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RESEARCH ARTICLE

Comparative Study of Sodium Fumarate, Mannitole and Furosemide Concerning Renal Warm Ischemia in Rabbits.

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ABSTRACT

While performing surgical treatment of the localized form of renal cell cancer by means of open or laparoscopic kidney resection, renal warm ischemia (RWI) is becoming the necessary aspect of the intervention. Using RWI allows to prevent parenchymal bleeding, to optimize operative conditions, to increase significantly the efficiency of hemostasis. However, an important problem is the probability of ischemic hypoxic damage of the secured part of the kidney tissue during RWI and renal functional impairment in the postoperative period.

Aim of the study – comparative study of nephroprotective activity of sodium fumarate, mannitole and furosemide using experimental model of 30- and 60-minute renal warm ischemia in rabbits.

Materials and methods: The experiments were carried out on 360 conventional male-rabbits of the "Chinchilla" breed weighed 2,6±0,3 kg which were allocated into 10 groups. The control group №1 included intact animals, the control group №2 included the rabbits having been operated on without clamping the renal artery. Animals from the trial groups (№3-№10) were given the experimental model of 30- and 60-minute RWI. In groups №3 and №4 medication was not provided. Other rabbits were performed renal warm exsanguination on the background of sodium fumarate (groups №5 and №6 - 1,5 ml/kg IV), lasix (groups №7 and №8 - 3,0 mg/kg IV) and mannitole (№9 and №10 - 1,0 g/kg IV). There was studied the effecct of RWI on the kidney tissue ultrastructure and the levels of NGAL, cystatin-C and creatinine in blood and urine.

Results: Experimental pharmacologically non-corrected 30-minute RWI in trial animals induced swelling and edema of the final part of microvilli of the proximal tubules epithelium, increase of lysosome number in the hyaloplasm of epithelial cells, appearance of flaky content of medium electronic density in the lumens of distal tubules and collecting tubes, as well as sharp peak-like increase of NGAL and cystatin-C in blood and urine. Increasing the time of exsanguination up to 60 minutes was accompanied by the growth of severity and scales of the observed disturbances. In groups where sodium fumarate, lasix and mannitole were used the observed ultrastructural disturbances were the least pronounced, whereas sodium fumarate demonstrated the best nephroprotective activity. In case of using mannitole the intensity of the observed disturbances was less than in the groups where mannitole, lasix or sodium fumarate were not provided. Lasix and sodium salt of fumaric acid showed a higher nephroprotective activity. The best results were received in the animals protected by sodium fumarate.

Conclusions: The studied medications produced a nephroprotective effect regarding renal ischemia of rabbits, sodium fumarate in the greatest degree, furosemide – less and mannitole – the least. Use of sodium fumarate allows to protect and stimulate the kidney tissue maximum effectively during oxygen deprivation of the ischemized organ.

KEYWORDS:
renal warm ischemia, kidney resection, ischemic hypoxic damage, pharmacological nephroprotection, antihypoxants sodium fumarate.

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INTRODUCTION

The term “renal warm ischemia” (RWI) is defined as a temporary stop of blood flow to the kidney by means of intraoperative clamping of the renal artery during open or laparoscopic organ resection , which is the method of choice for surgical treatment of the localized form of renal cell cancer (RCC) 1,2

Nowadays need for such kind of surgery is constantly increasing. According to the findings from Russian Center for Information Technology and Epidemiological Studies in Oncology P.A. Hertsen Moscow Oncology Research Center, in 2011-2014 occurrence of RCC in adults of Russian Federation increased by 1,2% within a year, from 2014 to 2016 yearly growth was 1,7%, and from 2016 to 2017 - 2,6%. From 2011 to 2017 prevalence of RCC increased from 78,5 cases per 100 000 people to 114,7 cases, among them the frequency of RCC in stages T1 and T2 increased from 54,2% to 63,9% within the same period 3

Including RWI into the scheme of such interventions is obviously one of the factors of their successful outcome as it allows to prevent parenchymal bleeding, to optimize operative conditions, to increase significantly the efficiency of hemostasis 4. However, RWI remains to be ischemia – a typical pathological process having a complex of pathological and protective-adaptive reactions realizing in the form of morphological, metabolic and functional disturbances of the ischemized tissue – renal tissue in this case.

There are three fragments of pathogenesis of structural-functional disorganization of the renal tissue on performing surgical removal of the kidney area damaged by cancer: vascular, obstructive and reperfusive. The first two fragments are activated by clamping the renal artery, the latter – by derestricting the blood flow into the intrarenal bloodstream 5,6

While clamping the renal artery in terms of blood supply cessation to the microvasculature of the renal parenchyma, the primary specific factor damaging kidney cells is hypoxia. The immediate consequence of its action is the inhibition of ATP-synthetic functions of mitochondria and lack of adenosine triphosphate in effector nephrocytes, whereas, in terms of oxygen deprivation the maximum vulnerability is proved for epithelial cells of S-3 segment of proximal tubules having the greatest glycolytic activity. While realizing the mechanisms of hypoxic damage nephron dysfunctions appear or increase 7–12

Traditionally, by the time of RWI, there is exsanguination lasting up to 10 minutes, from 10 to 30 minutes and longer than 30 minutes. Some researchers note that in the first case no functional disturbances of renal tissue appear, in the second case – reversible structure and function disturbances are observed. If restriction of blood supply to the kidney lasts more than 30 minutes, there is a high probability of fatal damage of effector nephrocytes. On the whole, ischemic impact is considered to be “safe” if it lasts not more than 20-25 minutes [Seryogin, 2012].

There are also other researchers who have a tougher view on the issue of the allowable time of warm ischemia. So, Patel A.R. et al. (2011) and Thompson R.H. et al. (2010, 2012) emphasize that each minute of blood supply stop to the kidney on surgery influences the remote functional outcomes of kidney resection

. It’s worth noting that not all the kidney tissue and not synchronically is involved in urine formation, therefore the argument mentioned above is quite debatable.

At present, the mechanisms of hypoxic cell alteration is studied in details, the identity of cause-and-effect chains for the cells of different type and origin is defined, dependence of new disturbances of intracellular homeostasis on hypoxia time is shown. So, for instance, it’s experimentally proved that within the first 5 minutes of oxygen deprivation there is a decrease of intracellular ATP level in 2-4 times. Within the following 10 minutes, hyper concentration of calcium ions as activators of membranous phospholipase is formed in the cytoplasm and mitochondria. Then, from the 15th to 30th minute of hypoxia, there starts the breakdown of phospholipids of mitochondria membranes associated with the activity of active membranous phospholipase, characterized by the increase of their permeability, the inhibition of the processes of Ca^{2+} ions accumulation as well as the dissociation of the oxidative phosphorylation and decline of mitochondria activity indices – the coefficients of oxidative phosphorylation and respiration control from 0 to 1 respectively. Within the following half an hour, it’s possible to observe the transitory increase of the intensity of mitochondria respiration, then after 60-90 minutes from the beginning of the hypoxic impact, mitochondria damage gets to be irreversible leading to the cell death 16–19

This scenario of hypoxic alteration on the molecule-cellular level, which is standard for all the cells regardless of their tissue and organ type, agrees with the conclusions of many researchers stating that, firstly, the time of warm ischemia is the principal factor increasing or decreasing the baneful effect of oxygen deprivation and able to predefine the postoperative degree of the functional competence of the uropoetic system 20; secondly, even in cases when the time of RWI doesn’t exceed 20-25 minutes, postoperative decline of the kidney function is observed in more than 20% patients 21.

At present a lot of publications confirm a high relevance of the scientific research dealing with developing the methods of renal tissue protection on preforming the operations involving RWI. There are two directions: the first one is focused on reducing the time of RWI and/or its scales (the techniques of “zero ischemia”, selective parenchymal ischemia, super selective tumor devascularization, superselective embolization of the arteries supplying the tumor, controlled hypotonia, “cold ischemia” with perfusing chilled solutions through the kidney bloodstream or covering it with ice, etc.) 22–24. The second one is associated with the pharmacological

support of the renal parenchyma during renal warm ischemia 25. Here, regarding the mechanisms of the effector nephrocytes damage in terms of RWI, the most proven and efficient is the use of pharmacological medication with antihypoxic type of action and the use of precursors of high-energy bonds.

At present, antihypoxic medicines are used in different forms of pathology involving hypoxic impairment. In such cases the result of antihypoxant action is the rise of the energy status of the damaged cells, the removal of the imbalance between needs for ATP and the level the ATP biosynthesis

The present-day drugs of antihypoxic action are classified into five groups: 1) antioxidant inhibitors of fatty acids (perhelexine, aethomoxire, trimethazidine, ranolazine, meldonium); 2) succinate-containing drugs (reamberin, cytoflavin, remaxol, oxymiaethylaethylpyridine succinate) and succinate-forming (sodium oxybutirate, polyoxyfumarine, confumine); 3) natural components of the respiratory chain (cytochrome C, ubichinon); 4) artificial redox-systems (oliphen or hypoxen); 5) high-energy compounds (phosphocreatine) 27.

At present all the listed drugs are applied in clinical practice and are widely and successfully used in cardiology, neurology, ophthalmology, gynecology and other fields of medicine 27. But at the same time there are few and varied publications concerning the problems of antihypoxic protection of the renal tissue including the issues of antihypoxic nephroprotection in terms of RWI. These marked circumstances served as a motivation to carry out this study. The aim was the comparative study of the nephroprotective activity of mannitole, sodium fumarate and furosemide using the experimental model of 30- and 60-minute renal warm ischemia.

MATERIALS AND METHODS OF THE STUDY

The experiments were carried out on 360 conventional male-rabbits of the “Chinchilla” breed weighed 2,6±0,3 kg. The ethical principles of dealing with animals were followed according to the requirements of «European Convention for the Protection of Vertebral Animals Used for Experimental and Other Scientific Purposes. CETS No. 123».

To achieve the aims of the study we worked out a method of modeling the intraoperative warm ischemia of the renal tissue which involved applying microvascular renal artery clamp after midline laparotomy and skeletization of the kidney pedicle. Vascular clamping lasted 30 and 60 minutes. After taking the samples of the kidney parenchyma the renal artery blood flow was restored. The experimental surgical intervention was finished by controlling hemostasis and closing the wound of the anterior abdominal wall with single interrupted vicryl sutures. During the surgery the animals were provided with anesthetic management (zoletil, 25 mg/kg IV; rometar, 2% 1,0-1,5 ml IM; halothane-oxygen mixture). To prevent microbe infection bicilline-5 dosed 1 500 000 UI/kg was administered intramuscular intraoperative.

Before the beginning of the experiments all the animals were allocated into 10 groups (2 control groups and 8 trial groups), each having 36 animals. Control groups №1 and №2 included intact rabbits and the rabbits having “false” surgery without clamping the renal artery. In all the trial groups while performing an experimental intervention each animal was subjected to the model of renal warm ischemia lasting 30 minutes in groups №3, №5, №7 and №9, and 60 minutes in groups №4, №6, №8 and №10.

In groups №3 and №4 the intervention was performed without pharmacological nephroprotection, the rabbits from groups №4 and №5 were introduced sodium salt of famaric acid (sodium fumarate) single dosed 1,50 ml/kg intravenously 24 hours and 2 hours before the operation. As the comparison medication there was used lasix (groups №7 and №8) and mannitole (groups №9 and №10). Both medicines were administered intravenously 10 minutes before applying microvascular renal artery clamp: lasix dosed 3,00 mg/kg, mannitole dosed 1,00 g/kg.

All the animals were studied in terms of the macro- and ultrastructural features of the renal tissue. To estimate macrostructural characteristics of the kidney visual evaluation of the organ was performed. The condition of ultrastructural components of the renal tissue was analyzed by the method of transmission electron microscopy of the biopsy material of the renal parenchyma in FSBE “Research Institute of Influenza” Ministry of Health of the Russian Federation using an electron microscope JEOL JEM 1011 having the point image resolution 0,3 nm and lattice image resolution 0,14 nm, magnification of the objects x100 -1 000 000. Digital electron micrograph photography was performed using the camera Morada.

After 2, 12, 24 and 72 hours after the experimental intervention as well as at the end of the first, second, third and fourth week of the postoperative period all the rabbits were measured the levels of NGAL, cystatine-C, L-FABP, KIM-I and creatinine in blood serum and/or in urine.

To process the received data there were used the methods of variational statistics, a set of applied programs “STATISTICA 6” found in “Microsoft Excel 2002”. Differences were considered meaningful in $p<0,05$.

RESULTS OF THE STUDY

In all the animals having RWI the longitudinal and transverse size of the kidney diminished by 5% compared to that of the rabbits from the control group №2. There was also observed the turgor decrease, paleness and coldness of the kidney surface.

According to the findings of the electron microscopy, shown in Figure 1, after 30-minute RWI and 60-minute reperfusion in the proximal tubules there is observed the increased number of

lysosomes and vacuolization of the cytoplasm of epithelial cells, pear-shape of the final segments of the microvilli, signs of slight swelling and edema of the brush border. In the lumens of the distal tubules and collecting tubes presence of flaky content is detected. In the animals that didn't get any medication, these signs occur in the mass. In the groups, where sodium fumarate, lasix and mannitole were used, the mentioned ultrastructural disturbances were the least expressed, however sodium fumarate showed the best nephroprotective activity.

All the revealed changes of the renal ultrastructure ischemized for 30 minutes also took place after 60-minute RWI, but the degree of their expression was much higher (Figure 2).

Besides, new disturbances appeared which were absent after the renal artery occlusion of less duration. Among them – aggregation and agglutination of the corpuscles in the glomerular and peritubular capillaries; change of the form of the proximal tubules microvilli by replacing the finger-shaped configuration for the pear-shaped or bubble-shaped; destruction of the cytoskeleton of epithelial cells of the proximal tubules in the form of depolymerization and fragmentation of microtubules and myofilaments; clusters of friable flaky substance interspersed with granular detritus both in distal and proximal tubules; swelling and vacuolization of the epitheliocyte cytoplasm of the distal tubules and collecting tubes with thickening of their walls and decreasing of the lumen diameter. After 60-minute warm ischemia of the renal parenchyma without pharmacological correction the marked ultrastructural signs of hypoxic alteration of the renal tissue were maximum evident. The use of lasix and mannitole slightly allowed to reduce the degree of the impairment.

The use of sodium fumarate reduced the occurrence of such disturbances to single cases. After 30-minute RWI and introduction of this chemical compound the changes of the kidney ultrastructure restricted to rare pear-shaped dilatations of the microvilli ends and not numerous clusters of friable flaky substance in the lumens of the distal tubules and collecting tubes.

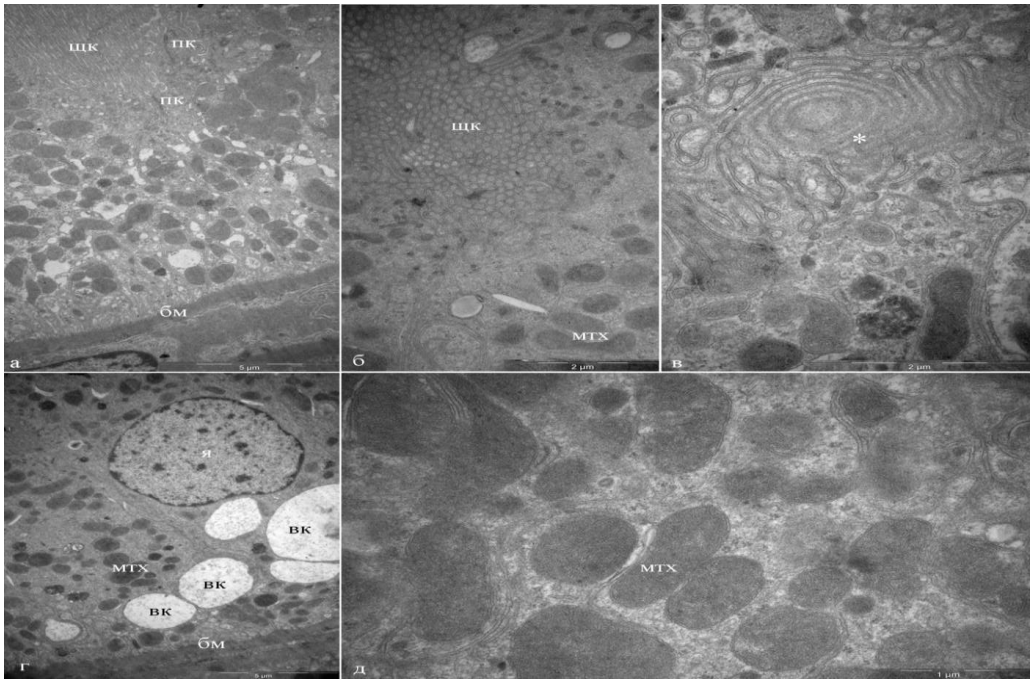
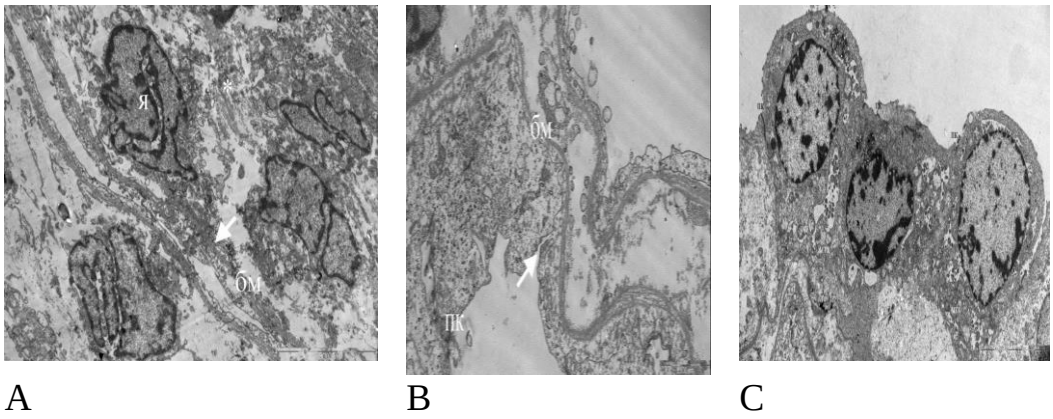


Fig.1: Ultrathin histological section after 30-minute warm ischemia and 60-minute reperfusion of the kidney (contrast study in alcohol solution of uranyl-acetate and aqueous solution of lead citrate). a – general view of proximal tubule epithelium, x200000; b – swelling of the brush border, x500000; c – merge of the membranes of microvilli of the brush border and formation of labyrinthine membrane structure (star), x500000; d – vacuoles in the cytoplasm of proximal tubule cells x200000; e – mitochondria of proximal tubule cells preserve their normal structural organization.
Keys: BB – brush border, BM – basal membrane, M – mitochondria, V – vacuoles, N – nucleus.



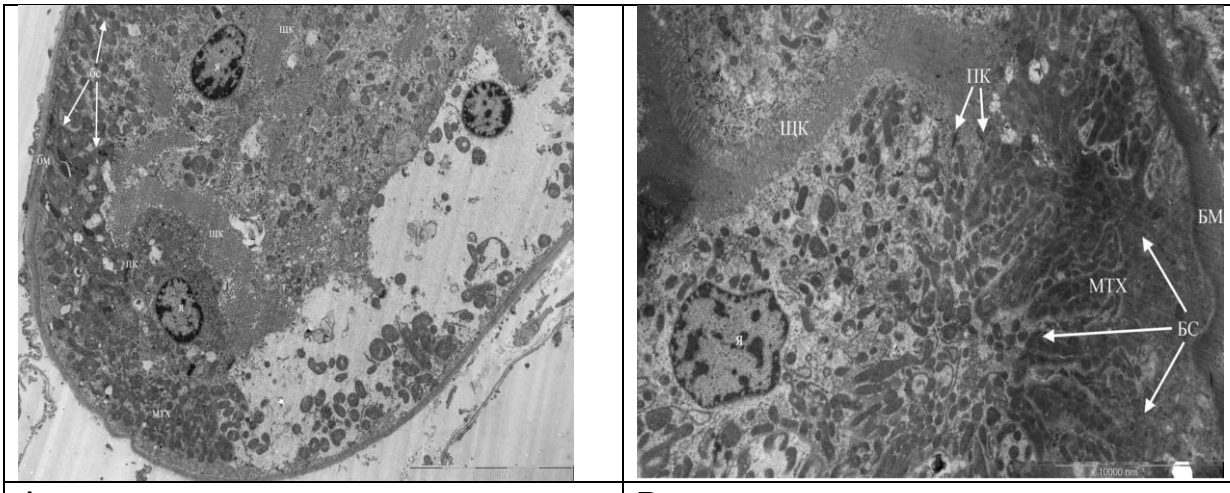
A B C

Fig.2: Ultrathin histological section after 60-minute warm ischemia and 60-minute reperfusion of the kidney. Contrast study in alcohol solution of uranyl-acetate and aqueous solution of lead citrate. A – a proximal tubule, x100000, numerous death of epithelial cells with fragmentation of their cytoplasm (star) and exposure of the basement membrane areas (arrow). B – a thin part of Henle's loop, x20000, partial watering of the epithelial cells cytoplasm and wholeness disturbance of single dense contacts (arrow). However, most dense contacts preserve normal organization. C – a distal tubule, x20000. Fragmentation of mitochondria into small round structures, with partial loss of cristas.
Keys: EN – epitheliocyte nuclei, BM – basal membrane, DC – dense contacts

As shown in Figure 3, after 60-minute warm exsanguination performed with the use of sodium fumarate, in the proximal part of the renal tubules most epithelial cells preserve the brush border in its intact form (or, perhaps, there is a very rapid regeneration of the brush border); pear-shaped and bubble-shaped dilatations of the microvilli occur only in single cases. In the epithelial cells of the proximal tubules there are visible basal folds associated with numerous mitochondria marked along the apical-basal axis, cell contact with the basal membrane, nearly full preservation of the system of the isolating dense contacts defining the wholesome of the epithelial layer and its functional polarization. Only in single cases there is observed an increased number of lysosomes, fragmentation of cytoskeleton microtubules and myofilaments in the cytoplasm of epithelial cells of the proximal tubules. All these signs bring the ultrastuctural organization of the proximal tubules in terms of fumarate-mediated nephroprotection closer to the normal state and make it absolutely different from the picture of nearly complete destruction of the proximal tubules epithelium after 60-minute RWI performed without medication support.

According to the image in Figure 3A, despite of the considerable decline of pathomorphological changes in the proximal tubule on using sodium fumarate, in some cases there is observed a cell death of tubular epitheliocytes. However, only the death of single cells neighbouring with the normal epitheliocytes in the same tubule is meant in such cases. The animals having 60-minute warm exsanguination of the kidney and not receiving sodium fumarate were noted to have a mass death of epitheliocytes.

As shown in Figure 3C, 3D and 3E, in terms of fumarate-mediated nephroprotection on 60-minute RWI, the ultrastructure of more distal nephron segments (thin segment of Henle's loop, distal tubule, collecting tube) is quite similar to that one in the control conditions. There is noted a much better preservation of the distal tubule mitochondria associated with the basal folds of the cell membrane compared to their fragmentation and degradation of the cristas after 60-minute warm exsanguination in the animals not receiving sodium fumarate while ischemic stress without nephroprotection (Figure 3D).



A B

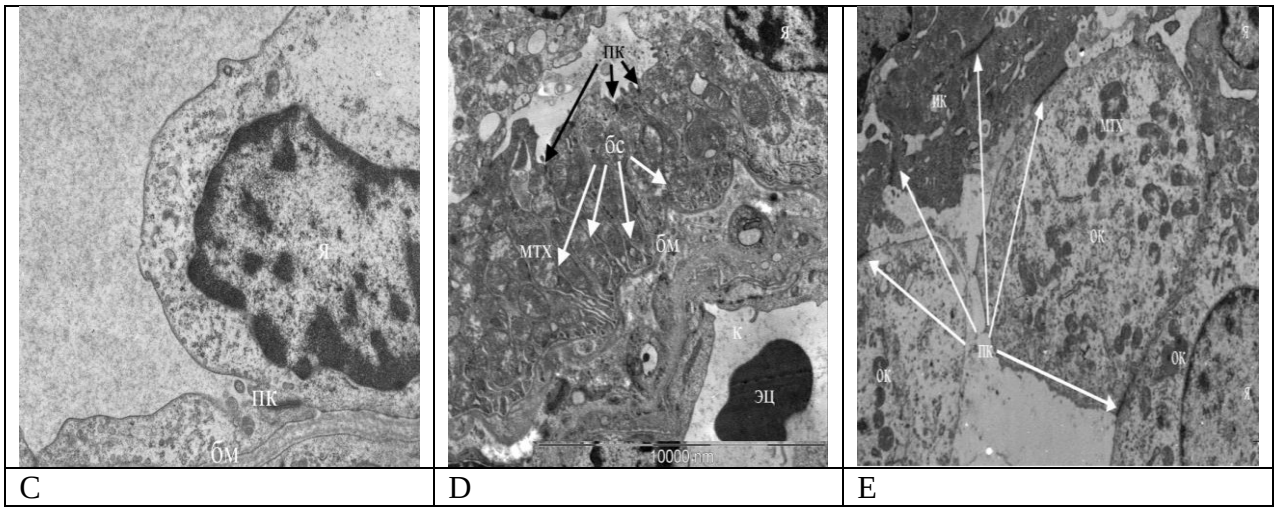
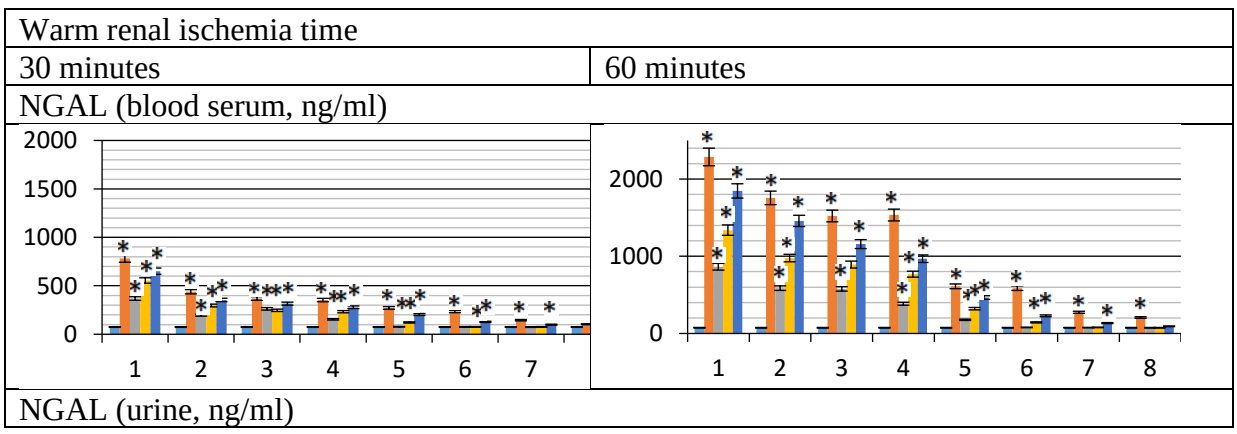


Fig.3: Ultrathin section of the renal tissue after 60-minute WRI and 60-minute reperfusion with the use of 15% aqueous solution of sodium fumarate. Contrast study in alcohol solution of uranyl-acetate and aqueous solution of lead citrate. A, B - the proximal tubule, x20000, A (down to the right) - necrotic death of some epitheliocytes on preserving the normal ultrastructure of other cells as a part of the epithelial layer; C - a thin part of Henle's loop, x20000; D - the distal tubule, x20000; E - the collecting tube, x20000.
Keys: BB - brush border, EN - epitheliocyte nucleus, M - mithochondria, BF - basal folds, BM - basal membrane, DC - dense contacts, E - erytrocytes, MC - main cells of the collecting tube, IC - intercalary cells of the collecting tube.

Changes of NGAL and cystatin-C concentrations in blood serum and urine and creatinine level in blood serum after 30- and 60-minute WRI (pharmacologically non-corrected and performed with the use of sodium fumarate, lasix and mannitole) are shown in Figure 4.

NGAL concentration in blood serum 2 hours after the experimental operation with 30- and 60-minute WRI was sharply, peak-like increased in 10 and 31 times in the animals with pharmacologically non-corrected exsanguination, when using sodium fumarate – in 5 and 11 times, lasix – in 7 and 18 times, mannitole – in 9 and 25 times. Then there was a gradual decline of this index. Normalization occurred after two weeks in the rabbits protected with sodium fumarate regardless the WRI time, a week later in the groups receiving lasix and two weeks later in the animals having non-corrected ischemia and in all the animals receiving mannitole. During the final measuring NGAL level in blood remained increased after 60-minute pharmacologically non-corrected RWI.

As well as in blood serum, NGAL level in urine was increased after 2 hours of intervention: in 50 and 68 times in the animals having 30- and 60-minute WRI without medicine support (p=0,039 and p=0,034, respectively), in 23 and 37 times in the groups using sodium fumarate (p=0,02 and p=0,005, respectively), in 40 and 42 times in the rabbits receiving lasix (p=0,039 and p=0,034, respectively) and in 41 and 55 times when using mannitole (p=0,010 and p=0,001, respectively). Then the value of this index gradually decreased. Differences with the control NGAL level in urine disappeared at the end of the observation period in the groups with pharmacologically non-corrected 30- and 60-minute RWI and in the groups using mannitole. After performing the experiment and introducing lasix normalization occurred a week earlier. In the rabbits protected with sodium fumarate preoperative NGAL level in urine was restored in a week after 30-minute RWI and in two weeks after 60-minute exsanguination.



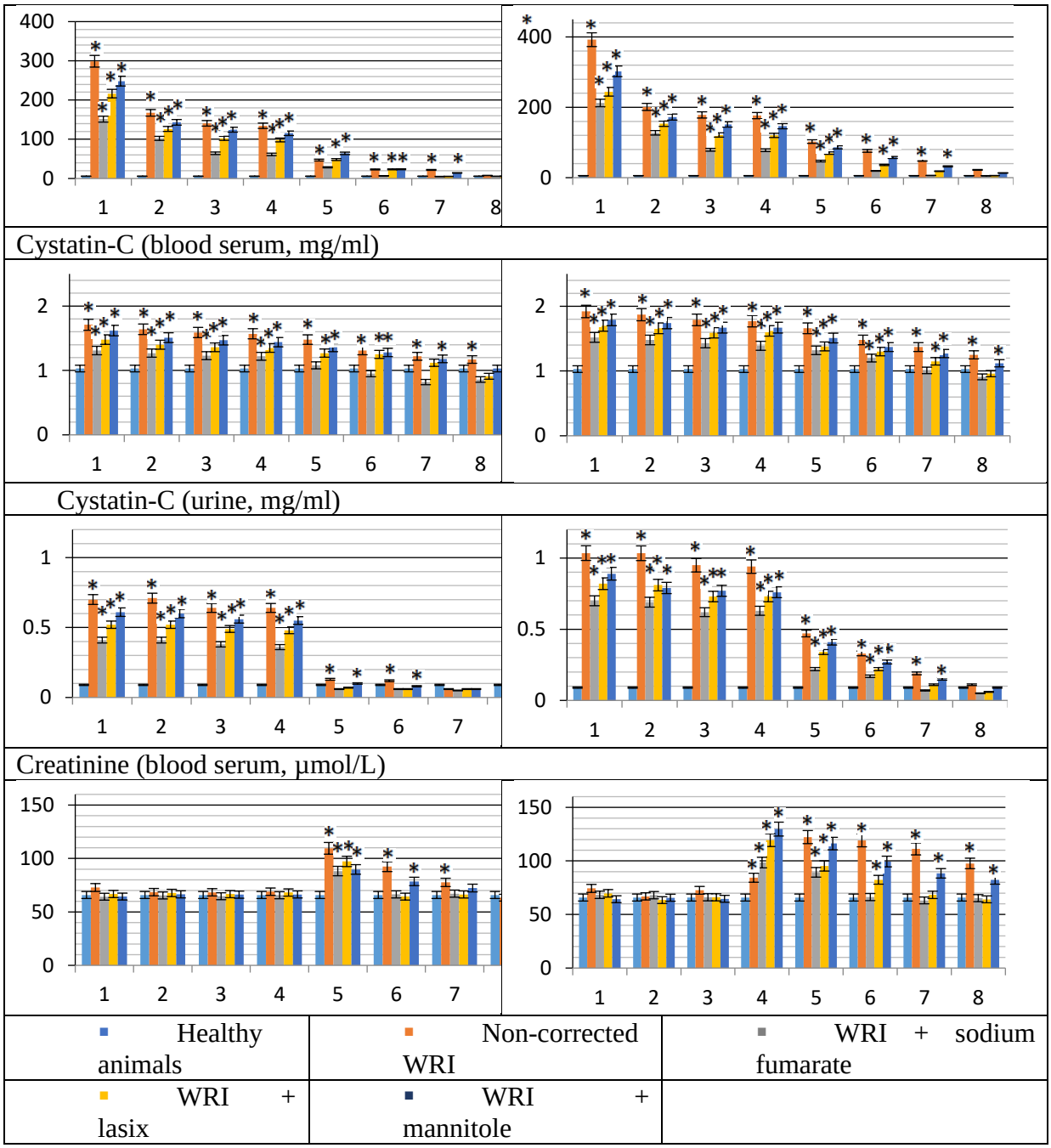


Fig.4: Influence of medicine support during 30- and 60-minute warm renal ischemia upon the dynamics of tissue markers of acute kidney damage in blood serum and urine in the rabbits after 2(1), 12(2), 24(3) and 72(4) hours and in 7 (5), 14 (6), 21 (7) and 28 (8) days after the experimental intervention.
Keys: * - statistically meaningful differences between the indices in control animals and rabbits from trial groups ($p < 0,05$).

Cystatin-C level in blood after 30- and 60-minute clamping of the renal artery without medicine support was increased within the whole observation period with its maximum during the first 2 hours, exceeding its value by 64% and 85%, respectively. In terms of fumarate-mediated protection in 2 hours after 30-minute RWI, the index level increased only by 27%, and became normal on the seventh day. After introducing lasix, in the first 2 hours after 30- and 60-minute exsanguination the index value increased by 42% and 65%, after introducing mannitole – by 56% and 72%. Then this index gradually declined, normalization occurred not earlier than on the twentieth day and only in the animals with 30-minute RWI.

In the rabbits of group №3 and group №4 in the first three days after pharmacologically non-corrected renal warm ischemia lasting 30 minutes cystatin-C level in urine increased in 8 times, after 60-minute RWI – in 12 times; the index normalization was noted at the end of the third and fourth week of monitoring, respectively.

In terms of using sodium fumarate, in the first three days after RWI lasting 30 minutes cystatin-C level in urine increased in 5 times, however, on the seventh day it returned to its initial value. On increasing the time of exsanguination to 60 minutes this substance level in urine increased in 8 times and became normal nor earlier than at the end of the third week after the

experiment start.

During the first 72 hours after 30- and 60-minute RWI and introducing lasix, cystatin-C concentration in urine increased in 6 and 9 times compared to the initial value (p=0,030 and p=0,006, respectively). Decrease of cystatin-C in urine to its initial value was observed on the 7th day, if the renal warm ischemia time didn't exceed 30 minutes, and at the end of the third week of the experiment after 60-minute exsanguination.

In the rabbits receiving mannitole, during the first 72 hours after 30-minute exsanguination of the renal tissue cystatin-C level in urine increased in 6-7 times (p=0,025 and p=0,030, respectively), after 60-minute RWI – in 8-10 times (p=0,032 and p=0,011, respectively). Then gradual decline of the index was observed. The results on the twenty-first and twenty-eighth day didn't differ meaningfully from the preoperative value.

Increase of creatinine level in blood serum after modelling RWI was noted only in seven days after 30-minute ischemia and on the third day after 60-minute exsanguination, whereas the maximum concentration was observed in terms of pharmacologically non-corrected RWI, less high – with mannitole action, even lower – on using lasix, the lowest – in the animals receiving sodium fumarate.

DISCUSSION

According to the results of the study, sodium fumarate, introduced intravenously in a single dose 1,50 ml/kg 24 hours and 2 hours before the experimental operation with modelling RWI of different time (30 and 60 minutes), greatly restricts the expression of acute ischemic damage of the renal tissue, whereas the main element of its pathogenesis is an energy status decrease of epithelial cells of the kidney proximal tubules associated with oxygen deprivation.

It is experimentally confirmed by, firstly, differences between ultrastructural features of the renal tissue in the animals having 30- and 60-minute RWI with the use of sodium fumarate and without any medication support, in favor of sodium salt of fumaric acid; secondly, - statistically meaningful differences between the features of postoperative dynamics of NGAL and cystatin-C in blood serum and urine, creatinine in blood serum – also in favor of sodium fumarate.

Besides, according to the results of electron-microscopic investigation of the renal tissue and the laboratory staged analysis of biomarkers of acute kidney injury in blood and urine, nephroprotective activity of sodium fumarate greatly exceeds that of lasix and mannitole.

The use of succinic and fumaric acids and their derivatives in pharmacotherapy of the cases related to hypoxy and deficient formation of macroergic compounds is based on later inhibition of the activity of FAD-mediated succinate-oxidase fragment of the citrate cycle in the cells deprived of oxygen, compared to NAD-dependent elements. Therefore, even during oxygen deprivation there is a chance to support the energy-forming function of mitochondria within a certain period. It is conditioned by the presence of necessary substrates in mitochondria, perhaps, exogenous succinates found, for instance, in mexidole, cytoflavin or reamberin. Besides, recharging the pool of mitochondrial succinates can be provided by external introducing of succinate-forming compounds, including sodium oxybutirate, sodium fumarate and polyoxyfumarine.

After exogenous introducing of sodium fumarate into the inner medium and its electrolytic dissociation, fumaric acid anions (fumarates) easily overcome common cellular and mitochondrial membranes. In terms of hypoxy in mitochondria there occurs transformation of fumarates into succinates recharging mitochondrial pool of substartes of FAD-dependent succinate-oxidase step of Krebs cycle and therefore increasing ATP formation within a certain time, for instance, time of kidney warm exsanguination.

Sufficiency of the energy status of the ischemized cells during RWI provided by exogenous introducing of sodium fumarate becomes, firstly, the factor preventing the inhibition of ATP-dependent transmembrane transport of ions, alteration of cellular and intracellular membranes, loss of potassium ions and accumulation of calcium in hyaloplasm with activating the membrane phospholipase, rise of intracellular colloid-osmotic pressure and cells swelling, release of active lysosomal hydrolases, impairment of the cell genetic apparatus and start of apoptic program and other disturbances leading to irreversible cell alteration and death; secondly, the factor promoting the preservation of the functional potential of the renal parenchyma during RWI and competence of the kidney function in the postoperative period.

The results of the performed investigation fully agree with the opinions of many researchers about the expediency and efficiency of using the medicines of antihypoxic type of action, particularly succinate-forming compounds, to prevent and correct ischemic-hypoxic disturbances in the clinical practice.

CONCLUSIONS

The studied medicines produced a nephroprotective effect in terms of renal warm ischemia of the rabbits: in the highest degree on using sodium fumarate, then furosemide and in the least degree – mannitole.

Using sodium fumarate allows to protect and stimulate the renal tissue maximum effectively during oxygen deprivation of the ischemized organ.

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