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Effects of Perioperative Fluid Management on Endothelial Glycocalyx in Radical Cystectomy: A Randomized Clinical Trial

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What's known on the subject? and What does the study add?

Major abdominal surgeries are known to cause large amounts of fluid shifts *in vivo*, occasionally depending on the fluid therapy modality. Theoretically, excessive fluid replacement leads to glycocalyx damage; however, it is not well established how to follow-up such damage and its clinical implications. In this study, biochemical degradation products of glycocalyx and their relationship with liberal fluid therapy are demonstrated, although there may not be any clear change in hemodynamic monitoring.

Abstract

Objective: The endothelial glycocalyx layer (EGL) is the interface between the blood and the endothelium that regulates permeability. This study compared the effects of liberal and restrictive fluid therapies on atrial natriuretic peptide (ANP) release and EGL products in radical cystectomy surgery. We hypothesized that a liberal regimen would damage the glycocalyx layer, resulting in a higher serum EGL product concentration than restrictive therapy.

Materials and Methods: Patients were randomized into two groups for restrictive (group R) or liberal (group L) regimens. Group R received 2 mL/kg/h Ringer's lactate and 2 mcg/kg/h norepinephrine infusion, whereas group L received only Ringer's lactate infusion at 10 mL/kg/h rate during the surgery. Preoperative and postoperative blood samples were obtained to evaluate ANP levels and glycocalyx degradation products. The stroke volume index, cardiac index, stroke volume variation, and systemic vascular resistance index parameters were recorded at 30-min intervals throughout the surgery. The length of stay in the hospital and intensive care unit and postoperative complications were recorded.

Results: The study was completed with 39 patients. Postoperative ANP levels were higher in group L in both between- and within group examination ($p<0.05$). EGL constituents; syndecan-1 and hyaluronan concentrations, were higher in group L ($p<0.05$). Advanced hemodynamic parameters indicated insignificant changes between the groups ($p>0.05$). Postoperative complications and length of stay data were similar ($p>0.05$).

Conclusion: ANP, hyaluronan, and syndecan-1 concentrations can be used as an indirect measurement method to show EGL damage and hypervolemia in major urologic surgeries. Advanced hemodynamic monitoring was ineffective for confirming hypervolemia.

Keywords: Fluid shifts, atrial natriuretic peptid, hemodynamic monitorization, liberal fluid therapy, radical cystectomy

Introduction

Major abdominopelvic surgeries are known to be extensive operations that cause large fluid shifts among the tissues and occasionally require high volume of intraoperative fluid replacement. Adopting proper perioperative fluid management is essential, but the correct therapy is still debated in the literature (1). Ongoing studies are now focusing on the micro

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level; investigating the dynamics of intravascular fluid by taking "endothelial glycocalyx" (EGL) into consideration, which may help define a suitable approach (2,3). An endogenous hormone, atrial natriuretic peptide (ANP), is secreted from the atrium of the heart due to mechanical wall stress which damages the EGL (4).

Conventionally, perioperative fluid therapy aims to provide adequate nutrient and oxygen delivery to the organs and tissues while avoiding hypotension, which may cause hypoperfusion. However, this approach may result in infusing quite large amounts of fluid with possible adverse effects on the organs (5). Organ perfusion disorders can be observed with hypovolemia, and when shifted to the hypervolemic side, complications such as pulmonary edema, prolonged mechanical ventilation, anastomotic leaks, and infection can be encountered (6).

The data regarding the fluid amount affecting EGL shedding is mostly investigated in critical care settings, and anesthesia-related results are yet to be investigated (7). We hypothesized that glycocalyx damage markers would be significantly higher in patients who receive liberal fluid therapy. The aim of this study was to investigate the relationship between liberal fluid replacement and EGL shedding during the perioperative period. Our primary outcome was the change in serum ANP concentrations, and secondary outcomes were structural EGL products (hyaluronic acid, heparane sulfat, syndecan-1) concentrations, advanced cardiac hemodynamic parameters, total usage of fluid, vasopressor, and blood products, length of intensive care unit (ICU) and hospital stay, and complications.

Materials and Methods

This prospective, single-center, double-blind, randomized trial was approved by the local Clinical Research Ethics Committee of İstanbul University, İstanbul Faculty of Medicine (2018/374) and registered at clinicaltrials.gov (NCT04780490). After obtaining informed consent, the study was performed on patients with American Society of Anesthesiologists physical status II-III who underwent radical cystectomy with urinary diversion under general anesthesia between April 2018 and June 2020. A computed system (www.graphpad.com) was used for randomization to generate numbers and divide patients into two groups, and the numbers were stored in opaque sealed envelopes by an external person. The exclusion criteria were hepatic dysfunction (impaired liver function tests), cardiac dysfunction (ejection fraction <35%), renal dysfunction (glomerular filtration rate <30 or creatinine >2 mg/dL), and known coagulapathies. Informed consent was obtained from all participants. The patients and postoperative data assessors were blinded to the groups.

Anesthesia Management

After arrival to the operating room, standard monitorization (electrocardiography, non-invasive blood pressure, and pulse oximetry) was performed on all patients. Before general anesthesia induction, an epidural catheter was inserted at T9-T10 level using a 16-gauge Tuohy needle in which the catheter placement was checked with a 3 mL 2% lidocaine (Jetmonal®, Adeka, İstanbul, Turkiye) test dose. In the postoperative period, 0.1% bupivacaine (Marcain®, Astra Zeneca, Cambridge, UK) infusion was administered to all patients via a PCA device (PCA Ambulatory infusion pump, CADD-legacy, Smiths Medical MD, Minnesota, USA), epidurally, for up to 48 h (basal infusion: 6 mL/h, PCA dose: 4 mL/h, lockout time: 30 min, 4-hour limit: 26 mL).

Standard anesthesia induction with midazolam (0.05 mg/kg IV, fentanyl 2 mcg/kg IV, propofol 2 mg/kg IV, and rocuronium (0.06 mg/kg IV) was provided. Controlled mechanical ventilation was set to keep $EtCO_2$ between 35 and 40 mmHg, positive end-expiratory pressure at 5 mmHg, and tidal volume at 6-8 mL/kg based on ideal body weight. Sevoflurane was used for maintenance to achieve a minimum alveolar concentration of 0.8-1.

Once safe induction and maintenance are provided; a pulse contour analysis device, the Vigileo™ system (Edwards Lifesciences LLC, Irvine, CA, USA) using the FloTrac™ Sensor via arterial cannulation, was installed in all patients. Using this monitor, advanced hemodynamic parameters like stroke volume index (SVI), cardiac index (CI), stroke volume variation (SVV), and systemic vascular resistance index values were recorded at 30-min intervals throughout the surgery. Despite this specific monitoring, the operating anesthetist was blinded to the parameters to follow our fluid protocol.

Fluid Management

Sealed envelopes were opened upon patient entry to the operating room. According to the randomization; restrictive fluid therapy group (Group R) was replaced with 2 mL/kg/h Ringer's lactate along with 2 mcg/kg/h norepinephrine IV infusion during the surgery. In case of a mean arterial pressure (MAP) drop below 65 mmHg, norepinephrine dosage was increased up to 8 mcg/kg/h. If further hypotension was observed, a 250 mL bolus of Ringer's lactate was administered. The liberal fluid therapy group (group L) was replaced with 10 mL/kg/h Ringer's lactate throughout the surgery. Similar to the other group; the hypotension periods were intervened with bolus Ringer's lactate (250 mL) without norepinephrine boluses or infusion. In case of observed hypotension after two consecutive fluid boluses, norepinephrine IV 0.1 mcg/kg bolus was administered to group L. Blood loss exceeding 500 cc was intervened with an equal

amount of colloid solution (voluven balanced®, Fresenius Kabi AG, Stans, Switzerland), and an erythrocyte suspension (ES) was transfused if the blood gas analysis reflected a hemoglobin drop below 8 g/dL (<9 g/dL for patients with ischemic heart disease) in both groups. In case of uncontrolled hypotension, the patients were excluded from the study.

Preoperative and postoperative 1st and 2nd day laboratory parameters, including hemoglobin (g/dL), hematocrit (%), albumin (g/dL), total protein (g/dL), urea (mg/dL), creatinine (mg/dL), and C-reactive protein (mg/dL), were recorded. The postoperative total amount of given crystalloid, blood products, and urine output were also recorded for secondary analyses. As a postoperative complication, acute kidney injury (AKI) occurrence was evaluated in the early postoperative period under KDIGO classification (8). Creatinine levels were also examined on the postoperative 6th month in order to observe chronic kidney disease occurrence. Length of hospital stay (LOS), gastrointestinal (constipation, ileus, anastomotic leak), cardiovascular, neurologic, and infectious complications were also recorded.

Determination of the ANP and Glycocalyx Constituents

Peripheral venous blood samples (10 mL) were taken before the induction of anesthesia and at the end of the surgery and were examined at the department of medical biology of the institute. The blood samples were centrifuged at 3500 RPM for 10 min, and the serum fraction was frozen and stored at 80 °C until required for the assay, which was thawed only once as appropriate. Serum levels of human syndecan-1/CD138, human heparan sulfate, human hyaluronic acid, and human ANP molecules were measured using an enzyme-linked immunosorbent assay (ELISAs kit, Invitrogen).

Statistical Analysis

Based on the assumption of a 30% change in serum ANP concentrations with liberal fluid therapy; and with a desired power of 0.8 and alpha error of 0.05, at least 17 participants were required for each group. Considering a possible drop-out ratio of 10%, 38 patients were planned to be enrolled in the current study. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 21.0. Categorical data were analyzed using descriptive statistics. Homogeneity of the data was assessed with Kolmogorov-Smirnov test, and the t-test or Mann-Whitney U test was used for between-group data comparison according to the normality of the data. Repeated measure analysis of variance (ANOVA) was performed for intragroup recurrent measurements. All categorical variables were compared for the study outcome using Fisher's exact test or the w2 test. A p-value of <0.05 was considered statistically significant.

Results

In each group, 22 patients were enrolled. However, one patient was excluded from group L because of intraoperative aberrant tachyarrhythmia, and four patients were excluded from group R because of missing follow-up data, including blood samples. Therefore, the current study was completed with 39 patients (Figure 1).

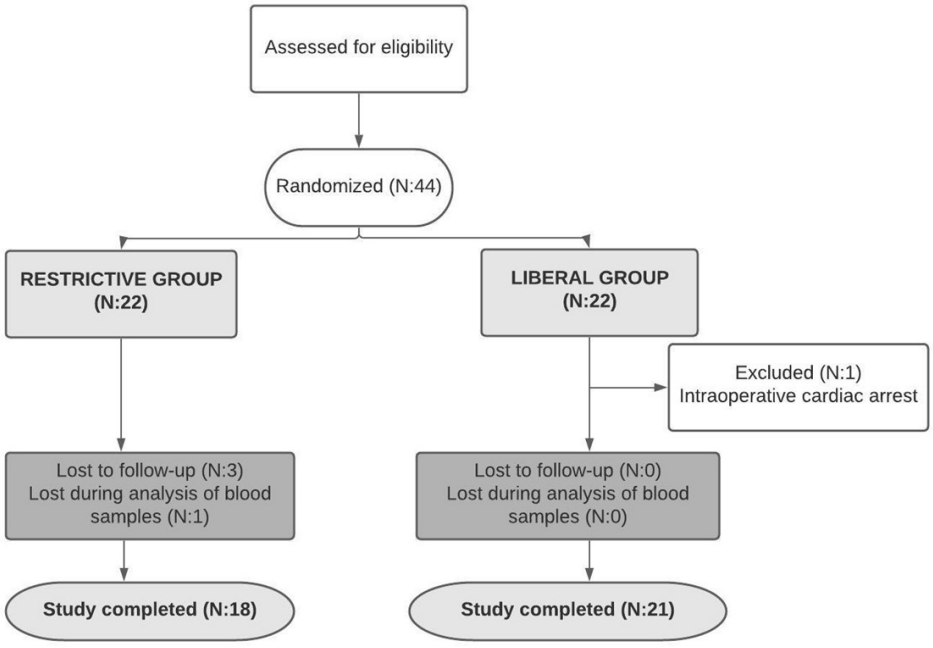

Figure 1. Study design flowchart (CONSORT diagram)

Demographic data were not different between the groups except for body weight. Anesthesia and surgical durations were also similar between the groups (p>0.05). Group R was given less fluid, which was compatible with the study design (1105 mL vs. 3790 mL, p<0.001). However, group L patients required a higher volume of colloid use (485 mL vs. 769 mL, p<0.05). The number of patients who required vasopressor use was significantly higher in group R, as expected; however, occasional vasopressor need was observed in group L, either (p<0.001). Intraoperative total amount of ES and fresh frozen plasma (FFP) consumption was similar between the groups (p>0.05) (Table 1). As summarized in "Table 2", intraoperative hemodynamic variables including cardiac output measurements were statistically similar at all predefined time points of the surgeries (p>0.05).

Postoperative laboratory parameters did not differ between the groups (p>0.05; Table 3). The situation was the same for postoperative 1st and 2nd day crystalloid replacement also (2846 mL vs. 3112 mL, 2482 mL vs. 2700 mL, respectively; p>0.05). Additionally, there was no difference in terms of the amount of ES and FFP replaced on the postoperative 1st and 2nd day (p>0.05). However, the urine output on both postoperative 1st and 2nd days was significantly lower in group R than in group L (1704 mL vs. 2481 mL, 1476 mL vs. 2304 mL, respectively; p<0.05). Six patients in group R and five patients in group L

Table 1. Demographic, clinical characteristics, intraoperative fluid parameters and postoperative complications of the groups

Characteristics	Group R (n=18)	Group L (n=21)	p
Sex (female/male)	3/15	4/17	0.3
Age (years)	62.29±9.52	64.41±10.66	0.5
Body weight (kg)	82.82±16.70	71.82±11.73	**0.02***
Height (cm)	171.35±9.99	167.23±7.09	0.1
BMI (kg/m²)	29.19±20.22	27.18±19.33	0.6
ASA II	13	15	0.8
ASA III	5	6	0.8
Hypertension (n)	10	10	0.4
Diabetes mellitus (n)	2	3	0.8
Ischemic heart disease (n)	2	2	0.8
COPD (n)	2	3	0.8
Active smoker (n)	10	13	0.9
Duration of anesthesia (min)	350.21±85.47	336.57±75.12	0.1
Duration of surgery (min)	322.5±80.14	296.76±69.81	0.1
Crystalloid infused (mL)	1105.88±319.12	3790.90±1078.75	**<0.001****
Colloid infused (mL)	485±209.56	769.23±330.11	**0.01***
Vasopressor usage (n)	18	4	**<0.001****
Length of ICU stay (hours)	19.7±8.4	21.4±6.15	0.8
Length of hospital stay (days)	11.3±8.4	12.1±7.3	0.7
Complications			
Gastrointestinal Anastomotic leak Constipation Ileus	 1 5 1	 2 3 3	0.7
Cardiovascular Ventricular tachycardia	 0	 2	0.4
Neurologic Seizure	 0	 1	0.9
Genitourinary Pyelonephritis Urosepsis Urinary tract infection Surgical wound infection	 0 1 4 3	 1 2 4 3	0.5
Exitus	1	1	1

ASA: American Society of Anesthesiologists, BMI: Body mass index, COPD: Chronic obstructive pulmonary disease, ICU: Intensive care unit, *: p<0.05, **: p<0.001, n: Number of patients

Table 2. Intraoperative hemodynamic parameters			
	Group R (n=18)	Group L (n=21)	p
HR (beats/min)			
Post-induction	77.11±17.84	76.72±12.53	0.9
30th min	73.00±14.72	70.72±12.53	0.6
60th min	68.41±15.35	68.50±13.26	0.9
90th min	69.05±14.23	69.40±13.26	0.9
120th min	76.76±13.65	68.77±11.33	0.4
End of surgery	78.31±6.77	82.82±10.71	0.1
MAP (mm Hg)			
Post-induction	88.17±19.16	92.45±25.90	0.5
30th min	83.41±15.67	84.68±13.87	0.7
60th min	79.23±12.57	85.27±13.65	0.1
90th min	83.58±11.62	84.54±16.08	0.8
120th min	84.00±8.97	81.40±15.84	0.5
End of surgery	71.43±14.94	75.82±11.85	0.3
SVI (mL/m²/beat)			
Post-induction	39.17±15.88	38.31±10.31	0.8
30th min	37.11±16.38	38.90±9.02	0.6
60th min	37.64±11.81	36.90±10.88	0.8
90th min	39.29±13.45	34.22±9.58	0.1
120th min	36.00±13.28	40.36±10.34	0.2
End of surgery	45.25±14.25	38.60±10.37	0.1
CI (L/min/m²)			
Post-induction	2.76±0.90	2.66±1.06	0.7
30th min	2.72±0.85	2.71±0.91	0.9
60th min	2.36±0.52	2.55±0.90	0.4
90th min	2.50±0.53	2.48±0.64	0.9
120th min	2.41±0.47	2.67±0.87	0.2
End of surgery	3.20±1.14	2.88±0.78	0.3
SVV (%)			
Post-induction	13.33±7.40	10.73±3.45	0.1
30th min	12.46±5.82	10.95±3.67	0.3
60th min	13.33±4.89	13.26±4.94	0.9
90th min	13.53±3.44	13.00±5.26	0.7
120th min	15.06±5.40	12.86±4.29	0.1
End of surgery	11.06±5.17	12.43±4.96	0.4
SVRI (dyne. s. cm⁻⁵/m²)			
Post-induction	32179.14±545.22	2222.56±738.27	0.8
30th min	2157.21±546.96	2182.76±674.84	0.9
60th min	2413.57±668.94	2193.30±616.37	0.3
90th min	2260.71±791.12	2392.30±838.92	0.6
120th min	2321.14±659.25	2270.39±659.25	0.8
End of surgery	1810.22±641.76	2049.22±626.60	0.2

HR: Heart rate, MAP: Mean arterial pressure, SVI: Stroke volume index, CO: Cardiac output, CI: Cardiac index, SVV: Stroke volume variation, SVRI: Systemic vascular resistance index

experienced creatinine elevation above 0.3 mg/dL in the early postoperative period, which was compatible with stage 1 AKI. However, none of the patients developed chronic kidney disease during the 6-month postoperative follow-up. Gastrointestinal, cardiovascular, neurologic, and infectious complications did not differ statistically among the groups (p>0.05). Accordingly; three of the group L patients experienced ileus and two experienced anastomotic leak, whereas one patient in group R experienced ileus and one other patient experienced anastomotic leak. It was similar on the wound infection aspect. Only one patient from each group developed a surgical wound infection (Table 1). The median length of ICU stay (19.7±8.4 hours in group R vs. 21.4±6.15 hours in group L, p>0.05) and hospital stay (11.3±8.4 days in group R vs. 12.1±7.3 days in group L, p>0.05) were similar (Table 1).

Our primary outcome; postoperative serum ANP concentrations were higher than preoperative values in group L (84.31±14.05 pg/mL and 55.64±15.38 pg/mL, respectively; p<0.05). The situation was the same for hyaluronan and syndecan-1 levels, also (p<0.05). Interestingly, restrictive therapy group postoperative ANP concentrations was quite close to the preoperative

Table 3. Preoperative, postoperative 1st and 2nd-day laboratory values			
	Group R (n=18)	Group L (n=21)	p
Preoperative			
Hemoglobin (g/dL)	12.24±2.34	12.15±2.19	0.9
Hematocrit (%)	37.36±7.12	36.22±6.32	0.6
Albumin (g/dL)	3.98±0.45	4.15±0.82	0.6
Total protein (g/dL)	6.67±1.01	6.58±1.10	0.6
Urea (mg/dL)	35.26±7.81	49.89±8.21	0.2
Creatinine (mg/dL)	1.02±0.25	1.29±0.45	0.8
C-reactive protein (mg/dL)	6.38±5.35	7.99±6.07	0.2
Postoperative 1st day			
Hemoglobin (g/dL)	10.21±1.69	9.92±2.24	0.9
Hematocrit (%)	30.92±5.18	28.98±4.28	0.1
Albumin (g/dL)	3.23±0.38	2.95±0.39	0.2
Total protein (g/dL)	5.60±0.76	5.01±0.46	0.1
Urea (mg/dL)	37.96±11.10	45.15±23.88	0.9
Creatinine (mg/dL)	1.23±0.35	1.30±0.51	0.8
C-reactive protein (mg/dL)	77.95±38.98	75.17±46.58	0.8
Postoperative 2nd day			
Hemoglobin (g/dL)	9.52±1.57	9.49±1.45	0.7
Hematocrit (%)	28.98±5.14	28.58±4.41	0.2
Albumin (g/dL)	3.08±0.38	3.06±0.50	0.8
Total protein (g/dL)	5.39±0.71	5.34±1.05	0.8
Urea (mg/dL)	46.17±19.36	46.72±25.68	0.4
Creatinine (mg/dL)	1.10±0.32	1.31±0.55	0.9
C-reactive protein (mg/dL)	160.00±62.74	165.91±102.16	0.6

values (55.81±9.98 pg/mL vs. 55.83±10.49 pg/mL; respectively; p>0.05). In line with this; postoperative serum hyaluronan and syndecan-1 concentrations were significantly lower in group R than in group L (14.19 ng/L vs. 19.45 ng/L and 3.99 pg/mL vs. 6.97 pg/mL; p<0.05, respectively). Of note, preoperative and postoperative comparison of heparan sulfate did not change significantly in both groups (p>0.05). Within-group analysis did not show any statistically significant change in ANP, heparan sulfate, hyaluronan, and syndecan-1 concentrations comparing the preoperative and postoperative values for group R (p>0.05) (Table 4).

Discussion

Our results support the relationship between the intraoperative liberal fluid regimen and EGL disintegration, which is attributed to elevated serum ANP concentration. As it was well demonstrated under "experimental" settings before; acute normovolemic hemodilution via limited colloid replacement is superior to excessive volume loading in terms of EGL protection (7). Although the data are quite sparse; clinical studies also exhibited similar outcomes. Belavić et al. (9) investigated three different groups as restrictive (1 mL/kg/h), low liberal (5 mL/kg/h), and high liberal (15 mL/kg/h) for minimally invasive surgeries and concluded that the high liberal crystalloid infusion group was associated with increased serum EGL constituents. Our current clinical study is consistent with the aforementioned findings. Accordingly, higher infusion rates causing hypervolemia are related to EGL damage regardless of the fluid (crystalloid or colloid) and surgery type (minimal invasive or open abdominal). Of note, only heparan sulfate did not increase with liberal therapy, which is compatible with the previous study (9). Heparanase enzyme is secreted from mast cells when activated by inflammation, and ANP receptors do not exist in the mast cell surface (10). Therefore, hypervolemia-induced ANP release may not affect heparan sulfate shedding into the circulation.

Table 4. Summary of preoperative and postoperative ANP, heparan sulphate, hyaluronan and syndecan-1 levels

	Group R (n=18)	Group L (n=21)	p**
ANP (pg/mL)			
Preoperative	55.83±10.49	55.64±15.38	0.6
Postoperative	55.81±9.98	84.31±14.05	**0.003**[a]
p*	0.4	**0.004**	
Heparan sulphate (ng/L)			
Preoperative	47.42±10.72	44.48±15.19	0.9
Postoperative	47.29±13.17	46.45±14.98	0.4
p*	0.4	0.2	
Hyaluronan (ng/L)			
Preoperative	13.93±6.21	13.00±3.56	0.7
Postoperative	14.19±5.19	19.45±5.99	**0.04**[b]
p*	0.09	**0.03**	
Syndecan-1 (pg/mL)			
Preoperative	4.04±1.69	4.76±1.97	0.8
Postoperative	3.99±1.55	6.97±1.87	**0.04**[a]
p*	0.6	**0.04**	

[a]: Student's t-test, [b]: Mann Whitney-U test. p*: ANOVA significance level within group analysis, p**: Significance level for between group analysis, ANP: Atrial natriuretic peptide

As seen in the revised starling equation, basic physiology has been evolving recently. Traditional capillary "reabsorption" is now a denied concept that was believed to protect intravascular fluid content initially. It is firmly underlined that the EGL layer is responsible for adjusting "the filtration" which occasionally preserves intravascular volume in case of hypovolemia or hypotension, and there is no "reabsorption" (3,11,12). Therefore, it is quite understandable why the EGL represents high importance. However, EGL cannot be the sole factor limiting hyperfiltration in cases of hyperhydration, which leads to "interstitial edema". Recent volume kinetics studies have shown that increased infusion rate is related to increased half-life in the peripheral space (13,14). High amounts of fluid retention may cause side effects in specific organ systems, such as pulmonary or urinary impairment (15).

MAP is one of the most important determinants of vascular filtration. Li et al. (16) clearly demonstrated that lower MAP is related to lower filtration, which causes more plasma dilution. Preserving individuals' hemodynamic parameters in a healthy window during surgery is a major concern in everyday anesthesiology practice. The tendency to replace higher amounts of fluid may arise due to the intention of avoiding hypotension. However; our results revealed that fluid restriction did not cause any significant drop in the MAP, SVI, CI, or SVV. Moreover; hyperhydration did not cause hypertension or increased cardiac output. These data are quite similar to Belavić et al.'s (9) study. As an exception, they demonstrated a relatively low MAP after anesthesia induction with restrictive fluid therapy compared with high liberal fluid therapy. Possibly, our restrictive regimen, which is supported with norepinephrine infusion, did not conduct the same situation because hypotension is due to vasodilation and norepinephrine is an alpha-1 adrenergic agonist. Note that Belavić et al. (9) did not exhibit any hypotension period with restrictive therapy, also. To our knowledge; data regarding intraoperative fluid regimen and its relation with advanced cardiac output measurement are quite sparse in the literature.

Clinical investigations that were presented in the early 2000s underline an observed lower postoperative complication rate, which may reach a 35% drop with intraoperative restrictive fluid therapy (17-21). Our current sample size was inadequate to compare postoperative complications; however, several studies

have demonstrated increased AKI incidence with restrictive regimen (22,23). Of note, long-term follow-ups did not exhibit chronic kidney disease in any patient who developed AKI in this study. Both restrictive and liberal fluid regimens have their own conflicts in terms of micro- or macrovascular complications. However, a quick return of bowel function and decrease in the LOS was achieved with enhanced recovery after surgery modalities for radical cystectomy patients in whom liberal fluid therapy is externalized (24,25). For this particular patient group, managing fluid therapy under the guidance of urine output is not possible because it is unmeasurable. Therefore, cardiac output measuring devices are considered valuable. However, we can only claim that advanced hemodynamic parameters may only prevent extreme fluid restriction, which eventually leads to low cardiac output, and as observed in this study; too much fluid replacement is not detectable with these hemodynamic variables occasionally. Therefore, biomarkers would be advantageous for recognizing excessive fluid replacement.

Study Limitations

This study represents a solid scientific basis since it is applied for major abdominopelvic surgery and examines biochemical findings along with advanced hemodynamic variables to evaluate the EGL structure. However, the total number of participants is a limitation for comparing postoperative clinical outcomes.

Conclusion

Compared with the restrictive fluid regimen, the intraoperative liberal fluid regimen causes elevated ANP secretion and EGL shedding in radical cystectomy patients without any significant change in static and dynamic hemodynamic parameters. Therefore, serum ANP concentrations may be used as an indicator of excessive fluid replacement. Further studies should focus on the clinical and laboratory effects of the chosen fluid regimen by considering recent physiological concepts such as the Revised Starling Equation, volume kinetics, and fluid distribution.

Ethics

Ethics Committee Approval: This prospective, single-center, double-blind, randomized trial was approved by the local Clinical Research Ethics Committee of İstanbul University, İstanbul Faculty of Medicine (2018/374) and registered at clinicaltrials.gov (NCT04780490).

Informed Consent: Informed consent was obtained from all participants.

Authorship Contributions

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