusion, mortality, radical cystectomy surgery, red blood cell transfusion

Öz

Amaç: Bu çalışmada intraoperatif ve postoperatif ilk 24 saatlik dönemde eritrosit transfüzyonu ve/veya inotropik/vazopresör ajan infüzyonunun 30 günlük ve bir yıllık sağkalımı etkisinin araştırılması amaçlanmıştır.

Gereç ve Yöntem: Bu çalışmaya final analizinde Kasım 2011 ile Ocak 2019 arasında radikal sistektomi ve üriner diversiyon operasyonu geçiren 133 hasta dahil edildi. Perioperatif anestezi yönetimi erken postoperatif yoğun bakım hasta takipleri esas alındı.

Bulgular: İntraoperatif kırmızı kan hücresi transfüzyonu ile bir yıllık mortalite oranları arasında istatistiksel olarak anlamlı bir ilişki bulunmuştur. Yoğun bakım ünitesinde yapılan eritrosit transfüzyonu ile postoperatif 30 günlük mortalite oranları arasında istatistiksel olarak anlamlı bir ilişki bulunmuştur. Yoğun bakım ünitesinde vazopressör/inotrop ajan infüzyonu ile postoperatif 30 günlük mortalite arasında istatistiksel olarak anlamlı bir ilişki bulunmuştur.

Sonuç: Radikal sistektomi ve üriner diversiyon operasyonu geçiren hastalarda intraoperatif eritrosit, inotrop/vazopresör ilaç uygulaması ve yoğun bakımda postoperatif ilk 24 saat içinde eritrosit transfüzyonu hem erken hem de geç dönemde daha düşük sağkalım oranları ile ilişkilidir. Gelecekteki çalışmalar, perioperatif kan yönetimi ve hasta hemodinamisinin korunması ile ilgili erken ve geç dönem sonuçları etkileyebilecek farklı stratejiler geliştirmeye ve uygulamaya odaklanmalıdır.

Anahtar kelimeler: İnotrop/vazopresör infüzyonu, mortalite, radikal sistektomi cerrahisi, kırmızı kan hücresi transfüzyonu

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INTRODUCTION

Radical cystectomy and urinary diversion surgery (RCUD) are often associated with a high frequency of complications due to patients' complex intervention protocols and frequent comorbidities of non-primary pathologies. These patients require a multidisciplinary approach at every stage of the treatment, from the preoperative stage to the postoperative follow-up[1].

Regional or general anesthesia techniques are used in the anesthesia plan in radical cystectomy and urinary diversion (RCUD) surgeries[2]. Intraoperative fluid management, transfusion requirements, hypothermia prevention, antibiotics, and thromboembolism prophylaxis are considered as part of standard care. Postoperative period follow-ups and advanced recovery protocols, including pain control, ambulation, and early return of bowel functions are recommended. Radical cystectomy (RC) is associated with significant blood loss and the need for transfusion. Perioperative blood transfusion (PBT) rates in the RC procedure range from 15% to 66%. PBT involves serious risks such as transfusion-related lung injury, infection, and allergic reactions. It has been reported that perioperative blood transfusion may be an independent predictor of mortality in patients undergoing radical cystectomy[3,4]. Red blood cells (RBC) and fresh frozen plasma (FFP) transfusion may cause adverse effects on the immune system due to suppression of cytotoxic cells, the release of immunosuppressive prostaglandins, and inhibition of interleukin 2. The ideal plan for PBT is still debated in major oncologic surgery, especially for elderly comorbid patients[5].

This study aimed to present our experience in perioperative and early postoperative intensive care management and follow-ups in patients who underwent RCUD operation for muscle-invasive bladder cancer and to evaluate the effects of perioperative management and practices on mortality.

MATERIALS AND METHODS

This retrospective study was approved by the Baskent University Medical and Health Sciences Research Board (Project no: KA20 /72) and was funded by the Baskent University Research Fund. The data were collected from patients and hospital electronic database records who underwent radical cystectomy and urinary diversion operation between November 2011 and December 2019 at Baskent University Faculty of Medicine Adana and Ankara Hospitals. In our institutions, all patient data is stored in electronic media and files are archived since November 2011. For this reason, to prevent data loss, 2011, the date of transition to the electronic database of our hospitals, was determined as the study's start date.

Study design

During the preoperative evaluation, age, gender, American Society of Anesthesiologists (ASA) physical status score, and the presence of comorbidities were recorded for all patients. Patients who developed metabolic complications (e.g., hyperchloremic metabolic acidosis, hyponatremia), pulmonary embolism, ureteroileal anastomotic leak, ileus, and who underwent relaparotomy in the postoperative period were excluded from the study. All patients with a 10 g dl^{-1} and above preoperative hemoglobin value were prepared for the operation. The operation date, duration of operation, intraoperative hemodynamic unexpected conditions [hypotension (systolic arterial pressure (SAP)<90 mmHg), hypertension (SAP>140 mmHg), bradycardia (heart rate (HR)<60 min^{-1}), tachycardia (HR>100 min^{-1})], inotrope-vasopressor drug requirement, bleeding amount, crystalloid infusion volume, transfusion amount and types were recorded. As the first option, 0.02 mg noradrenaline bolus was administered intravenously (iv) to our patients in case of hypotension. If indicated, noradrenaline infusion was administered at doses of 0.005 - 0.1 μg kg^{-1} min^{-1} as a vasopressor agent for hypotension.

In all patients, 0.9% NaCl infusion was initiated by establishing an intravenous route with a 21 Gauge branule in the preoperative period. Standard anesthesia monitoring with 5-lead ECG, pulse-oximetry, temperature, invasive arterial blood pressure from the radial artery, and central venous pressure monitoring were provided.

A standard anesthesia plan is applied to patients who undergo an RCUD operation in our clinics. Intubation was administered via a 2 mg kg^{-1} IV propofol, 0.4-0.5 mg kg^{-1} rocuronium bromide, and 1μg kg^{-1} fentanyl at anesthesia induction. Anesthesia was maintained with a 2% sevoflurane inhalation anesthesia using a 50% nitrous oxide and 50% oxygen mixture. When necessary, repeated doses of

rocuronium bromide were administered at 0.15 mg kg^{-1}. During the preemptive multimodal analgesia protocol, 0.1 mg kg^{-1} IV morphine sulfate, 10 mg kg^{-1} paracetamol, and 20 mg tenoxicam were administered to our patients for postoperative analgesia. For our patients with an intraoperative epidural catheter, 8-10 ml 0.25% bupivacaine was administered in the postoperative care unit, followed by 4-6 ml/hour infusion of 0.0625% bupivacaine through an epidural catheter.

These patients are then followed up in the Surgical Intensive Care Unit (ICU) for the first 24 postoperative hours according to the routine practice of our clinics. During the first 24 hours of surgical ICU follow-up of the patients, transfusion needs, unexpected hemodynamic events, [hypotension (SAP<90 mmHg), hypertension (SAP>140 mmHg)], and vasopressor agent infusion needs were recorded. It was also recorded if they were readmitted within 48 hours after being discharged from the intensive care unit. Postoperative early period (first 30 days) and late postoperative period (1 year) mortality of the patients were recorded.

Outcomes

Primary outcomes of interest were: (1a) association between intraoperative red blood cell, fresh frozen plasma transfusion, and 30-day and 1-year mortality and (1b) the association between intraoperative inotropic agent requirement and 30-day and 1-year mortality. Secondary outcomes of interest were: (2a) association between unexpected hemodynamic events and 30-day and 1-year mortality and (2b) association between readmission to the intensive care unit and 30-day and 1-year mortality.

Statistical analysis

The conformity of numerical variables to normal distribution was examined with the Kolmogorov Smirnov test of normality, and no numerical variables were distributed normally ($p<0.05$). Descriptive statistics were given by considering the median (minimum-maximum) for numerical variables n (%) for categorical variables. Pearson Chi-square test was used to evaluate independent categorical data, Generalized Fisher (Fisher-Freeman-Halton) Exact test was used when Pearson Chi-square test was not suitable. Type I error probability was determined as $\alpha=0.05$ in all statistical analyzes, and all analyzes were performed using the IBM SPSS v25 program.

RESULTS

The 139 patients who underwent RCUD surgery at Baskent University School of Medicine Adana and Ankara Hospitals between November 2011 and December 2019 are included in this study. A total of 6 patients, two patients with pulmonary embolism, four patients who underwent laparotomy due to ileus and ureteroileal anastomotic leakage in the postoperative period were excluded from the study. In the final analysis, 133 patients were included in the study. Patient demographics, ASA physical status, comorbidities, operation duration, intraoperatively delivered crystalloid fluid, bleeding amount, RBC, and FFP amount are shown in Table 1.

General anesthesia was administered to 120 (90.2%) patients and intraoperative epidural catheter replacement for postoperative analgesia along with general anesthesia to 13 (9.8%) patients. When the intraoperative hemodynamic parameters of patients were evaluated, hypotension was observed to have developed in 45.1% and hypertension in 6%. Intraoperative noradrenaline infusion was administered in 7.5% of the patients with hypotension.

According to the patients' hemodynamic data, in the first 24 postoperative hours of ICU follow-up, 57.1% of the patients had normal hemodynamics, while 36.1% developed hypertension, and 6.8% had hypotension. Data regarding inotrope/vasopressor agent and transfusion requirement in ICU 24 hour follow-up and readmission to ICU in the first 48 hours are shown in Table 2. The amount of RBC transfusion administered within the ICU was 0.35 units on average (min-max 0-2), and the FFP transfusion was 0.65 units on average (min-max 0-4). It was found that 6 (4.5%) died in the postoperative 30-day period, and 11 (8.3%) died in the postoperative 1-year period.

When we look at the relationship between intraoperative hemodynamics and postoperative 30-day mortality, it was found that 2 of 65 hemodynamically stable, 4 of 60 patients with hypotension died, and none of the 8 patients with hypertension died. When the relationship between intraoperative hemodynamics and postoperative 1-year mortality was evaluated, it was found that 4 of 65 hemodynamically stable patients, 5 of 60 patients with hypotension, and 2 of 8 patients with hypertension died. There was no statistically significant relationship between postoperative 30-day

and one-year mortality with intraoperative hemodynamic parameters (p> 0.05) (Table 3). There were no deaths among the 22 patients who were not administered intraoperative RBC. Eleven of the 100 patients who were administered 1-9 units of RBC died.

There was no statistically significant relationship between intraoperative RBC transfusion and postoperative 30-day mortality (p> 0.05). The relationship between intraoperative RBC transfusion and one-year mortality was found to be statistically significant (p = 0.003) (Table 3).

Table 1. Patient demographics

Variable	
Age (Years) [min-max (Median)]	
Sex	
Male n (%)	110 (82.7%)
Female n (%)	23 (17.3%)
ASA physical status n (%)	
2	87 (65.4%)
3	46 (34.6%)
Comorbidities (%)	
No comorbidity	26.7%
Hypertension	31.4%
Type II diabetes mellitus	15.7%
Coronary artery disease	12.2%
Chronic obstructive pulmonary disease	7%
Congestive heart failure	2.3%
End-stage renal disease	1.2%
Stage 4 chronic kidney disease	1.7%
Cerebrovascular disease	1.2%
Valvular heart disease	0.6%
Operation duration (minute) [min-max (Median)]	155-615 (195.17]
Intraoperative crystalloid fluid (mililiter) [min-max (Median)]	1000-7000 (3119.32)
Intraoperative bleeding amount (mililiter) [min-max (Median)]	200-4000 (924.06)
RBC (unit) [min-max (Median)]	0-9 (2.18)
FFP (unit) [min-max (Median)]	0-7 (2.09)

Table 2. Data regarding inotrope/vasopressor agent and transfusion requirements and readmission to ICU

	Yes	**No**
ICU inotropic agent infusion requirement	5.3%	94.7%
ICU transfusion requirement	46.6%	53.4%
First 48 h ICU readmission	9%	91%

§ICU: Intensive Care Unit

There was no statistically significant relationship between intraoperative FFP transfusion postoperative 30-day and 1-year mortality (p> 0.05) (Table 3). There was no statistically significant relationship between intraoperative inotrope/vasopressor infusion, postoperative 30-day, and 1-year mortality (p> 0.05) (Table 3).

In the first 30-day mortality, during the ICU follow-up period, 3 of 96 patients who did not receive RBC transfusion and 3 of 37 patients who received 1-2 units of RBC transfusion died. The relationship between RBC transfusion in the ICU and postoperative 30-day mortality was found to be statistically significant (r = 0.176, p = 0.021) (Table 3). No statistically significant relationship was found between RBC transfusion in the ICU and one-year postoperative mortality (p>0.05) (Table 3). There was no statistically significant relationship between FFP transfusion in ICU, postoperative 30-day, and one-year mortality (p> 0.05) (Table 3).

In the ICU follow-up, 4 of 126 patients who did not receive vasopressor/inotrope agent infusion, and 2 of 7 patients who received vasopressor/inotrope agent infusion died. The relationship between

vasopressor/inotrope agent infusion in the ICU and postoperative 30-day mortality was found to be statistically significant (r = 0.273, p = 0.001) (Table 3). There was no statistically significant relationship between intraoperative inotrope/vasopressor infusion in ICU follow-ups and one-year postoperative mortality (p>0.05) (Table 3). There was no statistically significant relationship between readmission to the ICU within 48-hours, postoperative 30-day, and one-year mortality (p> 0.05) (Table 3).

Table 3. Perioperative management and follow-up of patients

Variable	Postoperative 30-day mortality	Postoperative 1-year mortality
	p	p
Intraoperative Hemodynamics	0.617	0.243
Intraoperative Red Blood Cell Transfusion	0.262	0.003*
Intraoperative Fresh Frozen Plasma Transfusion	0.392	0.131
Intraoperative Inotrope/Vasopressor Infusion	0.680	0.531
Red Blood Cell Transfusion in ICU	0.021*	0.787
Fresh Frozen Plasma Transfusion in ICU	0.426	0.729
Inotropic agent infusion requirement in ICU Follow-Up	0.001*	0.400
Readmission to the ICU within First 48-Hours	0.652	0.993

§ICU: Intensive Care Unit, *: p<0.05

DISCUSSION

For localized muscle-invasive bladder cancers and in selected cases of non-muscle-invasive cancers, removing the entire bladder via radical cystectomy and creating a urinary diversion is often recommended as the most effective treatment[6]. RCUD operations are associated with significant perioperative morbidity and mortality rates, ranging from 30% to 70% of patients[7]. Patients with muscle-invasive bladder cancer have increased surgical complication rates due to cardiovascular comorbidity, diabetes, and obesity. Age alone is not an independent risk factor for complications after radical cystectomy[8]. It has been reported that the one-year survival rate in muscle-invasive non-metastatic bladder cancer is 66%, and the rate of patients with three or more comorbidities according to the Charlson comorbidity index is 8%[9]. Patients undergoing radical cystectomy with pelvic lymph node dissection have 10-year recurrence-free survival rates of 50-59% and overall survival rates of approximately 45%[10].

General anesthesia or combined epidural anesthesia and general anesthesia are applied during the anesthesia management of RCUD operations[11]. Multimodal analgesia is used in postoperative pain management for many types of surgeries. Agents used in this process include paracetamol, nonsteroidal anti-inflammatory drugs, and opioids[12]. Epidural analgesia for perioperative pain management in abdominal surgery is standard internationally[13]. The general anesthesia protocol is applied to our standard clinical practice in line with this literature information. For postoperative analgesia, multimodal IV analgesia strategy and additional epidural analgesia are used in selected cases. Radical cystectomy operations are characterized by remarkable blood loss and transfusion requirements. Intraoperative blood loss and the need for transfusion in urological procedures are increasingly being studied[14]. In several recent radical cystectomy studies, the average estimated blood loss has been reported to range from a few hundred to approximately 2,000 ml[15-17]. Chang et al. reported that in 297 patients who underwent radical cystectomy, the average blood loss was 600 ml and the average need for blood transfusion was two units (range 1-10)[14]. In our series, the mean estimated blood loss was 900 ml, and the average blood transfusion requirement was two units (range 0-9).

Radical cystectomy is one of the most complicated urological surgical procedures, and its perioperative early mortality rates range between 0.3% and 5.7%[18]. In an analysis where more than 2,500 patients who underwent radical cystectomy were examined, Hollenbeck et al. observed many factors such as patient's age, functional status, ASA score, kidney function, anesthesia type, operation duration, and

blood transfusion requirements were indicators of complications[19].

Bleeding is a major source of surgical morbidity and is often managed by RBC transfusion. RBC transfusion is necessary for improving tissue perfusion and oxygenation in some clinical situations. Intraoperative blood loss and RBC transfusion are highly interrelated but much more challenging to measure reliably and prone to errors[20]. Transfusion is a life-saving treatment; however, the evidence shows that transfusion is associated with many worse outcomes, such as multiple organ failure, transfusion-related acute lung injury, and death risk[21]. Mechanisms likely to explain the decreased survival rates include PBT, defined as transfusion-related immunomodulation and the induction of immunosuppressive effects[22,23]. Cell-derived microparticles originating from blood cells are thought to play an essential role in transfusion-related effects. RBC microparticles can cause immunosuppression by reducing the release of several cytokines such as TNF-α, IL-8, or IL-10. Furthermore, infusion of growth factors (vascular endothelial growth factor and transforming growth factor β) may create stimulation of cancer cell proliferation[24-26].

Many studies show that transfusion is associated with cancer recurrence and cancer-specific survival[27-29]. Zuckerman et al. reported that in 74,962 patients who underwent gastrointestinal cancer surgery, perioperative RBC transfusions were independently associated with higher all-cause mortality, which was observed far beyond the early postoperative period. It was independent of short-term postoperative morbidity and mortality and the scope of cancer[30].

Diamantopoulos et al. reported in their retrospective cohort study involving 747 patients who underwent radical cystectomy that intraoperative blood transfusion was independently associated with lower overall survival and recurrence-free survival, but not with postoperative blood transfusion[31]. In our study, intraoperative blood transfusion was significantly associated with a decrease in one-year survival, especially in the early postoperative period (first 24 hours), reducing postoperative 30-day survival.

The perioperative period, in which fluid and vasoactive drugs were frequently used to prevent hypovolemia, vasodilation, and decreased cardiac output, is characterized by a temporary but significant deterioration of normal physiology[32]. Norepinephrine has both alpha-1 and beta-1 receptor agonist effects. Norepinephrine is a vasoactive drug used to increase organ perfusion due to its vasoconstrictor effects under impaired vascular tone or reduced cardiac output. At the same time, further fluid administration may cause hypervolemia, tissue edema, and cardiorespiratory complications. Vasoactive agents are widely used in the perioperative period and are administered according to blood pressure and other hemodynamic goals[33,34]. Mizota et al. reported that in a retrospective cohort study of 2776 patients who underwent major abdominal surgery, postoperative invasive respiratory or vasopressor support was associated with higher hospital mortality and lower long-term survival when limiting their analysis to 30-day survivors[35]. In our study, a 30-day mortality rate was also found to be significantly higher in patients who received inotrope/vasoconstrictor drug support due to hemodynamic instability in the first 24 postoperative hours.

Our study has some limitations. First, this study has all the limitations of the observational retrospective study design. Additionally, the small sample size makes it difficult to detect clinical differences due to confounding factors. Second, we did not investigate the effects of existing comorbidities on early and 1-year survival in muscle-invasive non-metastatic bladder cancer. Third, as this was a two-center study, we did not evaluate pathological data. Another limitation was that we did not have our patients' preoperative tumor biomarker levels. These data could have provided more precise information regarding tumor progression and survival. All these multiple variables can be more clearly evaluated by planning a more extensive and longer-term study, including a randomized controlled trial that includes pathological evaluation, examination of tumor markers, and better definition of perioperative risks.

In conclusion, intraoperative RBC transfusion, inotrope/vasopressor drug administration, and RBC transfusion in the first 24 hours of ICU follow-up are associated with lower survival rates in both early and late periods in radical cystectomy surgery. Future studies should focus on developing and implementing different strategies for perioperative blood management and maintenance of patient hemodynamics that may affect early and late outcomes.

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