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Preservation Solution with Curcumin for Vascular Surgery

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Abstract

The object of the study was the annular segments of the descending thoracic aorta of male «Wistar» rats, the annular segments of the great saphenous vein, the radial and internal thoracic arteries of a human. In the process of work, experimental studies were carried out to assess the viability of isolated vessels under various conditions of their conservation. For this purpose, the isometric contractions of isolated arteries and the functional state of their endothelium were evaluated before and after vessel preservation in bicarbonate buffer with curcumin encapsulated in polyvinpyrrolidone, 2% papaverine solution, and Custodial cardioplegic solution. Solutions were studied in aerated and non-aerated form. Vasospasm of isolated vessels was assessed using norepinephrine at a concentration of 10^{-5}M and KCl 75 mM. Endothelial function was assessed using the endothelium-dependent vasodilator acetylcholine 10^{-3}M. The preservation temperature was varied from 23°C to 4°C. Based on the results of the studies, it was found that the developed composition of a non-aerated preservative solution based on a bicarbonate buffer: NaCl – 118,5 mM, KCl – 4,7 mM, $CaCl_2$ – 2,5 mM, $MgSO_4$ – 1,2 mM, KH_2PO_4 – 1,2 mM, $NaHCO_3$ – 25 mM, curcumin – 1,5 μM, glucose 11 mM, pH 7,4; *t* = 4,0°C provides 100,0% preservation of the endothelial function of the vessels within 24 hours. Under these conditions, standard preservative solutions provided significantly less vascular protection: Custodial, 64–66%, 2% papaverine, 2%, and saline, 1%.

Keywords: preservative solution; bicarbonate buffer; vascular surgery; encapsulation in polyvinylpyrrolidone; flavonoid curcumin

Introduction

Among the cardiovascular diseases, the main place is occupied by ischemic heart disease (IHD) – a pathological condition with absolute or relative impairment of myocardial blood supply due to damage to the coronary arteries. Its treatment is symptomatic and depends on the clinical form. A sudden change in the nature of the disease, accompanied by instability of the patient's clinical status, is life-threatening. In such cases, traditional antianginal therapy is often ineffective and the patient's condition requires surgical intervention. In 1960, the American surgeon R.H. Goetz introduced coronary artery bypass grafting (CABG) into clinical practice – an operation in which myocardial blood supply is improved by connecting the coronary vessels below the site of their damage to the aorta using a shunt. Currently, coronary artery bypass grafts are used from the internal mammary artery (*A. mammaria*), radial artery (*A. radialis*) and great saphenous vein (*V. saphena magna*). However, in the early postoperative period, one of the main complications is graft occlusion, which occurs primarily due to their spasm [1]. The use of the radial artery in coronary surgery is currently limited to bypass grafting of occluded coronary arteries [2]. The main reasons for radial artery graft closure are its spasm and intimal hyperplasia. The radial artery, unlike elastic arteries (such as the internal mammary artery), is characterized by increased receptor-mediated contractility to various stimuli, which is realized not only through α-adrenergic receptors, thromboxane receptors, but also through activation of RhoA and Ba-sensitive Kir receptors [3]. Therefore, the choice of cardiovascular agents for the prevention of radial artery vasospasm is a complex task.

Antispasmodics (from the Greek spasmos – cramp, spasm and lyticos – releasing, relieving) are drugs that weaken or completely eliminate spasms of the smooth muscles of internal organs and blood vessels. Myotropic antispasmodics (MS) are a large group of drugs with various mechanisms of action that mediate their direct effect on smooth muscle cells.

The modern classification of MS is as follows

I. Non-selective MS:

phosphodiesterase inhibitors: isoquinoline derivatives (papaverine, drotaverine); xanthine derivatives (theophylline, euphylline); various (bencyclane, pinaverium bromide, adiphenin, arpenal, etc.).

II. Selective MS:

calcium channel inhibitors: phenylanilamine derivatives (verapamil); benzothiazepine derivatives (diltiazem); dihydropyridine derivatives (nifedipine, nitrendipine); potassium channel activators (minoxidil, diazoxide); nitric oxide donors (sodium nitroprusside, nitroglycerin, etc.) [4].

Papaverine (Papaverinum) is an opium alkaloid that has a myotropic spasmolytic effect on smooth muscles. It is used in Belarus to preserve blood vessels. According to modern concepts, papaverine inhibits phosphodiesterase (PDE) in muscles, which leads to an increase in the concentration of cAMP and relaxation of smooth muscles associated with its accumulation. On the other hand, papaverine has an effect similar to calcium antagonists. Unlike other opium alkaloids, it does not affect the central nervous system. A 2% solution is produced in 2 ml ampoules. However, the pharmacological drugs currently used to prevent spasms do not completely resolve this problem [5]. In addition, it is known that the use of drugs from some groups or their combinations is more effective in the intraoperative period, and others – in the postoperative period. The use of calcium antagonists after myocardial revascularization with radial artery grafts in patients with coronary artery disease does not completely prevent myocardial ischemia in the postoperative period. Despite the fact that intimal hyperplasia rarely contributes to the development of serious stenosis of venous grafts, it often provokes late stenoses and occlusions that occur against the background of progressive atheromatous deviations [6]. Therefore, the attending physician still does not have convincing criteria for choosing a pharmacological agent for a specific patient, taking into account his physiological characteristics. As a consequence of this fact – the development of postoperative complications and limitation of the use of a muscular vessel of a sufficiently large diameter [7, 8]. During surgical manipulations, the shunt is subject to temperature changes, which leads to a contraction of its walls. In addition, temperature changes affect the effectiveness of various drugs. When a section of artery is cooled sharply from 37°C to 22°C, contraction is observed; however, if cooling is done gradually, contraction is not observed and there is a decrease in the basic vascular tone, the strength of the reaction to norepinephrine, and the maximum response to KCl. With subsequent heating to 37°C, the strength of the reaction to norepinephrine and KCl was restored, and the basic vascular tone increased [9]. The protective effect of the cardioplegic solution «Custodiol», popular in global clinical practice, is based on the inhibition of oxidative and activation processes of the neuromuscular and secretory types in membrane structures [10]. The pharmacological action of the solution «Custodiol» allows for effective protection of the heart under conditions of general moderate hypothermia during cardiac ischemia lasting up to 180 min. The solution «Custodiol» is also used to relieve vasospasm of blood vessels [11]. The drug contains a histidine buffer, which eliminates the need for peroxygenation and determines the intracellular mechanism of tissue protection. Composition of the solution «Custodiol»: (mM/l) histidine 180,0; histidine hydrochloride monohydrate 18,0; tryptophan 2,0; sodium chloride 15,0; potassium chloride 9,0; magnesium chloride hexahydrate 4,0; calcium chloride dihydrate 0,015; α-ketoglutaric acid 1,0; mannitol 30,0; manufacturer «Dr. Franz Kohler Chemie GmbH» (Germany). The effectiveness of vasotransplants is largely predetermined by the procedures for their preparation and storage before implantation, which is why the search for universal drugs that prevent spasms and dysfunction of the endothelium of various shunts has recently intensified [8]. Damage to the endothelial structure due to vasospasm and thrombosis can subsequently lead to atherosclerotic damage to the implant. Based on the above, the selection of components to increase the effectiveness of buffer mixtures used to prevent spasms of the vascular graft is quite complex.

The aim of our work was to study the possibilities of a new solution for preserving the endothelium and preventing spasm of human vascular transplants. Materials and methods of the study. Preparation of the experimental solution – bicarbonate buffer containing the flavonoid curcumin encapsulated in polyvinylpyrrolidone. The bicarbonate buffer was a Krebs-Henseleit solution containing: NaCl – 118,5 mM, KCl – 4,7 mM, $CaCl_2$ – 2,5 mM, $MgSO_4$ – 1,2 mM, KH_2PO_4 – 1,2 mM, $NaHCO_3$ – 25 mM, glucose 11 mM, saturated with carbogen (O_2/CO_2 in the ratio 95%/5%), pH 7,4, t = 37,0°C. The content of

curcumin in the bicarbonate buffer was 1,5 μM. To increase the solubility of curcumin in water, we used polyvinylpyrrolidone (PVP), a polymer of the monomer N-vinylpyrrolidone. PVP is soluble in water and other polar solvents. In dry form, PVP has the appearance of a white or light yellow layered hygroscopic powder that easily absorbs up to 40% of its weight in atmospheric water, the molar mass is 2500–2500000 grams/mol, the density is 1,2 g/cm³, the melting point is 150–180°C (Fig. 1). PVP is used as an auxiliary agent to increase the solubility of drugs in liquid and semi-liquid dosage forms. In our studies, PVP was dissolved in water at a ratio of 25 g per 100 ml of water. Then 1 g of curcumin was added (Fig. 1). The mixture was thoroughly mixed and sublimated in a freeze dryer.

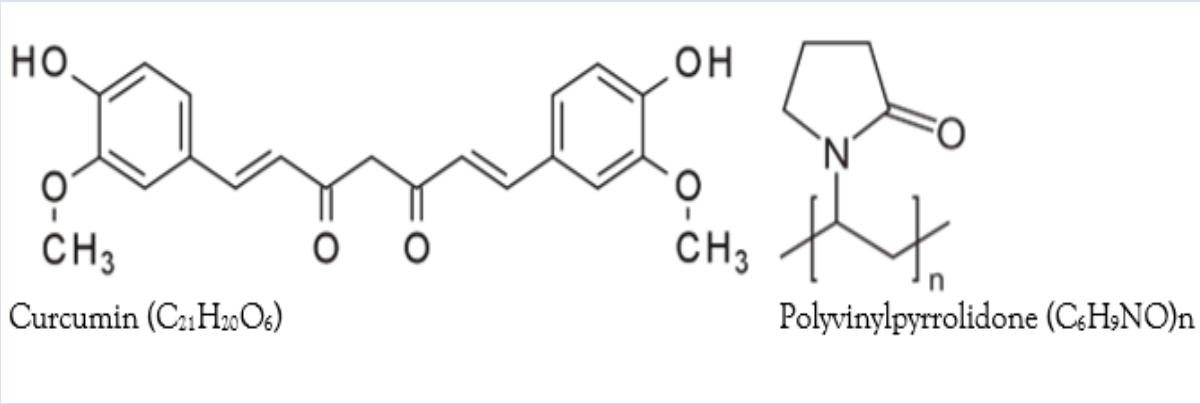

Figure 1: Chemical structure of the main components of the experimental solution

Conducting the research. The object of the study was ring segments of the descending thoracic aorta of male «Wistar» rats (weight 350–400 g) with intact endothelium. Preparation of aortic specimens and recording of vascular responses to the action of vasoactive substances were performed according to the method described by R.F. Furchgott. [12]. Rats were subjected to thoracotomy under urethane anesthesia (1,0 g/kg). The aorta was carefully cleaned of blood, the middle fragment was excised and cut into rings 3 to 4 mm long. The segments were placed in 6-ml vessels containing carbogenated Krebs-Henseleit solution at 37°C and fixed horizontally on an isometric voltage sensor of the «MultiMyograph DMT 610P» multichannel system (Denmark). Changes in voltage were amplified and transmitted to a computer for subsequent analysis. All segments of the descending thoracic aorta were stretched for 1 hour at a resting stress of 30 mN. Segments that relaxed less than 50% were excluded from further experiments. The effect of the preservative properties of curcumin added to a bicarbonate buffer was studied. A 2% papaverine solution and «Custodiol» were used as comparison drugs.

The experimental design was as follows

1. Isometric tension of rat arterial segments was recorded, which was defined as the initial tension.
2. 10^{-5}M norepinephrine was added to activate vascular contraction.
3. 10^{-3}M acetylcholine was introduced into the solution and the ability of vessels to endothelium-dependent relaxation was assessed.
4. Vessel segments were placed in the tested preservative solution for 24 hours in a thermostat at a temperature of 4,0°C.
5. Isometric tension of rat arterial segments was recorded after preservation, which was defined as the test tension.
6. 10^{-5}M norepinephrine was added to activate contraction of the drugs.
7. 10^{-3}M acetylcholine was introduced into the solution and the ability of the preparations to cause endothelium-dependent relaxation after preservation was assessed.

The objects of the study were ring segments of the great saphenous vein of the leg, the radial and internal thoracic arteries of humans, provided by the Institute of Cardiology of Belarus. The vessels were removed from patients during surgery and transported to the place of the experiment in a thermos in Krebs-Henseleit solution saturated with oxygen. The vein and arteries were cut into rings 3–4 mm long. The obtained segments were divided into 2 groups: 10^{-5}M norepinephrine was used as a vasoconstrictor for one group of vessels, and 75 mM KCl solution for the other. The segments were placed in 6-ml vessels containing carbogenated Krebs-Henseleit solution at 37°C and fixed horizontally on an isometric voltage

sensor of the «MultiMyograph DMT 610P» multichannel system (Denmark).

The experimental design was as follows

1. Constrictor was added. When the values reached a plateau, isometric tension of vessel segments was recorded, which was defined as the initial tension.
2. The experimental group of vessels was placed in a bicarbonate buffer solution (BBS) + curcumin for 30 min, after which the constrictor was added again.
3. When the values reached a plateau, isometric tension of vessel segments was recorded, which was defined as the test tension.

Statistica 10.0 was used for statistical processing of the obtained results.

Results and discussion

The study of the preservative properties of standard solutions of Custodiol, papaverine, physiological solution, flavonoid curcumin, added to bicarbonate buffer (BCB), showed that the studied substances can be divided into 3 groups according to their ability to preserve the endothelial function of isolated arteries (when compared with BCB) (Table 1). In the first group (BKB curcumin + 1,5 μM in PVP), BKB, BKB + O_2 with the addition of a vasodilator, a complete 100% relaxation of the aortic segments occurred (Table 1), which indicates the preservation of endothelial function after preservation in solutions of the indicated drugs for 24 hours. In the second group (Custodiol + O_2, Custodiol), a decrease in isometric tension by 65–87% was observed, while in the third group (papaverine 2%, 0,9% NaCl) – only by 0,8–1,6%. It should be noted that in isolated arterial strips after 24 hours of preservation, in almost all studied samples of solutions, the reaction to norepinephrine significantly (by 1,5–2,1 times) increased. The exception was BCB+curcumin 1,5 μM, where after preservation the value of test contraction was practically no different from the initial value (106,0%) (Table 1). The effect of the remaining drugs (except papaverine and NaCl) caused an increase in the test isometric contraction tension (163,6–214,7% of the initial value). Papaverine.

Table 1: Response of isolated thoracic aorta segments of male «Wistar» rats to norepinephrine (NE 10^{-5}M) and acetylcholine (Ach) for 24 hours

Investigational drugs	Number of vessels	NE 10^{-5}M	NE 10^{-5}M in 24 h	NE 24 h/NE %	Ach after 24 hours, %
BKB+curcumin 1,5 μM	8	17,6±3,2	18,66±2,2	106,0	101,3±1,9* †
BKB	10	13,79±1,2	26,52±2,2	192,3	87,9±3,6†
BKB+O_2	10	14,27±3,1	30,6±1,8	214,4	85,4±4,5†
Custodiol+O_2	8	14,92±0,9	26,12±2,1	175,0	65,9±3,1
Custodiol	8	14,2±1,7	27,6±3,4	194,4	63,6±4,3
Papaverine 2%	7	13,71±1,6	5,2±1,7	37,9	1,6±0,5
0,9% NaCl	6	15,3±2,8	1,5±0,9	9,8	0,8±0,3

*Note: * – differences are significant compared to BKB; † – compared to Custodiol.*

NaCl after preservation caused only minor contractions of the aortic segments (9,8–37,9% of the initial value). The study of the effect of curcumin on the contractility of human vascular segments showed that BCB + curcumin 1,5 μM promotes an increase in their resistance to restenosis, which is expressed in a decrease in isometric contraction tension. Thus, when using the great saphenous vein with repeated addition of NE 10^{-5}M and KCl 75 mM in the control group, there is an increase in the contraction force of the segments by 134,7% and 129,5%, respectively, while in the experimental group a decrease in isometric tension was observed (by 87,1% for NE 10^{-5}M and 94,2% for KCl 75 mM) (Fig. 2).

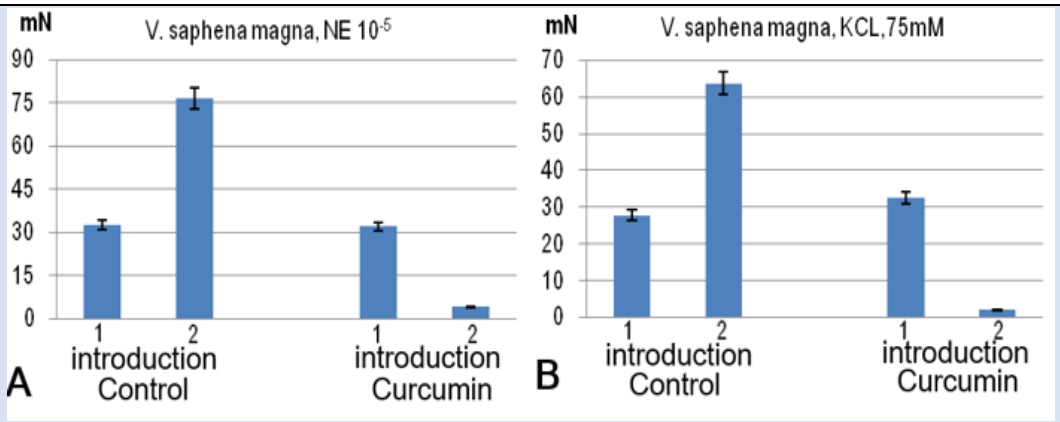

Figure 2: Change in isometric tension of segments of the great saphenous vein of the human leg (*V. saphena magna*) in the control and experimental groups upon addition of: A) – norepinephrine 10^{-5}M (NE 10^{-5}); B) – KCl 75 mM

A similar trend is observed when studying the segments of the radial and internal thoracic arteries. When studying the segments of the radial artery, the isometric tension in the control group increased by 117,7% for NE 10^{-5}M and by 163,4% for KCl 75 mM, while in the experimental group it decreased by 90,3% for NE 10^{-5}M and by 84,8% for KCl 75 mM (Fig. 3).

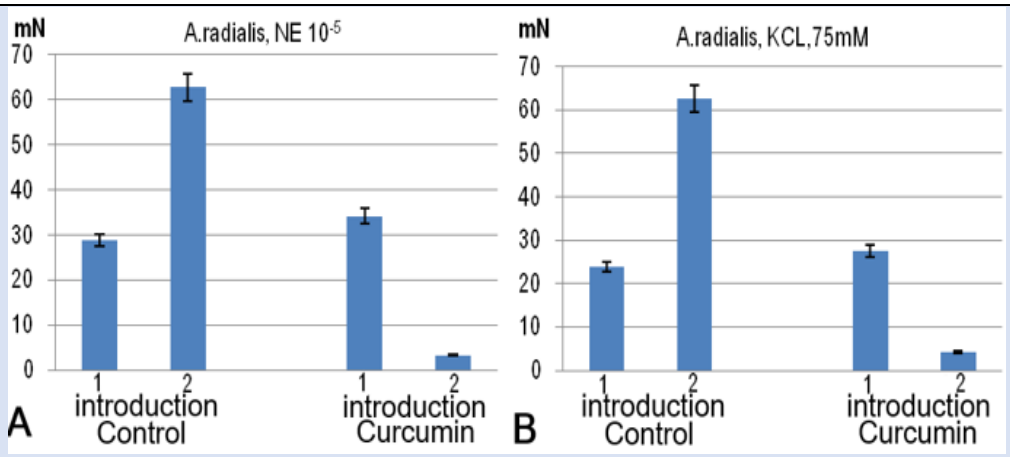

Figure 3: Change in isometric tension of the human radial artery segments (*A. radialis*) in the control and experimental groups with the addition of: A) norepinephrine 10^{-5}M (NE 10^{-5}); B) KCl 75 mM

For the segments of the internal thoracic artery, the following changes were observed with repeated addition of vasoconstrictors: isometric tension in the control group increased by 74,8% for NE 10^{-5}M and by 117,0% for KCl 75 mM, in the experimental group, isometric tension decreased by 92,2% for NE 10^{-5}M and by 78,2% for KCl 75 mM (Fig. 4).

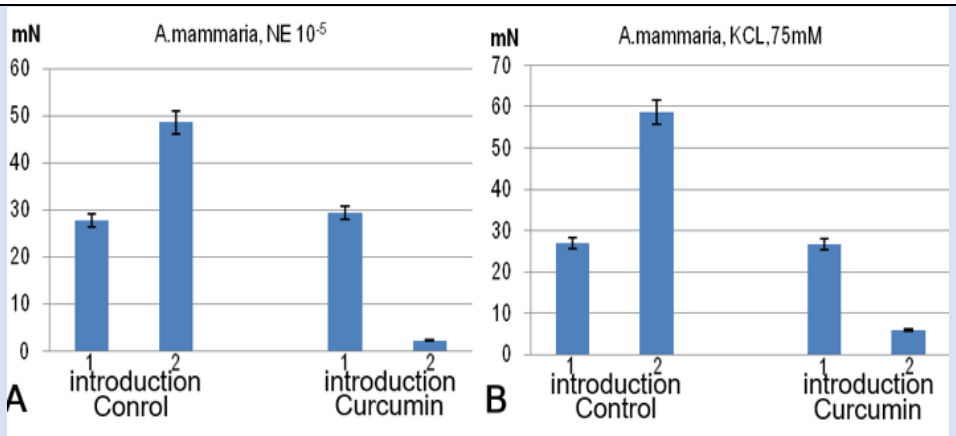

Figure 4: Change in isometric tension of segments of the human internal mammary artery (A. mammaria) in the control and experimental groups with the addition of: A) – norepinephrine 10^{-5}M (NE 10^{-5}); B) – KCl 75 mM

The conducted studies on the evaluation of the effectiveness of curcumin on human vessels: the internal mammary artery, radial artery and great saphenous vein of the human leg showed that the bicarbonate buffer with curcumin reduced the isometric tension of the segments of the studied vessels both with the addition of norepinephrine and with the action of potassium chloride by several times compared to the initial values. In the control group, there was an increase in this indicator with the addition of these vasoconstrictors by two times. Over 800,000 coronary artery bypass grafting surgeries are performed worldwide each year, 500,000 of which are performed in the United States. In Europe, «Custodiol» is used in 2 million surgeries per year. Transplants implanted into the arterial circulation are subject to significant denudation and proliferation of the endothelium, as well as migration of medial cells into the intima. Early occlusion (before discharge from the hospital) occurs in 8–12% of transplants, 15 to 30% are blocked by the first year, and 50% of them stop functioning after 10 years. [8, 13] This is associated with damage to the vessel during extraction, storage, and transportation. Modern transplantology assigns the task of protecting organs and tissues, including the prevention of vasospasm, to preservative solutions aimed at the comprehensive preservation of the structural and functional integrity of the transplant. Since the main cause of vasospasm is damage and disruption of the endothelium of vascular implants during preparatory activities, such solutions are used immediately from the moment of removal of biological material from the donor and before transplantation into the recipient's body. The viability of the transplant directly depends on the quality of the preservative homogeneous system and/or on the cardiovascular agents used. Despite the large number of cardiovascular agents that prevent vasospasm, an active search is underway for an effective drug that prevents the development of graft restenosis during CABG. We have conducted studies of the preservative properties of curcumin encapsulated in pyrrolidone added to a bicarbonate buffer. «Custodiol» and a 2% papaverine solution were used as comparison drugs. For this purpose, segments of the descending thoracic aorta were preserved in solutions of the above-mentioned drugs for 24 hours, after which the contractility of the vessel and the viability of its endothelium were studied. The results of our studies indicate that the bicarbonate buffer with curcumin encapsulated in pyrrolidone was more effective in preventing allograft spasm and preserving their endothelial function compared to «Custodiol», a drug widely used in vascular surgery today. Curcumin is a yellow bioflavonoid found in the roots of turmeric (Curcuma longa). It is known for its anti-inflammatory, antioxidant, and antiproliferative properties [14]. When studying the effect of curcumin on blood vessels, it was found that curcuminoids have the ability to both relax and constrict the walls of arterioles, affecting α- and β-adrenergic receptors [15]. The manifestation of this or that effect depends on the concentration of curcumin in the solution: subnanomolar doses of curcumin relaxed the walls of arterioles, and micromolar doses had vasoconstrictor properties. The implementation of the project to develop a formula for a solution based on a bicarbonate buffer with curcumin will create a new dosage form of the drug for preserving allografts used in cardiovascular surgery. The price of this solution will not exceed 1-2 USD per liter.

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Conclusions

1. We have developed a composition of a solution for vascular surgery, which is a bicarbonate buffer (Krebs-Henseleit solution: NaCl – 118,5 mM + KCl – 4,7 mM + $CaCl_2$ – 2,5 mM + $MgSO_4$ – 1,2 mM + KH_2PO_4 – 1,2 mM + $NaHCO_3$ – 25 mM + glucose 11 mM + saturation with carbogen (O_2/CO_2 in a ratio of 95%/5%), pH 7,4, t = 37,0°C), containing 1,5 μM curcumin encapsulated by sublimation in polyvinylpyrrolidone.

2. The developed solution for vascular surgery had the following properties:

– antispasmodic (preventing spasm) action,
– endothelioprotective (preserving the ability to relax) action.

3. The effectiveness of the solution for vascular surgery developed by us exceeds the effect of a similar drug «Custodiol» that is currently widely used in vascular surgery.

4. The cost of the solution for vascular surgery developed by us is lower than the well-known analog of the drug «Custodiol» (price 70 USD per 1 l).

Conflicts of Interest

The authors declare no conflicts of interest.

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