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## Features of Conservative Treatment of Acute Pancreatitis in Elderly Patients

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**Abstract.**

The results of conservative treatment of 45 patients with acute pancreatitis being treated as inpatients in pancreatology center of Ivano-Frankivsk Regional Clinical Hospital from 2011 to 2015 were analyzed. Two groups of patients were formed. Group I included 17 patients at the age from 50 to 65 years (the average age was  $57.2 \pm 4.8$  years). Group II included 13 patients at the age of 65 years and older (the average age was  $69.8 \pm 3.9$  years) - the main group. On the second-third day of treatment in patients of the comparison group infusion volume was about 55 (48;59) ml/kg/day; in patients of the main group it was 50 (48;54) ml/kg/day (the difference was statistically insignificant in a 95% confidence interval -  $W=78.5$ ,  $P=0.19$ ). In patients of the main group during treatment with low molecular weight heparin there were observed marked changes in the activated partial thromboplastin time. On the third day of treatment with low molecular weight heparin in patients of the main group the activated partial thromboplastine time constituted  $43.65 \pm 0.92$ s indicating the increase in the index by 83.0 % compared to the initial level. On the seventh day of treatment in this group of patients APTT was  $47.17 \pm 0.98$ s ( $p < 0.001$ ). In the comparison group it constituted  $27.54 \pm 1.03$ s; on the 7<sup>th</sup> day it was  $29.50 \pm 1.54$ s compared to the initial level. Intensive therapy of acute pancreatitis in elderly patients has a number of features associated with reduced functional reserves of organs and systems and provides restrictive approach to the choice of medications and their dosage.



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### **Problem statement and analysis of the recent research**

Acute pancreatitis (AP) is an actual problem in the emergency gastrointestinal surgery and intensive care and remains one of the most severe and life threatening diseases of abdominal cavity organs [1, 2].

In 2009, according to UN data, the quantity of people of senior age group in the world was 743 million (11% of total population), and by 2050 it shall be 2 billions (22% of total population of the planet). In Ukraine, by 2050 the persons of advanced and old age will have constituted approximately 38 % of population [1, 2]. During the last decade, increase in AP in patients of advanced and old age was registered. In 65% of patients of senior age group, AP course is relatively mild and effectively treated with conservative approach [2]. In Ukraine, the cases of AP constitute 102 per 100 000 of population, total lethality ranges from 4 to 15%, in cases of acute necrotizing pancreatitis (ANP) it constitutes 24-60%. The post-surgery lethality achieves 70% [3]. At the same time, lethality in case of AP in patients of senior group remains high, and in the cases of ANP it may reach 42-70% [4,5].

Due to the peculiarities of the physiological processes, concomitant polymorbidity, development of mutual resistance syndrome in persons of advanced age, the course of AP is frequently characterized by the development of multiorgan dysfunction. Based on the above mentioned, disciplined approach to the intensive care and surgical treatment of such patients is required. The problem of selection of the optimal schemes of infusion therapy as an integral part of complex treatment remains among the matters that need advanced study [3,4,5].

**The objective** of the research was to analyze and study the peculiarities of conservative therapy administration in case of acute pancreatitis in patients of senior age group.

### **Materials and methods of the research**

To achieve the objective, we analyzed the results of the conservative treatment of 45 patients with AP treated at Pancreatology Center of Ivano-Frankivsk Oblast Clinical Hospital during the period from 2011 to 2015.

The research criteria for inclusion of patients were as follows: 1) AP confirmed by clinical, instrumental, laboratory and (or) preoperative data; 2) manifestations of pancreatogenic shock in the onset of disease. The exclusion criterion was lethal result before 24 hours from the moment of hospitalization. Out of 45 patients only 30 patients completely corresponded to the inclusion criteria of this research.

Patients were divided into two groups for objectification of the study. The first group included 17 patients with AP at the age from 50 to 65, average age  $57.2 \pm 4.8$  (average value  $\pm$  standard deviation). The second group included 13 patients with AP at the age from 65 and senior, average age  $69.8 \pm 3.9$  (main group). All the patients were hospitalized at the intensive care unit for correction of hypovolemia, hypoxemia, dyselectrolytemia, glycemia control, monitoring of vital function, situational therapy. The scope and composition of infusion therapy in AP patients were checked twice per day.

Patients with enzyme peritonitis were administered laparoscopic sanitation and abdominal drainage. Open surgical interventions in case of infectious necrotizing pancreatitis required change of intensive care approach taking into consideration the pre-surgery condition of patients and existing complications (hemorrhage, septic shock). Review of the specific features of infusion therapy under such circumstances was beyond the scope our study.

Statistical analysis of research results was represented in median and quartile values (Me (0,5L; 0,5U) – median (lower, upper quartile), for comparison we used the methods of non-parametric statistics, in particular, for comparison of two odd groups of data – Mann-Whitney criterion (STATGRAPHICS Plus Version 5.1 software).

### Results of the research and their discussion

Control of pain syndrome and neurovegetative disorders frequently leading to shock condition during the first hours of the disease, takes an important place in the complex of medical measures. One should remember that narcotic pain medications are vagomimetic agents and cause such undesirable effects as spasm of sphincter of Oddi, increase in pressure in the bile ducts, increase in pancreatic juice enzyme activity. Therefore, administration of morphine and its derivatives in case of AP is contraindicated. Moreover, the patients of this category undergo the serious risk of respiratory and hemodynamics depression in case of administration of narcotic pain medications. In the experimental group nonnarcotic analgesics (Ketanov 10 mg every 4-6 hours, Dexalgin 50 mg every 8 hours, and also Ketorol or Riabal) were administered that not always delivered the expected result.

Epidural prolonged analgesia with 0.2% solution of Ropivacaine (Naropin) for anaesthetization was additionally used in the main group of patients. Such methodology, in addition to good analgesic effect, facilitated improvement of perfusion in the splanchnic zone and stimulation of the intestinal peristaltic. For epidural analgesia the epidural space was catheterized on the level Th7-Th8 or Th8-Th9. During the first 2-3 days, Ropivacaine was administered through the infusion pump with the speed of 5-8 ml /hour, further, the patient was transferred to bolus dosing of medication 6-8 ml every 3 hours. Bolus administration of Ropivacaine did not prevent the patients from activation and was safe in the conditions of compensated hypovolemia.

Massive sequestration of liquid in the "third space" in case of AP, including the loss of liquid in the parapancreatic cellular tissue, free abdominal cavity, pleural cavities, and accumulation of liquid in the lumen of the intestine and so on, may reach approximately 3-10 liters and lead to severe total hypoperfusion and pancreatic ischemia. For this reason, timely and sufficient by scope infusion therapy has extremely important significance.

In order to provide high intensity infusion therapy to patients, we catheterized one central vein (v. jugularis interna or v. subclavia with catheter of 1.4 mm in diameter) and one-two peripheral veins (catheters "Venflon 18 G"). Basic solutions for hypovolemia correction included crystalloids (0.9% sodium chloride solution, lactated Ringer's solution). If rapid infusion of 2.5-3.0 l of these solutions was not sufficient to achieve average blood pressure (Av.BP) over 65 mmHg, infusion of 1.5-2.0 l of synthetic colloid solutions, derivatives of Hydroxiethyl starch or Sodium Carbomer (Refortan, Venofundin, Gelofusine) was additionally used. In case the target value (Av.BP) was not achieved, we included sympathomimetics and inotropic agents into the intensive therapy scheme - dofamin±norepinefrin±dobutamine.

The effectiveness of infusion therapy and liquidation of total hypoperfusion were manifested by the improvement of consciousness level of patients, warmer and pink skin, reduction of capillary blood flow regeneration (less than 4 s), hourly diuresis more than 0.5 ml/kg/hour, level of Av.BP more than 65 mmHg, level of central venous pressure (CVP) more than 8 mmHg.

After elimination of the pancreatogenic shock manifestations, the basis of infusion therapy further consisted of crystalloid solutions in combination with glucose, insulin and potassium mixture (GIP) and preparations for parenteral alimentation (system "three in one" – "Kabiven" or "Oliclinomel"). The daily volume of solutions for intravenous infusion depended on perspiration, losses as a result of drainage, nasogastral probe and so on, and was ranging from 3 to 5 liters.

We analyzed the volume and composition of parenteral infusion solutions, hourly diuresis and frequency of sympathomimetics administration in patients of both groups.

The volume of solutions that were transfused to patients with AP of the first group during the first day of pancreatogenic shock treatment was 102 (95; 110) ml/kg/day, n=17. In the second group of patients this value was 90 (85; 98) ml/kg/day, n=13 (difference is statistically significant in 95% confidence interval - Mann-Whitney criterion  $W=43.0$ ,  $P=0.005$ ). Thus, advanced and old age patients with AP needed transfusion of infusion solutions in less volume to achieve target value of CVP.

In order to maintain Av.BP on the level of more than 65 mmHg, sympathomimetics were administered to 10 (77.0 %) of 13 patients of the main group, and to 6 (35.0 %) of 17 patients of the experimental group. However, this difference in both groups was statistically insignificant -  $\chi^2=3.59$ ,  $P=0.058$ . In our opinion, fast prescription of sympathomimetics and inotropic agents enables to maintain systemic hemodynamic values and reduce the intravenous infusion volume.

Hourly diuresis during the first day of treatment in patients of the experimental group constituted 0.7 (0.5; 0.9) ml/kg/hour, main group – 0.2 (0.15; 0.6) ml/kg/hour (difference was statistically significant -  $W=56.0$ ,  $P=0.023$ ). According to the analysis, despite the intensive infusion therapy, patients of advanced and old age had anuria before administration of combination of dofa $\pm$  dobutamine indicating age reduction of functional capacity of the kidneys, and also myocardium dysfunction, that though indirectly but also causes deterioration of renal perfusion. The latter is proved by the results of bedside echocardiography in 6 patients of the main group with ejection fraction of the left ventricle not more than 40-50%. In order to prevent the additional kidney injury in patients with oliguria, we avoided transfusion of hyperosmolar colloids.

On the second and third day of treatment the volume of infusion in patients of the experimental group was average 55 (48; 59) ml/kg/day, in patients of the main group - 50 (48; 54) ml/kg/day (difference was statistically insignificant in 95% confidence interval -  $W=78.5$ ,  $P=0.19$ ). GIP mixture constituted approximately half of infusion therapy scope in patients of both groups, and its administration enabled correction of isolated deficit of water and potassium. Irrespective of GIP, steady hyperglycemia occurred in all 13 patients of the main group and in 12 (70.5%) patients of the experimental group ( $\chi^2=2.71$ ,  $P=0.099$ ). Presence of hyperglycemia in majority of patients of both groups may show injury of not less than 50% of the pancreatic tissue.

Emergence of the significant peripheral swellings/inflammations was the result of negative consequences of aggressive infusion therapy, especially in patients of senior age group with AP, even in case of maximally justified volume of synthetic colloid solutions administration. In case of intensive infusion therapy on early stages of AP treatment (pancreatogenic shock) in the conditions of “capillary flow” syndrome, the transfused crystalloid and colloid solutions partially accumulate and lag in the interstitial space that causes general hyper hydration. The latter can be associated with hypovolemia confirming low CVP levels. The above mentioned causes significant difficulties in selection of quantitative and qualitative composition of agents for further infusion therapy. Prescription of synthetic colloid solutions in order to increase the volume of circulating blood in combination with loop diuretic for elimination of hyperhydration was not always effective. The use of restrictive approach in infusion therapy strategy of the pancreatogenic shock treatment with early prescription of sympathomimetics enables to reduce the total daily volume of intravenous infusions. In our opinion, the attempts of maintaining the target CVP cannot be of priority, and we cannot consider its level to be marker of hypovolemia severity. Under such conditions, in daily practical work the adequate volume of infusion therapy can be proved by patients’ consciousness according to Glasgo scale, in addition to echocardiography data, and sufficient hourly diuresis.

Blood products were used according to the strict indications. Packed red cells were prescribed in case of hemoglobin value in the peripheral blood less than 70 g/l (in patients with severe ischemic heart disease or significant pathology of the central nervous system – less than 90-100 g/l). Fresh frozen plasma was used in case of confirmed hypo coagulation. The volume of intravenously transfused solutions was reduced as soon as renewal of the effective intestinal peristaltic and possibility of enteral alimentation of patient was observed. In case of albumin level in blood less than 30 g/l, expressed peripheral swellings caused by prior aggressive infusion therapy in the conditions of “capillary flow” syndrome, we considered the possibility of transfusion of 10% donor albumin in quantity of 200 ml.

In order to prevent thromboembolic complications, we used low molecular weight heparin (LMWH). The medication was administered in standard doses, subcutaneously into the lateral abdominal wall. Convenience and simplicity of LMWH use, absence of expressed side effects and need of frequent laboratory monitoring, make them the first choice agents in prevention of thrombohemorrhagic complications in patients of advanced age with ANP.

We observed changes of activated partial thromboplastine time (APTT) and index reflecting the processes of blood coagulation according to the inner mechanism in patients of the main group on the background of LMWH administration. On the third day of treatment with LMWH, the APTT in patients of the main group constituted  $43.65 \pm 0.92$  sec indicating the increase in value by 83.0 % as compared to the initial level. On the seventh day of treatment, the APTT in patients of the mentioned group was  $47.17 \pm 0.98$ s ( $p < 0.001$ ). In the experimental group, APTT on the third day was  $27.54 \pm 1.03$  s., on the seventh –  $29.50 \pm 1.54$ s as compared to the initial level.

The aforecited affirms prevailing of hyper coagulation processes in patients of advanced age with ANP of the experimental group which was more expressed on the third day of the study.

In seven days after beginning of treatment with LMWH, the functional activity of thrombocytes in patients of the main group was characterized by the established extension of reduced chronometric parameters of thrombocytes aggregation as compared to the values of patients of the experimental group. In particular, the latent period of thrombocytes aggregation – by 18.6%, aggregation time – by 14.0%, reduction of aggregation level – by 11.8% ( $p < 0.05$ ), as compared to the initial values. Twofold reduction of IV thrombocyte factor activity indicates reduction of intensity of intravascular thrombocyte aggregates formation.

The level of fibrinogen produced by parenchymal cells of the liver in blood plasma of patients of the main group was not significantly different from the normal values, and during the period of hospitalization was on average level of  $3.52 \pm 2.12$  g/l. In patients of the experimental group this value during hospitalization constituted  $2.23 \pm 1.13$  g/l with respect to the norm ( $p < 0.05$ ). The mentioned values are characteristic of reduction of the liver protein synthesis function.

The indices of XIII factor of blood coagulation activity (fibrinase), enzyme that directly participates in formation of fibrine clot, in patients of the main and experimental groups practically would not differ on the first day after surgery and corresponded to the values of norm ( $p > 0.05$ ). However, this value in patients of the experimental group increased to 15.8 % on the third day, and to 18.6 % on the seventh day as compared to the initial level of the group. Increase in this value shows reduction of fibrinase activity that is a pre-condition for intensification of hyper coagulation processes.

Analysis of the received data proves that patients that were not treated with LMWH for prevention of trombohemorrhagic complications, had total potential of hemocoagulation increasing as a result of increase of thrombogenesis intensity by external and internal activation ways, activation of primary hemostasis platelet elements and reduction of anticoagulation potential.

Summarizing the above described information, it is worth noting that the acute pancreatitis intensive therapy in patients of senior age group has a series of peculiarities related with reduction of the functional reserves of the systems and organs and involves restrictive approach to selection of medications and respective dosing. For effective treatment of the pancreatogenic shock it is required to use intravenous infusion in less scope. Development of the myocardium dysfunction requires timely administration of inotropic agents. In case of high risk of kidney injury, the hyperosmolar colloid solutions should not be administered.

### Conclusions

1. Patients of senior age group with acute pancreatitis need transfusion of less volume of infusion solutions for achievement of target parameters of system hemodynamics as compared to patients of younger age.



2. Majority of patients of senior age group with acute pancreatitis have persistent acute myocardium dysfunction causing the need of urgent administration of inotropic agents during the initial phase of treatment.
3. Restrictive approach to infusion therapy in patients of senior age group at early stages of acute pancreatitis treatment with proactive prescription of dofamin enables reduction of emergence of excessive peripheral swellings and inflammations risk caused by the “capillary flow” syndrome.

### Perspectives of research in the field

Study of the peculiarities of acute pancreatitis conservative treatment in patients of senior age group will allow avoiding a number of complications related to reduction of the functional reserves of systems and organs and involves restrictive approach to selection of medications and their dosing.

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