Evaluation of volemic status during combined extracorporeal detoxification in patients with severe acute pancreatitis: a retrospective observational study

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Abstract

INTRODUCTION: The morbidity and mortality of severe acute pancreatitis (SAP) remains high. Intensive therapy aimed at stopping hypovolemia, systemic endotoxicosis is a debatable problem. **OBJECTIVE:** Improving treatment results in patients with SAP by assessing the dynamics of volumetric criteria and the degree of fluid therapy (FT). **MATERIALS AND METHODS:** The study included 25 patients. First, study group of 9 patient, used standard therapy in conjunction with selective hemoperfusion and continuous veno-venous hemofiltration. Second, control group of 16 patients, who received standard intensive care. FT in the groups was 2.5–3.5 ml/kg/h. Volemic parameters were measured by transpulmonary thermodilution. The central venous pressure and the diameter of the vena cava inferior were assessed. Comparative analysis was performed between two groups. **RESULTS:** FT in the amount of 58.7 (52.4–59.4) ml/kg/day in group 1, and 58.3 (54.2–61.4) ml/kg/day in group 2 in the first day, up to 83.9 (72.4–86.1) and 79.3 (72.4–84.1) ml/kg/day, was observed by day 3 ($p < 0.05$), according to the results of transpulmonary

Оценка волемического статуса на фоне применения комбинированной экстракорпоральной детоксикации у пациентов с тяжелым острым панкреатитом: ретроспективное наблюдательное исследование

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Реферат

АКТУАЛЬНОСТЬ: Заболеваемость и летальность тяжелого острого панкреатита (ТОП) остается высокой. Интенсивная терапия, направленная на купирование гиповолемии, системного эндотоксикоза, является дискуссионной проблемой. **ЦЕЛЬ ИССЛЕДОВАНИЯ:** Улучшить результаты лечения пациентов с ТОП путем оценки динамики волюметрических критериев и степени достаточности инфузионной терапии (ИТ). **МАТЕРИАЛЫ И МЕТОДЫ:** В исследование были включены 25 пациентов, которых распределили на две группы: в группе 1 ($n = 9$) применяли стандартную терапию совместно с селективной гемоперфузией и непрерывной вено-венозной гемофильтрацией. В группе 2 ($n = 16$) проводилась стандартная интенсивная терапия. ИТ в группах составила 2,5–3,5 мл/кг/ч. Волемические параметры измеряли методом транспульмональной термодилюции. Оценивали центральное венозное давление, диаметр нижней полой вены. Выполняли сравнительный анализ между группами. **РЕЗУЛЬТАТЫ:** ИТ в объеме 58,7 (52,4–59,4) мл/кг/сут в группе 1 и 58,3 (54,2–61,4) мл/кг/сут в группе 2

thermodilution. From the 1st to the 3rd day, Global end-diastolic volume index increased from 345 (328–412) to 648 (590–690) ml/m² in group 1, and from 375 (348–413) to 654 (599–701) ml/m² in group 2 ($p < 0.05$). Intrathoracic blood volume index increased from 440 (420–510) to 780 (750–840) ml/m² in group 1 and 430 (417.5–465) to 750 (665–780) ml/m² in group 2 ($p < 0.05$). Extravascular lung water index and pulmonary vascular permeability index by 5 days in group 2 increased by 1.8 — 11 (10.5–11.8) and 2.2 times — 6.5 (5.75–7), respectively ($p < 0.05$). **CONCLUSIONS:** FT 3.5 ml/kg/h, reaches isovolemia by the 3rd day of therapy. The use of extracorporeal detoxification methods in complex therapy is accompanied by an improvement in clinical and laboratory parameters.

KEYWORDS: pancreatitis, hemoperfusion, hemofiltration, continuous renal replacement therapy, fluid therapy, transpulmonary thermodilution, central venous pressure, vena cava inferior

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в первые сутки, до 83,9 (72,4–86,1) и 79,3 (72,4–84,1) мл/кг/сут, наблюдалось к 3-м суткам ($p < 0,05$) по результатам транспульмональной термодилюции. С 1-х по 3-и сутки индекс глобального конечного диастолического объема увеличился с 345 (328–412) до 648 (590–690) мл/м² в группе 1 и с 375 (348–413) до 654 (599–701) мл/м² группе 2 ($p < 0,05$). Индекс внутригрудного объема крови увеличился с 440 (420–510) до 780 (750–840) мл/м² в группе 1 и с 430 (417,5–465) до 750 (665–780) мл/м² в группе 2 ($p < 0,05$). Индекс внесосудистой воды в легких и индекс проницаемости легочных капилляров к 5-м суткам в группе 2 увеличились в 1,8 — 11 (10,5–11,8) и 2,2 раза — 6,5 (5,75–7) соответственно ($p < 0,05$). **ВЫВОДЫ:** ИТ 3,5 мл/кг/ч, достигает изоволемии к 3-м суткам терапии. Применение в комплексной терапии методов экстракорпоральной детоксикации сопровождается улучшением клинико-лабораторных показателей.

КЛЮЧЕВЫЕ СЛОВА: панкреатит, гемоперфузия, гемофильтрация, непрерывная заместительная почечная терапия, инфузионная терапия, транспульмональная термодилюция, центральное венозное давление, нижняя полая вена

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Introduction

Acute pancreatitis (AP) is a disease characterized by acute inflammation of pancreatic ducts and histologically presents as cell (acinous) destruction. Despite of all advantages of modern medicine, overall incidence of acute pancreatitis maintains on the level of 15–85 individuals per population of 100 000 people and there is no tendency to reduce. Severe acute pancreatitis connected with constant organ failure (cardiovascular, respiratory and/or renal), impacts

approximately 20–30 % of patients and associated with high hospital lethality of more than 35.2 % [1, 2].

Complex intensive care in early phase of AP has a range of features, based on pathogenetic mechanisms of disease development. High vascular penetration, liquid sequestration into extra cellular fluid compartment, retroperitoneal space, abdominal and pleural space lead to severe hypovolemia which together with constitutional endotoxicosis are the foundation-stone of multiple-organ-failure syndrome [3].

Efficacy of intensive care depends on starting date (so called open therapeutic window, limited with the first 72 hours from the beginning of the disease), according to experimental studies data [4]. One of the most significant task of intensive care is the choice of the volume of infusion therapy (IT). The most particular strategy shall be considered as the one which demonstrated that the volume of 5.8 ml/kg/hour (massive infusion therapy) lead to an increase of lethality compared to IT in volume of 3.8 ml/kg/hour (moderate infusion therapy) [5]. However, authors themselves mention about insufficiency of evidence base with recommendation of these volume load. There is only one randomized trial about mild AP treatment in the literature, where advantage IT in the volume of 3.8 ml/kg/hour compared to 1.8 ml/kg/hour has been demonstrated [6]. Meta-analysis of 2021 year shows that IT of higher volume connected with higher risk of organ disfunction and adverse outcome compared to standard IT of mean volumes [7]. It should be noted that uncontrolled massive IT associated with adverse outcome on the background of the development of pulmonary overhydratation, wet brain and increase in intra-abdominal pressure [8, 9].

It is commonly believed throughout the world community for a long time, that IT sufficiency has the following typical criteria: achieving the volume of urination more than 0.5–1 ml/kg per hour, mean blood pressure more than 65 mm Hg, central venous pressure (CVP) 8–12 mm Hg, mixed venous saturation more than 70 %. Additional criteria may be considered as the following: normalization of the level of lactate, urea and reduction of laboratory criteria of hemoconcentration [10].

CVP determination for a long time considered to be one of simple and achievable bedside method of volume status determination. However, there are a lot of evidences that CVP has low sensitivity and specificity in the hydration status assessment. Nonetheless, world data show that CVP has been continuously used due to its simplicity, availability and the possibility of initial assessment of hydration [11, 12].

In the last decade determination of inferior vena cava diameter (IVC diameter) is considered to be the actual method of assessment of hydration status. Ultrasonographic assessment of IVC diameter is one of the best predictors of volemia among the numerous methods of monitoring [13]. However, controversial results of some trials warn that ultrasound should be used carefully due to large variability of data [14].

Method of transpulmonary thermodilution (TPTD) is currently the "gold standard" of volume status determination. Global end-diastolic volume index (GEDVI) is one of the most essential indicator of preload among many parameters [15]. This criterion is recommended to use not only for optimization of conducted infusion therapy but also as control point for goal-oriented dehydration [16, 17].

Thus, the assessment of hydration status with the answer to the question about sufficiency of infusion load is complicated and up to this point unsolved problem of medicine in general. There is always the necessity of balancing on the border between hypo- and hyperhydration when choosing a strategy of infusion therapy and correction methods. And only an inquisitive mind of a specialist together with modern achievements in medicine and numerous research papers probably help us answer to the raised question.

Objective. To improve the results of the treatment of patients with severe acute pancreatitis (SAP) by means of the assessment of volumetric criteria and the rate of sufficiency of infusion therapy (IT).

Materials and methods

Monocentric retrospective observational study includes 25 patients who underwent treatment in intensive care unit (ICU) of Pirogov City Clinical Hospital No 1 with the diagnosis "acute pancreatitis, severe disease". Diagnostic of acute pancreatitis conducted accordingly to revised classification Atlanta 2012 [18]. The presence of sepsis as multiple-organ-failure syndrome due to infection was determined in accordance with the criteria of joint conference SCCM/ESICM as of 2016 year as ≥ 2 scores of SOFA scale [19].

Study phases and tasks

On the first phase of our research (part 1) the following tasks were set:

1. To reveal and assess clinical laboratory criteria of hypovolemia, acid-base balance disturbance in patients with severe acute pancreatitis.
2. To fulfill dynamic assessment of volumetric parameters in patients with severe acute pancreatitis.
3. To assess the sufficiency of infusion therapy in patients with severe acute pancreatitis during 5 days of complex intensive care.

On the second phase of our study (part 2) the following tasks were set:

1. To reveal clinical laboratory markers of systemic endotoxemia in patients with severe acute pancreatitis.
2. To study the impact of combined method of extracorporeal detoxification on general clinical parameters, organ dysfunction and disease outcomes.

Entry criteria:

- presence of severe acute pancreatitis;
- induction of multiple-organ-failure syndrome (≥ 2 scores according to the SOFA scale) longer than 48 hours.

Patients exclusion criteria from the study:

- terminal state of a patient;
- pregnancy;
- patients under 18 years old;
- oncological diseases or chronical diseases in decompensation stage.

When patients were admitted to intensive care unit, severity of patient's condition and the risk of adverse outcome were assessed according to the APACHE II scale, intensity of multiple-organ-failure was assessed by the SOFA scale. The dynamic was evaluated on a daily basis.

The vital functions of organs and systems were monitored on a 24-hour basis: invasive measuring of blood pressure (iBP), central venous pressure (CVP), intra-abdominal pressure (IAP), heart rate (HR), hemoglobin saturation of arterial (SaO_2) and central venous blood with oxygen, arterial and venous blood gases rates, acid-base balance (ABB) and water-electrolytic balance (WEB) were carried out. Clinical (hemoglobin, hematokrit, red blood cells, leucocytes, thrombocytes, leucogram) and biochemical (total protein, albumin, total bilirubin, aspartate transaminase (AsAT), alanine transaminase (AlAT), urea, creatinine, alkaline phosphatase, pancreatic amylase, C-reactive protein and others), hematological (aPTT, INR, fibrinogenous) blood analyses were evaluated on a daily basis. Worst rate for the last day was considered when conducting statistic analysis.

Spiral computed tomography of abdominal space with bolus contrasting was performed for the evaluation of prevalence of the process in the pancreas gland and surrounding tissues. Balthazar scale was used for quantity assessment of severity of the process [20].

Volume status in patients estimated by means of CVP measurement and diagnostic ultrasound (DUS) with IVC diameter and lower hollow vein collapse index ([IVCmax – IVCmin) / IVCmax] × 100) determination. Detailed analysis of haemodynamics and personalized correction of volume load performed according to PiCCO plus methodology with the use of additional block to Philips monitor (China). Patients' central vein (internal jugular or subclavian) as well as femoral artery were preliminary cateterized. The monitor was calibrated before start of using. Thermodilution was conducted with 0.9 % solution of NaCl maintained at +4 °C in the form of 5 boluses, 20 ml each. Measurements were held 3–4 times a day. The following parameters were monitored: global end-diastolic volume index (GEDVI), intrathoracic blood volume index (IBVI), extravascular lung water index (ELWI), pulmonary vascular permeability index (PVPI).

All patients underwent complex intensive care, including vasopressor support, infusion therapy, parenteral feeding and/or nutritional support of nutritional mixture through nasogastric/intestinal probe, prevention of formation of stress-ulcers of gastro-intestinal tract, respiratory support, pain management, prevention of thromboembolic disorders, antibacterial therapy conducted during infected acute pancreatitis (C-reactive protein > 150 mg/L, procalcitonin more than 3.8 ng/ml) or the presence of alternative infection source. Basic infusion therapy composed of solutions of isoosmolar crystalloids (sterofundin-ISO or isotonic solution of sodium chloride). Sufficiency of conducted therapy was assessed by means of classical criteria of achieving urinary excretion rate more than 0.5–1 ml/kg per hour; mean blood pressure more than 65 mm Hg; central venous pressure 8–12 mm Hg; saturation of central venous blood with oxygen more than 70 %, results of IVC diameter measuring, TPTD results. The main goal of infusion therapy was considered as the correction of acid-base and hydro-electrolytic balances disturbance.

During the study the patients were separated into two clinical groups. The first group included 9 patients, whose treatment consisted of standard complex intensive care with the use of combined method of extracorporeal detoxification (ECD), included simultaneous or sequential conducting of selective hemoperfusion (SH) and veno-venous hemofiltration. The second group included 16 patients, who treated in accordance with the standards of complex intensive care. Extrarenal indications were taken as indications for starting of ECD conduction for patients treatment of the first group: significant hydro-electrolytic disturbance (pH ≤ 7.15, lactate ≥ 2.0, BE ≤ –2.0), maintained or increased doses of vasopressor support, reduced general condition of patients (SOFA scores increasing), which could not be stabilized during 48 hours, on the background of standard complex intensive care. Operation of selective hemoperfusion (SH) was conducted using Efferon CT extracorporeal blood adsorber. Extended venovenous hemofiltration (EVVHF) in the mode of postdilution performed with the use of MultiFiltrate device (Fresenius Medical Care).

Statistical analysis

Obtained data were presented as median and interquartile range (25^{th} and 75^{th} percentile). Shapiro—Wilk test was used to characterize the normality of data distribution. Mann—Whitney and Kruskal—Wallis non-parametric tests were used to check statistical hypothesis (between the groups). Wilcoxon criterion was used to determine the confidence of attributes changes during observation in dynamic (intragroup or paired). Fisher's exact test was used to reveal the differences of quality attributes between the groups. The value of first level mistake with $p < 0.05$ was accepted as statistical significance criterion.

Results

The main clinical laboratory symptoms were analyzed in the study groups at the time when the patients were admitted to intensive care unit (Table 1).

Table 1. The main clinical and laboratory parameters of patients in the study groups at the time of admission to the ICU

Rate	Group 1 (*n* = 9) Me (Q1–Q3)	Group 2 (*n* = 16) Me (Q1–Q3)	*p*-value
Male, *n*	6	9	1.0
Female, *n*	3	4	
Age, years	55 (40–59)	64 (46–68)	0.13
Weight, kg	95 (87–111)	93 (88; 100)	0.92
X-ray computer tomography, scores	8 (7–9)	7 (6–8)	0.21
SOFA, scores	7 (6–8)	6 (5–8)	0.39
APACHE II, scores	26 (25–26)	24 (22–25)	0.053
KDIGO, stage	0–I	0–I	1.0
SBP, mm Hg	51 (58–72)	60 (52.3–75.3)	0.47
Heart rate, per minute	115 (112–118)	114 (107–125)	0.83
Erythrocytes, $\times 10^{12}$/L	5.61 (5.27–5.67)	5.7 (5.32–5.9)	0.35
Hemoglobin, g/L	170 (159–176)	169 (166–184)	0.86
Hematocrit, %	51.5 (51–61.8)	54.1 (51–56.1)	0.97
Thrombocyte, $\times 10^{9}$/L	185 (168–194)	180 (164–185)	0.81
pH	7.14 (7.11–7.17)	7.12 (7.1–7.15)	0.47
BE	–10.2 (–10.3 … –9.4)	–8.1 (–12.1 … –5.8)	0.51
Lactate, mmol/L	8.2 (7.3–8.5)	5.8 (5.2–6.8)	0.11
Leucocyte, $\times 10^{9}$/L	14.9 (14.5–15.5)	17.6 (14.2–18.1)	0.23
CRP, mg/L	315.6 (290.4–364.4)	222 (215.6–275.3)	0.053
PCT, ng/ml	4.5 (2.85–7.8)	3.95 (3.59–4.94)	0.89
IL-6, pg/ml	1624.3 (1426.5–1684.3)	1529.8 (1440.9–1670.9)	0.96
Urea, mmol/L	10.2 (9.2–15.2)	12.5 (9.9–15.9)	0.61
Creatinine, mkmol/L	128 (98.3–181)	182 (114–294.7)	0.22
CKD, ml/min/1.73 m^2	58 (45–62)	62 (56–69.5)	0.18
GEDVI, ml/$м^2$	345 (328–412)	375 (348–412)	0.36
IVC diameter, cm	0.8 (0.7–1.1)	0.7 (0.6–0.8)	0.11
CVP, cm water column	0 (0–1)	1 (0–1)	0.56
PaO_2/FiO_2, mm Hg	280 (276–290)	280 (260–280)	0.58
ELWI, ml/kg	3 (3–4)	3.5 (3–4.25)	0.9
PVPI	1 (1–2)	2 (1–2)	0.5
Infusion, ml/kg/day	57.5 (52.4–59.4)	58.3 (54.2–61.4)	0.64

CRP — C-reactive protein; CT — disease severity index according to computed tomography with Balthazar contrast; CVP — central venous pressure; dVCI — diameter of the vena cava inferior; ELWI — index of extravascular water in the lungs; GEDI — index of global end-diastolic volume; GFR — glomerular filtration rate; HR — heart rate; IL-6 — interleukin-6; MAP — mean arterial pressure; PaO_2/FiO_2 — the ratio of the partial pressure of oxygen in arterial blood to the fraction of oxygen in the inhaled gas (syn. — oxygenation index, hypoxemia index, Horowitz index); PCT — procalcitonin; PVPI — pulmonary vascular permeability index.

Note: Data are presented as Me (Q1–Q3). Statistical differences between groups (*p*-value) were assessed using the Money—Whitney *U*-test, for quantitative (binary) Fisher's exact test data.

At study entry clinical groups were totally comparable to one another and didn't differ from one another statistically significantly ($p > 0.05$ for all parameters).

Assessment of hematological criteria

Dynamic of main hematological parameters in clinical groups under study from the first till the fifth days of the treatment is presented in Table 2.

The data presented in the Table shows that there are no statistically significant differences in erythrocytes dynamic between the groups 1 and 2, from the first to the fifth days ($p = 0.34$; 0.2; 0.44; 0.11; 0.07). However, it should be noted that on the background of conducted intensive care in both groups there is a significant decrease of the parameter concentration by the third day compared to the source data ($p < 0.05$). The same situation is observed when analyzing the parameters of hemoglobin and hematocrit. Thus, the tendency of patients hemoconcentration at the date of their admission to intensive care unit in both groups is clearly evidenced, which is in accordance to pathogenetic scheme of AP development which means sequestration of the liquid into interstitial and extraperitoneal space, abdominal and pleural cavity. This pathological process is coexisted with significant events of hypovolemia which both from native and foreign authors' point of view make disease state and prognosis heavier [2, 3]. In our case we can observe that normovolemia in both groups in all clinical parameters reaches all its reference range by the third day of study. From other authors' point of view the main goal should be achieving normovolemia by 1–2 days of complex intensive care. However, opinions about terms of sufficiency of volume load greatly contradictory and associated both with positive and negative moments either in near-term or in long-term perspective [21–23].

Infusion load and volume parameters assessment

Analysis of high volume load from the first till the fifth days of intensive care is presented on Fig. 1.

On this figure we can watch relevant increase of the volume of infusion load beginning from the first day of intensive care with values of 58.7 (52.4–59.4) ml/kg/day in the group 1, and 58.3 (54.2–61.4) ml/kg/day in the group 2 to 83.9 (72.4–86.1) and 79.3 (72.4–84.1) ml/kg/day by the 3rd day accordingly ($p = 0.02$ and $p = 0.01$ for each group accordingly). Conducted intergroup analysis hasn't revealed any relevant differences between the volumes of IT since the 1st till the 5th days of therapy ($p = 0.64$; 0.95; 0.55; 0.07; 0.19).

By the 5th day the volume of volume load has been decreased to 27.8 (24–28.7) and 22.3 (19.3–26.4) ml/kg/day in each group accordingly ($p = 0.009$ and $p = 0.008$). Relevant differences between the groups hasn't been registered ($p = 0.19$). Thus, it should be noted that maximal volume of water load falls on the third day of intensive care with futher decrease of its intensity. Fluid volumes since the first, the second and the third days of intensive care correspond to moderate infusion therapy [5–7].

Such parameters as CVP, IVC diameter, GEDVI, IBVI were analyzed in order to determine the adequacy

Table 2. Main hematological criteria in the study groups

Parameters	Groups	Day 1	Day 2	Day 3	Day 4	Day 5w
Erythrocytes, ×10⁹/L	Group 1 ($n = 9$) Me (Q1–Q3)	5.61 (5.27–5.67)	5.23 (5.1–5.3)	4.9* (4.83–4.92)	4.2* (3.89–4.6)	3.8* (3.7–3.99)
	Group 2 ($n = 16$) Me (Q1–Q3)	5.7 (5.32–5.9)	5.38 (5.19–5.73)	5.3* (4.32–5.36)	4.9* (4.57–5.0)	4.23* (4.1–4.79)
Hemoglobin, g/L	Group 1 ($n = 9$) Me (Q1–Q3)	170 (159–176)	161 (154–169)	144* (140–158)	134* (132–143)	128* (122–133)
	Group 2 ($n = 16$) Me (Q1–Q3)	169 (166–184)	166 (163–167)	159* (150–162)	150* (137–157)	146* (132–153.5)
Hematocrit, %	Group 1 ($n = 9$) Me (Q1–Q3)	51.5 (51–61.8)	50.6 (49.2–53.5)	46.1* (45.5–49.3)	38.8* (37.2–43.7)	37.4* (33.4–41)
	Group 2 ($n = 16$) Me (Q1–Q3)	54.1 (51–56.1)	51.8 (49.9–54.7)	48.7* (41.2–49.3)	44* (42.6–48.2)	42* (38.15–45.15)

Note: Data are presented as Me (Q1–Q3). Statistical differences between groups were assessed using the Mann—Whitney *U*-test, intragroup differences using the Wilcoxon test.

* Statistically significant differences (Wilcoxon test, $p < 0.05$) in the concentration of erythrocytes, hemoglobin and hematocrit compared with 1st day.

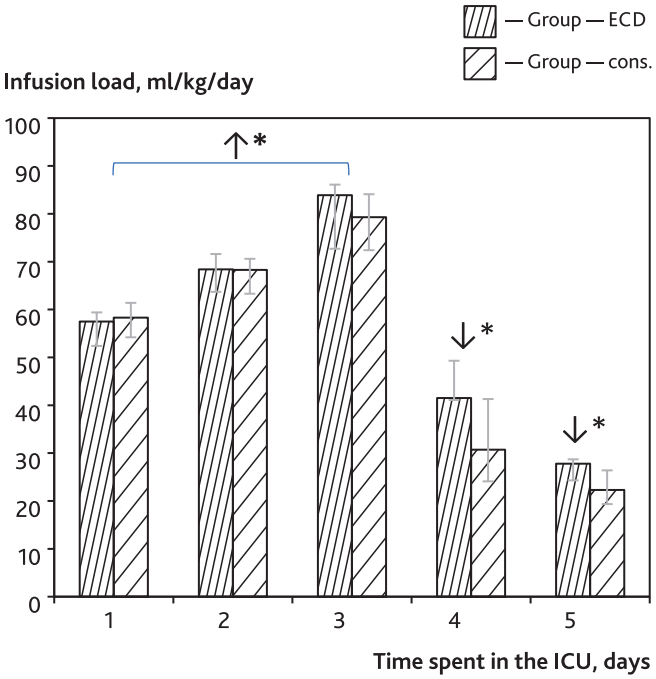

Fig. 1. Results of the volemic load analysis

Конс. — standard therapy (group 2); ЭКД — extracorporeal detoxification (group 1).

Note. Data are presented as median (25–75th percentiles). Statistical differences between groups were assessed using the Mann—Whitney *U*-test, intragroup differences using the Wilcoxon test.

* Statistically significant differences (Wilcoxon test, $p < 0.05$) in the volume load of both groups between the 1st and 5th days of therapy.

of preload or volume status in patients. The results of this analysis are presented in Table 3.

Analysis of obtained CVP values since the 1st till the 5th days of intensive care in both study groups demonstrated slow increase of rates with relevant difference from source values measured when patients were admitted ($p = 0.008$; 0.007; 0.008; 0.007) for the first group and ($p = 0.003$; .0003; 0.003; 0.014) for the second group accordingly. Considering the same conditions of entry and conducted infusion therapy, there was no relevant difference between the groups ($p = 0.6$; 0.9; 0.9; 0.4; 0.2). However, it should be noted that the lower borderline of acceptable reference range of this parameter was reached only by the fifth day of complex intensive therapy, which in modern conditions is considered to have an extremely out-of-date result and low informativeness. The same thought was suggested by many native and foreign authors pointing to a low informativeness and poor accuracy of this method of volume status assessment [11, 12].

Table 3. Dynamics of volemic load criteria during five days of intensive care

Parameters	Groups	Day 1	Day 2	Day 3	Day 4	Day 5
CVP, cm water column	Group 1 (n = 9) Me (Q1–Q3)	0 (0–1)	3 (2–3)*	4 (4–5)*	6 (6–7)*	8 (7–8)*
	Group 2 (n = 16) Me (Q1–Q3)	1 (0–1)	3 (2–3)*	5 (4–5)*	6 (6–5)*	7 (7–8)*
IVC diameter, cm	Group 1 (n = 9) Me (Q1–Q3)	0.8 (0.7–1.1)	1.1 (1.1–1.4)*	1.5 (1.3–1.6)*	1.8 (1.6–1.9)*	2.0* (1.8–2.2)
	Group 2 (n = 16) Me (Q1–Q3)	0.7 (0.6–0.8)	0.9 (0.7–0.9)*	1.1 (0.9–1.2)*	1.5 (1.2–1.6)*	1.6 (1.5–1.8)*
GEDVI, ml/m²	Group 1 (n = 9) Me (Q1–Q3)	345 (328–412)	510* (440–540)	648* (590–690)	714* (680–760)	756* (720–780)
	Group 2 (n = 16) Me (Q1–Q3)	375 (348–413)	512* (473–606)	654* (599–701)	726.5* (660–783)	770* (725–815)
IBVI, ml/m²	Group 1 (n = 9) Me (Q1–Q3)	440* (420–510)	640* (520–720)	780* (750–840)	880* (820–920)	910* (890–930)
	Group 2 (n = 16) Me (Q1–Q3)	430* (417.5–465)	580* (550–616)	750* (665–780)	845* (785–853)	890* (860–905)

Note: Data are presented as Me (Q1–Q3). Statistical differences between groups were assessed using the Mann—Whitney *U*-test, intragroup differences using the Wilcoxon test.

* Statistically significant differences (Wilcoxon test, $p < 0.05$) in the values of CVP, DIVC, global diastolic volume (GEDI), intrathoracic blood volume (ITBI) compared with 1st day.

Also slowly increase of rates since the first till the fifth days with relevant difference from the second day of intensive care (p = 0.009; 0.009; 0.009; 0.01) for the first group and (p = 0.02; 0.008; 0.009; 0.022) for the second clinical group accordingly is also observed when analyzing the results of d IVC. Intergroup differences according to this criterion haven't been obtained (p = 0.064). However, it should be noted that minimal reference values in both groups were achieved only by the fourth day of intensive care as in the previous group, which is exetremely slow and has outdated character and liable to flexibility, considering changeable scheme of therapeutic process [14].

The analysis of IBVI and GEDVI parameters shows similarly results. Positive increase of IBVI parameter is observed with relevant difference for the first group since the third day of intensive care (p = 0.01; 0.009; 0.009) and for the second group since the second day of intensive care (p = 0.01; 0.01; 0.01; 0.02). Analysis of dynamic of the GEDVI parameter demonstrated relevant increase of rates for the first group since the third day of the therapy (p = 0.01; 0.009; 0.009) and for the second group since the third day of the therapy accordingly (p = 0.014; 0.017; 0.026; 0.001). Relevant differences between the study groups haven't been observed (p = 0.56; 0.21; 0.08; 0.06; 0.16 and p = 0.36; 0.53; 0.77; 0.69; 0.67 accordingly) with a background of sufficient and dedicated infusion therapy for IBVI and GEDVI parameters.

However, it should be noted that GEDVI and IBVI reached minimal values of volume sufficiency by the end of the second and the beginning of the third day compared to previous criteria (CVP and d IVC), which may be considered as relatively acceptable temporal frames for assessment of conducted volume load. The most acceptable result in the sense of prevention of short-terms and long-terms adverse effects and outcomes of the disease is the achievement of normovolemia by the end of the second and the beginning of the third day, according to native and foreign authors. Uncontrolled massive infusion therapy for patients in critical condition is associated with adverse outcome in presence of pulmonary overhydratation, cerebral edema and intra-abdominal pressure. Any strategy for the achievement of normovolemia both towards increase and towards decrease can be associated with risks and influence on prediction and outcome of the disease. Meanwhile, there no general consensus on this point in the literature [3–10, 21–23]. Nevertheless, in joining the opinion of worldwide researches, we would like to emphasize that TPTD is the most optimal and close to ideal control method and to the full extent justifies imposed tasks on the assessment of volume status [15–17, 34].

Analysis of extravascular water index in lungs is presented on the Fig. 2.

Conducted intragroup analysis of extravascular water index in lungs has been demonstrated relevant decrease of ECD in the first group in relation to the first day of the therapy (p = 0.02; 0.01; 0.01; 0.03), maintaining in the frames of reference value and the second group (conservative therapy) accordingly (p = 0.01; 0.01; 0.01; 0.02), but significantly exceeds acceptable limits. It should be noted that the increase of the index in the second group has high rate of relevance by the fifth day (p < 0.001). The increase of extravascular water in lungs in one group and the decrease in the other is clearly observed in intragroup comparison of study groups since the third till the fifth days of intensive therapy (p = 0.01; 0.001; 0.001).

Similar situation is observed with dynamic of pulmonary capillaries permeability index which is shown on Fig. 3.

Presented on the Figure data show relevant intragroup increase of pulmonary capillaries permeability index in both groups since the first day till the fifth day of intensive care: for the first group (p = 0.02; 0.008; 0.02; 0.036) but maintaining within the reference values by the fifth day and the second group accordingly (p = 0.01; 0.01; 0.016; 0.031), which by the fifth day higher than twice of acceptable limits. Analysis of intragroup differences of pulmonary capillaries permeability index revealed relevantly best rates in group 1, which treated with combined extracorporeal detoxification, in comparison with conservative therapy of the second group, and since the fourth day of intensive care these differences have high level of relevance (p = 0.0007; 0.0008).

Thus, it can be concluded that the use of combined extracorporeal detoxification in the group 1 probably enables to control volume load of a patient, contributes to decrease of the risk of pulmonary tissue failure by means of decreasing the pulmonary capillaries permeability and extravascular water in lungs, which is positively connected with better outcomes of the disease, according to the opinion of some authors [24, 25].

Respiratory function assessment

Respiratory index (PaO_2/FiO_2) was the main parameter which we used to assess lungs malfunction, the dynamic of this rate is shown in Fig. 4.

We paid particular attention to the frequency of ALV usage in the study groups. Analysis (Fisher's test) showed that there are no relevant differences in the frequency of ALV on the first day between the groups: 55.5 (5/9) and 61.5 (8/13) accordingly. By the 5th day the frequency of respiratory support in the group 1 was 88.9 % (8/9) and 92.3 % (12/13) accordingly (p = 0.72).

Thus, after obtained data have been analyzed, we can suggest that complex intensive care on the background of systemic toxicosis is associated with capillary leakage syndrome and accumulation of extravascular water in lungs with decrease of respiratory index, however the use of combined method of extracorporeal detoxication has positive effect on prosthesis of pulmonary function (decrease of endogenic toxicosis, pulmonary capillaries penetrance, extravascular lung water) in the form of earliest respiratory index normalization, which apparently can influence not only on ALV duration but also on the outcome

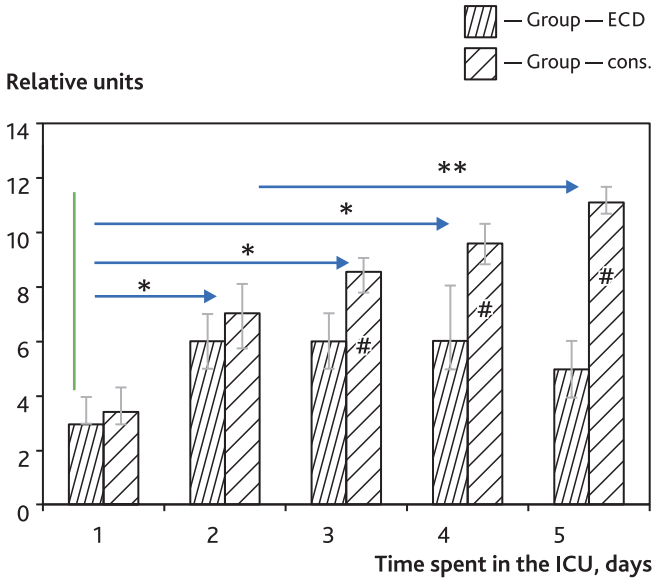

Fig. 2. The results of the analysis of the dynamics of the index of extravascular water in the lungs

Конс. — standard therapy (group 2); ЭКД — extracorporeal detoxification (group 1).

Note. Data are presented as Me (Q1–Q3). Statistical differences between groups were assessed using the Mann—Whitney *U*-test, intragroup differences using the Wilcoxon test.

* Statistically significant differences (Wilcoxon test, $p < 0.05$) in the index of extravascular water in the lungs in the group 1 and group 2 between the 1st and 2nd, 1st and 3rd, 1st and 4th days of therapy.

** Statistically significant differences (Wilcoxon test, $p < 0.001$) of extravascular water in the lungs in the group 1 and group 2 between the 1st and 5th days of therapy.

\# Statistically significant differences (Mann—Whitney *U*-test, $p < 0.05$) of extravascular water in the lungs between groups.

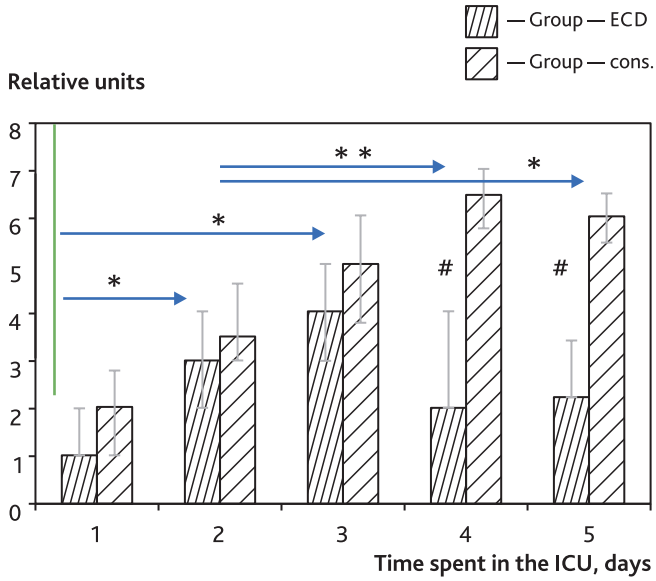

Fig. 3. Results of analysis of the pulmonary capillary permeability index

Конс. — standard therapy (group 2); ЭКД — extracorporeal detoxification (group 1).

Note. Data are presented as Me (Q1;Q3). Statistical differences between groups were assessed using the Mann—Whitney U-test, intragroup differences using the Wilcoxon test.

* Statistically significant differences (Wilcoxon test, $p < 0.05$) in the index of pulmonary capillary permeability in the 1st and 2nd groups between 1st and 2nd, 1st and 3rd, 1st and 5th days of therapy.

** Statistically significant differences (Wilcoxon test, $p < 0.001$) in the pulmonary capillary permeability index in the 1st and 2nd groups between the 1st and 4th days of therapy.

\# Statistically significant differences (Mann—Whitney U-test, $p < 0.05$) index of pulmonary capillary permeability between groups.

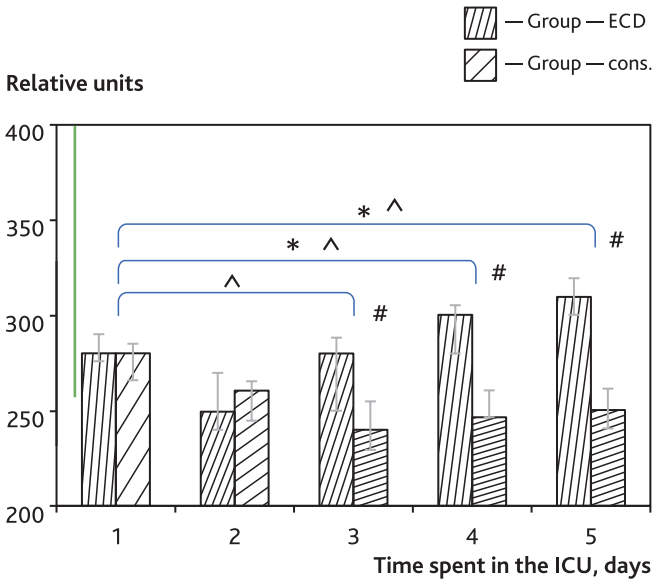

Fig. 4. Results of the analysis of the respiratory index (PaO_2/FiO_2)

Конс. — standard therapy (group 2); ЭКД — extracorporeal detoxification (group 1).

Note. Data are presented as Me (Q1–Q3). Statistical differences between groups were assessed using the Mann—Whitney *U*-test, intragroup differences using the Wilcoxon test.

* Statistically significant differences (Wilcoxon test, $p < 0.05$) of the respiratory index (PaO_2/FiO_2) in the group 1 between 1st and 4th, 1st and 5th days therapy.

^ Statistically significant differences (Wilcoxon test, $p < 0.05$) of the respiratory index (PaO_2/FiO_2) in group 2 between the 1st and 3rd, 1st and 4th, 1st and 5th days therapy.

\# Statistically significant differences (Mann—Whitney *U*-test, $p < 0.05$) in respiratory index (PaO_2/FiO_2) between groups.

of the disease in general as long-term result [26–28]. Meanwhile, the absence of relevant changes of the frequency of ALV in both groups apparently based on small quantity of patients and the results can be different when the quantity of participants increased.

Hospital lethality analysis

Comparative analysis of lethality while the participants were treated in in-patient clinic hasn't revealed any statistically relevant differences between the groups ($p = 0.19$). However, positive effect of different methods of extracorporeal detoxication were observed by many authors both in native and in foreign literature.

Discussion

Currently sufficiency and quality principles of infusion therapy are attached a huge value. Due to this, such term as fluid resuscitation was introduced. Meaning and value of early dedicated therapy in patients with acute pancreatitis have been unknown [8], but according to many authors it can improve process and outcome of the disease [33].

The results obtained in the process of our study confirmed the fact that patients with severe acute pancreatitis have severe hypovolemia by the moment of admission to RICU, which is evidenced by the data of transpulmonary thermodilution: IBVI, GEDVI, IVC diameter and CVP measurement (*see* Table 3). Sequestration, high losses and capillary leakage syndrome lead to severe hemoconcentration which is represented by the level of hematocrit, hemoglobin and erythrocytes (*see* Table 2). The results obtained by our team emphasize the importance and significance of early dedicated infusion therapy wich is in accordance with opinions of native and foreign authors [1, 3, 7, 8, 33].

The important result of our study is the data which conform the fact that conduction of infusion therapy in the volume of 57.5–58.3 ml/kg/day in the first day, 68.3–68.4 ml/kg/day in the second day and 79.3–83.9 ml/kg/day in the third day (*see* Fig. 1), is not sufficient which is evidenced by the results of CVP monitoring, IVC diameter and the data of transpulmonary thermodilution (*see* Table 3). It should be noted that transpulmonary thermodilution (PICCO-monitoring) is most specific and valuable marker of adequacy of volume load, and on the basis of the results of this method normovolemic parameters were achieved by the end of the second day compared to CVP and IVC diameter values (*see* Table 3) which was confirmed by hematological criteria in the form of hemodilution symptoms (*see* Table 2). According to opinion of some authors, it is worth to achieve the signs of normovolemia by the first and second days, however other authors state the fact that rapid and massive infusion therapy is associated with risks of organ failure and adverse outcomes [7–9, 21–23]. The data about quantity and speed of IT in patients with severe acute pancreatitis stay discussable, controversial and far from solving [3–10, 21–23, 33].

Data showing rapid normalization of respiratory index (Horowitz index) (*see* Fig. 4) on the background of the conduction of complex ECD compared to the group treated with conservative therapy look particularly encouraging and curious ($p < 0.05$). In our view this result was achieved due to possible complex impact of extracorporeal detoxication on markers of systemic toxicosis as a consequence of decrease of pulmonary vascular permeability index ($p < 0.05$) (Fig. 3), as well as correction of volemic component in the form of ELWI decrease ($p < 0.05$) (*see* Fig. 2), which wasn't observed in the group of conservative therapy.

Thus, the results of our study definitely evidence that transpulmonary thermodilution is the earliest and most relevant method of volume load monitoring. Increase of the volume of infusion therapy has pathogenic and reasonable character. Conduction of complex intensive care in association with the use of extracorporeal detoxication methods extremely positively impacts on clinical laboratory symptoms, severity of organ failure and the risk of adverse outcome. It should be mention that introduction of modern methods of detoxication can be useful as an instrument of control of volume status and reversal of adverse outcomes of excessive infusion therapy in the opinion of many popular authors [16, 17, 34].

Conclusion

The conduction of infusion therapy from the first till the third days in the volume of 3.5 ml/kg/hour helps to achieve normovolemia by the second-third days of complex intensive care, which confirms by classical laboratory symptoms and data of transpulmonary thermodilution and in our point of view this result is not sufficient.

Transpulmonary thermodilution method is the most optimal method of volumetrical parameters in conditions of complex intensive care conduction and massive volume load. Isovolemia is achieved by the second-third days based on the results of TPTD compared to classical method of IVC diameter and CVP control by the fourth and fifth days accordingly.

Inclusion the method of combined extracorporeal detoxication in standard complex intensive care provides earliest normalization of respiratory function of lungs by means of modeling of ELWI and PVPI concentration which is reflected in the increase of respiratory index.

In our point of view, the increase of volume load during the first 72 hours of intensive care till 5-6 ml/kg/hour (120–144 ml/kg/day) in connection with combined extracorporeal detoxication is the most effective, pathogenetically reasonable and rational in the conditions of significant hypovolemia and hemoconcentration and help to prevent

organ failure on the background of dynamic modulation of volumetric parameters which is probably improve the results of treatment and disease outcomes in general.

Disclosure. The authors declare that they have no competing interests.

Author contribution. All authors confirm the compliance of their authorship, according to international ICMJE criteria (all authors made a significant contribution to the development of the concept, research and preparation of the article, read and approved the final version before publication).

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