

USE OF PLASMAPHERESIS IN HYPERTRIACYLGLYCEROLEMIA – INDUCED ACUTE PANCREATITIS

Použitie plazmaferézy pri hypertriacylglycerolémii – indukovanej akútnou pankreatitídou

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Abstract

Introduction. Acute pancreatitis (AP) remains one of the most complex problems of emergency abdominal surgery. One of the determined reasons for the AP development is hypertriacylglycerolemia. The frequency of hypertriacylglycerolemia-induced AP ranges from 10 to 38%.

Materials and methods. There were analyzed the results of the treatment of 57 patients with hypertriacylglycerolemia-induced AP, who were in the surgical department of the since 2018 to 2022. The main group of patients (37 (64.91%) included 29 (78.37%) men and 8 (21.62%) women with a median age of 42 years (Q1 – Q3 = 31 – 55). Plasmapheresis was used in patients of the main group, in addition to conservative treatment. The first session of plasmapheresis was started no later than a day after hospitalization and diagnosis of hypertriacylglycerolemia-induced AP.

Results. After the treatment, which included medicinal treatment and plasmapheresis, the level of glucose in the patients' blood decreased slightly. Among people without DM, the level of glucose in the blood was 4.90 mmol/l (4.45 – 5.30), in people with DM – it was on average 8.30 mmol/l (7.95 – 8.70) and decreased at only 7.78%. When using plasmapheresis in patients of the main group, the level of triacylglycerols decreased at 27.79 % compared to the initial values ($p < 0.05$). In the control group, where only conservative treatment was performed, the level of triacylglycerols decreased at only 3.22% ($p > 0.05$).

Conclusions. Early diagnosis of hypertriacylglycerolemia-induced acute pancreatitis and timely medicinal treatment using plasmapheresis made it possible to reduce the level of triacylglycerols in patients of the main group at 27.79% compared to the initial values ($p < 0.05$) (Tab. 2, Fig. 2, Ref. 29). Text in PDF www.lekarsky.herba.sk.

KEY WORDS: hypertriacylglycerolemia-induced acute pancreatitis, plasmapheresis, level of triacylglycerols. Lek Obz 2024, 73 (3): 85-90

Abstrakt

Úvod. Akútna pankreatitída (AP) zostáva jednou z najvážnejších komplikácií pri akútnej operácii brucha. Jedným z prejavov vývijajúcej sa AP je hypertriacylglycerolémia. Častotť výskytu AP v súvislosti s hypertriacylglycerol émiou sa pohybuje od 10 % do 38 %.

Materiál a metódy. Analyzovali sa výsledky liečby 57 pacientov s AP vyvolanou hypertriacylglycerol émiou, ktorí boli na chirurgickom oddelení od roku 2018 do roku 2022. Hlavná skupina pacientov (37 (64,91 %) zahŕňala 29 (78,37 %) mužov a 8 (21,62 %) žien s mediánom veku 42 rokov (Q1 – Q3 = 31 – 55). Plazmaferéza sa okrem konzervatívnej liečby používala u všetkých sledovaných pacientov. Prvá aplikácia plazmaferézy sa začala najneskôr deň po diagnostikovaní AP vyvolanej hypertriacylglycerol émiou.

Výsledky. Po liečbe, ktorá zahŕňala konzervatívnu liečbu a plazmaferézu, hladina glukózy v krvi pacientov mierne klesla. Pacienti bez DM mali hladinu glukózy v krvi 4,90 mmol/l (4,45 – 5,30), pacienti s DM – priemerne 8,30 mmol/l (7,95 – 8,70), pokles bol o 7,78 %. Pri použití plazmaferézy sa u sledovaných pacientov hladina triacylglycerolov znížila o 27,79 % v porovnaní s počiatočnými hodnotami ($p < 0,05$). V kontrolnej skupine, kde bola vykonaná iba konzervatívna liečba, sa hladina triacylglycerolov znížila iba o 3,22 % ($p > 0,05$).

Záver. Včasná diagnóza akútnej pankreatitídy v dôsledku hypertriacylglycerol émie a včasná liečba pomocou plazmaferézy umožnili znížiť hladinu triacylglycerolov u pacientov hlavnej skupiny o 27,79 % v porovnaní s počiatočnými hodnotami ($p < 0,05$) (tab. 2, obr. 2, lit. 29). Text v PDF www.lekarsky.herba.sk.

KLÚČOVÉ SLOVÁ: akútna pankreatitída, hypertriacylglycerol émia, plazmaferéza, hladina triacylglycerolov.

Lek Obz 2024, 73 (3): 85-90

Introduction

Acute pancreatitis (AP) remains one of the most complex problems of emergency abdominal surgery, which is caused by the growth of necrotic forms of the disease, purulent-septic complications, and significant economic costs for the treatment of patients (1, 2). Lethality in AP is 4.5 – 15%; in complicated forms it can

reach 60 – 85%, and in the fulminant course of the necrotic AP, complicated by the multiple organ failure, even 100% (3). One of the determined reasons for the AP development is hypertriacylglycerolemia. The frequency of hypertriacylglycerolemia-induced AP ranges from 10 to 38% (4, 5).

Hypertriacylglycerolemia is characterized by a concentration of triacylglycerols in the blood plasma of more than 2.0 mmol/l, an increase in the level of remnants of chylomicrons and intermediate particles of low-density lipoproteins (6, 7). Familial combined hypertriacylglycerolemia (FHTG), uncorrected diabetes mellitus (DM), alcohol abuse, taking a number of medications, and pregnancy, especially in the III trimester, contribute to an increase in the concentration of triacylglycerols (8). Hereditary hypertriacylglycerolemia is determined exclusively by an increase in the level of very low-density lipoproteins (VLDL), which is associated with endothelial dysfunction, leukocyte activation, and insulin resistance (9, 10).

When studying the mechanisms of hypertriacylglycerolemia-induced AP, it was found that an increase in the level of triacylglycerols and chylomicrons and their hydrolysis lead to the accumulation of toxic free fatty acids that damage mitochondria by inhibition of the mitochondrial complexes I and V, which is accompanied by a decrease in the level of acinar ATP and necrosis of pancreatic gland (PG) cells (11).

It has been determined that the systematic use of alcohol and fatty food stimulates an increase in the level of VLDL, excessive secretion of cholecystokinin and enzymes of the pancreas, which is a contributing factor to its fatty infiltration (12). Free fatty acids increase the signs of local inflammation, cause a cytotoxic "hit" not only on acinar cells, but also on the capillary epithelium, as a result of which the viscosity of the secretion in the PG ducts increases and acidosis progresses (13). The final stage of this inflammatory cascade is the premature activation of trypsinogen with the development of interstitial or necrotic AP (14, 15). In addition, hypercholesterolemia leads to oversaturation of bile with the cholesterol and the formation of biliary sludge/stones, which significantly increases the risk of developing biliary AP (16).

The recurrent course of the disease is considered to be a peculiarity of hypertriacylglycerolemia-induced AP, while the severity of the patient's condition is more often depends with the level of triacylglycerols in the blood (17, 18). The disease is often accompanied by pancreatogenic shock, the development of severe endogenous intoxication, which, with inadequate medicinal treatment, leads to purulent-septic complications and multiple organ failure (19, 20).

Various methods are used to reduce the level of lipoproteins in the blood of patients, and to correct endogenous intoxication (21, 22). Good results of patients' treatment were demonstrated when using extracorporeal treatment methods, in particular, plasmapheresis (23, 24). When using plasmapheresis, the improvement in the rheological properties of blood, a positive effect on indices of the body's bradykinin system, and a significant decrease in LDL levels were noted (25). At the same time, according to the eighth revision of the American Society of Afferent Therapy

guidelines (2019), patients with severe hypertriacylglycerolemia-induced AP were assigned to category III (the optimal role of apheresis has not been determined – decision-making should be individual), class 1C (26). Therefore, there is an urgent necessity to further study the effect of plasmapheresis on the manifestations of endogenous intoxication, and the reduction of the aggressiveness of the etiological factor in patients with hypertriacylglycerolemia-induced AP (27). Aim: to determine the effect of plasmapheresis on changes in lipid metabolism and glycemia level in patients with hypertriacylglycerolemia-induced acute pancreatitis.

Materials and methods

This cohort study involved of 57 patients with hypertriacylglycerolemia-induced AP, who were in the surgical department of the since 2018 to 2022. The main group of patients 37 people included 29 (78.37%) men and 8 (21.62%) women with a median age of 42 years (Q1 – Q3=31 – 55). Plasmapheresis was used in patients of the main group, in addition to conservative treatment. The control group 20 people included 15 (75.00%) men and 5 (25.00%) women, median age 39 years (Q1 – Q3=37 – 45). The patients of the control group were used only medicinal conservative treatment; plasmapheresis was not performed. Inclusion criteria were patients with different forms of hypertriacylglycerolemia-induced pancreatitis. Exclusion criteria were patients with oncological diseases, postoperative patients, including after endoscopic retrograde cholangiopancreatography. Plasmapheresis was performed in the first ten days for various forms of the disease.

There was used the classification of AP enacted at the international symposium in Atlanta in our work (2012) (29), with some additions of the working group of experts of the World Congress of Emergency Surgery, Edinburgh, Scotland (2021).

According to this classification, a comparative analysis of patients of the main and control groups is presented in the form of a table (Tab. 1).

To analyze the results of spiral computed tomography, there was used the classification of O. I. Dronov and co-authors (2013) (28). According to the criteria of this classification, 24 (64,86%) patients of the main group with pancreatic necrosis: 9 (24.32%) patients were diagnosed with subtotal surface necrosis of the PG, 6 (16.21%) patients were diagnosed with subtotal transmural PG necrosis, 4 (10.81%) patients were diagnosed with total surface PG necrosis, and 5 (13.51%) patients were diagnosed with total transmural necrosis of the PG.

To make the diagnosis of the disease, the criteria defined by the guideline for the diagnosis and treatment of AP (China, 2021) (1) were used. In particular, the presence of at least two of the three diagnostic criteria for AP should be present: abdominal pain, the level of lipase in the blood serum, which exceeds 3-fold the

Table 1. Comparative analysis of patients of the main and control groups with hypertriacylglycerolemia-induced AP to risk factors and nature of pancreatic necrosis.

Diagnostic	Main group (n=37)		Control group (n=20)	
	Absolute number	P (%)	Absolute number	P (%)
Interstitial hypertriacylglycerolemia-induced AP	13	35.13	4	20.00
Focal necrosis of the pancreas	19	51.35	11	55.00
Total-subtotal pancreatic necrosis	5	13.51	5	25.00
Aseptic pancreonecrosis	21	56.75	12	60.00
Infected pancreonecrosis	7	18.91	3	15.00
Acute isolated liquid formations of the omentum bag and retroperitoneal space	9	24.32	5	25.00
Regular alcohol consumption	17	45.94	7	35.00
The presence of DM	16	43.24	5	25.00
Violation of glucose tolerance	4	10.81	6	30.00
High cholesterol level	8	21.60	0	00.00*
Body max index \geq 25	16	43.24	8	40.00

* - statistically significant difference compared to the indices of the main group.

upper limit of the norm, as well as characteristic signs of the disease determined by the use of instrumental examination methods. In addition, to make the diagnosis of hypertriacylglycerolemia-induced AP, the level of triacylglycerols in the blood serum was determined, which should exceed the index of 2.0 mmol/l. The level of total protein, total cholesterol, triacylglycerols, VLDL, LDL, HDL in blood serum and the atherogenicity coefficient were determined in all studied patients with hypertriacylglycerolemia-induced AP after hospitalization.

Therapeutic plasmapheresis was performed using the "DigiPla 90" device (China), in a volume of 30 - 50% of circulating plasma under the control of the level of total protein in the blood. The first session of plasmapheresis was started no later than a day after hospitalization and diagnosis of hypertriacylglycerolemia-induced AP. Depending on the clinical picture of the disease, plasmapheresis included 1 - 3 cycles of blood exfusion with the removal of 300 to 1500 ml of plasma and the return of the patient's own erythrocyte mass to the bloodstream. The ratio of exfusion volumes was 50% - blood components, 25% - protein-containing solutions, 25% - saline solutions. All patients tolerated the plasmapheresis sessions well, there were no side effects or complications.

Contraindications to the use of plasmapheresis were: unstable hemodynamics, pronounced hypoproteinemia (blood protein level below 50 g/l), thrombocytopenia (platelet count below $150 \times 10^9/l$), anemia (hemoglobin < 80 g/l).

The criteria for the effectiveness of the treatment of patients with hypertriacylglycerolemia-induced AP in the main group and the comparison group were considered to be a decrease in the average indices of the lipid spectrum, in particular, triacylglycerols, total cholesterol, and VLDL cholesterol.

Data analysis was performed using the licensed statistical analysis package IBM SPSS 26.0 for Windows.

The indices obtained during the study are represented by the median and interquartile range (25th and 75th percentiles). Non-parametric tests (Mann - Whitney, Wilcoxon ones) were used to check statistical hypotheses. A critical level of statistical significance was set at 95% ($p=0.05$), indicating a low probability of obtaining a forecast by chance. The identification of potential determinants that slow down the recovery process, was performed by calculating the odds ratio (OR) with a 95% confidence interval (CI).

Results of the research

It was determined that the average level of blood glucose in the main group of patients without diabetes mellitus before the start of treatment was 5.10 mmol/l (4.30 - 5.70), in patients with DM this index was 9.00 mmol/l (8.70 - 9.58) ($p < 0.001$). After the treatment, which included medicinal treatment and plasmapheresis, the level of glucose in the patients' blood decreased slightly. Among people without DM, the level of glucose in the blood was 4.90 mmol/l (4.45 - 5.30) ($p > 0.05$), in people with DM - was on average 8.30 mmol/l (7.95 - 8.70) and decreased at only 7.78% ($p < 0.001$).

An opposite situation was observed in the control group. Before the treatment (among people without DM) the average level of glycemia was 5.80 mmol/l (4.90 - 6.50), in people with DM the level of glycemia was 9.70 mmol/l (9.20 - 9.85) ($p < 0.001$). Thus, in patients without DM, the level of glycemia after the treatment remain was 5.67 mmol/l (4.95 - 6.30), and decreased only at 2.24% ($p > 0.05$). Among people with DM, the average level of blood glucose after the treatment was 9.05 mmol/l (8.57 - 9.19), so it decreased at 6.70% and was statistically significant ($p > 0.05$).

Before the treatment, all patients had a significant increase in the level of almost all indices of lipid metabolism - cholesterol, triacylglycerols, LDL, VLDL, HDL, atherogenicity coefficient. The level of protein in the blood remained within the normal range (Tab. 2).

Table 2. Changes in the main indices of lipid metabolism in patients with acute pancreatitis in the main and comparison groups on the third day after the treatment.

	Indices	Main group				Control group			
		Before the treatment		After the treatment		Before the treatment		After the treatment	
		Me	Q ₁ - Q ₃	Me	Q ₁ - Q ₃	Me	Q ₁ - Q ₃	Me	Q ₁ - Q ₃
1	Total protein, g/l	78.05	75.21 - 80.12	77.12*	75.25 - 78.73	75.36	73.14 - 79.87	75.74	73.24 - 78.92
2	Cholesterol, mmol/l	7.34	6.46 - 7.98	5.59*	5.12 - 6.18	7.75	7.24 - 8.33	7.01^#	6.69 - 7.85
3	Triacylglycerols, mmol/l	3.85	3.59 - 4.05	2.43*	2.00 - 2.76	3.74	3.39 - 4.12	3.09^#	2.92 - 3.73
4	LDL, mmol/l	4.01	3.48 - 4.26	2.59*	2.21 - 2.84	3.79	3.63 - 4.12	3.11^#	2.78 - 3.39
5	VLDL, mmol/l	1.51	1.38 - 1.68	1.45*	1.34 - 1.54	1.54*	1.45 - 1.68	1.48	1.39 - 1.59
6	HDL, mmol/l	1.26	1.17 - 1.32	1.22*	1.14 - 1.27	1.26	1.21 - 1.32	1.21^	1.16 - 1.27
7	CA	4.93	4.24 - 5.40	3.72*	3.19 - 4.15	5.11	4.71 - 5.79	5.04^#	4.36 - 5.61

LDL - low-density lipoproteins; HDL - high-density lipoproteins; CA - atherogenicity coefficient; * - statistically significant difference compared to the indices of the main group before the treatment; ^ - statistically significant difference compared to the indices of the comparison group before the treatment; # - statistically significant difference compared to the values of the main group after the treatment.

When using plasmapheresis in patients of the main group, the level of triacylglycerols decreased at 36.88% compared to the initial values ($p < 0.001$). In the comparison group, where only conservative treatment was performed, the level of triacylglycerols decreased at only 17.5% ($p > 0.05$) during the same period of time. If before the treatment, triacylglycerole levels of the patients in the main and comparison groups were approximately the same, then a statistically significant difference between these indices was already observed during the 2nd - 4th day (Fig. 1). In the main group of patients, a faster decrease in the level of triacylglycerols in the blood was observed; it was already noticeable 24 hours after beginning of the treatment (Fig. 1).

The patient's gender and body mass index influenced the rate of normalization of triacylglycerole level in a main group. Thus, the male gender of patients almost halves the chances of normalization of the triacylglycerols level in the blood (OR = 1.86; 95% CI: 1.24 - 5.46; $p < 0.05$), and the body mass index is 25.0 and higher - contributed to the rate of normalization of the level

of triacylglycerols in the blood even more (OR = 2.54; 95% CI: 1.46 - 8.56; $p < 0.05$), (as indicated in Fig. 2).

Figure 2. Determinants affecting the rate of decrease in the level of triacylglycerols in the blood of patients with acute pancreatitis.

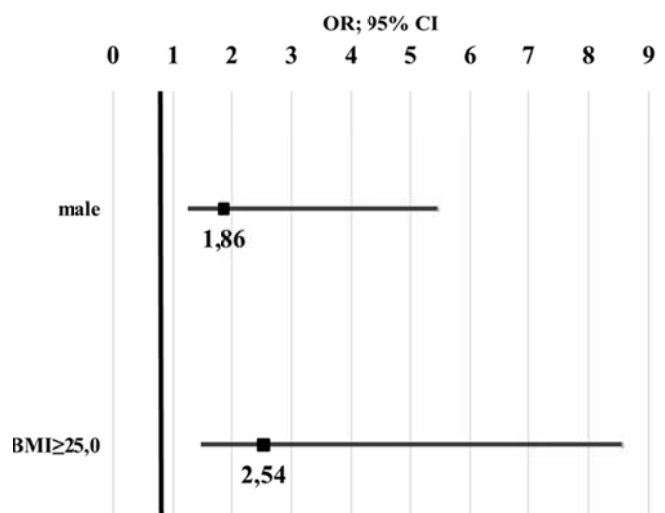
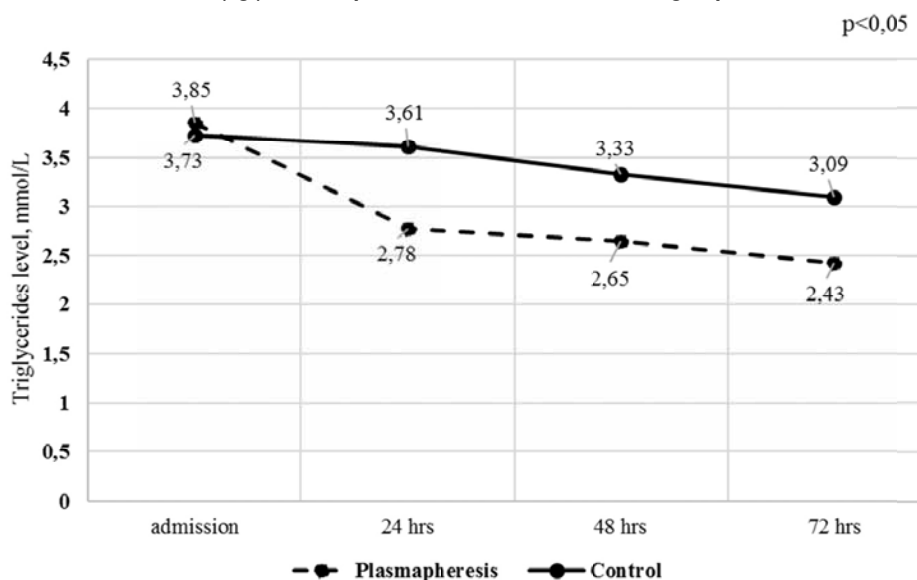


Figure 1. Decrease in the level of blood triacylglycerols in patients of the main and control groups.



During the treatment of patients of the main group with hypertriacylglycerolemia-induced AP, where plasmapheresis was used, and patients of the comparison group during the first two weeks of the disease, no fatal consequences were noted.

Discussion

The use of plasmapheresis and full medical treatment in patients with hypertriacylglycerolemia-induced AP of the main group provided a decrease in the level of glucose in the blood, an average, at 11.2% ($p < 0.001$), which had a significant effect on the overall course of acute pancreatitis. A similar situation was noted in patients of the comparison group, in which the use of only conservative treatment contributed to a decrease in the blood glucose level, an average, at 1.64% and was not statistically significant ($p > 0.05$).

Instead of this, the results of the studies performed indicate a significant decrease in lipid metabolism indices in the main group of patients with hypertriacylglycerolemia-induced AP. Thus, a significant decrease in the level of triacylglycerols in the blood was already noted in the patients of the main group during the 2nd day after the treatment; this was not noted in the comparison group. ($p > 0.05$). This coincides with the provisions and guidelines for the use of therapeutic apheresis in clinical practice of the American Apheresis Society guidelines (26). In addition, very low density lipoprotein levels and atherogenicity coefficient were statistically significantly decreased in the patients of the main group.

When analyzing the gender and body mass index of patients more than 25.0 and above, as indices that can influence the reduction of the level of triacylglycerols in the blood in hypertriacylglycerolemia-induced AP, it was determined that excessive body weight and male gender reduce the chances of normalization of the triacylglycerols level in the blood at almost 50%. The same data are provided by a number of other researchers who consider excess body weight to be a risk factor for the severe course of the disease (1, 3, 4).

When performing plasmapheresis in patients with hypertriacylglycerolemia-induced AP, we've noted a high level of "therapeutic compliance", which is also indicated by the studies of a number of authors (24, 25).

The given above results cause further interest in making research in this direction, in particular, regarding the determination of the effectiveness and other effects of the hypolipidemic effect of plasmapheresis in the complex treatment of hypertriacylglycerolemia-induced AP.

Conclusion

1. A pronounced hypolipidemic effect in patients with hypertriacylglycerolemia-induced acute pancreatitis occurs after the first plasmapheresis session and is accompanied by a significant decrease in the lipid profile.

2. Early diagnosis of hypertriacylglycerolemia-induced acute pancreatitis and timely medicinal treatment using plasmapheresis made it possible to reduce the level of triacylglycerols in patients of the main group at 27.79% compared to the initial values ($p < 0.05$).

*All procedures in studies involving human participants, were performed in accordance with the ethical standards of the institutional ethics committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This investigation was approved by the Ethics Committee (Meeting Minutes No. 94/16, February 16, 2016).

The written informed consent was obtained from each participant.

The authors declare no conflict of interest.

The data that support the findings of this study are available from the corresponding author upon reasonable request. No funding was received for this study.

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Accepted for publication September 19, 2023.

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