



# Evaluating intraoperative norepinephrine versus fresh frozen plasma in patients undergoing cytoreductive surgery and HIPEC to reduce renal insult

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## ABSTRACT

**Objective:** This study aims to compare the efficacy of intraoperative norepinephrine infusion versus plasma in reducing renal insult during cytoreductive surgeries.

**Methods:** Sixty patients (ASA I–III) of both genders were included in the study. Plasma group: received early fresh frozen plasma and RBCs in ratio exceeded 1:1, and norepinephrine group: received continuous low-dose norepinephrine (0.05–0.1 mic/kg/min).

**Results:** Both groups were comparable for their clinical characteristics and distribution of demographic data. Plasma group had significant elevation of their intraoperative heart rate with significant reduction in their mean arterial blood pressure values compared to norepinephrine group ( $30.3 \pm 4.1$  versus  $17.9 \pm 4.5$  bpm and  $-21.6 \pm 2.2$  versus  $-16.1 \pm 2.3$  mmHg, respectively,  $p < 0.001$ ) with preserved urine output ( $748.3 \pm 92.4$  for norepinephrine group versus  $693.3 \pm 117.2$  ml for plasma group,  $p = 0.048$ ) and better renal outcome ( $0.2 \pm 0.1$  mg/dl increase in serum creatinine level for norepinephrine group versus  $0.3 \pm 0.1$  mg/dl for plasma group,  $p < 0.001$ ). Additionally, patients in the norepinephrine group required less intraoperative blood and fresh frozen plasma transfusion ( $3.1 \pm 1.8$  units) compared to the plasma group ( $4.3 \pm 1.3$  units),  $p < 0.001$ .

**Conclusion:** Norepinephrine infusion can play a promising role in maintaining hemodynamic stability with adequate tissue perfusion and better renal outcome in patients undergoing CRS/HIPEC procedures.

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## KEYWORDS

CRS; HIPEC; plasma; norepinephrine; renal injury

## 1. Introduction

Cytoreductive surgery (CRS) and heated intraperitoneal chemotherapy (HIPEC) evolved as a standard approach for management of peritoneal carcinomatosis [1]. The procedure was first described by Sugarbaker in the mid-90s as a possible treatment option for patients with peritoneal malignant implants. CRS/HIPEC include surgical excision of macroscopic tumor tissues, affected solid organs and peritonectomy, followed by application of intraperitoneal chemotherapy to eradicate residual microscopic tumor cells [2–4]. The advanced nature of the surgical procedure leads to major metabolic and hemodynamic changes during the perioperative period [5]. CRS/HIPEC is accompanied by major blood loss with subsequent transfusion of excessive amounts of blood and blood products [6]. Chemotherapy applied to the peritoneal cavity is heated to  $42^{\circ}\text{C}$ – $43^{\circ}\text{C}$ . Thus, the procedure carries the risk of major fluid shift and temperature changes, which can lead to organ failure in susceptible patient population [7]. Acute kidney injury (AKI) is one of the major postoperative complications following CRS/HIPEC procedure [8]. Several

factors can contribute to the development of AKI. These include low perfusion secondary to hypotension, major fluid shift as well as the nephrotoxic effect of used chemotherapeutic agents [9]. Early plasma transfusion is advocated in CRS/HIPEC for restoration and maintenance of blood pressure. Plasma has been tested to improve surgical outcome and the need for blood substitute in CRS/HIPEC procedures [6]. Hyperthermia induced during the HIPEC phase results in circulatory vasodilatation with consequent decrease in mean arterial blood pressure and renal perfusion, thus precipitating increased incidence for development of AKI. Norepinephrine is a vasopressor agent with predominant  $\alpha$  activity; hence, it causes adequate vasoconstriction of vessels with subtle myocardial affection [10]. It plays an important role in restoring kidney perfusion during vasodilatation states [11]. The aim of the current study is to compare the efficacy of infusing low dose norepinephrine versus fresh frozen plasma in maintaining intraoperative hemodynamic stability and protection against development of AKI in patients undergoing CRS/HIPEC procedures.

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## 2. Patients and methods

### 2.1. Ethical considerations

After approval of the institutional review board of the National Cancer Institute – Cairo University IRB (201,920,025.2P), this parallel double-blinded (patient and data assessor) randomized controlled study was done in the period from October 2020 to May 2022. A written informed consent was taken from all patients enrolled in the study. The study followed Declaration of Helsinki 1975 and was prospectively registered at clinicaltrials.gov (NCT 04683614).

### 2.2. Inclusion and exclusion criteria

Adult patients of both genders with World Health Performance Status  $\leq 2$ , aged from 18 to 65 years old, ASA I, II and III scheduled for CRS/HIPEC operations were included consecutively. Exclusion criteria included patient's refusal, impaired renal or liver functions and patients with cardiovascular or cerebrovascular disease.

### 2.3. Patient enrollment

Patients meeting eligibility criteria were consecutively recruited throughout the study period from National Cancer Institute preoperative anesthesia assessment clinic by the anesthesia resident. Randomization was generated using a computer system randomization. After obtaining a written informed consent, patients were allocated into one of two studied groups by anesthesia resident using closed envelope technique to receive either fresh frozen plasma or low dose norepinephrine 0.05–0.1  $\mu\text{g}/\text{kg}/\text{min}$ .

### 2.4. Anesthetic consideration and intervention

In the holding area, patients were pre-medicated with 2 mg intravenous (IV) midazolam after fixation of 20 G cannula. Before induction of anesthesia, pulse oximetry, electrocardiogram (ECG) and non-invasive automated blood pressure monitors were connected to the patient. Induction of anesthesia was done by propofol 2 mg/kg, fentanyl 2  $\mu\text{g}/\text{kg}$  and rocuronium 0.5 mg/kg followed by endotracheal intubation and controlled mechanical ventilation with 50% Fio<sub>2</sub>. Then anesthesia was maintained using positive pressure ventilation, tidal volume 6–8 ml/kg with end tidal sevoflurane 1.5–2.5% and rocuronium. Starting from induction of anesthesia, heart rate (HR), peripheral oxygen saturation (SpO<sub>2</sub>) and invasive blood pressure monitoring using General Electric Datex- Ohmeda 3030, Carestation 620 B40 monitor (Madison, USA), core body temperature, end tidal CO<sub>2</sub> and urine output were continuously monitored. Ultrasound guided central venous line insertion was done after induction of anesthesia. First generation

cephalosporin antibiotic was given 30 minutes prior to skin incision; a booster dose was given after 4 hours. Core body temperature was continuously monitored using nasopharyngeal probe, where during the hyperthermic chemotherapy phase the infused fluids flow was managed to keep the increase in temperature less than 0.5°C every minute while hypothermia was managed through forced warm air and heated matters.

Perioperative analgesic protocol was carried through intravenous perioperative analgesia by means of intraoperative morphine sulphate 0.1 mg/kg and postoperative patient-controlled analgesia (PCA) with morphine sulphate in a regimen of 1 mg/bolus and 15 minutes lockout interval and a maximum dose of 30 mg/24 hours.

In both groups, crystalloids were the main fluid used for replacement of deficit, maintenance and urine output. Initially, blood loss was replaced with crystalloids in 3 to 1 ratio in hemodynamically stable patients. In both groups, when blood pressure values were recorded to be 20% below the baseline despite of adequate crystalloid replacement, then plasma group received fresh frozen plasma and packed RBCs in ratio exceeding 1:1 and norepinephrine group received norepinephrine infusion 0.05–0.1  $\mu\text{g}/\text{kg}/\text{min}$ .

In both groups, blood transfusion was indicated in case of tachycardia > 100 beats/min, decreased MAP < 65 mmHg, decreased urine output < 0.5 ml/kg/hr and/ or hemoglobin level  $\leq 7$  g.

For patients who were allocated to the plasma group, in case of reduction of MAP 20% below the baseline not responding to crystalloid infusion and not associated with hemoglobin drop, FFP infusion was started with 1 or 2 units according to each patient hemodynamic response.

For patients who were allocated to the norepinephrine group, norepinephrine infusion was prepared in 160  $\mu\text{g}/\text{ml}$  by adding 8 mg norepinephrine to 0.9% saline and delivered through a 50 ml syringe pump. Norepinephrine was initially started through a bolus of 10  $\mu\text{g}$  then the infusion was continued in a dose of 0.05  $\mu\text{g}/\text{kg}/\text{min}$  and escalated as needed according to each patient hemodynamic response to a dose of 0.1  $\mu\text{g}/\text{kg}/\text{min}$ . The infusion was stopped in case of observed elevation of MAP  $\geq 20\%$  above the preoperative baseline then resumed when MAP reduced below 65 mmHg.

In both groups in case of persistent hypotension with reduction of MAP  $\geq 20\%$  and/or MAP  $\leq 65$  mmHg, vasopressors were added and escalated according to the local institutional protocol and adjusted to each patient hemodynamic response.

### 2.5. Surgical technique

Surgical technique of our treatment consisted of tumor resection and removal of the involved organs and peritoneum. The surgical procedure started with dissection

of the parietal peritoneum from the abdominal wall, during which time the peritoneum remained closed. Then the peritoneum was then opened so that full access to the peritoneal cavity was possible. Peritoneal Carcinomatosis Index (PCI) was used to score the extent of peritoneal involvement at the time of surgery as reported in the 13-region and lesion size system [12].

Then CRS was done according to the disease extension: (1) greater omentectomy, right parietal peritonectomy, right colon resection; (2) pelvic peritonectomy with sigmoid colon resection hysterectomy; (3) antrectomy, cholecystectomy, lesser omentectomy, and dissection of the duodenal-hepatic ligament; (4) right-upper-quadrant peritonectomy and Glissonian capsule resection; (5) left-upper-quadrant peritonectomy-splenectomy and left parietal peritonectomy; and (6) other intestinal resection and/or abdominal mass resection.

Following the surgical procedures, all sites and volumes of residual disease were recorded using the Completeness of Cytoreduction (CCR) score as CC0 for no residual disease, CC1 for microscopic residual disease ( $<0.25$  cm), CC2 for macroscopic residual disease ( $0.25$ – $2.5$  cm) and CC3 for gross residual disease ( $>2.5$  cm) [2]. Then the abdomen was explored for hemostasis to prevent blood loss during HIPEC or after abdominal closure.

In gynecological malignancies, HIPEC treatment consisted of carboplatin  $800$  mg/m<sup>2</sup> diluted in 3 L of normal saline administered via IP perfusion for approximately 90 min in the hyperthermic phase at approximately  $41$ – $43^{\circ}\text{C}$  using closed technique [13].

In colorectal cancer patients, mitomycin ( $35$  mg/m<sup>2</sup>) or oxaliplatin ( $360$  mg/m<sup>2</sup>) was administered [14].

## 2.6. Outcome measures

Our primary outcome measure was renal insult, which was defined as an increase  $\geq 0.3$  mg/dl [15] in creatinine level after 24 hours above the preoperative baseline. Secondary outcome measures included intraoperative hemodynamics, urine output, total intraoperative fluid volume and total volume of blood and blood products.

## 2.7. Sample size calculation and statistical methods

Sample size was calculated on OpenEpi program version 3 and according to previous research done by Angeles and colleagues [16] who stated in their study that from 66 patients included, the incidence of post-operative acute kidney injury was 48%, and adjusting the confidence interval to 95% and the power of the test to 80%, the minimum sample size needed for this study was found in 57 patients. Six patients were added to compensate for any possible attrition.

The collected data were coded, tabulated and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 28.0, IBM Corp., Chicago, USA, 2021. Quantitative data tested for normality using Shapiro-Wilk test, then if normally distributed described as mean  $\pm$  SD (standard deviation), then compared using independent t-test (unpaired comparisons) and paired t-test paired comparisons. Qualitative data are described as number and percentage and compared using Chi-square test and Fisher's Exact test for variables with small, expected numbers. The level of significance taken at P value  $< 0.050$  was significant, otherwise was non-significant.

## 3. Results

Eighty-six patients were initially assessed for eligibility and 24 patients were excluded from the study. Sixty-three patients were randomized in norepinephrine group (32 patients) and in plasma group (31 patients), after exclusion of patients with change in their surgical plan; finally, 60 patients were included in the study (Figure 1).

Both groups were comparable regarding their demographic data, clinical characteristics and duration of surgery (Table 1).

Intraoperative heart rate values showed a statistically significant elevation for plasma group compared to norepinephrine group ( $30.3 \pm 4.1$  versus  $17.9 \pm 4.5$  bpm, respectively) ( $p < 0.001$ ). Meanwhile, there was a statistically significant reduction in systolic ( $-16.2 \pm 2.0$  versus  $-21.8 \pm 2.1$  mmHg), diastolic ( $-16.0 \pm 2.7$  versus  $-21.5 \pm 2.2$  mmHg) and mean blood pressure ( $-16.1 \pm 2.3$  versus  $-21.6 \pm 2.2$  mmHg) values for plasma group compared to norepinephrine group,  $p < 0.001$  (Fig 2–5).

Higher dose norepinephrine infusion above  $0.1$   $\mu\text{g}/\text{kg}/\text{min}$  was needed in 7 (23.3%) patients of the plasma group versus 4 (13.3%) patients in the norepinephrine group after experiencing persistent hypotension with  $\text{MAP} < 65$  mmHg.

Although the volume of infused intravenous fluids and colloids were significantly higher in norepinephrine group compared to plasma group ( $9.2 \pm 1.0$  versus  $7.4 \pm 0.8$  L) and ( $1.4 \pm 0.2$  versus  $0.9 \pm 0.2$  L), respectively,  $p < 0.001$ , on the other hand, the number of transfused FFP and packed RBCs units were found to be significantly lower in norepinephrine group compared to plasma group ( $3.1 \pm 1.8$  and  $3.2 \pm 1.9$  U versus  $4.4 \pm 1.3$  and  $5.2 \pm 1.4$  U), respectively ( $p < 0.001$ ). Number and percent of patients who needed massive blood transfusion (defined as transfusion of  $\geq 5$  units of PRBCs and FFP) were comparable in both groups where 6 (20%) patients in norepinephrine group versus 9 (30%) patients in plasma group needed massive blood transfusion. Urine output values were significantly higher for norepinephrine group compared to plasma group ( $748.3 \pm 92.4$

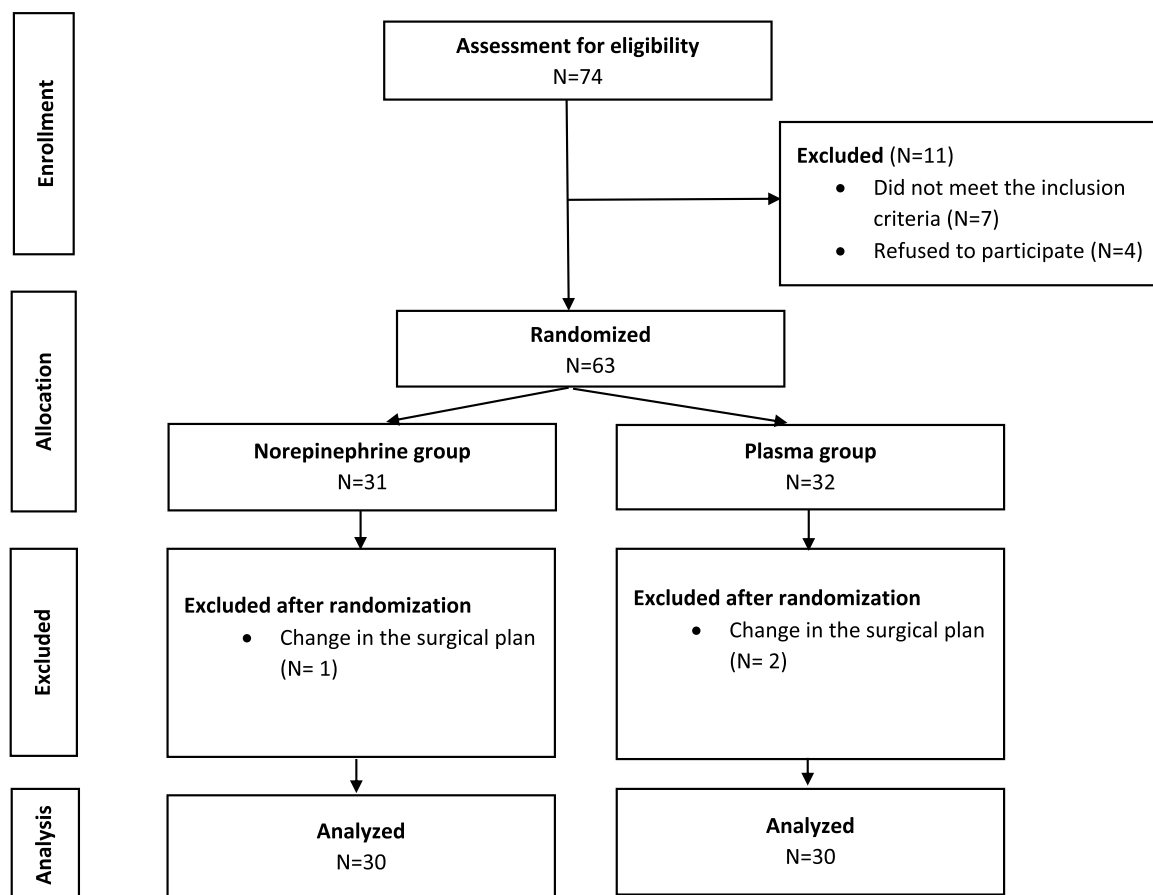


Figure 1. Consort flow chart.

Table 1. Comparison according to demographic data, clinical characteristics and duration of surgery.

Variables	Norepinephrine (N = 30)	Plasma (N = 30)	p-value
Age (years), Mean± SD	43.3 ± 10.2	42.1 ± 10.6	^0.648
BMI (kg/m <sup>2</sup> ), Mean± SD	28.2 ± 4.0	27.7 ± 3.7	^0.655
Sex (n, %)			
Male	16 (53.3%)	18 (60.0%)	#0.602
Female	14 (46.7%)	12 (40.0%)	
Hypertension (n, %)	12 (40.0%)	14 (46.7%)	#0.602
Diabetes mellitus (n, %)	8 (26.7%)	10 (33.3%)	#0.573
ASA grade (n, %)			
I (no comorbid)	14 (46.7%)	12 (40.0%)	#0.503
II	6 (20.0%)	10 (33.3%)	
III	10 (33.3%)	8 (26.7%)	
Operation duration (hours) Mean± SD	8.3 ± 0.8	8.4 ± 0.9	^0.579

BMI: body mass index. ^Independent t-test. #Chi square test. \$Fisher's exact test

versus 693.3 ± 117.2 ml), respectively (p = 0.048). Only 14 patients in norepinephrine group needed diuretics compared to 25 patients in plasma group, (p = 0.003), and the total amount of diuretics used showed a statistically significant lower values for norepinephrine group compared to plasma group, (24.3 ± 5.8 versus 37.2 ± 7.9 mg), respectively (p < 0.001) (Table 2).

Both groups were comparable regarding baseline serum creatinine; however, although serum creatinine at hour-24 increased significantly in both groups compared to baseline values (p = 0.033), the increase in serum

creatinine level was significantly higher for plasma group when compared to norepinephrine group (0.3 ± 0.1 versus 0.2 ± 0.1 mg/dl), respectively, p < 0.001 (Table 3).

#### 4. Discussion

The current study results revealed higher incidence of acute kidney injury represented as elevation in serum creatinine level after 24 hours postoperatively in patients who received fresh frozen plasma (0.3 ± 0.1 mg/dl) when compared to those who received norepinephrine infusion (0.2 ± 0.1 mg/dl) during CRS/HIPEC surgeries. Patients who received continuous infusion of low dose norepinephrine were more hemodynamically stable, with maintained urine output (748.3 ± 92.4 for norepinephrine group versus 693.3 ± 117.2 ml for plasma group) and better renal outcome.

Several studies investigated the increased incidence of AKI associated with HIPEC [8,9,17]. Maintaining adequate tissue perfusion and renal function is the cornerstone of perioperative anesthetic management for CRS/HIPEC surgeries. Multiple factors can contribute to worsening patient outcome including hypotension, hypovolemia, transfusion of blood and blood products in addition to the used nephrotoxic drugs [18]. Increased intraoperative blood loss was identified as a major risk

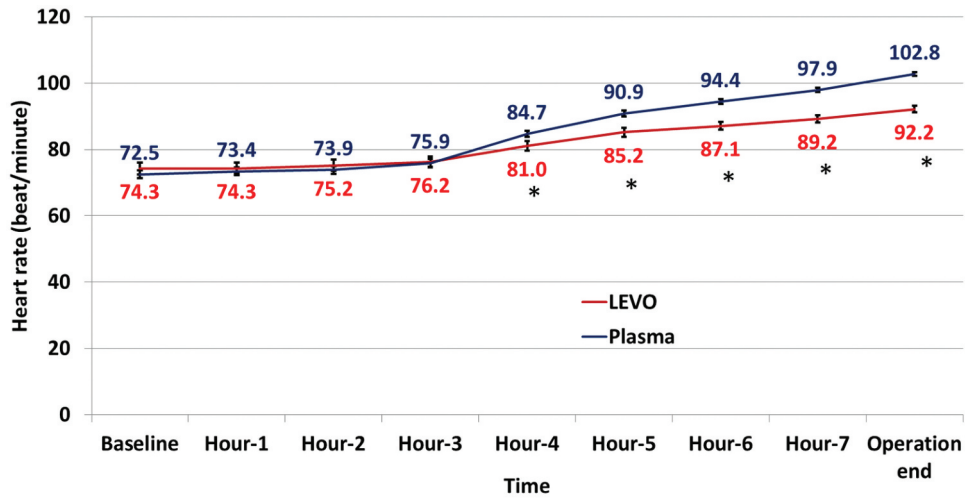


Figure 2. Perioperative heart rate values in the two studied groups.

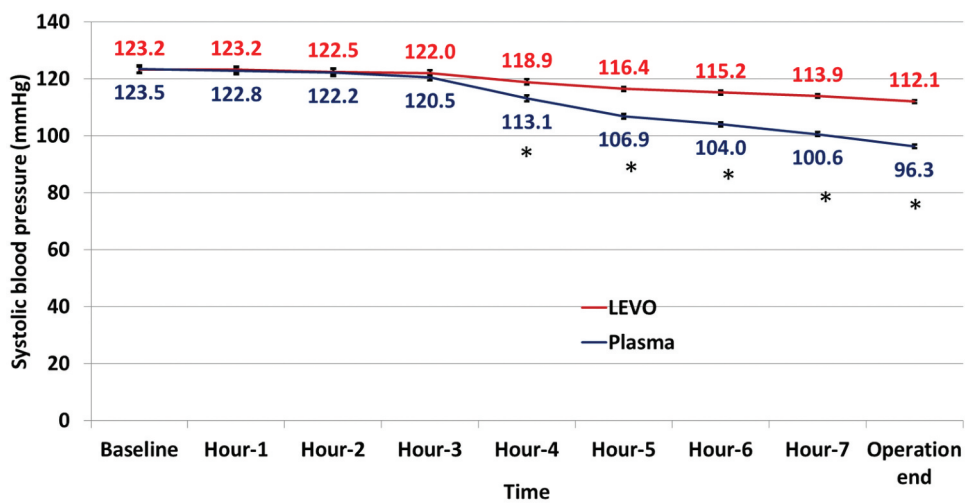


Figure 3. Perioperative systolic blood pressure values in the two studied groups.

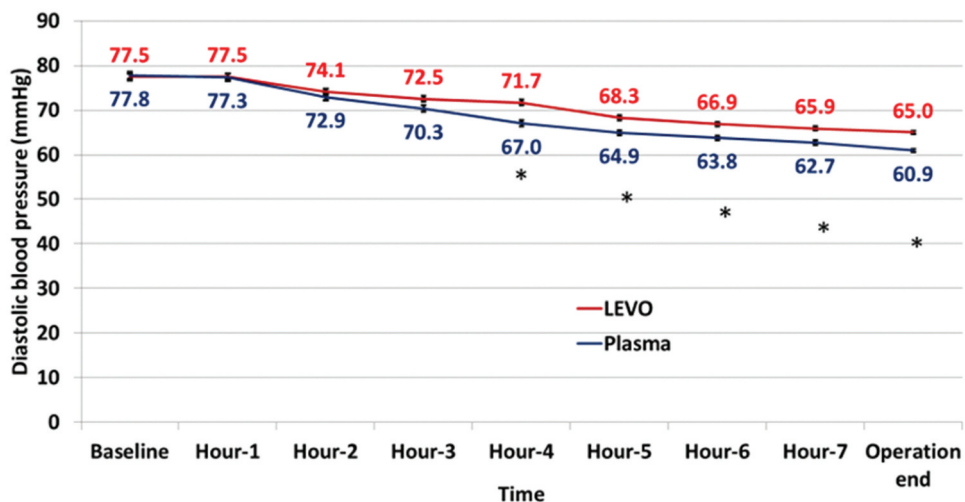


Figure 4. Perioperative diastolic blood pressure values in the two studied groups.

factor of acute kidney injury [5]. It is documented in the literature that CRS/HIPEC procedures are associated with increased incidence of massive blood transfusion [19–21]. Administration of FFP in HIPEC procedures

reduces intraoperative blood transfusion and can maintain stable hemodynamics [6]. Early administration of fresh frozen plasma (FFP) helps in clot stability during blood loss as it reach in antifibrinolytic agents [22].



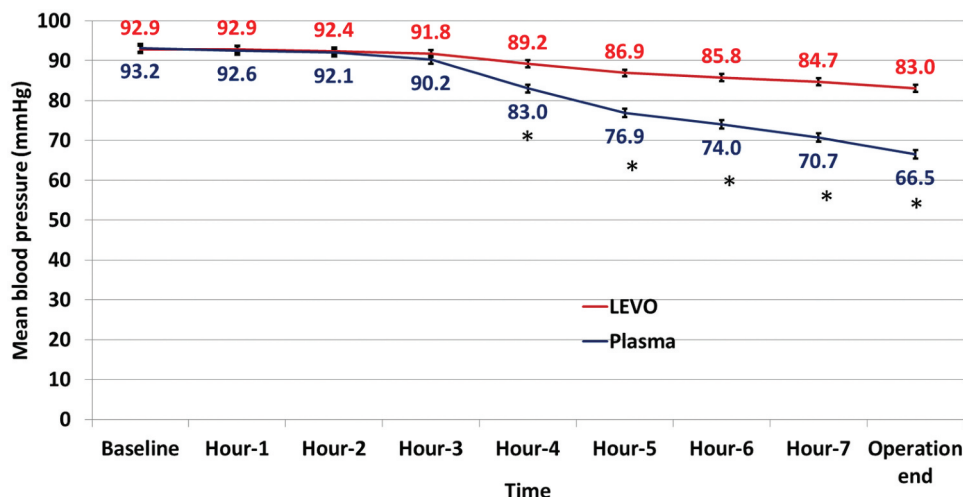


Figure 5. Perioperative mean arterial blood pressure values in the two studied groups.

Table 2. Comparison regarding diuretics needed intraoperative blood transfusion and fluid input& output.

Variables	Norepinephrine (N = 30)	Plasma (N = 30)	p-value	Effect of norepinephrine relative to plasma	
				Relative risk	95% CI
Diuretics need	14 (46.7%)	25 (83.3%)	#0.003*	0.56	0.37–0.85
Diuretics (mg), Mean± SD	24.3 ± 5.8 (N = 14)	37.2 ± 7.9 (N = 25)	^<0.001*	Mean ± SE −12.9 ± 2.4	95% CI −17.8–8.0
FFP units (units), Mean± SD	3.2 ± 1.9	5.2 ± 1.4	^<0.001*	−2.1 ± 0.4	−2.9–1.2
PRBCs units (units), Mean± SD	3.1 ± 1.8	4.4 ± 1.3	^0.0026*	−1.4 ± 0.4	−2.2–0.5
IV fluids (L), Mean± SD	9.2 ± 1.0	7.4 ± 0.8	^<0.001*	1.8 ± 0.2	1.3–2.2
IV colloids (L), Mean± SD	1.4 ± 0.2	0.9 ± 0.2	^<0.001*	−0.4 ± 0.1	0.2–0.6
Urine output (mL), Mean± SD	748.3 ± 92.4	693.3 ± 117.2	^0.048*	55.0 ± 27.2	0.5–109.5

RBC: Red blood cells. IV: Intravenous. ^Independent t-test. #Chi square test. \*Significant. CI: Confidence interval

Table 3. Comparison regarding serum creatinine.

Time	Norepinephrine (N = 30)	Plasma (N = 30)	^p-value	Effect of norepinephrine relative to plasma	
				Mean± SE	95% CI
Baseline	0.70 ± 0.29	0.72 ± 0.27	0.713	−0.03 ± 0.07	−0.17–0.12
Hour-24	0.9 ± 0.3	1.0 ± 0.3	0.033*	−0.2 ± 0.1	−0.3–0.0
Change	0.2 ± 0.1	0.3 ± 0.1	<0.001*	−0.1 ± 0.0	−0.2–0.1
#p-value	<0.001*	<0.001*			

Data presented as Mean± SD. #Change = hour-24–baseline, negative values indicate reduction. SE: Standard error. CI: Confidence interval. ^Independent t-test. #Paired t-test. \*Significant

Additionally, using FFP helps in improvement of patients' acid-base state as it acts as a buffer in acidotic patients which came in contrast to crystalloid usage that has an acidic nature [6]. On the other hand, transfusion of blood and blood products carry the risk transfusion related infection and increased incidence of acute lung injury [23]. Another concern is the increased incidence of cancer recurrence associated with blood transfusion [24]. Saxena and colleagues advocated a protocol near to the current study adopted plasma group regimen. They observed that their protocol that utilized early administration of fresh frozen plasma with restricting crystalloid resuscitation reduced the overall need for blood and blood products. However, their results did not monitor the renal outcome; otherwise, they investigated a global outcome of transfusion needed [25]. In a study done by Naffougie and colleagues, they concluded that increased blood loss was identified as a major predictor of acute kidney injury following CRS/

HIPEC procedures, resulting in further postoperative complications [8]; this augments the results of the current study which reported that using norepinephrine resulted in lower incidence of acute kidney injury.

Patients undergoing major surgeries or having systemic inflammation or sepsis usually suffer from systemic hypotension despite proper fluid replacement and normal cardiac output due to vasodilatation [26]. We assumed that using norepinephrine can prevent AKI in patients undergoing CRS/HIPEC; as during prolonged surgeries, norepinephrine can maintain blood pressure, cardiac output and splanchnic circulation [27]. The systemic response to the hyperthermic phase of HIPEC is thought to mimic sepsis and septic shock [28]; thus, vasopressors can play a promising role in maintaining hemodynamic stability and adequate tissue perfusion. This data explains better renal outcome in the norepinephrine group, which had higher blood pressure than the plasma group, so we can conclude that

norepinephrine is a more powerful tool in maintaining blood pressure to treat hypotension resulting from HIPEC therapy. Initiating vasopressor therapy in addition to fluid therapy is recommended by Kidney Disease Improving Global Outcome (KIDGO) in patients who are at risk of developing AKI [29]. Norepinephrine increases renal perfusion pressure through increasing the renal vascular resistance. In a retrospective analysis by Kajdi and colleagues on 54 patients diagnosed with peritoneal carcinomatosis who underwent 57 CRS/HIPEC procedures, they reported that 55 patients needed norepinephrine infusion in a range of (0.5 to 30)  $\mu\text{g min}^{-1}$  to maintain stable mean arterial blood pressure [5]. In another study by Colantonio and colleagues, they reported that adding vasopressors to goal-directed fluid therapy compared to standard fluid therapy in patients undergoing CRS/HIPEC surgeries results in better postoperative outcome with reduced complications [14]. A systematic review by Deng and colleagues investigating the effect of using perioperative vasoactive drugs during major abdominal surgeries showed that using vasoconstrictor drugs as norepinephrine can improve perfusion with restoration of adequate vascular tone, reduce postoperative complications and promote a better outcome [30]. Hence, adding low dose norepinephrine during CRS/HIPEC procedures can be beneficial in protecting against hypoperfusion, with consequent value in reducing the incidence of postoperative acute kidney injury.

Angeles and his colleagues reported that reduced intraoperative urine output can be considered as an independent risk for acute kidney injury. Additionally, they observed that incidence of AKI was higher in patients who received less intraoperative fluids. Thus, proper peri-operative hydration is crucial to preserve kidney function and maintain adequate urine output [16]. Hakeam et al. came to the same conclusion [31]. These results go with our findings as norepinephrine group utilized more intraoperative fluids ( $9.2 \pm 1.0$ ) and maintained better urine output ( $748.3 \pm 92.4$ ) that explain the lower incidence of renal insult ( $0.2 \pm 0.1$ ).

Adding epinephrine to intraperitoneal chemotherapy was investigated by Pili-Floury and colleagues, and they observed that the experimental group had lower rates of renal insult. This lowered incidence of renal injury could be explained by the role of epinephrine in maintaining hemodynamics and renal perfusion [32]. Clearly, the design of our study that examined systemic administration of norepinephrine allowed more objective assessment of norepinephrine effect.

We can tell that HIPEC is a quiet complicated procedure with many aspects to be addressed. Consequently, a designed approach that maintain the balance between haemodynamics, the need of blood products, renal perfusion and diuresis is needed. Finally, any comparison should test final outcome rather than single parameter.

## 5. Conclusion

Using norepinephrine infusion can play a promising role in maintaining hemodynamic stability with adequate tissue perfusion and better renal outcome in patients undergoing CRS/HIPEC procedures.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

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