ORIGINAL ARTICLE

CONTENTS

Effect of infusion solutions on circulating blood volume through different administration routes in animal models of peritonitis

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ABSTRACT

Aim: To compare the effects of different administration routes of various infusion solutions on the dynamics of circulating blood volume (CBV) in an experimental rat model of peritonitis.

Materials and Methods: The experiment involved 100 male white rats, three months old, weighing 200–220 g, born to different dams. Peritonitis was modeled by a single intraperitoneal injection of a 10% suspension of fresh rat feces. During the study, following the development of peritonitis in the animals, the dynamics of neutral red dye concentration in the gastric perfusate were measured. This was done using 0.9% sodium chloride solution and 10% albumin solution, administered via three different routes.

Results: It was determined that intraosseous administration of both 0.9% NaCl solution and 10% albumin solution had a statistically significant impact on CBV in peritonitis. The 10% albumin solution demonstrated a longer hemodynamic effect. Additionally, extraperitoneal administration of the 10% albumin solution was also effective.

Conclusions: 1. Administration of 0.9% sodium chloride and 10% albumin solutions in experimental peritonitis in animals results in an increase in circulating blood volume (CBV) when administered by the intraosseous route, with increases of 30% ($P \leq 0.01$) and 45% ($P \leq 0.001$), respectively. 2. The 10% albumin solution, administered extraperitoneally as a bolus infusion, significantly enhanced the secretion of neutral red dye into the perfusate, which correlated with its effects on CBV and improved microcirculation in the gastric mucosa.

KEY WORDS: albumin, acute peritonitis, circulating blood volume, 0.9% sodium chloride solution

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INTRODUCTION

Peritonitis is an inflammatory reaction of the peritoneum, capable of rapid generalization, leading to sepsis and septic shock, and in complicated cases, resulting in a mortality rate of up to 80% [1]. Literature highlights causes of peritoneal sepsis, including undrained fluid collections, interloop abscesses, inadequate surgical sanitation of the abdominal cavity during operations, immune defects, severe comorbid conditions, and subsequent endothelial dysfunction, enteropathy, and endotoxemia, progressing to multi-organ failure syndrome [2]. Shortly after massive invasion of bacterial agents, mesothelial damage, cytokine release, altered absorptive capacity of the peritoneum, intestinal paralysis, and intra-abdominal hypertension develop [3]. The cytokine cascade results in endothelial dysfunction and microcirculatory blockages [4, 5]. Critical interventions to save patients' lives include adequate volumetric resuscitation to restore oxygen delivery to tissues, normalization of circulating blood volume (CBV) and cardiac output, early antibiotic administration, and combating multi-organ failure [6, 7]. Strategies like the «open abdomen» approach, vacuum systems, and modern sepsis therapy significantly improve survival rates [8].

AIM

The aim of this study was to compare the effects of different administration routes of various infusion solutions on the dynamics of circulating blood volume (CBV) in an experimental rat model of peritonitis.

MATERIALS AND METHODS

The experiment was conducted on 100 male white rats, 3 months old, weighing 200-220 g. All rats were offspring of different dams, born a few days apart. At three months of age, the rats were randomly divided into groups. All animal experiments adhered to international guidelines for biomedical research involving animals, in accordance with the «General Principles of Animal Use», approved by the First National Congress on Bioethics, and aligned with the «European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes» and national legislation [9]. The experiments were conducted in compliance with the European Council Directive 86/609/EEC of November 24, 1986, on the care and use of laboratory animals. The study was approved by the Ethical Committee of the Educational and Scientific Center «Institute of Biology and Medicine», Taras Shevchenko National University of Kyiv, Ukraine, in September 2001. The rats were housed in the vivarium of the «Institute of Biology and Medicine» under standard conditions of temperature (21°C), lighting (12/12-hour light-dark cycle), humidity, and diet (complete laboratory animal feed K-12-4, «Rizan-1», Ukraine), in accordance with the «Standard Rules for the Arrangement, Equipment, and Maintenance of Experimental Biological Clinics (Vivariums)» [10]. Each group was further subdivided into subgroups based on the objectives of the study. To model peritonitis, the rats received a single intraperitoneal injection of a 10% suspension of fresh rat feces. The suspension was administered through a single puncture along the midline in the umbilical region of the abdomen to a depth of 2 mm. It was prepared using isotonic sodium chloride solution and filtered once through a double layer of gauze. A volume of 0.5 ml of the suspension per 100 g of body weight was used to induce peritonitis [11, 12]. Twenty-four hours after peritonitis induction, the rats were enrolled in the experiment. During the study, following the development of peritonitis in the animals, the dynamics of the concentration of neutral red dye in the gastric perfusate were measured. This was done using 0.9% sodium chloride solution and 10% albumin solution, administered via three different routes. The CBV dynamics were assessed using the neutral red dye clearance method through the gastric mucosa. This method relies on the dilution of the dye in circulating blood as blood volume increases (i.e., with a rise in CBV). A corresponding decrease in dye concentration occurs when the dye diffuses through the gastric mucosa, facilitated by hydrochloric acid perfusion of the mucosa [13]. At the 30th minute of the experiment, the animals were divided into three groups based on the routes of administration of 0.9% NaCl solution and 10% albumin solution, with the control group consisting of intact animals. The groups were as follows: Group 1: Intravenous administration. Group 2: Intraosseous administration. Group 3: Extraperitoneal administration. The volume of the administered solutions was 1 ml. Each group was further divided into two subgroups: Subgroup 1: Received 0.9% NaCl solution. Subgroup 2: Received 10% albumin solution. Before the experiment, the rats were weighed using «AXIS AD-50» electronic scales (Poland). Microsurgical instruments and materials from «Surgiwell» (Pakistan) were used for surgical procedures.

For general anesthesia, urethane («Sigma», China) was used at a dose of 1.1 g/kg body weight, administered intraperitoneally. The depth of anesthesia was evaluated by assessing the flexor reflex of the forelimb. Euthanasia was performed by overdose of anesthesia.

The rats were fasted for 12 hours prior to the experiment, with free access to water. During the experiment, tracheotomy and midline laparotomy of the abdominal cavity were performed. The stomach and duodenum were exposed, and a ligature was placed below the pyloric sphincter. An input catheter was introduced into the stomach and secured at the level of the tracheotomy incision. An output catheter was inserted through a duodenal incision into the stomach and fixed above the incision in the duodenum and below the pyloric sphincter. Using a peristaltic pump (MINIPULS GILSON, USA), the perfusion solution was delivered into the stomach through the input catheter at a constant rate (15 ml over 15 minutes). During the first 10 minutes, the stomach was perfused with physiological saline to stabilize blood flow in the gastric mucosa. For the next 15 minutes, an HCl solution with a pH of 2.0 was used. To maintain a constant level of dye in the plasma, a loading dose of neutral red (2 mg per 100 g body weight) was injected into the tail vein of the animals. Every 15 minutes over a 2-hour period, perfusates were collected from the stomach, and the optical density of each perfusate was measured using a «Synergy HT» spectrophotometer at a wavelength of 276 nm. Distilled water was used as the zero reference. The concentration of neutral red in the perfusates was determined using a previously constructed calibration curve.

The statistical analysis of results was performed using methods of variance statistics with the software Statistica 8.0. The Shapiro-Wilk W-test was used to check for normality. The reliability of the identified changes was evaluated using analysis of variance (ANOVA), and the results were presented as M±SD. Differences between groups were considered statistically significant at a significance level of $P < 0.05$ [14]. Graphs and histograms were created using Microsoft Excel.

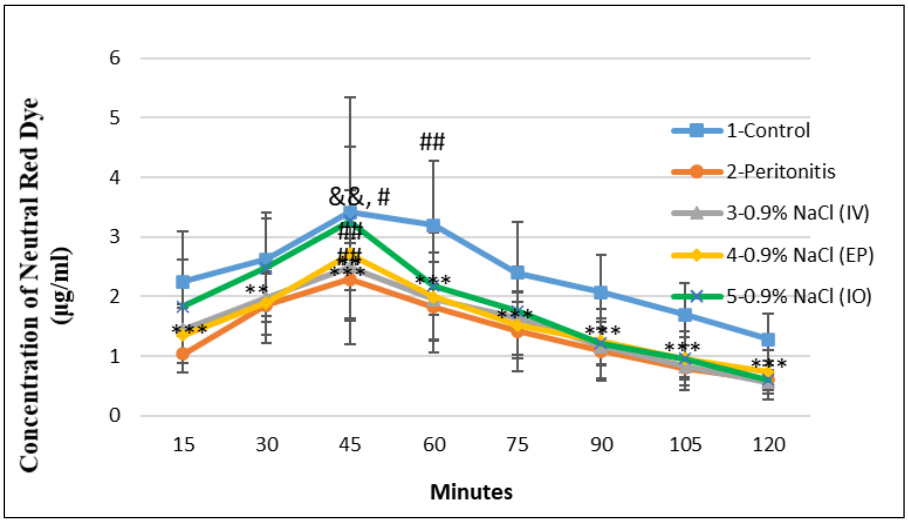

Fig. 1. Concentration of Neutral Red Dye in Gastric Perfusate of Rats After Administration of 0.9% NaCl Solution: 1 – Control, 2 – Peritonitis, 3 – Intravenous Administration (IV), 4 – Extraperitoneal Administration (EP), 5 – Intraosseous Administration (IO). P ≤ 0.01 *P ≤ 0.001 compared to control; #P ≤ 0.05, ##P ≤ 0.01, ###P ≤ 0.001 compared to the 30th minute within each administration group
Picture taken by the authors

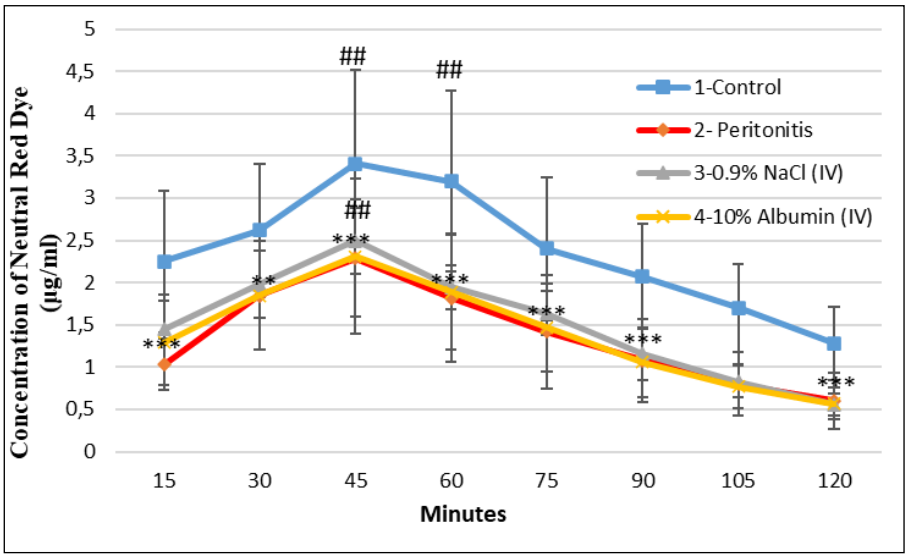

Fig. 2. Concentration of Neutral Red Dye in Gastric Perfusate of Rats After Administration of 10% Albumin Solution: 1 – Control, 2 – Peritonitis, 3 – Intravenous Administration (IV), 4 – Extraperitoneal Administration (EP), 5 – Intraosseous Administration (IO). P ≤ 0.01 *P ≤ 0.001 compared to control; #P ≤ 0.05, ##P ≤ 0.01, ###P ≤ 0.001 compared to the 30th minute within each administration group
Picture taken by the authors

RESULTS

The control group consisted of animals without peritonitis, which received an intravenous injection of neutral red dye at the 15th minute of the study to assess the dynamics of its secretion through the gastric mucosa.

In the second phase, dye secretion by the gastric mucosa was studied in animals with induced peritonitis who did not receive an infusion bolus of 0.9% NaCl solution or 10% albumin. The 10% albumin solution used in the study was the «Albuven» preparation, produced by BIOPHARMA PLASMA LLC, Ukraine. The active ingredient, human albumin, was present in a concentration of 100 g of total protein per 1000 ml of solution, with at least 96% being albumin. The auxiliary substances included sodium caprylate, sodium chloride, sodium hydroxide, and water for injections, with a sodium content not exceeding 160 mmol/L. Based on pathophysiological and pathomorphological data, significant fluid redistribution into inflamed peritoneal layers was anticipated during peritonitis, with subsequent dye saturation in these regions. At the beginning of the study (15th minute), the CBV deficit in peritonitis was 45.78%, likely not due to dye dilution but rather to its intense redistribution into inflamed areas. By the 60th minute, the CBV deficit was 53.4%, and by the 120th minute, the deficit remained at 46.9%.

The third phase involved determining the concentration of neutral red dye in the gastric perfusates after administering a bolus infusion of 0.9% NaCl or 10% albumin in animals with induced peritonitis. When administering 0.9% NaCl physiological solution to animals with modeled peritonitis, the following patterns were established. In the group receiving intravenous administration of 0.9% NaCl, significant differences from the control group were observed from the very beginning of the experiment. Specifically, the concentration of neutral red in the gastric perfusate differed by: 35.6% at the 15th minute, 24.4% at the 30th minute, 26.7% at the 45th minute, 39.1% at the 60th minute, 31.7% at the 75th minute, 43.9% at the 90th minute, 51.2% at the 105th minute, and 56.2% at the 120th minute, respectively.

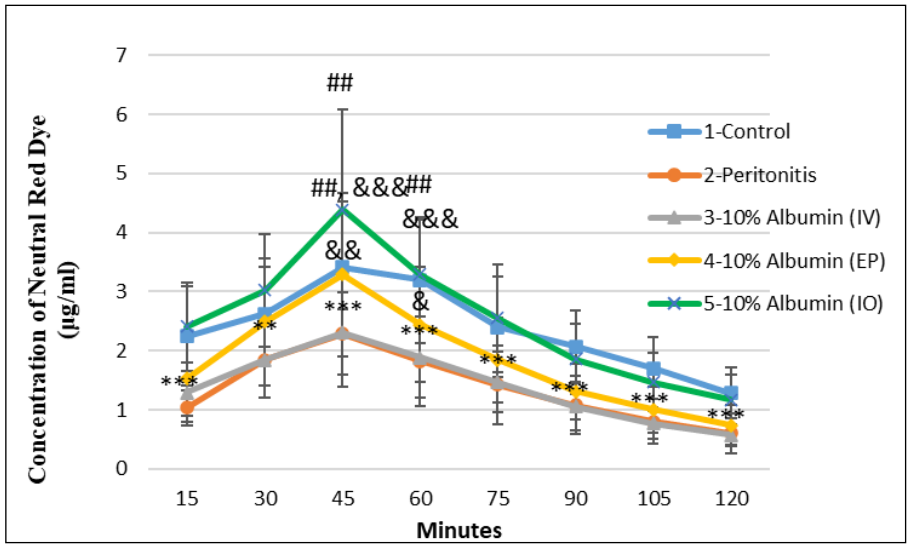

Fig. 3. Concentration of Neutral Red Dye in Gastric Perfusate of Rats After Intravenous Administration of 0.9% NaCl and 10% Albumin Solutions:
1 – Control, 2 – Peritonitis, 3 – 0.9% NaCl Intravenously (IV), 4 – 10% Albumin Intravenously (IV). P ≤ 0.01, *P ≤ 0.001 compared to control; #P ≤ 0.05, ##P ≤ 0.01, ###P ≤ 0.001 compared to the 30th minute within each administration group
Picture taken by the authors

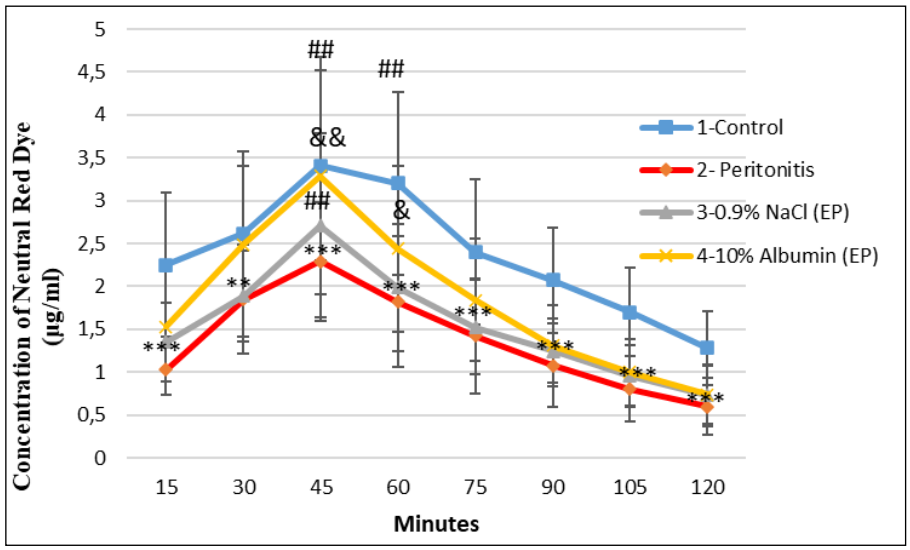

Fig. 4. Concentration of Neutral Red Dye in Gastric Perfusate of Rats After Extraperitoneal Administration of 0.9% NaCl and 10% Albumin Solutions:
1 – Control, 2 – Peritonitis, 3 – 0.9% NaCl Extraperitoneally (EP), 4 – 10% Albumin Extraperitoneally (EP). P ≤ 0.01, *P ≤ 0.001 compared to control; #P ≤ 0.05, ##P ≤ 0.01, ###P ≤ 0.001 compared to the 30th minute within each administration group
Picture taken by the authors

When analyzing the group with extraperitoneal administration of physiological solution in rats with peritonitis, significant differences from the control group were observed as follows: 40% at the 15th minute, 27.9% at the 30th minute, 37.8% at the 60th minute, 36.67% at the 75th minute, 39.6% at the 90th minute, 43.5% at the 105th minute, and 42.9% at the 120th minute, respectively.

When analyzing the group with intraosseous administration of physiological solution in rats with peritonitis, significant differences from the control group were observed at the following time points: 31.9% at the 60th minute, 26.7% at the 75th minute, 41.5% at the 90th minute, 43.5% at the 105th minute, and 53.1% at the 120th minute, respectively. The CBV deficit, compared to the 45th minute (where it was 44%), decreased to 31.9% at the 60th minute. However, by the 120th minute, the CBV deficit increased again to 53.1%.

The summarized data are presented in Fig. 1.

When comparing the effects of 0.9% NaCl solution administered via different infusion routes, notable changes were observed with intraosseous administration, which showed a statistically significant difference at the 45th minute compared to the peritonitis group (29.9%). At the 15th minute, the CBV deficit was 43.7%, and following an intravenous bolus of 0.9% NaCl, the CBV deficit at the 45th minute decreased to 29.9%, a result not observed with other routes (extraperitoneal or intravenous). This finding demonstrates the significant effectiveness of the intraosseous route for infusion therapy.

The second series of experiments analyzed the impact of different administration routes on CBV dynamics using a 10% albumin solution in rats with induced peritonitis. Significant differences in neutral red dye concentrations in gastric perfusates were observed at all time points, similar to the first series of experiments.

For rats with peritonitis, the concentration parameters of perfusates differed from the control group as follows: 15th minute: 54%, 30th minute: 29.4%, 45th minute: 32.8%, 60th minute: 43%, 75th minute: 40.8%, 90th minute: 47.8%, 105th minute: 48.8%, 120th minute:

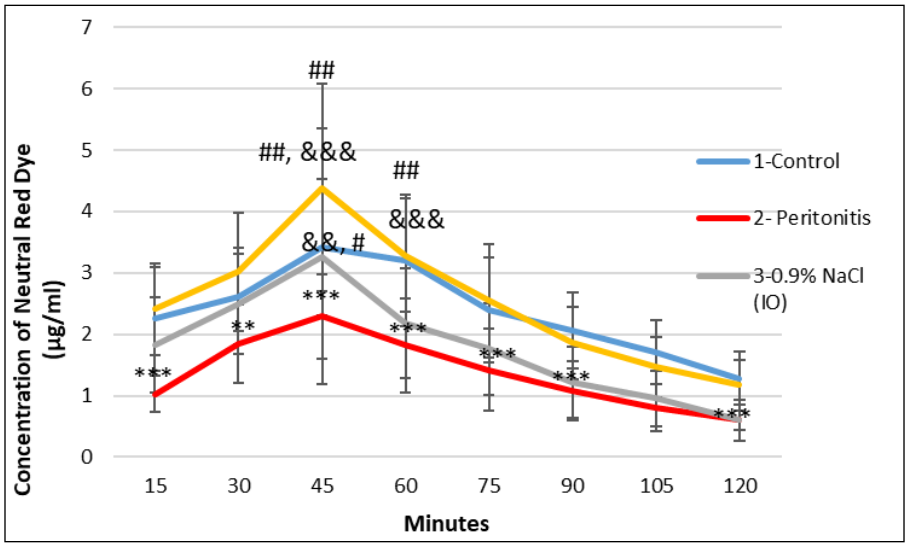

Fig. 5. Concentration of Neutral Red Dye in Gastric Perfusate of Rats After Intraosseous Administration of 0.9% NaCl and 10% Albumin Solutions:
1 – Control, 2 – Peritonitis, 3 – 0.9% NaCl Intraosseously (IO), 4 – 10% Albumin Intraosseously (IO). $P \leq 0.01$
*$P \leq 0.001$ compared to control; #$P \leq 0.05$, ##$P \leq 0.01$, ###$P \leq 0.001$ compared to the 30th minute within each administration group
Picture taken by the authors

53%. The concentration changes in perfusates depended on local hemodynamic changes, gastric mucosal perfusion, its absorptive and secretory capabilities, dye redistribution, and «paralysis» of microcirculation. The results of the second phase of the experiment are presented in Fig. 2.

Following the induction of peritonitis, a 10% albumin solution was administered to the experimental animals via three infusion routes: intravenous, extraperitoneal, and intraosseous. Intravenous administration of albumin solution resulted in significant changes in concentration from the control group, starting at the 15th minute with a 42.67% difference. These significant changes persisted across all measured intervals: 30th minute: 29.4%, 45th minute: 32.3%, 60th minute: 40.9%, 75th minute: 38.7%, 90th minute: 48.8%, 105th minute: 54.7%, 120th minute: 55.5%. The CBV deficit with intravenous administration of 10% albumin in peritonitis was: 42.7% at the 15th minute, 40.9% at the 60th minute, 55.5% at the 120th minute. Intraosseous administration of albumin solution showed significant changes in the concentration of neutral red dye in gastric perfusates. At the 45th minute, there was a 38.7% difference compared to the 30th minute within-group analysis. Compared to the peritonitis group, the differences were 47.8% at the 45th minute and 44.7% at the 60th minute. The 10% albumin solution administered extraperitoneally significantly altered the concentration of neutral red in the perfusates. At the 45th minute, there was a 30.4% difference compared to the peritonitis group. At the 60th minute, the difference was 25.4% compared to the peritonitis group. Additionally, when compared to the control group, significant changes were observed at: 23.7% at the 60th minute, 23.3% at the 75th minute, 36.7% at the 90th minute, 41.2% at the 105th minute, and 42.2% at the 120th minute. These findings indicate the effective impact of 10% albumin solution on CBV dynamics when administered via intraosseous and extraperitoneal infusion routes.

Comparative characteristics of CBV dynamics using identical substances (0.9% NaCl solution and 10% albumin solution) administered via different infusion routes are presented in Fig. 3, Fig. 4, Fig. 5.

In the comparative analysis of neutral red dye concentration curves in gastric perfusates following intravenous administration of 0.9% NaCl and 10% albumin solutions, the dynamics of dye secretion did not significantly differ between the two groups and the peritonitis group. Similarly, as observed in the control group, the peak secretion of neutral red dye occurred between the 45th and 60th minutes.

Following extraperitoneal administration of the studied solutions, a significant dynamic of dye secretion was observed in rats receiving 10% albumin compared to the peritonitis group. At the 45th minute, a 30.4% difference was noted. At the 60th minute, a 25.4% difference was recorded. In contrast, 0.9% NaCl administered via the extraperitoneal route showed no significant effect on CBV.

In a comparative analysis of neutral red dye concentration curves in animals receiving intraosseous bolus administration of 0.9% NaCl and 10% albumin solutions, a significant hemodynamic effect was observed. For 0.9% NaCl, at the 45th minute, there was a 29.9% difference compared to the peritonitis group. For 10% albumin, significant differences were noted at the 45th minute (47.8%) and the 60th minute (44.7%). This indicates CBV changes of 30% at the 45th minute in the 0.9% NaCl group and 48% and 45% at the 45th and 60th minutes, respectively, in the 10% albumin group. These results are reflected in the increased secretion of the dye through the gastric mucosa.

Thus, intraosseous administration of both 0.9% NaCl solution and 10% albumin solution demonstrated significant effects on CBV, with the latter showing a more prolonged hemodynamic effect. The extraperitoneal route of administering 10% albumin also proved effective.

DISCUSSION

The primary goal of fluid therapy is to ensure adequate oxygen delivery to tissues by normalizing cardiac output and restoring microcirculation. CBV deficit, particularly in peritonitis, significantly depends on capillary losses, renal and respiratory function, cumulative fluid balance, and fluid redistribution into the «third space» [15]. Combining infusion fluids with vasopressor therapy to achieve a mean arterial pressure (MAP) of 65 mmHg is essential for addressing these issues. Recommendations for the initial administration of 30 ml/kg crystalloids within the first three hours during septic shock have low evidence quality and are currently under revision. Experts now favor personalized infusion therapy, dynamic fluid balance assessment, and advanced hemodynamic monitoring with dynamic circulatory parameter evaluation [16, 17]. Categorizing patients into «responders» (those with a hemodynamic response to infusion therapy) and «non-responders» helps prevent fluid overload from excessive infusions [18]. Over time, infusion fluids redistribute into the interstitial space, leading to polycompartment syndrome, which primarily affects parenchymal organs (liver, kidneys), myocardium, lungs, and the intestinal wall [19]. Currently, early-stage infusion therapy for peritonitis is considered «liberal» and «massive», but if the patient's condition does not stabilize, the approach should shift toward restriction. These principles are described in the phased shock therapy concept (ROSE): R - Resuscitation, O - Optimization, S - Stabilization, E - Evacuation. Each phase involves specific strategies for fluid therapy [20]. Albumin use for primary stabilization in septic shock resistant to crystalloid therapy has moderate evidence strength, with recommendations favoring the use of 20-25% albumin solutions [21, 22]. While albumin increases MAP, it does not impact mortality compared to crystalloids [23-26]. Crystalloids remain the solutions of choice and should be balanced to avoid excessive chloride ions. Hemodynamic effects similar to those outlined in modern guidelines were observed in this study, with a significant hemodynamic impact demonstrated by the intraosseous administration of 10% albumin solution. The extraperitoneal route, which also proved effective with 10% albumin, requires further research and methodological refinement.

Traditional routes for administering infusion solutions include intravenous (IV) and intraosseous routes [27]. The intraosseous route offers advantages in patients with difficult peripheral venous catheterization, in emergency or battlefield conditions, but requires specialized equipment and skills [28]. However, it is associated with a high rate of infectious complications, such as osteomyelitis, and limited duration of access. Common access points include the tibial tuberosity, humerus, and sternum. The effect of intraosseous infusion is comparable to intravenous infusion in terms of stabilization speed and the range of administered medications. The retroperitoneal route has not been widely studied in intensive care for peritonitis. Nevertheless, some reports indicate its use in conservative treatment of aortic aneurysms, involving prolonged infusion of tetracycline-class antibiotics [29]. This route has been effectively employed for regional blocks, including paranephric, solar plexus, and sympathetic trunk ganglia blockades [30]. Considering the anatomical and physiological features of retroperitoneal lymphatic drainage into the thoracic cavity, the proximity of the sympathetic trunk, and compartmentalization of retroperitoneal structures, this route may be useful for administering certain antibiotics, albumin solutions, and more.

CONCLUSIONS

1. Administration of 0.9% sodium chloride and 10% albumin solutions in experimental peritonitis in animals results in an increase in circulating blood volume (CBV) when administered by the intraosseous route, with increases of 30% ($P \leq 0.01$) and 45% ($P \leq 0.001$), respectively.
2. The 10% albumin solution, administered extraperitoneally as a bolus infusion, significantly enhanced the secretion of neutral red dye into the perfusate, which correlated with its effects on CBV and improved microcirculation in the gastric mucosa.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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