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VIOLATION OF RENAL TRANSPORT OF SODIUM IONS UNDER CONDITIONS OF SKELETAL TRAUMA OF DIFFERENT SEVERITY, COMPLICATED BY BLOOD LOSS

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Abstract

Objective: to find out the features of renal transport of sodium ions in the early period after skeletal trauma of different severity, complicated by blood loss.

Materials and methods: In experiments was used 60 non-linear white rats, 180-200 grams weight, which were on a standard vivarium diet. All animals were divided into four groups: control (6 animals) and three experimental (in all experimental groups 18 animals).

The control group included the rats that were taken just to anesthesia (thiopental sodium, 40 mg per 1 kg). In the first experimental group, under the conditions of thiopental-sodium anesthesia (40 mg per 1 kg body weight intraperitoneally), a moderate severity of closed trauma was modeled and caused a closed fracture of the femoral bones. In the second experimental group was modeled blood loss of 20-22% volumes of circulating blood with the introduction of autoblood into the abdominal cavity at a rate of 0.5 ml per 100 g of animal weight. In the third experimental group, additionally, the adjacent thigh was broken. After 1, 3 and 7 days in experimental animals, the functional status of the kidneys was determined by the method of water loading. Diuresis was determined.

After two hours of urine sampling the animals, in conditions of thiopental-sodium

anesthesia (80 mg per 1 kg of body weight intraperitoneally), were taken out from the experiment.

In urine and blood serum, concentration of sodium ions was determined. Proximal and distal transport of sodium ions and its excretion with urine were calculated.

Results and their discussion. It has been established that isolated skeletal trauma (thigh fracture) in the period of early manifestations of traumatic disease (up to 7 days) is accompanied by a significant decrease in proximal and distal transport of sodium ions, which leads to a significant increase in their excretion with urine. Additional modeling of blood loss on the background of isolated skeletal trauma has deepened the revealed violations. The proximal and distal transport of sodium ions further decreased, reaching the maximum of disturbances in 3 days. This fact indicates a certain sensitivity of transport processes of sodium ions to hypoxia caused by blood loss. However, in the case of a fracture of the adjacent thigh (deepening of the skeletal trauma), the violation of the investigated processes became even more pronounced. Violation of proximal transport of sodium ions reached a maximum after 7 days, distal - after 3 days.

Violation of proximal and distal transport of sodium ions was accompanied by an increase in the excretion of sodium ions in the urine. However, during the 1 and 3 days of the post-traumatic period in all experimental groups, despite the loss of blood and the increase in the severity of skeletal trauma, the magnitude of sodium excretion was almost the same, indicating the intensive involvement of adaptive-compensatory mechanisms. An additional confirmation of this assumption is the fact that after 7 days in the case of isolated skeletal trauma, sodium excretion increases, at a time which, after simulating blood loss and fracture of the adjacent thigh, the rate remains at the previous level.

Conclusion. In conditions of skeletal trauma complicated by blood loss, there is an increase in the disturbance of proximal and distal transport of sodium ions in comparison with the isolated skeletal trauma observed during the acute period of traumatic diseases (1 day of the post-traumatic period) and in the period of early manifestations (3-7 days). Under these conditions, the excretion of sodium ions in the urine increases, which is stable during the experiment and does not depend on the severity of skeletal trauma and additional blood loss.

Key words: skeletal trauma, blood loss, proximal and distal sodium transport.

Introduction. Disorders of the kidney function play an important role in the pathogenesis of trauma. Today, it has been proved that kidney dysfunction, both in the context of direct trauma, and as a result of secondary damage due to the systemic response of

the body to inflammation leads to acid-alkaline, water-electrolyte, osmotic and colloid-osmotic imbalances. In turn, these violations lock the next "false" pathological circle, causing pathological deviations of cardiovascular system, respiration, metabolism [1, 2].

Nowadays, an actual problem is the increase in the frequency of terrorist attacks and local armed conflicts [3]. Under these conditions, there is a significant frequency of acute blood loss and mechanical damage of limbs, which in 80-90% of cases is the main cause of the deaths of injured and wounded [4]. The development of traumatic shock, the fall of systemic blood pressure causes hemodynamic disorders and hypoxia in the internal organs, which is the trigger mechanism for the development of multiple organ failure syndrome and is one of the immediate causes of death in both the early and late post-traumatic period [5].

In our previous studies, was shown that simulation of skeletal trauma complicated by blood loss leads to significant accumulation of secondary products of lipid peroxidation in the cortical and cerebellar layers of the kidney, depletion of the enzymatic layer of antioxidant defense, displacement of antioxidant-prooxidant correlation in the direction of predominance of prooxidant mechanisms that increase from the first to the seventh days of the post-traumatic period [6, 7].

Under these conditions, the activity of superoxide dismutase in the cortical and cerebellar layers is significantly reduced, low molecular weight peptides accumulated, indicating a violation of the processes of glomerular filtration and its dependence on the activity of the enzymatic system of antioxidant defense [8]. The diuresis decreases, the velocity of glomerular filtration and the creatinine excretion slow down [9].

Detected violations should affect the ion-regulating function of the kidneys.

Objective: to find out the features of renal transport of sodium ions in the early period after skeletal trauma of different severity, complicated by blood loss

Materials and methods: In experiments was used 60 non-linear white rats, 180-200 grams weight, which were on a standard vivarium diet. All animals were divided into four groups: control (6 animals) and three experimental (in all experimental groups 18 animals).

The control group included the rats that were taken just to anesthesia (thiopental sodium, 40 mg per 1 kg). In the first experimental group, under the conditions of thiopental-sodium anesthesia (40 mg per 1 kg body weight intraperitoneally), a moderate severity of closed trauma was modeled and caused a closed fracture of the femoral bones [7]. In the second experimental group was modeled blood loss of 20-22 % volumes of circulating blood with the introduction of autoblood into the abdominal cavity at a rate of 0.5 ml per 100 g of animal weight. In the third experimental group, additionally, the adjacent thigh was broken.

After 1, 3 and 7 days in experimental animals, the functional status of the kidneys was determined by the method of water loading [10]. This was done in 2 hours to euthanasia:

through a metal probe into the stomach was introduced heated to 30 ºC water in the volume of 5 % of the body weight of the animal. Urine was collected for 2 hours and diuresis was determined.

After two hours of urine sampling the animals, in conditions of thiopental-sodium anesthesia (80 mg per 1 kg of body weight intraperitoneally), were taken out from the experiment.

In urine and blood serum, concentration of sodium ions was determined by a standardized method for the biochemical analyzer Humalazer 2000. Proximal and distal transport of sodium ions and its excretion with urine were calculated [10].

All traumatic experiments were carried out in accordance with the general rules and regulations of the European Convention for the Protection of Vertebrate Animals used for research and other scientific purposes (Strasbourg, 1986), the General Ethical Principles of Animal Experiments (Kyiv, 2001), the Law of Ukraine «On the Protection of Animals from cruel behavior» (2006), as well as in accordance with «Scientific and practical recommendations for the maintenance and operation of laboratory animals».

The received digital data was subject to statistical analysis. The probability of differences between the experimental groups was estimated using Mann-Whitney's nonparametric criterion.

Results and their discussion. As can be seen from table. 1, with an isolated thigh fracture compared with the control group after 1 day of the post-traumatic period, a statistically significant decrease in the proximal transport of sodium ions was noted by 33.8% ($p < 0.05$).

After 3 days, the indicator further decreased - by 44.9% ($p < 0.05$), which was also significantly lower than in 1 day (by 16.8%, $p < 0.05$). After 7 days, the indicator increased by 21.6% ($p < 0.05$) compared to the previous one, but continued to remain lower than in control by 21.6% ($p < 0.05$).

Additional blood loss led to a further decrease of sodium ions proximal transport: after 1 day - by 56.4% ($p < 0.05$), after 3 days - by 74.8% ($p < 0.05$), after 7 days - by 70,6% ($p < 0,05$). In the case of fracture in both thighs and additional blood loss, the indicator was accordingly lower than the control level by 65.4, 78.6 and 82.5% ($p < 0.05$). It should be noted that in groups 2 and 3 the index reached the minimum value after 3 days and remained at the same level to 7 days ($p > 0,05$).

Table 1 – Proximal transport of sodium ions (mkmol·min^{-1}) per 100 g of animal weight in the dynamics of the early period after skeletal trauma of different severity, complicated by blood loss (Me (LQ;UQ)) - median (lower and upper quartile)

Type of trauma	Control	The duration of the post-traumatic period		
		1 day	3 days	7 days
Group 1 Thigh fracture	66,28 (63,31; 68,30) (n=6)	43,86* (41,63; 45,71) (n=6)	36,51*1 (34,53; 37,60) (n=6)	44,38*3 (42,04; 47,34) (n=6)
Group 2 Thigh fracture + blood loss + hematoma		28,88* (24,68; 30,46) (n=6)	16,70*1 (15,24; 20,40) (n=6)	19,47*1 (17,80; 20,93) (n=6)
Group 3 Fracture of both thighs + blood loss + hematoma		22,95* (21,64; 24,59) (n=6)	14,16*1 (13,14; 15,71) (n=6)	11,57*1 (11,36; 13,20) (n=6)
p_{1-2}		<0,05	<0,05	<0,05
p_{1-3}		<0,05	<0,05	<0,05
p_{2-3}		<0,05	>0,05	<0,05

Notes. Here and in other tables:

1. * – the differences regarding the control group are statistically significant (p<0,05);

2. p_{1-2} - probability of difference of the indicator between groups 1 and 2; p_{1-3} - between groups 1 and 3; p_{2-3} - between groups 2 and 3.

Comparison of experimental groups among themselves showed that after 1 day with an increase in the severity of injury, the indicator decreased and in group 2 was 34.2% less than in group 1 (p_{1-2}<0,05). In group 3, proximal transport of sodium ions was 47.7% lower than in group 1 (p_{1-3}<0,05) and 20.5% - in comparison with group 2 (p_{2-3}<0,05). After 3 days, the indicator in groups 2 and 3 was statistically significantly lower than in group 1 (54,2 and 61,2 %, p_{1-2}<0,05, p_{1-3}<0,05) After 7 days the index again became more severe with increasing severity (p_{1-2}<0,05, p_{1-3}<0,05, p_{2-3}<0,05).

Similar disturbances occurred also by the size of distal transport of sodium ions (table 2). After the isolated skeletal trauma, the index in comparison with the control group decreased by 11,4% (p <0,05) in 1 day, in 3 days - by 21,4% (p <0,05), after 7 days - by 17 , 5% (p <0.05). It should be noted that after 3 days the index became 11.3% less than after 1 day (p <0.05), increased by 7 days (p <0.05 compared with 3 day) and reached the level of 1 day (p>0,05).

Table 2 - Distal transport of sodium ions (mkmol 2 hours^{-1}) per 100 g of animal weight in the dynamics of the early period after skeletal trauma of different severity, complicated by blood loss (Me (LQ; UQ)) - median (lower and upper quartile)

Type of trauma	Control	The duration of the post-traumatic period		
		1 day	3 days	7 days
Group 1 Thigh fracture	5,08 (5,03; 5,27) (n=6)	4,50* (4,27; 4,65) (n=6)	3,99*1 (3,90; 4,03) (n=6)	4,19*3 (4,10; 4,38) (n=6)
Group 2 Thigh fracture + blood loss + hematoma		3,45* (3,00; 3,51) (n=6)	2,68*1 (2,59; 2,81) (n=6)	2,60*1 (2,50; 2,69) (n=6)
Group 3 Fracture of both thighs + blood loss + hematoma		2,59* (2,53; 2,71) (n=6)	2,36*1 (2,36; 2,42) (n=6)	2,11*1,3 (2,01; 2,25) (n=6)
p_{1-2}		<0,05	<0,05	<0,05
p_{1-3}		<0,05	<0,05	<0,05
p_{2-3}		<0,05	<0,05	<0,05

After additional blood loss, the indicator for 3 days decreased and became 47.2% compared to the control ($p < 0.05$) and 22.3% compared to 1 day ($p < 0.05$). At practically the same level, the indicator remained up to 7 days ($p>0,05$). In group 3 under conditions of fracture of both thighs and blood loss, the index gradually decreased from 1 to 7 days - correspondingly by 49.0, 53.8 and 58.5% ($p < 0.05$), and after 7 days was statistically significantly lower, than in 1 and 3 days ($p < 0.05$).

Comparison of experimental groups among themselves showed that in all terms of observation, the indicator with increasing severity of trauma became significantly lower ($p_{1-2}<0,05$, $p_{1-3}<0,05$, $p_{2-3}<0,05$).

Analysis of the excretion of sodium ions showed (table 3), that after a thigh fracture compared with the control group, the indicator in 1 day has increased significantly (5.65 times, $p < 0.05$), remained at the same level to 3 days and repeatedly increased after 7 days, which was statistically significantly higher than the control, and with the post-traumatic period ($p < 0.05$). In conditions of additional bleeding, the index increased and in all terms of observation more than 5 times exceeded the level of control ($p < 0.05$). After the fracture of both thighs and bleeding (group 3), the index in comparison with the control group in all terms of observation increased similarly as in group 2.

Table 3 - Excretion of sodium ions with urine (mkmol·min^{-1}) per 100 g of animal weight in the dynamics of the early period after skeletal trauma of different severity, complicated by blood loss (Me (LQ; UQ)) - median (lower and upper quartile)

Type of trauma	Control	The duration of the post-traumatic period		
		1 day	3 days	7 days
Group 1 Thigh fracture	0,020 (0,019; 0,021) (n=6)	0,113* (0,100; 0,114) (n=6)	0,113* (0,106; 0,119) (n=6)	0,121*1,3 (0,120; 0,124) (n=6)
Group 2 Thigh fracture + blood loss + hematoma		0,104* (0,100; 0,108) (n=6)	0,102* (0,096; 0,107) (n=6)	0,102* (0,092; 0,110) (n=6)
Group 3 Fracture of both thighs + blood loss + hematoma		0,098* (0,092; 0,102) (n=6)	0,096* (0,091; 0,104) (n=6)	0,096* (0,092; 0,106) (n=6)
p_{1-2}		>0,05	>0,05	<0,05
p_{1-3}		>0,05	>0,05	<0,05
p_{2-3}		>0,05	>0,05	>0,05

Comparison of experimental groups among themselves showed that after 1 and 3 days, the magnitude of excretion of sodium ions did not indicate significant differences between experimental groups (p_{1-2}>0,05, p_{1-3}>0,05, p_{2-3}>0,05). However, after 7 days in group 2 and 3 the indicator was statistically significantly higher than in group 1 (18.6%, p_{1-2}<0,05 and 26.0%, p_{1-3}<0,05).

The obtained results indicate that isolated skeletal trauma (thigh fracture) in the period of early manifestations of traumatic disease (up to 7 days) is accompanied by a significant decrease in proximal and distal transport of sodium ions, which is manifested by a significant increase in their excretion with urine. Similar disorders were observed in the acute period of traumatic disease after an experimental trauma and other authors [11, 12].

Additional simulation of blood loss on the background of isolated skeletal trauma deepened the revealed violations. The proximal and distal transport of sodium ions further decreased, reaching the maximum of disturbances in 3 days. This fact indicates a known sensitivity of transport processes of sodium ions to hypoxia caused by blood loss. However, in the case of a fracture of the adjacent thigh (deepening of the skeletal trauma), the violation of the investigated processes became even more pronounced. If the violation of proximal transport of sodium ions reached a maximum after 7 days, then distal - after 3 days. Taking

into account that additional thigh injuries deepen the systemic response of the body to inflammation, which is based on the enhanced formation of proinflammatory cytokines, it can be assumed that proinflammatory cytokines more influence the processes of distal transport of sodium ions.

Violations of proximal and distal transport of sodium ions were accompanied by an increase of excretion in urine. However, during the 1 and 3 days of the post-traumatic period in all experimental groups, despite the loss of blood and the increase in the severity of skeletal trauma, the magnitude of sodium excretion was almost the same. This fact indicates the intensive involvement of adaptive-compensatory processes, which, obviously, is based on a set of neurohumoral effects aimed at reducing diuresis and increasing the reabsorption of sodium and water. This mechanism is mediated through the effect of vasopressin and aldosterone, whose formation increases with blood loss [13]. An additional confirmation of this assumption is the fact that after 7 days in the case of isolated skeletal trauma, sodium excretion increases, while after simulating blood loss and fracture of the adjacent thigh, the index remains at the previous level.

Thus, in the case of skeletal trauma complicated by blood loss, there is an increase in the disturbance of proximal and distal transport of sodium ions compared with the isolated skeletal trauma, which is observed in the acute period of traumatic disease (1 day of the post-traumatic period), and in the period of its early manifestations (3 -7 days). Under these conditions, the excretion of sodium ions in the urine increases, which is stable during the experiment and does not depend on the severity of skeletal trauma and additional blood loss. The obtained results should be taken into account at development of methods of complex therapy of renal failure with the conditions of severe skeletal trauma complicated by blood loss.

Conclusions 1. Against the background of severe skeletal trauma, complicated by blood loss, in the acute period and the period of early manifestations of traumatic disease, proximal and distal transport of sodium ions is significantly reduced. Changes are deepened from the first to the seventh days of the post-traumatic period and are proportional to the severity of the injury.

2. Due to violation of proximal and distal transport of sodium ions their excretion with urine increases significantly, the degree of deviation which is practically the same, regardless of the severity of skeletal trauma and additional blood loss.

In the long run it is worth exploring in detail the features of the functional state of the kidneys in the period of early manifestations of traumatic disease in order to develop adequate

methods for correction of renal failure.

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