Translated by A.P. Strelkova

Venous Thromboembolic Complications in Patients with Acute Chemical Poisoning

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RELEVANCE Venous thromboembolic complications (VTEC) occur in patients hospitalized with various pathologies, complicate treatment and increase mortality. This problem has not received enough attention in toxicology.

AIM OF THE STUDY Conduct an analysis of VTEC in patients with acute chemical poisoning (AP).

MATERIAL AND METHODS The hospital patient records and pathological examination reports of 670 patients of the N.V. Sklifosovsky Research Institute for Emergency Medicine who died from VTEC in the period 2016–2022 were retrospectively analyzed. VTEC were confirmed by Doppler ultrasound during life or during pathological examination. Statistical analysis of the data was performed using the IBM computer program SPSS Statistics 26.0.

RESULTS VTEC were diagnosed in 245 patients. The proportion of VTEC increased from 20.2 to 46.7% over the years, and in cases of VTEC caused by psychopharmacological drugs, they were registered in 48.8% of cases. VTEC occurred twice more often in people over 60 years of age and 1.3-fold more often in women. Deep vein thrombosis of the right lower limb was predominant in all types of poisoning, and the prevalence of the lesion was mainly local. Concomitant cardiovascular diseases, oncological diseases, diabetes mellitus, and the development of pneumonia increased the risk of VTEC. Pulmonary embolism was observed in more than a third of cases of VTEC in patients with VTEC caused by psychopharmacological drugs, corrosive substances, and hypotensive and antiarrhythmic drugs.

CONCLUSIONS The characteristics of venous thromboembolic complications in acute chemical poisoning in general is similar to the complications indicated that arise in other pathologies, but has some features caused by the effect of specific chemicals on the body.

Keywords: venous thromboembolic complications, pulmonary embolism, acute chemical poisoning, psychopharmacological drugs, antihypertensive and antiarrhythmic agents, corrosive substances

For citation Belova MV, Ilyashenko KK, Sukhodolova GN, Kungurtsev EV, Polunin AV, Potskhveriya MM, et al. Venous Thromboembolic Complications in Patients with Acute Chemical Poisoning. *Russian Sklifosovsky Journal of Emergency Medical Care*. 2024;13(3):419–426. https://doi.org/10.23934/2223-9022-2024-13-3-419-426 (in Russ.)

Conflict of interest Authors declare lack of the conflicts of interests

Acknowledgments, sponsorship The study has no sponsorship

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ACP - acute chemical poisoning
antiHADs - antihypertensive and antiarrhythmic drugs
CS - corrosive substances
CVA - acute cerebrovascular accident
NPAS - narcotic and psychoactive substances
PE - pulmonary embolism
PPD - psychopharmacological drugs
VTEC - venous thromboembolic complications

Venous thromboembolic complications (VTEC) have been a serious problem for many decades in patients hospitalized with various pathologies. VTEC is a collective term that includes superficial and deep vein thrombosis, as well as pulmonary embolism (PE). These complications often determine the course and outcome of the underlying disease not only in the immediate but also in the long term [1].

According to literature data, mortality from VTEC in the USA and Europe reaches 300,000–600,000 cases per year and exceeds the number of deaths from acquired immune deficiency syndrome (AIDS), breast cancer, prostate cancer and car accidents combined [2, 3]. According to S. Bates et al., VTEC occurs in 0.5–2.2 cases per 1000 population depending on the population studied [4].

In the Russian Federation, according to the Association of Phlebologists, about 80,000 new cases are registered annually. In 60 years, the incidence of venous thrombosis increases several times and reaches 200 cases per 100,000 population per year. PE is registered annually with a frequency of 35–40 per 100,000 people [5].

Since the clinical picture of superficial and deep vein thrombosis in patients in the early stages of hospital stay is sometimes asymptomatic, in some cases the first manifestation of VTEC is sudden death. Thrombosis of any localization can be complicated by pulmonary embolism. However, in 90% of cases, its source is thrombi of the veins of the lower extremities, pelvic vein or inferior vena cava system [5]. Up to 60% of VTEC cases occur during or after hospitalization, and more than 40% of them can be prevented through prophylaxis, which makes VTEC the leading preventable cause of death in hospital [6]. VTEC is not the prerogative of any one medical specialty. According to domestic and foreign authors, the incidence of VTEC in hospital practice is 43% of patients in therapeutic departments and 16% in surgical departments of various profiles. Three-fold higher number of patients die from pulmonary embolism in therapeutic departments than in surgical departments. Analysis of autopsy results showed that pulmonary embolism as a cause of death accounts for 15.6% of all in-hospital mortality and up to 25% of postoperative mortality in surgical hospitals. PE accounts for 50% of deaths after appendectomy, cholecystectomy, herniotomy, 28–36% after operations on large joints. Pulmonary thromboembolism is the direct cause of death in 8 to 35% of cancer patients [7].

It should be noted that despite the relevance of this problem, not enough attention has been paid to toxicology.

The aim of the study was to conduct a retrospective analysis of VTEC in patients with ACPs.

MATERIAL AND METHODS

A retrospective study of hospital patient records (form No. 003/u) and pathological autopsy protocols (form No. 013/) was conducted. u) 670 patients of the N.V. Sklifosovsky Research Institute for Emergency Medicine, Moscow, who died from acute respiratory distress syndrome at different times from the moment of hospitalization during the period from 01.01.2016 to 31.12.2022. Among them, there were 211 people with poisoning with psychopharmacological drugs (PPD), 152 with corrosive substances (CS), 126 with narcotics and psychoactive substances (NPAS), 64 with alcohols, 55 with antihypertensive and antiarrhythmic drugs (antiHADs). The "Others" group, which included patients with poisoning with carbon monoxide (combustion products), paracetamol, plant poisons (aconite, colchicum, mushrooms), consisted of 62 patients. The age of the patients had a wide range from 18 to 97 years. There were 383 men and 287 women.

VTEC were diagnosed by ultrasound Dopplerography during life or thrombi and pulmonary embolism were detected during pathological examination. Statistical analysis of the data was performed using the *IBM SPSS Statistics* 26.0 computer program. The hypothesis of statistically significant differences in the frequencies of right-sided and left-sided thrombosis in the group of patients under consideration was tested according to the binomial distribution model using its approximate representation by the Gaussian distribution [8]. The significance level was set at $p<0.05$. Comparison of categorical data was performed using the two-sided χ^2 criterion.

RESEARCH RESULTS

When analyzing the material, it was found that VTEC occurred in 245 patients, i.e. in 36.56% of cases from the total number of deaths. Of these, 123 were men (50.2%) and 122 women (49.8%).

Fig. 1 shows the dynamics of the development of VTEC in acute exotoxicosis for the period from 2016 to 2022. It follows from it that, in general, during this time, there was a tendency towards an increase in the proportion of patients with these complications from 20.2% in 2017 to 46.6% in 2020. The increase in the proportion of VTEC (more than 40%) in 2020–2022 is noted.

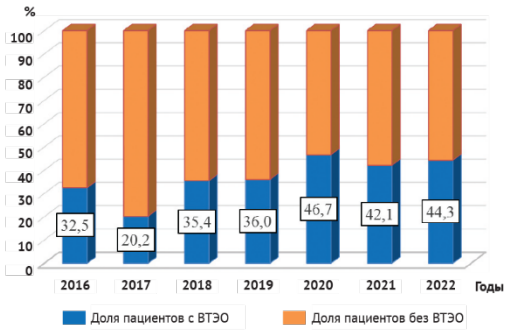

Fig. 1. Incidence of venous thromboembolic complications in deceased patients with acute chemical poisoning in 2016–2022

The incidence of VTEC was different in cases of poisoning with different groups of toxicants (Fig. 2). The diagram shows that the highest number of patients with VTEC were in the groups with PPD (103 of 211) and CS (55 of 152) poisoning, and the lowest number was in the groups with H (34 of 126) and alcohol (16 of 64) poisoning. In patients who died from antiHADs poisoning and in the "Other" group, VTEC were observed in 32.7% and 30.6%, respectively. Pairwise comparison of the incidence of VTEC in groups of people poisoned with different toxicants revealed that PPD poisoning statistically significantly increases the risk of VTEC compared to poisoning with other substances: CS (p = 0.022), NPAS (p = 0.0001); alcohols (p = 0.001); antiHADs (p = 0.047).

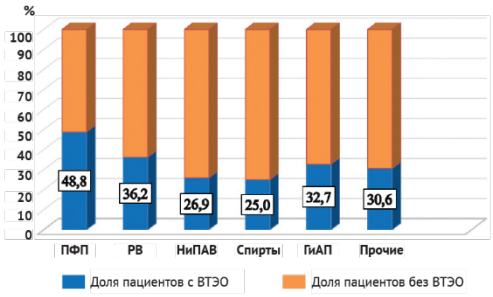

Fig. 2. Incidence of development of venous thromboembolic complications (VTEC) depending on the toxicants that caused poisoning

Notes: * — statistically significant difference in the incidence of VTEC in acute poisoning with psychopharmacological drugs (PPD) from poisoning with other toxicants. AntiHADs - antihypertensive and antiarrhythmic substances; NPAS - narcotic and psychoactive substances; CS - corrosive substances

Venous thrombosis occurs due to hemodynamic disturbances caused by slowing of blood flow, damage to the endothelium of the vascular wall, hypercoagulation and inhibition of fibrinolysis. One of the important reasons for slowing of blood flow is immobilization, leading to dysfunction of the muscular-venous pump of the legs. Significant - mechanisms initiating thrombosis include damage to the venous wall and disruption of the integrity of the endothelial layer. First of all, damage occurs due to oxidative stress, since powerful oxidants released by activated leukocytes cause death of endothelial cells with subsequent exposure of the subendothelial layer. These factors, with prolonged exposure, form a state of prothrombotic readiness [9]. These predictors of thromboembolic complications also occur in toxicological patients. Thus, we previously established microhemodynamic disturbances and a state of oxidative stress, most pronounced in acute poisoning with CS [10].

In our opinion, the high frequency of the above complications in PPD poisoning, along with the above factors, is associated with prolonged immobilization and hypoxia at the early stage of the disease, while in drug and alcohol poisoning, consciousness is restored much faster, and therefore motor activity is restored earlier. In the genesis of VTEC in acute CS poisoning, the major role of oxidative stress and systemic inflammatory response cannot be ruled out.

We assessed the influence of gender and age of patients on the incidence of VTEC (Table 1). Patients under 40 years of age were considered as a single group due to the fact that they develop lower extremity vein thrombosis less frequently than the older age group [11].

Table 1

Incidence of VTEC in patients of different gender and age

	Up to 40 years	41–50 years old	51-60 years old	61–70 years old	71–80 years old	Over 80 years old	Total
Men							
Quantity	122	64	61	49	38	49	383
VTEC	22	17	15	26	19	24	123
%	18	26.5	24.5	53.06	50	48.9	32.11
Women							
Quantity	27	21	28	30	64	117	287
VTEC	5	4	6	12	34	61	122
%	18.5	19.04	21.42	40	53.1	52.1	42.56

Note: VTEC - venous thromboembolic complications

It follows from Table 1 that VTEC were 1.3-fold (p = 0.006) more often occurred in women than in men. The incidence of VTEC in both men and women in the age groups up to 40 years and from 40 to 60 years did not differ statistically significantly (p = 0.30) and was about 19%. At the same time, VTEC were observed in almost half of patients over 60 years old. Thus, these complications are 2-fold (p = 0.0001) more often observed in older patients. Moreover, among men, the highest percentage of VTEC was reveaaled in patients aged 60–70 years, and among women — at an older age. According to the Association of Phlebologists, after 60 years, the incidence of venous thrombosis increases several times and reaches 200 cases per 100,000 population per year. PE is registered annually with a frequency of 35–40 per 100,000 people [5]. In our opinion, this is primarily associated with the development of metabolic disorders and cardiovascular diseases in older age groups.

An assessment was made of the incidence of VTEC depending on the presence of concomitant and background diseases (Table 2).

Table 2

Incidence of development of venous thromboembolic complications depending on concomitant diseases

Related diseases	Without VTEC (n =425)	With VTEC (n =245)	χ^2
Cardiovascular diseases	28.2% (120)	60.8% (149)	68.65; p <0.0001
Diabetes mellitus	4.9% (21)	25.3% (62)	59.38; p <0.0001
Malignant neoplasms	14.6% (62)	32.2% (79)	29.16; p <0.0001
Pneumonia	54.6% (232)	78.17% (193)	39.20; p <0.0001
CVA	0.9% (4)	7.35% (18)	20.08; p <0.0001

Note: VTEC - venous thromboembolic complications

The obtained results, presented in Table 2, showed that all the identified concomitant diseases contribute to the development of VTEC with a high degree of statistical significance. Thus, in patients suffering from diabetes mellitus, VTEC were diagnosed 5-fold more often, cardiovascular diseases 2.15-fold more often, and malignant neoplasms 2.2-fold more often than in similar groups without them.

The presence of a history of acute cerebrovascular accident (CVA), especially during the last 2 years, increased the risk of developing VTEC 8.2-fold. In the presence of several diseases, complications were even more common. Our data are consistent with the opinion of other authors, who also assign a priority role in the development of VTEC to diabetes mellitus, cardiovascular and oncological diseases, CVA [12].

Ultrasound examinations of the lower extremities were performed on patients at various times from the moment of admission to the hospital, most often in the period from the 1st to the 14th day. In 50 people (20.4%), no VTEC were detected during the first examination, conducted from the 1st to the 12th day. However, repeated examinations in the period up to the 23rd day showed the presence of thromboses of various veins of the lower extremities.

In 23 patients (9.4%) who died within 16 days from the moment of hospitalization, ultrasound examination of the veins was not performed, while deep vein thrombosis of the lower extremities and pulmonary embolism were detected in them during pathological examination.

A study was conducted to determine the localization of blood clots in patients in the study groups (Table 3).

Table 3

Location of lesions in patients with deep vein thrombosis of the lower extremities depending on the type of toxicant

View toxicant	Total observations	Localization of thrombus in the limb, *n* (%)		
		Right	Left	Both
PPD	103	54 (52.5)	14 (13.6)	35 (33.9)
CS	55	26 (47.3)	11 (20.0)	18 (32.7)
NPAS	34	18 (52.9)	6 (17.6)	10 (29.4)
Alcohols	16	9 (56.2)	4 (25.0)	3 (18.8)
AntiHADs	18	8 (44.4)	3 (16.7)	7 (38.9)
Other	19	12 (63.2)	3 (15.8)	4 (21)
Total	245	127 (51.8)	41 (16.7)	77 (31.4)

Notes: AntiHADS- antihypertensive and antiarrhythmic drugs; NPAS - narcotic and psychoactive substances; PPD - psychopharmacological drugs; CS - corrosive substances

It follows from the data in Table 3 that in 68.5% of patients with chemical etiology of ACP, regardless of the type of toxicant, thrombosis of the veins of the lower extremities was unilateral, but on the right side these complications occurred 3.1-fold more often than on the left. Thus, the right extremity is the most frequent localization of the lesion in all the studied groups of patients. It should be noted that in 31.4% of cases, bilateral lesions of the veins of the lower extremities occurred, more often in cases of poisoning with PPD and antiHADs.

In 2009, B.S. Sukovatykh et al. suggested a classification that allows assessing the prevalence of the thrombotic process. According to this classification, the assessment was carried out as follows: thrombosis of only one segment of the deep veins was considered local, thrombosis of the popliteal and superficial femoral veins was widespread, deep veins of the leg, popliteal and femoral veins were subtotal, deep veins of the leg, limb and pelvis were total [13] (Table 4).

Table 4

The prevalence of the thrombotic process in acute poisoning according to the classification of BS Sukovatykh et al. [13]

Type of toxicant, number of patients	Prevalence of thrombotic process, *n* (%)			
	Local	Common	Subtotal	Total
PPD, *n* = 103	49 (47.5)	19 (18.2)	6 (5.8)	29 (28.2)
CS, *n* =55	23 (41.8)	12 (21.8)	6 (10.9)	14 (25.5)
NPAS, *n* =34	16 (47)	7 (20.5)	6 (17.7)	5 (14.8)
Alcohols, *n* =16	8 (50)	3 (18.75)	2 (12.5)	3 (18.75)
AntiHADs, *n* =18	6 (33.3)	5 (27.8)	2 (11.1)	5 (27.8)
Other, *n* =19	12 (63.1)	2 (10.6)	2 (10.6)	3 (15.7)
Total, *n* =245	114 (46.5)	48 (19.6)	24 (9.79)	59 (24.1)

Notes: antiHADs - antihypertensive and antiarrhythmic drugs; NPAS - narcotic and psychoactive substances; PPD - psychopharmacological drugs; CS - corrosive substances

It follows from Table 4 that local thrombosis prevailed in the studied contingent of deceased patients. It is noteworthy that total thrombosis occurred in more than 25% of individuals with poisoning by PPD, antiHADs, and CS.

In 20 cases (8.16%), thrombosis of the central venous catheter was detected, mainly in patients with CS poisoning - 10.9% (6 people) and PPD 9.7% (10 people). In the remaining groups, catheter thrombosis was isolated.

During pathological examination, PE was confirmed in 79 patients (32.2%), and as the cause of death in 13 of them (5.3%).

The incidence of PE depending on the type of toxicant is shown in Fig. 3.

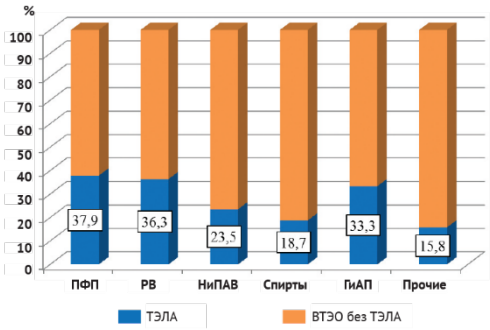

Fig. 3. Incidence of development of pulmonary embolism in deceased patients with VTEC in the course of acute chemical poisoning depending on the type of toxicant

Notes: VTEC - venous thromboembolic complications; antiHADs - antihypertensive and antiarrhythmic drugs; NPAS - narcotic and psychoactive substances; PPD - psychopharmacological drugs; CS - corrosive substances; PE - pulmonary embolism

From the presented diagram (Fig. 3) it follows that PE most often occurred in patients with poisoning with PPD (37.9%), CS (36.3%) and drugs affecting the cardiovascular system (33.3%).

We conducted a study that allowed us to identify the frequency of occurrence of PE depending on the prevalence of the thrombotic process (Table 5).

From the presented table it follows that PE develops in patients with varying prevalence of the process, but most often in case of the involvement of 4 or more veins.

CONCLUSION

The conducted studies have shown that the characteristics of venous thromboembolic complications in acute poisoning of chemical etiology are generally consistent with the specified complications arising in other pathologies. Thus, venous thromboembolic complications in acute chemical poisoning develop with the same frequency as in patients of therapeutic and surgical departments, statistically significantly higher in older people and with concomitant diseases [7]. However, there are some features due to the effect of specific chemicals on the body.

Table 5

Incidence of pulmonary embolism occurrence depending on the prevalence of the thrombosis

View toxicant	Local		Common		Subtotal		Total		Total	
	Number of patients		Number of patients		Number of patients		Number of patients		Number of patients	
	n	PE, *n* (%)	*n*	PE, *n* (%)	*n*	PE, *n* (%)	*n*	PE, *n* (%)	*n*	PE, *n* (%)
PPD	44	14 (31.8)	23	8 (34.7)	8	3 (37.5)	22	13 (59.1)	103	38 (36.9)
CS	20	6 (30.0)	17	6 (35.3)	8	3 (37.5)	10	5 (50.0)	55	20 (36.4)
NPAS	10	1 (10.0)	10	2 (20.0)	6	2 (33.3)	8	3 (37.5)	34	8 (23.5)
Alcohols	6	1 (16.7)	8	1 (12.5)	0	0	2	1 (50.0)	16	3 (18.7)
antiHADs	6	3 (50.0)	4	2 (50.0)	2	0	6	2 (33.3)	18	7 (38.9)
Other	8	1 (12.5)	2	0	4	1 (25.0)	5	1 (20.0)	19	3 (15.8)
Total	94	26 (27.6)	70	19 (27.1)	28	9 (32.1)	53	25 (47.1)	245	79 (32.2)

Notes: antiHADs - antihypertensive and antiarrhythmic drugs; NPAS - narcotic and psychoactive substances; PPD - psychopharmacological drugs; CS - corrosive substances; PE - pulmonary embolism

In various types of acute chemical poisoning, similar homeostasis disorders occur, and their intensity is associated with the characteristics of a specific toxicant, the severity and stage of intoxication. From the earliest stages of acute poisoning, the body of victims experiences disturbances in water-electrolyte balance, acid-base balance, hemorheology, central hemodynamics and oxidative stress [10]. Patients' low mobility leads to a decrease in the tone of the veins of the lower extremities and a decrease in the blood flow velocity in these areas. Puncture and catheterization of the central veins lead to vascular trauma, which is an additional factor in the development of venous thromboembolic complications.

The most frequent development of venous thromboembolic complications and pulmonary embolism in acute poisoning with psychopharmacological drugs, in our opinion, is associated with prolonged immobilization of patients, especially those in a comatose state, which leads to a slowdown in blood flow. Another important trigger for thrombotic complications is a violation of the integrity of the vascular endothelium, which can be due to oxidative stress developing in acute poisoning, to a greater extent in acute poisoning with corrosive substances. The third most important nosology for the occurrence of thrombotic complications of acute poisoning were hypotensive and antiarrhythmic drugs, accompanied by cardiotoxic shock and a critical slowdown in blood flow. In addition, such poisonings more often occurred in people suffering from cardiovascular diseases, and therefore initially having vascular damage of varying degrees.

Considering the numerous factors leading to increased thrombus formation and, as a result, the high incidence of venous thromboembolic complications in patients with toxicological profiles, further in-depth study of this problem is necessary to reduce the risk of developing severe, and often fatal, venous thromboembolic complications.

FINDINGS

1. An increase in the incidence of venous thromboembolic complications in acute poisoning was noted in the period from 2020 to 2022 (more than 40%). This complication occurs statistically significantly 2-fold more often (p = 0.0001) in patients over 60 years of age, and 1.3-fold (p = 0.006) in women compared to men.

2. In cases of poisoning: with psychopharmacological drugs, venous thromboembolic complications are observed in 48.8% of patients, with corrosive substances in 36.2%, with antihypertensive and antiarrhythmic drugs in 32.7%. In this background, pulmonary embolism was observed in 37.9%, 36.3% and 33.3% of cases, respectively.

3. The incidence of development of venous thromboembolic complications in the course of concomitant diseases is observed in 60.8% of cardiovascular diseases cases, in 32.2% of oncological diseases, in 25.3% of diabetes mellitus and in 78.2% of patients in the presence of pneumonia.

4. In all the studied poisonings, deep vein thrombosis of the right lower limb occurs statistically significantly 3-fold more often (p <0.001), and the prevalence of damage in these cases is mainly local.

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Received on 16/01/2024
Review completed on 02/26/2024
Accepted on 05/06/2024