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Experimental Study of ATP-Dependent Potassium Channels Activators Using Possibility in Surgery.

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ABSTRACT

Experiment is executed on white rats of the Wistar line. Studying of influence of a distant ishemic reconditioning, nicorandil and minoxidil on a condition of ishemic weak fabrics, and also selection of optimum doses of medications was carried out on model of the isolated integumentary flap on the pedicle. The received results showed that the pharmacological reconditioning nicorandil and minoxidil along with a distant ishemic reconditioning can be considered as the available universal instrument of prophylaxis and correction of consequences of a local ishemia in surgery. And medications are effective in the minimum dose which does not have the ghost effects, the reference for a medication in a routine dose.

Keywords: rats, an ishemia, an ishemic reconditioning, a pharmacological reconditioning, nicorandil, minoxidil.

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INTRODUCTION

The prospect of studying of a an ishemic reconditioning phenomenon for many years remains vital. Opening of a distant ishemic reconditioning proved that process has not local character, and represents the system of multilevel duplication including a humoral component [1]. The last gave rise to an age of pharmacological reconditioning. A number of medications capable to initiate process without ishemic episode is known, however this question continues to be open. The real research is devoted to studying of influence of ATP activators – dependent potassium channels of a nicorandil and minoxidil on a condition of ishemic weak fabrics.

TECHNIQUE

Experiment is executed on 80 white rats of the Wistar line weighing 220-250 g. Nicorandil studying of influence and minoxidil a condition of ishemic weak fabrics, and also selection of optimum doses of medications was carried out on model of the isolated integumentary flap on the pedicle. The rag all animal was found on second day of experiment under anesthetic on a forward abdominal wall by the 1-cm basis, 4-cm length, isolated in a sterile plastic bag, a wound took in a noose suture. The assessment of survival was made by means of measurement of the the survived fabric area for the 6th days of experiment. Further estimated the index of survival (IS) - the relation of the survived fabric area and the initial area of a rag ×100%. All animals were divided into 4 groups: I – control with model operation of a integumentary flap and introduction of Amylum (n=10); II – with model operation of a integumentary flap and carrying out a distant ishemic reconditioning (n=10), III – with model operation of a integumentary flap and introduction of a nicorandil: III And in a daily dose of 3,4 mg/kg (n=10), III In – 1,3 mg/kg (n=10), III With – 0,4 mg/kg (n=10); IV – with model operation of a integumentary flap and introduction of a minoxidil: IV And – in a daily dose of 2 mg/kg (n=10), IV In - 1 mg/kg (n=10), IV With – 0,25 mg/kg (n=10). Amylum in group I, medications in groups III and IV entered endogastric according to the identical scheme – for the first days of experiment, then every 48 hours, a distant ishemic reconditioning in group II carried out 30 and a minute applying a tourniquet on the left-hand lower extremity according to the same scheme [2].

RESULTS OF RESEARCH

At model operation of a integumentary flap on the pedicle the part of its length surpassing basis width no more than twice survives. We obviously found a rag at which length 4 times surpassed basis width.

For the sixth days of experiment in control group the area of the survived fabric of a rag made 1,59±0,03 cm2, an indicator of survival – 40% of the initial area (4 cm2) that corresponds to the results received by other researchers. Carrying out a distant ishemic reconditioning promoted reliable increase in survival of a integumentary flap in comparison with control group – to value of 2,36±0,09 cm2 (p <0,05), PV – 59%. Introduction of medications in all applied doses also promoted reliable increase in survival of a integumentary flap in comparison with control group, in group III A to 2,20±0,08 cm2 (p <0,05) PV – 55%, in group III B to 2,90±0,37 cm2 (p <0,05) PV – 72,5%, III With to 3,10±0,03 cm2 (p <0,05) PV – 77,5%, in group IV A to 2,40±0,03 cm2 (p <0,05) PV – 60%, in group IV B to 2,41±0,04 cm2 (p <0,05) PV – 60%, IV With to 2,50±0,04 cm2 (p <0,05) PV – 62,5%.

Thus, the distant ishemic reconditioning promotes increase in survival of the isolated integumentary flap on the pedicle. Nicorandil as well as minoxidil on this model in all applied doses have similar effect.

ATP-dependent potassium channels are the most probable effector link in a phenomenon of an ishemic reconditioning. Realization of their protective potential is connected with a membrane hyperpolarization owing to their opening, activation of system of nitrogen oxide and other mechanisms. Canals of this type are located on a plasmatic membrane of nervous cells, on an internal membrane of mitochondrions, are widely presented to endothelia and the smooth muscle cells of vessels. All their isoforms are capable to share in realization of protective effect of a reconditioning [3]. Activators of ATP-dependent potassium channels one of the most perspective medications for activation of process of a reconditioning, however the majority of researches is directed on studying of their effects on heart [4]. The result of the conducted research showed that the distant ishemic reconditioning promotes increase in survival of the isolated integumentary flap on the pedicle. Nicorandil as well as minoxidil on this model in all applied doses have similar effect.

Nicorandil also minoxidil are capable to activate equally the least sensing channels, however nicorandil in difference from a minoxidil is a hybrid of nitrate and the activator of potassium ATP-dependent channels [5]. In the conducted research we estimated not only influence of medications on ishemic weak fabrics, but also carried out selection of the most optimum dose of medications. The choice of doses was carried out according to the literary data devoted to the pilot studies on animals, the instruction on application of medications, and also scaling ratios of doses (mg/kg on mg/sq.m) for a rat and the person depending on body weight. It is known that the daily reconditioning leads to gradual cancellation of effect. Considering that the effect of a reconditioning starts weakening in 46 hours [6], we chose the scheme of introduction of a daily dose through the corresponding time term.

Minoxidil in a daily dose of 2 mg/kg, 1 mg/kg, 0,25 mg/kg renders equivalent effect on models of the isolated integumentary flap on the pedicle. Reliable differences between indexes in subgroups of group IV it is not revealed. In group with application of a nicorandil the indicator of survival authentically increases at decrease of a medication dose. It is known that both medications have the expressed hypotensive effect, however in minimum doses such ghost effect is not observed. The daily dose nicorandil 1,3 mg/kg (in terms of the person makes 15 mg/days) whereas the dose of 3,4 mg/kg is standard (in terms of the person of 40 mg/kg per day). Researches, showed that therapy of nicorandil 15 mg/days improved the clinical forecast at the coronary patients who are on a hemodialysis after an angioplasty [7]. These data allow to assume that the dose of a nicorandil of 15 mg/days provides adequate opening of K-ATF of channels. Besides in a number of researches it is proved that application of a medication in such dose deprives of it the ghost effects. Results of research and literary allow to assume that improvement of effect of a nicorandil at decrease of a dose is bound to nitrolike effect of a medication which the minoxidil does not have. One of mechanisms of development of ishemic adaptation stimulation of synthesis of nitrogen oxide under the influence of an ishemia and the subsequent reperfusion is considered. Data on participation of nitrogen oxide in realization of protective effect of a classical ishemic reconditioning are contradictory.

Separately it is worth stopping on "a nitrogen oxide hypothesis" a prepositional phrase of scientists led by R. Bolli in 1998 [8]. Its original positions are as follows.

- Nitrogen oxide plays a key role both initiations, and in a mediation of a "the second protective window" phenomenon;

- As the trigger of "the second protective window" nitrogen oxide acts during the first short-term ishemic episode when it causes the increased formation of NO (allegedly, at the expense of an endothelial NO sinthasy) and superoxidanionradicat. Interacting among themselves, NO and O2 form peroxinitritradikat. Peroxinitryt, in turn, activates ε-isoform C-protein kinases. Its stimulation can be also carried out and other fissile forms of oxygen which are O2 derivatives;

- Activation ε-isoform protein kinases With starts the complex alarm cascade including activation various tirosincanas, the mitogenactivated protein kinases and a transcription factor. These mechanisms lead to increase of the transcription of a gene induced NO synthase and, as a result, to increase of activity of this enzyme in a time interval of the delayed phase of protection of an ishemic reconditioning (day 2, following an original nomenclature of R. Bolli).

In development of an ishemic reconditioning two various isoforms NO synthase matter: calcium dependent endothelial, participating in early phases of process, and calcium dependent induced, generating nitrogen oxide for protection of a myocardium is later. It is revealed that at early stages of formation of a late phase of an ishemic reconditioning nitrogen oxide is synthesized due to activation endothelial, and later (in 24 hours) – at the expense of inductable NO synthase [9].

Authors of "a nitrogen oxide hypothesis" consider what exactly a superactivity inductable NO synthase, recorded in 24-72 hours after the initiated ishemic episode, is responsible for realization of protective effect of "the second window" of a reconditioning. It is necessary to emphasize once again that, according to R. Bolli, the trigger for development of "the second window" are also jet forms of oxygen, some of them react with nitrogen oxide and form other free radicals, such as peroxinitrit [10]. Nitroxyl, one more one-electron derivant of nitrogen oxide, provides protection similar to a reconditioning and larger, than immediately nitrogen oxide. That is the jet NO forms are necessary for protection against ishemic damage that

is confirmed in our research – effect of a nicorandil in a daily dose of 0,4 mg/kg 1,3 times better than effect from a distant ishemic reconditioning and a minoxidil in a minimum dose. At the same time in big concentration nitroxyl also peroxinitrit are capable to cause damage. The dose of donators of nitrogen oxide also defines possibility of application for a pharmacological reconditioning.

SUMMARY

The pharmacological reconditioning nicorandil and minoxidil along with a distant ishemic reconditioning can be considered as the available universal instrument of prophylaxis and correction of consequences of a local ishemia in surgery. And medications are effective in the minimum dose which does not have the ghost effects, the reference for a medication in a routine dose. The received results allow to conduct further researches of effects of a reconditioning nicorandil and minoxidil.

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