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ARAŞTIRMA / RESEARCH

Optimization of perioperative hemodynamics in cytoreductive surgery of ovarian cancer with malignant ascites

Malign asitli over kanserinde sitoredüktif cerrahide perioperatif hemodinamik optimizasyon

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Abstract

Purpose: In this study, we aimed to evaluate the effects of norepinephrine and albumin use in patients with epithelial ovarian cancer with malignant ascite in order to maintain plasma oncotic pressure and intravascular volume, to provide perioperative hemodynamic stabilization and tissue perfusion. In addition, it was aimed to compare in terms of postoperative intensive care admission, hospital stay and complications.
Materials and Methods: A total of 66 patients, 38 with ascites and 28 without ascites, who underwent cytoreductive surgery for ovarian cancer were included in this study. PVI and invasive arterial monitoring of the patients were performed after hemodynamic stabilization (after the start of surgery) (T_0). T_0, 1st hour (T_1) and 2nd hour (T_2) and postoperative (T_{postop}.) Ascites patients were composed of 3 subgroups which the ones received norepinephrine (NE) infusion, norepinephrine + albumin (NEA) infusion or only fluid therapy (FT). From the perioperative hemodynamic and laboratory data of the patients, tissue perfusion was evaluated with lactate, and hemodynamic status was evaluated with pleth variability index (PVI), perfusion index (PI) and mean arterial pressure (MAP).
Results: Demographic and clinical findings did not differ significantly between patients with and without ascites. Lactate level in NEA / NE group in Tpostop, PVI level in T1h, T2h and T_{postop} time frames were determined higher than the FT group. PI was found to be significantly lower

Öz

Amaç: Bu çalışmada malign asitli epitelyal over kanserli hastalarda plazma onkotik basıncı ve intravasküler volümü korumak, perioperatif hemodinamik stabilizasyon ve doku perfüzyonunu sağlamak amacıyla norepinefrin ve albümin kullanımının etkilerini değerlendirmeyi amaçladık. Ayrıca postoperatif yoğun bakıma yatış, hastanede kalış ve komplikasyonlar açısından da karşılaştırılması amaçlandı.
Gereç ve Yöntem: Bu çalışmaya over kanseri nedeniyle sitoredüktif cerrahi uygulanan 38 asitli ve 28 asitsiz toplam 66 hasta dahil edildi. Hastaların hemodinamik stabilizasyon sonrası (ameliyat başladıktan sonra) (T_0) PVI ve invaziv arter monitorizasyonu yapıldı. T_0, 1. saat (T_1) ve 2. saat (T_2) ve postoperatif (Tpostop.) hastaların kan gazı ve hemodinamik verileri kaydedildi. Asit hastaları, norepinefrin (NE) infüzyonu, norepinefrin + albümin (NEA) infüzyonu veya sadece sıvı tedavisi (FT) uygulanan 3 alt gruba ayrıldı. Hastaların perioperatif hemodinamik ve laboratuvar verilerinden doku perfüzyonu laktat ile, hemodinamik durumu plet değişkenlik indeksi (PVI), perfüzyon indeksi (PI) ve ortalama arter basıncı (MAP) ile değerlendirildi.
Bulgular: Demografik ve klinik bulgular asitli ve asitsiz hastalar arasında anlamlı farklılık göstermedi. Tpostop'ta NEA/NE grubunda laktat düzeyi, T1h, T2h ve Tpostop zaman dilimlerinde PVI düzeyi FT grubuna göre daha yüksek saptandı. PI'nin T2 zaman çerçevesinde önemli ölçüde düşük olduğu bulundu. Ameliyat sonrası yoğun bakıma yatış oranı NEA ve NE gruplarında daha yüksekti.

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in the T2 time frame. The postoperative ICU admission rate was higher in the NEA and NE groups. The duration of ICU stay in group NEA was shorter than in group NE. **Conclusions:** We recommend the use of low-dose NE with albumin to provide perioperative hemodynamic optimization, tissue perfusion and plasma oncotic pressure in surgery of ovarian cancer with malignant ascites. Despite high fluid replacement in these patients, the use of norepinephrine and albumin together may have an important role in preventing / reducing major complications in the perioperative period.
Keywords: Epitelial ovarian cancer, fluid-therapy, hemodynamic monitoring, malignant ascites

Grup NEA'da yoğun bakımda kalış süresi grup NE'ye göre daha kısaydı.
Sonuç: Malign asitli over kanseri cerrahisinde perioperatif hemodinamik optimizasyon, doku perfüzyonu ve plazma onkotik basıncı sağlamak için albümin ile düşük doz NE kullanımını öneriyoruz. Bu hastalarda yüksek sıvı replasmanına rağmen norepinefrin ve albüminin birlikte kullanılması perioperatif dönemde majör komplikasyonları önlemede/azaltmada önemli rol oynayabilir.

Anahtar kelimeler: Epitelyal ovaryan kanser, sıvı yönetimi, hemodinamik monitörizasyon, malign asit

INTRODUCTION

Ovarian cancer is among gynecological cancers with high mortality, with 5-year survival rates ranging from 30-50%[1]. Advanced stage ovarian cancer is characterized by intraabdominal ascites accumulation. Besides, major perioperative circulatory complications are common in patients with high amounts of ascites[2]. Therefore, it has a significant effect on anesthesiological treatment and postoperative morbidity.

During the intraoperative period of patients with ovarian cancer, the increased fluid need due to the amount of ascites causes hemodynamic imbalance by creating significant changes in circulating blood flow[3]. In intraoperative period, fluid loss due to surgery, as well as aspirated ascites and bleeding cause significant intravascular volume loss and reactively predispose to hypotension and tachycardia[4,5]. Malignant ascites is assumed to be an important risk factor promoting perioperative hemodynamic deterioration, however detailed data on the hemodynamic consequences of ascites on the systemic circulation in patients undergoing cytoreductive ovarian cancer surgery are still limited. Norepinephrine (NE) plays an important role in stimulating heart and circulatory functions[6]. NE is considered a vasopressor with minimal cardiac depressant effect[7]. However, there is not enough data in the literature regarding the need for albumin and NE infusion in the peroperative period in patients with ovarian cancer with malignant ascites.

In this study, as a primary outcome we aimed to evaluate the effects of NE and/or norepinephrine + albumin (NEA) infusion on hemodynamics and tissue perfusion and oxygenation in patients with ascites in the perioperative period, and to examine the relationship with the outcomes in postoperative period. And as a secondary outcome, we aimed to investigate whether there is a difference between the groups in terms of postoperative intensive care admission, hospital stay and complications.

MATERIALS AND METHODS

Study design and population

This retrospective study was conducted in Health Sciences University Istanbul Bakirkoy Dr. Sadi Konuk Training and Research Hospital Gynecological Oncology Clinic. Between January 2018 and April 2020, a total of 66 patients with ovarian cancer over the age of 18, 38 with ascites and 28 without ascites, were included in the study (Figure 1). Patients' ASA score was classified as 2-3 according to the recommendations of the American Society of Anesthesiologists[8] and laparotomic oncologic surgery. ASA 4 patients, patients with decompensated heart failure (ejection fraction of <30%), and not being able to tolerate a tidal volume of 8 mL/kg in mechanical ventilation (for accuracy of the Pleth Variability Index), with cardiac rhythm disorder, and the ones with liver or kidney failure and laparoscopic surgery were excluded from the study. The patients were divided into ascites (Group A) and those without ascites (Group FA). Group A was divided into 3 groups as those who did not use NE and albumin (Group FT), those who using only NE (Group NE), and those who using NE and albumin (Group NEA).

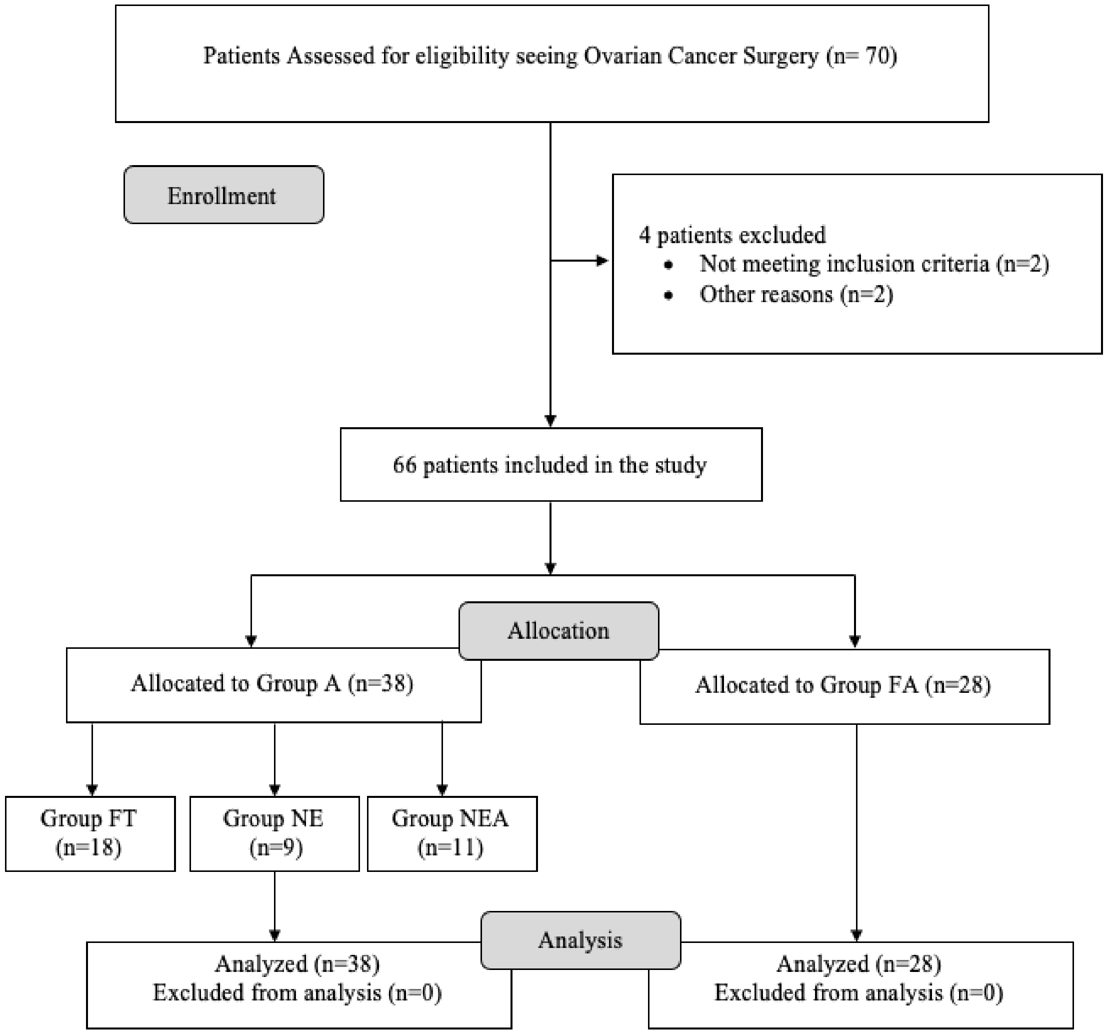

Figure 1. Classification of Ovarian Cancer patients according to intraoperative treatment management (flow chart of the study)

Group A: patients with ascites, Group FA: patients without ascites, Group FT: patients with fluid therapy, Group NE: patients with given norephinephrine, Group NEA: Patients with given norephinephrine and albumin

The study was planned in accordance with the Helsinki Declaration revised in Brazil in 2013. Informed consent forms were obtained from all patients. Ethics committee approval of the study were obtained from the Clinical Research Ethics Committee of Health Sciences University Istanbul Bakirkoy Dr. Sadi Konuk Training and Research Hospital (2020/220).

Anesthesia initial process

The same anesthetic procedure was routinely applied to all patients. Accordingly, clear fluid intake for up to 2 hours and solid feeding up to 6 hours preoperatively were allowed. Standard Electrocardiography (ECG), pulse oximetry, non-invasive blood pressure monitoring, and invasive and noninvasive arterial pressure measurements were made with a Datex S/5 monitor (Datex Ohmeda®, GE Healthcare, Chicago, IL, USA), and non-invasive hemodynamic fluid responsiveness sensor (Masimo Corporation, Radikal 7, USA) and pleth variability index (PVI)-perfusion index (PI) monitoring in the operating room were provided. Vascular access was opened with an 16-18 G catheter for all patient. After sedation with 0.03 mg/kg midazolam, epidural catheter was inserted at the T_{11-12} level for postoperative analgesia. All patients had an arterial line for arterial blood gas monitoring. In induction, 1 µg/kg fentanyl, 2-3 mg/kg propofol followed by 0.6 mg/kg rocuronium were used. The settings of patients' ventilator were adjusted in volume-controlled mode as I/E: 1/2 in tidal volüme and 8 ml/kg in frequency according to the patient's end tidal CO_2 value ($EtCO_2$: 35-45). Sevoflurane, remifentanil infusion and, when necessary, rocuronium were used for maintenance of anesthesia.

Peroperative fluid management

With induction, all groups were started with 6-8 ml/kg bolus crystalloid followed by 2 ml/kg crystalloid infusion. PVI follow-up, urine output, mean arterial pressure (MAP) and arterial blood gas data were evaluated for fluid requirement. The optimum value for PVI was standardized as 13 in light of the literature. Fluid challenge (250 cc) was performed in patients with PVI >13 and MAP< 65 mmHg. If the clinical situation persisted despite fluid challenge repeated twice, a bolus dose of 1-2 µg NE was administered twice at 5-minute intervals. If the hemodynamic instability persisted, NE infusion was started. Fluid infusion was continued in patients with PVI <13 and MAP > 65 mmHg.

In patients with bleeding, if arterial blood gas a target hemoglobin concentration within the target range (7.0–9.0 g/dL) and PVI >13%, they were administered blood products[9]. In patients with ascites, if large amounts of acid liquid (> 1000 ml) were aspirated; fresh frozen plasma (PVI > 13) or 20% human albumin 3 ml / kg was used to maintain and maintain oncotic pressure[9]. In addition, according to the input albumin value and the results of the albumin laboratory sent peroperatively, human albumin treatment was given when necessary.

PVI and invasive arterial monitoring of the patients were performed after hemodynamic stabilization (after the start of surgery) 15 minutes after anesthesia induction (T_0), 1st hour (T_1) and 2nd hour (T_2) and postoperative ($T_{postop.}$) PVI, hemodynamic parameters, arterial blood gas values, perioperative bleeding amount, amount of fluid infusion were recorded. At the end of the operation, patients were evaluated in terms of admission to the intensive care unit (ICU) according to their hemodynamic status. On postoperative 24th hour, we recorded ICU admission (patients who are indicated due to hemodynamic instability, taking inotrope infusion, respiratory distress, administration of massive blood transfusion, comorbidities), fever, length of ICU stay, and length of hospital stay (the lenght of hospital stay was defined as the postoperative follow-up in bed till to discharge). Survival assessment was made by calling the patients who were discharged on the 30th postoperative day.

Statistical analysis

Statistical evaluation was performed using the Statistical Package for Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc., Chicago, IL) program. The normal distribution of the data was evaluated with the Kolmogorov-Smirnov test. Categorical variables were expressed as numbers and percentages. Among the numerical variables, those with normal distribution were shown as mean±standard deviation, and those without normal distribution were shown as the median (min-max). Chi-Square analysis and Fisher's Exact Test were used to compare categorical variables between groups. The independent groups t-test or Mann Whitney U tests were used for the comparison of the quantitative measurements between the two groups, and the ANOVA (post hoc: Bonferroni test) or Kruskal-Wallis tests (post hoc: Dun's test) were used to compare the quantitative measurements between the groups more than two. In determining these tests, normality distribution was taken into account. The changes in laboratory findings between groups before and after the operation were evaluated with the mixed model for repeated measurements. A p value of <0.05 was considered significant in statistical analysis.

RESULTS

The mean age of the study population was 54.4±12.0 years and 62.1% (n:41) were ASA II and 37.9% ASA III (n:25). The demographic, clinical and laboratory findings of the patients are shown in Table 1. In Group A, preoperative ICU indication ratio (28.9% vs 7.1%; p=0.032) and median surgical time (420 vs 275; p<0.001) were found to be higher compared to Group FA, and mean hemoglobin (11.0±1.7 vs 11.7±1.5; p=0.044) levels were lower (Table 1).

Table 1. Preoperative demographic, clinical and laboratory findings

Variables	All population n=66	Ascite		p
		No n=28	Yes n=38	
Age, years	54.4±12.0	52.6±10.1	55.3±12.8	0.366
BMI, kg/m²	28.7±5.1	28.5±4.8	28.8±5.4	0.802
ASA, n(%)				
II	41(62.1)	21(75.0)	20(52.6)	0.077
III	25(37.9)	7(25.0)	18(47.4)	
Preoperative ICU indication, n(%)				
No	53(80.3)	26(92.9)	27(71.1)	0.032*
Yes	13(19.7)	2(7.1)	11(28.9)	
Surgery time, minutes	347(135-585)	275(145-450)	420(135-585)	<0.001*
Ascite volume (mL)		-	4600(1000-13000)	-
Hemoglobin, mg/dL	11.2±1.5	11.7±1.5	11.0±1.7	0.044*
Creatinine, mg/dL	0.6(0.3-1.7)	0.6(0.3-1.4)	0.6(0.3-1.7)	0.974

Numerical variables were shown as mean ± standard deviation or median (min-max). Categorical variables were shown as numbers (%). Abbreviations: BMI, body mass index; ICU, intensive care unit

Table 2. Perioperative clinical findings according to ascite levels

Variables	Grup FA n=28	Grup A			p
		Grup FT n=18	Grup NE n=9	Grup NEA n=11	
Bleeding volume, mL	350(50-2000)	500(200-1000)	**1200(300-1700)**	**800(500-1500)**	<0.001*
Urine volume, mL	110(50-1100)	200(150-750)	**500(180-1000)**	**360(120-850)**	<0.001*
Intravenous fluid replacement					
Crystalloid solution, n (%)	28(100.0)	18(100.0)	9(100.0)	11(100.0)	-
Level, mL	2225(812.5-3500)	2500(2000-5200)	5000(3500-6000)	5000(2500-7000)	<0.001*
Colloid solution, n (%)	10(35.7)	16(88.9)	9(100.0)	11(100.0)	<0.001*
Level, mL	0(0-500)	500(0-1000)	500(500-1000)	500(500-1000)	<0.001*
Total fluid volume, mL	2500(812.5-5300)	3550(2200-6800)	7200(5200-8400)	7400(4500-9700)	<0.001*
Erythrocyte replacement, n (%)					
None	19(67.9)	13(72.2)	-	1(9.1)	<0.001*
1 unit	2(7.1)	2(11.1)	1(11.1)	3(27.3)	
2 units	6(21.4)	3(16.7)	5(55.6)	4(36.4)	
3 units	1(3.6)	-	3(33.3)	3(27.3)	
Fresh frozen plasma, n (%)					
None	19(67.9)	7(38.9)	-	-	<0.001*
1 unit	1(3.6)	-	-	-	
2 unit	7(25.0)	10(55.6)	3(33.3)	2(18.2)	
3 unit	1(3.6)	-	1(11.1)	2(18.2)	
4 unit	-	1(5.6)	4(44.4)	5(45.5)	
5 unit	-	-	1(11.1)	2(18.2)	

Numerical variables were shown as median (min-max), Categorical variables were shown as numbers (%), * p <0.05 shows statistical significance, Bold characters are different from other groups (post hoc test).

Tablo 3. Clinical findings according to peroperative use of NE and NEA in presence of ascite

Variables	Grup FA n=28	Grup A			p
		Grup FT n=18	Grup NE n=9	Grup NEA n=11	
Hemoglobin (mg/dL)					
T0	11.0±1.7	10.4±1.1	10.2±1.0	10.6±0.5	0.109
T1	11.0±1.7	10.0±1.0	10.0±1.5	9.7±1.4	0.033*
T2	11.0±1.6	10.1±1.0	10.4±1.4	9.8±0.9	0.013*
Postoperatif	11.1±1.3	10.2±1.5	10.5±1.3	10.6±1.0	0.047*
p	0.996	0.670	0.050*	0.015*	
Hearth rate (beats/min)					
T0	82.0±17.1	79.4±10.0	82.0±11.1	85.1±15.4	0.591
T1	70.6±10.9	75.8±10.2	77.7±9.6	82.3±10.5	0.018*
T2	70.0±8.9	74.2±10.6	73.7±10.7	82.2±14.5	0.160
Postoperatif	84.0±11.2	86.3±12.0	88.0±8.5	91.5±18.2	0.399
p	<0.001*	<0.001*	0.016*	0.027*	
MAP (mmHg)					
T0	80.3±14.6	83.1±23.1	75.4±4.8	84.8±11.4	0.572
T1	75.9±14.1	83.2±11.4	72.6±5.5	80.5±9.3	0.099
T2	75.6±11.2	77.9±11.5	76.8±14.2	74.5±7.2	0.856
Postoperatif	86.3±13.9	81.8±10.1	76.7±6.2	81.5±8.8	0.147
p	0.001*	0.107	0.681	0.029*	
pH					
T0	7.5±0.1	7.5±0.1	7.5±0.1	7.5±0.1	0.086
T1	7.4±0.1	7.4±0.1	7.4±0.1	7.5±0.1	0.768
T2	7.4±0.1	7.4±0.1	7.4±0.1	7.4±0.1	0.373
Postoperatif	7.4±0.1	7.4±0.1	7.4±0.1	7.4±0.1	0.949
p	<0.001*	0.001*	0.001*	0.008*	
HCO3 (mmol/L)					
T0	24.0±2.0	24.8±1.5	24.5±2.9	23.5±2.1	0.085
T1	23.2±2.6	23.6±2.2	24.3±2.7	23.7±2.3	0.438
T2	23.2±2.4	24.2±2.1	24.0±2.2	23.3±2.3	0.374
Postoperatif	23.2±2.6	23.6±1.7	23.8±3.4	22.3±1.4	0.475
p	0.046*	0.021*	0.153	0.108	
Lactate (mEq/L)					
T0	0.9(0.1-2.8)	0.8(0.6-1.8)	0.9(0.7-1.4)	0.9(0.7-1.8)	0.439
T1	1.1(0.5-2.2)	0.8(0.6-2.0)	1.4(0.8-2.4)	0.9(0.7-2.0)	0.086
T2	1.2(0.4-6.3)	1.1(0.6-2.6)	2.0(0.6-2.8)	0.8(0.6-2.0)	0.047*
Postoperatif	1.4(0.9-6.5)	1.8(0.4-3.0)	3.8(0.7-6.4)	2(0.6-3.1)	0.009*
p	0.451	<0.001*	<0.001*	0.050*	
Base excess (mEq/L)					
T0	0.1 [(-8.9)-(4.4)]	0.6 [(-1.1)-(3.9)]	- 0.1 [(-2.6)-(6.9)]	- 0.8 [(-4.8)-(3.8)]	0.025*
T1	- 0.3 [(-14)-(2.9)]	- 0.9 [(-4)-(4.3)]	- 0.5 [(-2.5)-(6.9)]	0.8 [(-8.3)-(1.4)]	0.654
T2	-0.4[(-11)-(3.4)]	-0.9[(-4)-(3.6)]	-0.4[(-3.8)-(3.3)]	-1.0[(-4.0)-(3.8)]	0.542
Postoperatif	-0.5[(-13)-(3.2)]	-0.8[(-3)-(2)]	-0.6[(-5.0)-(7.5)]	-2.8[(-5)-(2)]	0.043*
p	0.019*	0.010*	0.145	0.049*	
PVI					
T0	12.0±3.5	11.1±2.5	11.0±2.1	12.5±3.3	0.661
T1	13.0±4.5	15.0±3.6	20.1±3.3	19.7±2.2	<0.001*
T2	12.6±3.5	13.3±2.0	20.0±2.6	19.8±3.4	<0.001*
Postoperatif	13.2±3.6	12.9±2.9	13.3±2.2	16.4±3.2	0.050*
pt	0.588	<0.001*	0.004*	<0.001*	
PI					
T0	3.6±1.1	3.4±1.0	3.2±0.7	3.4±1.0	0.101
T1	3.1±0.9	2.2±0.7	2.2±0.7	2.0±0.6	0.020*

T2	2.7±0.8	2.0±0.8	1.4±0.4	1.4±0.4	0.023*
Postoperatif	1.8±0.5	1.5±0.5	1.4±0.4	1.0±0.3	0.045*
pt	<0.001*	<0.001*	<0.001*	<0.001*	

Numerical variables were shown as mean ± standard deviation or median (min-max), * p <0.05 shows statistical significance, Bold characters are different from other groups (post hoc test).

Median bleeding level (p <0.001), and urine output (p <0.001) were found to be higher in Group NE compared to other groups. These findings were also higher in Group NEA compared to groups FT and FA. The total fluid volume level was similar in Group NE and Group NEA and was higher than in the other groups (p <0.001) (Table 2). There was no significant difference in laboratory findings between the main groups (Group A and Group FA) at the time of peroperative T0. The mean PVI values in T1 and T2 were statistically higher in the group NE and group NEA compared to other groups (p<0.001), and the PI values in T_{postop} were found to be significantly lower than the T0 time in all groups (p<0.001) (Table 3)..

Table 4. Perioperative clinical findings according to ascite levels

Variables	**Ascite**		**p**
	<5000 mL	**≥5000 mL**	
	n=20	**n=18**	
Perioperative findings			
Bleeding	650(200-1700)	1000(200-1700)	0.035*
Urine	275(150-750)	365(120-1000)	0.331
NE	3(15.0)	13(72.2)	0.001*
Intravenous fluid replacement			
Crystalloid solution, n (%)	20(100.0)	18(100.0)	-
Level, mL	2600(2000-4500)	5000(2000-7000)	<0.001*
Colloid solution, n (%)	18(90.0)	18(100)	0.515
Level, mL	500(0-1000)	500(500-1000)	0.055*
Total fluid volume (mL)	3950(2200-6000)	7450(3200-9700)	<0.001*
Albumin	2(10.0)	9(50.0)	0.011*
Erythrocyte replacement, n (%)			
None	13(65.0)	1(5.6)	<0.001*
1 unit	2(10.0)	4(22.2)	
2 units	5(25.0)	7(38.9)	
3 units	-	6(33.3)	
Fresh frozen plasma, n (%)			
0	7(35.0)	-	<0.001*
1	-	-	
2	12(60.0)	3(16.7)	
3	-	3(16.7)	
4	1(5.0)	9(50.0)	
5	-	3(16.7)	
Postoperative findings			
Hospitalization in ICU, n(%)	6(30.0)	16(88.9)	<0.001*
median duration, days	0(0-5)	1(0-5)	
Stay duratıon ın hospıtal, days	10(6-30)	10(1-28)	
Fever, n(%)	5(25.0)	3(16.7)	0.818
Complication, n(%)	6(30.0)	5(27.8)	0.999
Eviserasyon	2(10.0)	3(16.7)	0.457
Anastomotic leak	1(5.0)	1(5.6)	
Wound infection	3(15.0)	-	
Pulmonary edema, pleural effusion	-	1(5.6)	

Numerical variables were shown as mean ± standard deviation or median (min-max), Categorical variables were shown as numbers (%)., * p <0.05 shows statistical significance, Abbreviations: NE, norepinephrine; FFP, fresh frozen plasma; ICU, intensive care unit

The amount of bleeding, NE requirement, and perioperative albumin requirement were found to be higher in those with an acid content of 5000 ml and above compared to those below 5000 ml. In addition, the rate of ICU hospitalization in the postoperative period was found to be higher in these patients (Table 4)

Postoperative ICU hospitalization ratio (57.9% vs 7.1%; p <0.001), median length of stay in ICU (1 vs 0; p <0.001), and median length of stay in hospital (10 vs 8; p = 0.019) were higher in group A compared to group FA. The distribution of complications between the two groups did not differ significantly. No exitus was found in the postoperative period. In addition, the ICU hospitalization rate (p <0.001, duration of ICU stay (p <0.001), and duration of hospıtal stay groups (p =0.047) were found to be higher in Group NE/NEA compared to other (Table 5).

Table 5. Events and mortality according to NE and NEA use

Variables	Grup FA n=28	Grup A			p
		Grup FT n=18	Grup NE n=9	Grup NEA n=11	
Hospitalization in ICU, n(%)	2(7.1)	4(22.2)	9(100.0)	9(81.8)	<0.001*
Duration of ICU stay, days	0(0-1)	0(0-5)	**2(1-5)**	**1(0-4)**	<0.001*
Duration of hospıtal stay, days	8(3-30)	8(6-30)	**11(6-28)**	**10(1-27)**	0.047*
Fever, n(%)	3(10.7)	4(22.2)	-	4(36.4)	0.113
Complication, n(%)	5(17.9)	5(27.8)	3(33.3)	3(27.3)	0.721
Eviserasyon	2(7.1)	2(11.1)	1(11.1)	2(18.2)	0.757
Anastomotic leak	1(3.6)	1(5.6)	1(11.1)	-	
Wound infection	2(7.1)	2(11.1)	1(11.1)	-	
Pulmonary edema, pleural effusion	-	-	-	1(9.1)	

Numerical variables that do not show normal distribution are shown as median (min-max). Categorical variables were shown as numbers (%). * p <0.05 shows statistical significance. Bold characters are different from other groups (post hoc test).
Abbreviations: ICU, intensive care unit

DISCUSSION

Our study evaluated the important relationships of targeted fluid and vasopressor therapy with hemodynamic outcomes in the perioperative period according to the presence and level of ascites in patients with Epithelial Ovarian Cancer. Firstly, it was determined that Group A needed more fluid replacement, had low hemoglobin and high heart rate levels in the peroperative period. Hemodynamic changes were monitored with PI and PVI support in all patients. Fluid therapy, NE and/or NEA infusion were applied to the patients according to the response in these parameters. Our study is the first study evaluating intraoperative NE and NE + albumin infusion efficiency in patients with ovarian cancer with malignant ascites.

The presence of ascites in the ovarian cancer affects the respiratory and circulatory functions and weakens the tolerance to surgery and anesthesia[10]. Exudative loss in patients with ascites is due to increased vascular permeability and neovascularization of small peritoneal blood vessels[11]. There are various factors in malignant ascites that are secreted by tumor cells, increase vascular permeability and induce angiogenesis. An early step leading to angiogenesis is partial proteolysis of the vascular basal lamina, resulting in hyperpermeability[12]. This condition causes a significant fluid shift from the intravascular space to the peritoneal cavity and is considered the main mechanism of ongoing fluid loss during surgery[3]. These findings may explain the mechanism of increased fluid demands in the perioperative period in the ovarian cancer with malignant ascites cohort in accordance with our study.

In ovarian cancer patients with ascites, a rapid decrease in intra-abdominal pressure is observed following surgery, and this increases fluid shift from the intravascular space to the peritoneal cavity due to the increase in the hydrostatic pressure gradient. Low albumin concentrations in patients with high amounts of ascitic fluid affect circulating blood flow, contributing to decreased intravascular volume[13]. Albumin plays a key role in maintaining colloid osmotic pressure. In the perioperative period, albumin infusion can be used for hemodynamic support in patients with excessive crystalloid requirement, except for its role in regulating colloid osmotic pressure. Thus, it plays an important role in preventing perioperative complications[14]. In our study, although it was observed that higher crystalloid and colloid solutions were given in Group A, no difference was found in the perioperative laboratory findings (pH, HCO_3, BE) in the groups that were given albumin infusion and not. However, a lower dose of NE infusion was required in Group NEA. Perioperative PVI value and postoperative lactate level were found to be lower in Group NEA compared to Group NE. This may indicate that the administration of albumin to the patient leads to improvement in the maintenance of oncotic pressure and tissue perfusion. Although there was no difference between Group NE in terms of postoperative ICU hospitalization, it was observed that the duration of hospitalization in the ICU was shorter in Group NEA. These results obtained in group NEA are also compatible with other publications supporting that fresh frozen plasma transfusion can improve hemodynamic stability in patients with high ascites levels[3,15]. In the light of these findings, we can say that albumin infusion may play an important role in preventing perioperative complications in ovarian cancer patients with high volumes of ascites.

In response to increased fluid demands, hemodynamic imbalance may be observed in ovarian cancer patients with ascites. The use of NE can normalize stroke volume variation and therefore can be administered before fluid challenge[16,17]. In our study, although laboratory findings (Hb, creatine, Ph, WBC, CRP) were similar in groups with and without ascites during the perioperative basal period, high HR levels were observed. Low HR is associated with microvascular blood flow and blood flow heterogeneity[18]. Therefore, high HR in Group A may cause changes in circulating blood flow[3]. In our study; while more the amount of ascitic fluid and bleeding and more affected hemodynamics, since surgery is invasive for more advanced cancer, were expected in the subgroups given NEA and NE in patients with ascites; no difference was found between the other groups. This suggests that NE has an important role in preventing hypotension in cases of hypovolemia and hypoperfusion that develop despite fluid replacement in patients. However, low PI and high PVI hemodynamic measures play a key role in the administration of NE infusion[19]. In our study, while PI and PVI levels were similar in all groups at the beginning of the operation, lower PI and higher PVI levels were observed in Group A in later time intervals. This difference is striking, especially for those with an ascitic fluid amount>5000ml. While the increase in the PVI value indicates the fluid deficit, the accompanying decrease in the PI value indicates that there is a problem in tissue oxygenation and organ perfusion[19]. This situation was mostly supported by NE / NEA infusion in Group A. In the perioperative period, NEA infusion also contributes significantly to oxygen delivery. In insufficient oxygen supply, lactate levels are increased[20]. In our study, lactate levels did not differ in the intraoperative T0-1-2 time periods in Group NEA compared to other groups, but postoperative lactate levels were found to be high.

Ovarian cancer patients with ascites carry a significant risk of morbidity and mortality. Therefore, intraoperative fluid therapy is important for both surveillance and prevention of postoperative complications[21]. Amir et al. reported that increased intraoperative blood loss and preoperative ascitic fluid amounts increased the duration of postoperative ICU stay and that the operation times were similar in patients admitted to the service or ICU[22]. In independent clinical studies conducted by Puls et al.[23] and Kosary et al.[24], they found that patients without ascites had a higher 5-year survival rate than patients with ascites. In our study, a higher ICU admission rate and length of stay were observed in Group A. It was determined that this high rate was caused by the patients given NE / NEA infusion. The higher ascitic fluid level may be an important criterion for this group to be more critical patients. In addition to the detection of higher bleeding amount in these patients; requirement for fluid replacement, erythrocyte replacement and FFP are the other findings supporting our hypothesis. Although the complication rates in Group A were observed higher than Group FA, no statistical difference was found between the two groups. There was no mortality in any of the patients included in the study. In the light of these findings, we think that the effectiveness of NE and albumin therapy plays an important role in ovarian cancer patients with high ascites level.

Important limitations of our research; that it has a single-center planning and low sampling. Another limitation is the evaluation of 30-day survival results.

In conclusion, we recommend the use of low-dose NE with albumin to provide perioperative hemodynamic optimization, tissue perfusion and plasma oncotic pressure in ovarian Ca surgery with malignant ascites. In these patients, despite high fluid replacement, the use of Norepinephrine and Albumin together may have an important role in preventing/reducing major complications in the perioperative period. In order to investigate the potential effects of the results on the clinical outcome, it should be supported by prospective studies with larger samples.

Yazar Katkıları: Çalışma konsepti/Tasarımı: GÖY,GS Veri toplama: DA; Veri analizi ve yorumlama: GÖY, GS; Yazı taslağı: GÖY, GS; İçeriğin eleştirel incelenmesi: GÖY, GS,GOH; Son onay ve sorumluluk: GÖY, GS, DA, SK, GOH; Teknik ve malzeme desteği: -; Süpervizyon: GÖY, GS; Fon sağlama (mevcut ise): yok.
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