

# Indicators of cellular metabolism alterations in patients with traumatic disease due to hypoxia depending on a management regimen of intensive care

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

## Key words:

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**The aim** of this study was to evaluate changes in the level of erythrocyte metabolism under conditions of hypoxia in patients with traumatic disease in polytrauma depending on the components of intensive care (IC).

**Materials and methods.** A prospective study was carried out in 88 patients suffering from polytrauma in the period from 2015 to 2017. All the patients were divided into 2 groups, comparable by severity of trauma and condition. A special feature of the examined patients was the staged surgical correction in all cases according to the Damage Control concept.

Patients from the Control group received an intensive care according to the standard local clinical protocol in polytrauma. Patients randomized to the FDP group were treated with infusion of D-fructose-1,6-diphosphate sodium hydrate in addition to the standard care. Hemodynamic parameters and cellular metabolism indicators were monitored: on admission to the operating room, after 24 hours, on day 3, 5 and 14.

**Results.** The signs of hypovolemia were equally severe in both groups on admission to the operating room. The FDP group demonstrated more rapid stabilization of hemodynamics and improved myocardial contractility at the 3<sup>rd</sup> day of IC.

The monitoring of acid-base balance and carbohydrate metabolism showed the presence of compensated metabolic acidosis and energy deficiency. High indexes of lactate/pyruvate indicated a sharp imbalance in the ratio of aerobic/anaerobic metabolic processes. The analysis of ATP dynamics displayed impaired mitochondrial ATP production and inhibition of the glycolytic pathway of energy release.

**Conclusions.** Complementary systemic inflammatory response with the elevation of lactate level by the 5<sup>th</sup> day occurred in patients with traumatic disease who underwent staged surgical correction. Optimization of intensive care resulted in a faster restoration of the balance between aerobic and anaerobic metabolic processes, an increase in the level of ATP and the rate of 2,3-DPG production in erythrocytes contributing to adequate oxygen supply to the tissues, supporting cellular respiration and preventing the development of oxidative tissue damage, as well as helped to maintain compensatory mechanisms and reduce cellular hypoxia ensuring adequate metabolism of vital organs.

## Ключові слова:

травматична хвороба, гіпоксія, D-фруктозо-1,6-дифосфат натрієвої солі гідрату, метаболізм еритроцитів.

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## Показники клітинного метаболізму в умовах гіпоксії при травматичній хворобі залежно від схеми інтенсивної терапії

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**Мета роботи** – оцінити зміни рівня метаболізму еритроцитів в умовах розвитку гіпоксії у хворих на травматичну хворобу при політравмі залежно від складу інтенсивної терапії (ІТ).

**Матеріали та методи.** Здійснили проспективне дослідження 88 пацієнтів із політравмою (2015–2017 рр.). Хворих поділили на 2 групи, зіставні за тяжкістю стану. Особливістю пацієнтів було те, що в усіх випадках хірургічну корекцію, за концепцією Damage Control, виконували поетапно. Пацієнти контрольної групи (К) отримували традиційну інтенсивну терапію, хворим групи FDP додатково призначали інфузії D-фруктозо-1,6-дифосфат натрієвої солі гідрату. Досліджували параметри гемодинаміки, показники клітинного метаболізму на час надходження, через 24 години, на 3, 5, 14 добу.

**Результати.** Пацієнти обох груп під час надходження мали однаково виражені ознаки гіповолемії. У хворих групи FDP спостерігали швидшу стабілізацію показників гемодинаміки та поліпшення скорочувальної здатності міокарда на тлі ІТ (уже на 3 добу).

Моніторинг кислотно-лужного стану й вуглеводного обміну показав наявність компенсованого метаболічного ацидозу, дефіциту енергії. Високі значення індексу лактат/піруват свідчили про різкий дисбаланс співвідношення аеробних/анаеробних метаболічних процесів. У результаті аналізу динаміки АТФ визначили порушення мітохондріального вироблення АТФ та інгібування гліколітичного шляху звільнення енергії.

**Висновки.** У хворих на травматичну хворобу в разі хірургічної корекції поетапно відбувається додаткова активізація реакцій системної запальної відповіді, що супроводжується підвищенням рівня лактату до 5 доби. Оптимізація інтенсивної терапії призвела до швидшого відновлення рівноваги між аеробними та анаеробними метаболічними процесами, підвищення рівня АТФ, швидкості утворення 2,3-ДФГ в еритроцитах, тобто сприяла повноцінному забезпеченню тканин киснем, підтримці клітинного дихання та запобігала розвиткові окисного пошкодження тканин, сприяла підтримці компенсаторних механізмів і зменшенню гіпоксії.

## Показатели клеточного метаболизма в условиях гипоксии при травматической болезни в зависимости от схемы интенсивной терапии

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**Цель работы** – оценить изменения уровня метаболизма эритроцитов в условиях развития гипоксии у больных травматической болезнью при политравме в зависимости от состава интенсивной терапии (ИТ).

**Материалы и методы.** Проведено проспективное исследование 88 пациентов с политравмой в период 2015–2017 гг. Больных поделили на 2 группы, сопоставимые по тяжести состояния. Особенностью пациентов было то, что во всех случаях хирургическую коррекцию, согласно концепции Damage Control, выполняли поэтапно. Больные контрольной группы (К) получали традиционную интенсивную терапию, пациентам группы FDP дополнительно назначали инфузии D-фруктозо-1,6-дифосфат натрия соли гидрата. Изучали параметры гемодинамики, показатели клеточного метаболизма в момент поступления, через 24 часа, на 3, 5, 14 сутки.

**Результаты.** Пациенты обеих групп при поступлении имели одинаково выраженные признаки гиповолемии. В группе FDP наблюдали более быструю стабилизацию показателей гемодинамики и улучшение сократительной способности миокарда на фоне проведения интенсивной терапии (уже на 3 сутки). Мониторинг кислотно-щелочного состояния и углеводного обмена показал наличие компенсированного метаболического ацидоза, дефицита энергии. Высокие значения индекса лактат/пируват свидетельствовали о резком дисбалансе соотношения аэробных/анаэробных метаболических процессов. В результате анализа динамики АТФ отмечены нарушения митохондриальной выработки АТФ и ингибирования гликолитического пути освобождения энергии.

**Выводы.** У пациентов с травматической болезнью в случае хирургической коррекции поэтапно происходит дополнительная активизация реакций системного воспалительного ответа, что сопровождается повышением уровня лактата до 5 дня. Оптимизация интенсивной терапии способствовала более быстрому восстановлению равновесия между аэробными и анаэробными метаболическими процессами, повышению уровня АТФ и скорости образования 2,3-ДФГ в эритроцитах, то есть обусловила полноценное обеспечение тканей кислородом, поддержание клеточного дыхания и предотвращение развития окислительного повреждения тканей, способствовала поддержанию компенсаторных механизмов и уменьшению гипоксии.

**Ключевые слова:** травматическая болезнь, гипоксия, D-фруктозо-1,6-дифосфат натрия соли гидрата, метаболизм эритроцитов.

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Hypoxia is a condition characterized by a decrease in the level of providing the body with molecular oxygen ( $O_2$ ) or associated with a problem of gas utilization during the implementation of intracellular acid-base reactions [1,2].

Respiratory, circulatory, hemic and tissue hypoxia lead to a disruption of the processes of oxidative phosphorylation, the development of cellular hypoergosis, activation of the anaerobic pathway of energy supply, disorders of normal tissue metabolism [3]. At the cellular level, these shifts are realized in the destruction of cell membranes due to the effect of reactive oxygen species at a level that overwhelms the human antioxidative defense system. Activation of lipid peroxidation is developing very rapidly and occurs mainly in mitochondria of cells in the region of maximum damage [1,4]. In addition, signs of oxygen deficiency may be due to tissue and organ ischemia. However, under ischemic conditions, pathogenetic mechanisms of their formation are manifested not only by a decrease in oxygen tension in biological tissues affected, but largely due to inadequate delivery of energy substrates, primarily glucose [5]. In this connection, ischemia has to be regarded as more serious and dangerous phenomenon, since it underlies much faster reduction in cellular energy potential. At the same time, there is a decrease in the concentration of ATP, ADP, an increase in the concentration of AMP and inorganic phosphate in cells. It is known that ATP serves as a universal donor of energy for the vast majority of anabolic reactions, it is involved in the catabolism of carbohydrates, lipids and proteins and necessary to maintain the structural integrity of membranes, active transport of ions and other vital processes. Therefore, it becomes clear that any decrease in the ATP level entails disruption of a huge number of interdependent biochemical processes [6,7].

Currently, a universal mechanism of adaptation to hypoxia is the activation of anaerobic oxidation of glucose in erythrocytes and increase in 2,3-diphosphoglycerate

(2,3-DPG) level (allosteric regulator of hemoglobin affinity for  $O_2$ ). The following rule is very important to ensure adequate energy exchange under hypoxia. A higher concentration of 2,3-DPG in erythrocytes leads to easier hemoglobin- $O_2$  unloading to peripheral tissues. Amelioration of hypoxia was associated with activation of redox reactions and ATP synthesis in mitochondria [8].

Hypoxia is the key link in the pathogenesis of systemic inflammatory response syndrome, multiple organ failure syndrome (MOFS) and traumatic disease (TD). This is the result of impaired oxygen delivery to the tissues, increased energy consumption, hypoperfusion and ischemia [3,9]. Blood loss is the cause of reduced delivery of oxygen and substrates to cells. This reverses the body metabolism into an anaerobic pathway, which in its turn leads to a decrease in ATP synthesis and indirectly reduces heat production. At the molecular level, blood loss activates biochemical cascades of inflammation and apoptosis, leading to cellular damage and death [10–12].

Great efforts are being made in clinical and experimental studies to find ways to protect cells and tissues from harmful factors and to facilitate metabolic recovery after their exposure [13]. Numerous studies have shown that the administration of antioxidants and antihypoxants along with fluids led to a gradual increase in the survival rate of patients. This is due to a significant reduction in oxidative stress, inflammatory response intensity and normalization of homeostasis [14,15].

Thus, interest in the study of a conventional glycolytic intermediate, fructose-1,6-diphosphate (FDP), has increased recently due to confirmation of its beneficial effects. The various studies in vitro and in vivo evidence that FDP causes cell and tissue protection in a variety of harmful conditions and it may play a direct role in the regulation of many metabolic pathways. Moreover, recent literature describes protective effects of FDP against different harmful

**Table 1.** General characteristics of the patients involved in the study, M ± SD

Test characteristic, units	Control (n = 32)	FDP (n = 56)	Test	P
Mean age, years	35.2 ± 12.7	39.4 ± 12.7	t = 1.48	0.14
Body weight, kg	73.84 ± 11.86	73.15 ± 8.95	t = 0.22	0.83
t <sub>co</sub> , °C	35.77 ± 0.17	35.79 ± 0.19	t = 1.03	0.31
Blood loss, % CBV	35.21 ± 4.50	35.35 ± 4.90	t = 0.1	0.92
GCS, point	13.5 ± 0.5	13.5 ± 0.5	W = 864	0.79
APACHE-II, point	15.25 ± 2.70	15.84 ± 2.60	t = 0.85	0.39
ISS, point	26.8 ± 4.1	29.9 ± 4.5	t = 1.56	0.12
PTS, point	19.9 ± 6.4	20.7 ± 3.5	t = 0.62	0.54
RTS, point	5.971 ± 0.852	5.787 ± 0.783	W = 847.5	0.67
Scale of the Department of Military Surgery, condition at admission, point	21.3 ± 3.3	22.2 ± 2.8	W = 712.5	0.11
TRISS, point	0.829 ± 0.098	0.814 ± 0.096	t 0.62	0.54

t<sub>co</sub>: core body temperature; CBV: circulating blood volume; GCS: Glasgow Coma Scale; APACHE-II: Acute Physiology and Chronic Health Evaluation Score; ISS: Injury Severity Score; PTS: Polytrauma score, Hannover; RTS: Revised Trauma Score; TRISS: Trauma and Injury Severity Score.

factors on other tissues, such as brain, kidney, intestine, liver, heart and bone [13,16].

Although the protective properties of FDP have been extensively described in the current literature, the use of this substance in the complex treatment of traumatic disease has not been studied and remains open and relevant.

## Aim

The aim of this study was to evaluate changes in the level of erythrocyte metabolism under conditions of hypoxia in patients with traumatic disease (TD) in polytrauma depending on the components of intensive care (IC).

## Materials and methods

A prospective study of 88 patients (64 males and 24 females) suffering from polytrauma was carried out in the period from 2015 to 2017. All the patients were divided into 2 groups, comparable by severity of trauma and condition (Table 1).

Patients from the Control group received an intensive care according to the standard clinical protocol in polytrauma (Ministry of Health Care of Ukraine, Order No. 34, January 15, 2014). Patients randomized to the FDP group were treated with infusion of D-fructose-1,6-diphosphate sodium hydrate 150 mg/kg in addition to standard care. It was administered intravenously at a rate of 10 ml per minute over 10 days from the time of admission to the operating room [17]. The patients were randomized into the study groups using a random-number table. A special feature of the examined patients was the staged surgical correction in all cases according to the Damage Control concept. The volume of blood loss was assessed using Moore's formula [18]. Hemodynamic parameters were determined according to the method of integral rheography, developed by Kubicek and were processed on a DX-Reo complex by "DX-Complex" (Ukraine) [19]. A gas analyzer OPTI CCA-TS produced by "OPTI-Medical" was used to assess pulmonary gas exchange function and acid-base balance.

Indicators of cellular metabolism were monitored: at admission to the operating room, after 24 hours, on days 3, 5 and 14. The serum lactate level, whole blood pyruvate in the patients was performed by enzymatic photometric method [20]. The concentration of 2,3-diphosphoglyceric acid in erythrocyte suspension and ATP in erythrocytes was

determined by spectrophotometric method [21]. All studies were conducted in accordance with the Council of Europe Convention on the Protection of Human Rights and Human Dignity in Connection with the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (ETS No. 164) of 04.04.1997; the Helsinki Declaration of World Health Association (2008) and were approved by the Commission on Ethics and Bioethics of the School of Medicine V. N. Karazin Kharkiv National University. A written informed consent was obtained from each study participant or his legal representative, and all measures were taken to preserve patient anonymity.

Statistical processing of the results obtained was performed using the software IBM SPSS Statistics Premium Faculty Pack 20.0 and IBM SPSS Statistics Author Pack 20.0 (License No. 5725-A54). When comparing the results, depending on the normality of sample distribution, the Student t-test or the non-parametric Wilcoxon W-criterion were used to identify the significances.

## Results

The signs of hypovolemia were equally severe in both groups on admission to the operating room. It was a result of massive blood loss. All patients had hypotension (mean arterial pressure (MAP) was less than 65 mmHg) [22], tachycardia (heart rate (HR) exceeded 100 bpm), decrease in cardiac stroke index (CSI) (below 30 ml/m<sup>2</sup>) and cardiac index (CI) (less than 2.5 l/min/m<sup>2</sup>) [23] and a compensatory increase in total systemic vascular resistance (SVR) (Table 2). Further follow-up showed gradual stabilization of hemodynamics and improvements in myocardial contractility on the IC in both groups. A significant increase in MAP was observed as compared to the initial level (Control group by 40 %, FDP group by 58 %), cardiac stroke volume (CSV) (Control by 28 %, FDP by 44 %), CI (Control by 21 %, FDP by 57 %) on the 3rd day of hospital stay. In this case, the FDP group had significantly higher rates of hemodynamic parameter increase than the Control group. After the 5<sup>th</sup> day, both groups showed total hemodynamic compensation. Therefore, modified IC had an apparently positive effect on patients with TD at polytrauma.

The monitoring of acid-base balance showed compensated metabolic acidosis in both groups of injured at the time of admission (Control group: pH = 7.29 ± 0.02, BE = -1.9 ± 0.3 mmol/l, pCO<sub>2</sub> = 35.2 ± 1.3 mmHg;

**Table 2.** Hemodynamic changes in acute and early periods of traumatic disease in polytrauma, M ± SD

Index, units	Group	On admission	After 24 hours	On day 3	On day 5	On day 14
MAP, mm Hg	Control	60.0 ± 4.8	64.1 ± 5.6	84.4 ± 5.0	94.3 ± 4.7	101.2 ± 4.8
	FDP	62.4 ± 4.3	79.7 ± 9.45*	97.8 ± 3.7*	100.2 ± 5.3	101.1 ± 4.4
Hart Rate, bpm	Control	126.0 ± 5.2	114.0 ± 5.3	104.7 ± 7.6	96.7 ± 5.2	88.4 ± 3.8
	FDP	119.0 ± 4.2	105.0 ± 3.4*	98.7 ± 5.2*	91.8 ± 5.4	80.8 ± 4.1
CVP, mm H <sub>2</sub> O	Control	7.4 ± 4.2	18.0 ± 7.3	42.4 ± 4.5	48.2 ± 5.4	65.4 ± 3.3
	FDP	8.2 ± 4.8	22.1 ± 5.7*	49.5 ± 5.2	47.4 ± 6.3	71.2 ± 3.1
CSV, ml	Control	42.3 ± 6.2	42.1 ± 3.7	54.2 ± 3.2	60.4 ± 3.6	65.3 ± 3.6
	FDP	43.6 ± 4.2	54.8 ± 3.2*	61.9 ± 3.2*	63.7 ± 4.2	65.1 ± 3.5
CI, l/min/m <sup>2</sup>	Control	2.30 ± 0.21	2.50 ± 0.14	3.0 ± 0.3	3.0 ± 0.6	3.0 ± 0.4
	FDP	2.10 ± 0.34	2.90 ± 0.47*	3.3 ± 0.3*	3.2 ± 0.8	3.0 ± 0.2
CSI, ml/m <sup>2</sup>	Control	25.2 ± 3.2	25.2 ± 2.3	30.0 ± 2.9	34.8 ± 4.2	37.6 ± 4.2
	FDP	24.7 ± 3.2	28.1 ± 1.2	34.2 ± 5.5*	36.9 ± 6.1	38.9 ± 2.5
SVR, dyn·s·cm <sup>-5</sup>	Control	1584 ± 128	1737 ± 163	1497 ± 112	1205 ± 87	1095 ± 84
	FDP	1626 ± 187	1754 ± 111	1236 ± 121*	1087 ± 79*	1018 ± 65

\*: significance of differences between groups, P < 0.05.

**Table 3.** Dynamics of homeostasis indicators in the acute and early periods of traumatic disease in polytrauma, M ± SD

Index, units	Group	On admission	After 24 hours	On day 3	On day 5	On day 14
pH	K	7.29 ± 0.02	7.32 ± 0.01	7.32 ± 0.02	7.39 ± 0.02	7.44 ± 0.02
	FDP	7.31 ± 0.01	7.34 ± 0.01	7.39 ± 0.02*	7.43 ± 0.01*	7.45 ± 0.02
BE, mmol/l	K	-1.9 ± 0.3	-3.7 ± 0.1	-3.4 ± 0.2	-2.1 ± 0.1	-1.3 ± 0.1
	FDP	-2.1 ± 0.1	-3.1 ± 0.2*	-1.7 ± 0.2*	-1.6 ± 0.2*	-1.0 ± 0.1
pCO <sub>2</sub> , mmHg	K	35.2 ± 1.3	34.1 ± 1.1	36.3 ± 0.9	37.1 ± 1.2	35.4 ± 1.2
	FDP	34.8 ± 1.5	36.2 ± 1.2	37.0 ± 1.1	36.8 ± 0.8	35.8 ± 0.9
Glucose, mmol/l	K	7.8 ± 3.3	8.8 ± 1.2	7.3 ± 1.2	5.6 ± 0.8	4.3 ± 0.4
	FDP	7.9 ± 2.3	7.7 ± 0.9*	5.3 ± 0.8*	4.1 ± 0.4*	4.4 ± 0.5
Lactate, mmol/l	K	3.62 ± 0.11	4.22 ± 0.34	3.97 ± 0.38	2.20 ± 0.63	1.89 ± 0.71
	FDP	3.56 ± 0.16	4.35 ± 0.22	3.19 ± 0.27*	2.24 ± 0.25	1.90 ± 0.38

\*: significance of differences between groups, P < 0.05.

FDP group: pH = 7.31 ± 0.01, BE = -2.1 ± 0.1 mmol/l, pCO<sub>2</sub> = 34.8 ± 1.5 mmHg in venous blood). The normalization of pH and base excess in the FDP group occurred as early as on the 3<sup>rd</sup> day, whereas in the Control group – only on the 5<sup>th</sup> day (Table 3).

The compensatory mechanisms require increased energy expenditure in critical conditions. But the main pathogenic pathway related to centralization of blood circulation is energy deficiency in cells. This occurs as a result of metabolic switching to less energy efficient anaerobic pathway. This was confirmed by hyperglycemia of up to 7.8 ± 3.3 mmol/l in the Control group and 7.9 ± 2.3 mmol/l in FDP group (Fig. 1), as well as an increase in the lactate level to 3.62 ± 0.11 mmol/l and 3.56 ± 0.26 mmol/l, respectively, at the time of admission to the operating room. Increased lactate level is a consequence of hypoperfusion caused by MAP reduction in patients with traumatic shock, increased level of catecholamines in response to injuries, impaired oxidative phosphorylation and a balance between anaerobic and aerobic metabolism [24,25].

The analysis of anaerobic metabolism revealed increased level of pyruvate (Control group – 108.8 ± 22.2 mmol/l, FDP group – 117.1 ± 18.0 mmol/l) and lactate (Control group 3.62 ± 0.11 mmol/l, FDP group 3.56 ± 0.16 mmol/l) in both groups at the time of admission to the operating room. In the next stages of the study, the pyruvate level tended to gradually increase, probably due to the conversion to lactate in conditions of oxygen deficit, and then gradually normalized to the 14<sup>th</sup> day in patients of both groups. And

initially high index of lactate/pyruvate additionally pointed to a sharp imbalance in the ratio between aerobic/anaerobic metabolic processes (Fig. 2,3, Table 3).

The lactate level continued to increase after 24 hours indicating the further suppression of aerobic energy production pathway. The part of aerobic energy production increased early on the 3<sup>rd</sup> day. Moreover, in the FDP group patients who additionally received D-fructose-1,6-diphosphate sodium salt hydrate, the lactate level decreased significantly greater and faster than in the Control group (Control group – 3.97 ± 0.38 mmol/l, FDP group – 3.19 ± 0.27 mmol/l, P < 0.05) (Table 3). That was causally linked to the development of traumatic disease and potential body reaction in the systemic inflammatory response at the stage of additional surgery. The delayed surgery was performed in the Control group patients in the period of 4.7 ± 1.3 days, and in the FDP group patients – 4.5 ± 1.1 days.

Hypoperfusion and hypoxia lead to cellular dysfunction and a shift in the nature of metabolism toward the anaerobic pathway. In turn, glycolysis results in the development of lactic acidosis. The fluctuations in the concentration of main ischemia and hypoxia markers (lactate and pyruvate) reflect the delivery and consumption of the major energy substrate (glucose). It means adequate metabolism of vital organs [24,26].

The data analysis showed a decrease in ATP levels in both groups (Control group – 0.76 ± 0.12 μmol/ml and FDP group – 0.78 ± 0.15 μmol/ml). Moreover, within 24

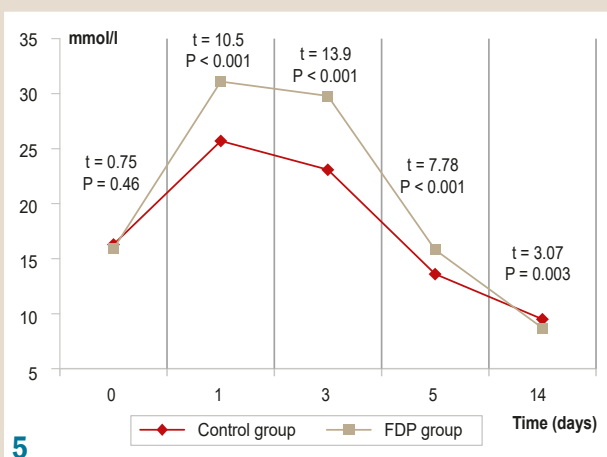
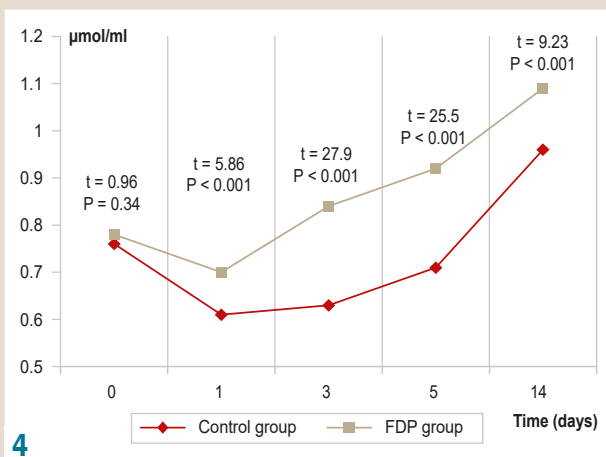
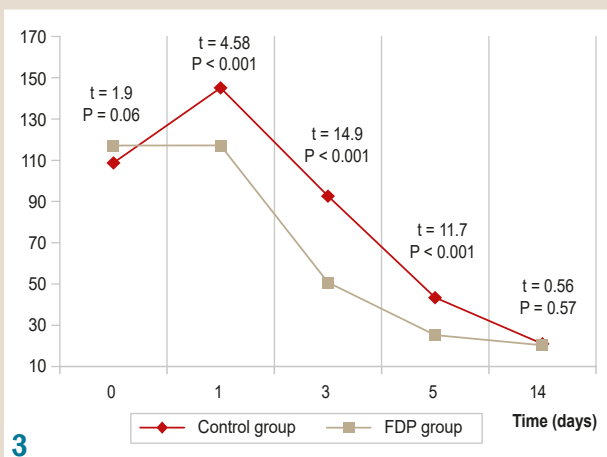
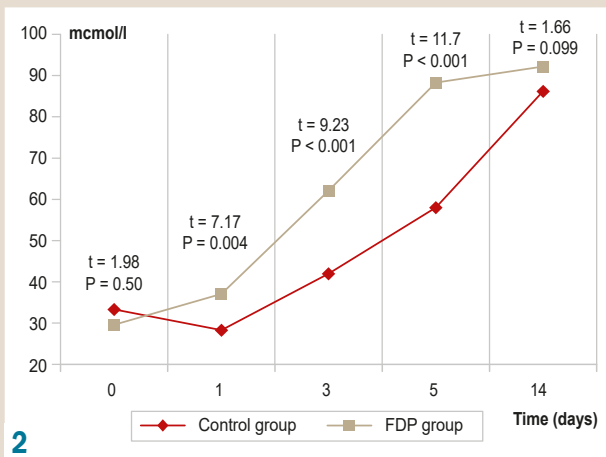
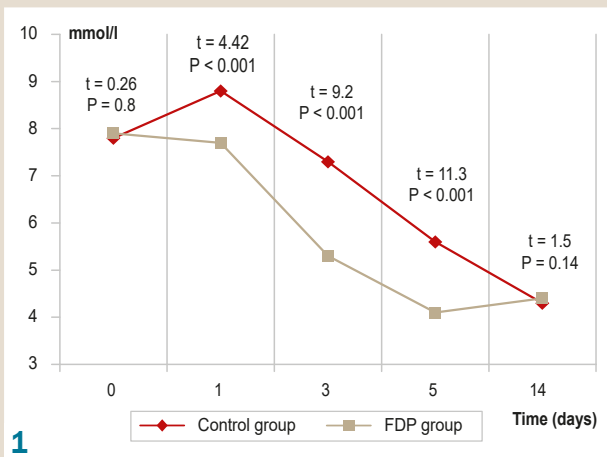


Fig. 1. Dynamics of glucose levels in patients of the studied groups.

Fig. 2. Dynamics of pyruvate levels in patients of the studied groups.

Fig. 3. Dynamics of the lactate/pyruvate index in patients of the studied groups.

Fig. 4. Dynamics of ATP levels in patients of the studied groups.

Fig. 5. Dynamics of 2,3-DPG levels in patients of the studied groups.

hours after the onset of hypoxia, the concentration of ATP continued to decrease. It was the evidence of impaired mitochondrial ATP production and inhibition of the glycolytic pathway of energy release. The systemic administration of D-fructose-1,6-diphosphate sodium salt hydrate to FDP patients increased energy potential and restored it by the 5<sup>th</sup> day of TD indicating its pronounced energy-stabilizing properties (Fig. 4). Fructose-1,6-diphosphate is an endogenous high-energy intermediate metabolite of the glycolytic pathway. A potential advantage of using exogenously administered D-fructose-1,6-diphosphate as the primary substrate

is that one molecule of glucose produces two molecules of ATP under anaerobic conditions. But one molecule of fructose-1,6-diphosphate, which is metabolized in the same conditions, produces four molecules of ATP since fructose-1,6-diphosphate does not require phosphorylation [27].

The analysis of the data obtained in the study also showed a significant increase in red blood cell 2,3-DPG in the patients of both groups even at admission to the operating room (up to 16.3 ± 1.3 mmol/l – the Control group, 15.9 ± 1.2 mmol/l – FDP group), which was more than 3 times higher than the normative values, and suggested



continuing effect of hypoxia. In our opinion, these changes indicated an increase in the reserve capacity of the oxygen transport system and were compensatory. By the end of the 1<sup>st</sup> day, a significant increase in 2,3-DPG was observed in both groups ( $25.7 \pm 2.1$  mmol/l – Control group and  $31.1 \pm 2.2$  mmol/l – FDP group,  $P < 0.001$ ). Thereafter, on the 3<sup>rd</sup> day of IC, 2,3-DPG level was  $29.8 \pm 2.2$  mmol/l in the FDP group patients, which was 82 % higher than the initial level and significantly ( $P < 0.001$ ) exceeded the level of this indicator in the Control group –  $23.1 \pm 2.2$  mmol/l. The gradual decrease to normal values occurred from the 5<sup>th</sup> to the 14<sup>th</sup> day (Fig. 5). We assumed that the data obtained were indicative of a higher level of erythrocyte availability for oxygen donation by reducing the affinity in FDP group. This was due to the uninterrupted functioning of the compensatory mechanisms in the absence of phosphate deficiency and it had been confirmed [28].

## Discussion

Intravenously administered FDP is capable of being actively transported into cells and acting as an alternative source of energy. It increases the production of ATP in conditions where phosphofructokinase is inhibited (e. g. by lactate) and preserves its own macroergic cell phosphates for pre-phosphorylation of hexoses. The relative ATP production by anaerobic glycolysis is greater for FDP than glucose [29,30].

Fructose-1,6-diphosphate is a substrate for the 2,3-diphosphoglyceric acid (2,3-DPG) formation. The concentration of 2,3-DPG in the red blood cells of adults is a functional value that varies depending on the body's oxygen demand. The maintenance of DPG in erythrocytes can decline or increase rapidly enough upon changes of an oxygen delivery mode [15,31].

Analyzing the clinical effects of FDP, several authors noted that it may restore inhibited glycolytic activity in the ischemic myocardium by regulating the effect on the glycolytic pathway, and also be a substrate for this pathway. Other researchers have shown that FDP reduces the area of tissue ischemia in experimental cerebral and myocardial infarction and improves hemodynamics after cardiac bypass [30]. Some data have demonstrated the absence of hypotensive effect of FDP that allows using it in patients with shock conditions and unstable hemodynamics [15]. In our study, FDP group has shown more rapid stabilization of hemodynamics and improvement of myocardial contractility in the course of IC on the 3<sup>rd</sup> day.

The results obtained after examination of polytrauma patients with TD indicated changes in cellular metabolic processes. The parameters tested were directly involved in the cellular oxygen metabolism. The violation of oxygen delivery to cells was a consequence of changes in systemic circulation that accompanied acute blood loss.

The maintenance of red blood cells energy metabolism is essential to prevent complications at the perioperative period in polytrauma patients. Evaluation of clinical efficacy of D-fructose-1,6-diphosphate sodium salt hydrate showed increasing proportion of aerobic energy production pathway as evidenced by a significantly ( $P < 0.001$ ) lower lactate levels by 20 % on the 3<sup>rd</sup> day, corresponding to the data of previous publications [6,8]. More rapid recovery of ATP from

the 1<sup>st</sup> to the 5<sup>th</sup> day ( $P < 0.001$ ) was found by analyzing the energy potential performance of erythrocytes. The increase in the reserve compensatory capacity of the oxygen transport system due to the increase in 2,3-DPG occurred at the end of the 1<sup>st</sup> day by 21 %. Therefore, the increased 2,3-DPG amount could have a positive effect on the processes of oxyhemoglobin dissociation under conditions of anaerobic metabolism in massive hemotransfusions with a relative reduction in functionally active form of 2,3-DPG [15].

Thus, the administration of the proposed therapy with the use of D-fructose-1,6-diphosphate sodium salt hydrate had a positive effect on the parameters of homeostasis.

## Conclusions

1. The increased lactate levels were found due to the complementary development of systemic inflammatory response by the 5<sup>th</sup> day at the stage of additional surgery in patient with traumatic disease.

2. The analysis of the results showed that the optimization of intensive care led to the faster restoration of the balance between aerobic and anaerobic metabolic processes, increase in the level of ATP and the rate of 2,3-DPG production in erythrocytes contributing to adequate oxygen supply to the tissues, supporting cellular respiration and preventing the development of oxidative tissue damage, as well as helped to maintain compensatory mechanisms and reduce cellular hypoxia ensuring adequate metabolism of vital organs.

3. Given this, the monitoring of cellular metabolism indicators might provide additional diagnostic information and allow the detection of trends in implicit pathological changes and the treatment quality assessment.

**Perspectives of further research** on this problem are presented in the study on relationships between morphological changes of red blood cells and indicators of cellular metabolism. Further studies on the effects of D-fructose-1,6-diphosphate sodium salt hydrate are needed.

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