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Research Article

Experimental assessment of immunoreactivity indices and effectiveness of pharmacotherapy schemes in surgical models of acute pancreatitis of various severity

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Abstract

Introduction: The investigation was aimed at assessment of immunoreactivity in the experimental groups of animals and evaluation of effectiveness of different combinations of pharmacological drugs used in the surgical models for the treatment of acute pancreatitis (AP) of various degrees of severity.

Materials and methods: As an object of research, sexually mature male individuals of mongrel white rats were used. Acute pancreatitis of various degrees of severity was caused by either a separate or simultaneous ligation of the pancreas ducts and an intraductal injection of the 50% bile solution in a dose of 0.2 mg/kg. Correction of immunoreactivity indices in the experimental animals was performed with the use of drug combinations producing immunomodulating, antioxidant and membrane protecting effects. Evaluation of the dynamics of immune parameters in rats was carried out using test systems from various manufacturers for laboratory analysis. The obtained findings were statistically processed with descriptive and variation techniques.

Results and discussion: The rats developed AP of various degrees of severity, and differently expressed shifts in immunoreactivity indices were observed. Assessment of immune and oxidant indices in experimentally induced acute pancreatitis of moderate and severe states revealed metabolic and immune disorders with anti-inflammatory effects which had various degrees of expression. Combination of immunomodulators, antioxidants and membranoprotectors exerted positive effects on the immunoreactivity state, but insignificantly decreased the mortality rate in the groups of experimental animals.

Conclusion: The combination of ferrovir, mexidol, phosphogliv, and its use for moderate and severe degrees of experimentally induced pancreatitis in rats decreases their mortality up to 12.9% and 19.8%. The combination of polyoxidonium, emoxipin and essentiale N exhibits positive clinico-laboratory effectiveness and lowers the mortality indices to statistically significant parameters – 11.8% и 19.6%, correspondingly, with $p < 0.05$.

Keywords

acute pancreatitis, pharmacological correction, experimental model of acute pancreatitis, immunoreactivity.

Introduction

Over the last 10 years, the mortality rate of the patients with acute pancreatitis (AP) getting specialized medical aid in surgical units of hospitals has remained about 20% of all the patients admitted to hostpital. An analysis of the causes of mortality evidences that adverse outcomes of the disease are up to 70% due to either early or late development of severe complications of AP caused by some background diseases. One of the etiological causes of AP is bile hypertension which develops as a side effect of obstructing the distal segment of the choledochus with a gall stone. It results in the bile reflux into the pancreatic duct and subsequent activation of pancreatic ferments, thus manifesting the disease. In such conditions, surgical treatment is used predominantly for removal of the developed complications, and the outcome of the disease depends, among other things, on the properly chosen medication, taking into account the existing impairments of the regulatory systems of the organism (nervous, endocrine and immune) as well as its immunoreactivity (Dibirov and Yuanov 2014; Andreev et al. 2015; Goltsov et al. 2015; Rakhimov 2017; Shabunin et al. 2018).

Unfortunately, the schemes of pharmacotherapy which could prevent the development of pathological conditions of the immune system and other regulatory systems have not been worked out so far. This is why the interest to AP modeling in the experimental animals seems to be justified as it makes it possible to compare the clinical picture of the disease as well as developing laboratory and morphological changes in the internal organs. In addition, experimental models allow us to give an objective assessment of the effect of drugs and their combinations in the correction of identified laboratory disorders, including immunoreactivity disorders, which will not only extrapolate the data obtained to the clinic, but also provide the best results in the treatment of moderate and severe AP (Denysiuk et al. 2015; Janisch and Gardner 2016; Schmidt et al. 2017; Nazarenko et al. 2019).

Materials and methods

All the study protocols were reviewed and approved by the Local Ethics Committee of National Kursk State Medical University (protocol No. 17, October 15, 2019). The experimental procedures met all requirements of the Russian National Regulations “Principles of Good Laboratory Practice”.

Design of the investigation

The experimental objects under investigation were sexually mature outbred white male rats, with the body weight 250–350 grams each. Modeling of biliary dependent pancreatitis was carried out according to the technique described below. Under general anesthesia (chlorhydrate was injected intra-peritoneally in a dose of 300 mg/kg), ductal bile was sampled from the common bile duct, without cannulating the major duodenal papilla, and with subsequent dilution of the bile sample with buffer solution to 50%. While modeling moderately severe AP, tourniquets were applied onto the common bile duct above and below the junction of the distal pancreatic duct, with a subsequent injection of 50% solution of bile with pH = 6,0 in a dose of 0,2 mg/kg into the segment of the common bile duct limited by the tourniquets. Fifteen minutes later, the distal pancreatic duct was ligated, the tourniquets were removed, and layered closure of the wound was done.

To model severe AP, tourniquets were applied onto the common bile duct above the junction of the distal pancreatic duct and below the junction of the proximal duct of the accessory pancreas. An injection of a 50% solution of bile with pH = 6.0 in a dose of 0.2 mg/kg was also made into the segment of the common bile duct delimited by tourniquets. Fifteen minutes later, ligation of the two pancreatic ducts, removal of the tourniquets, and layered wound closure were performed (Fig. 1) (Nazarenko et al. 2019).

Experimental groups

The following medical schemes were used for the animals:

1) combination of ferrovir (in a dose of 20 mg/kg, intramuscularly every 24 hours, № 10), mexidol (in a dose of 50 mg/kg, intra-abdominally every 24 hours, №10), and phosphogliv (in a dose of 800 mg/kg, in 1% starch suspension orally every 24 hours, №10),

2) combination of polyoxidonium (in a dose of 0,03 mg, intramuscularly every 24 hours, №10), emoxipin (1 ml of 1% solution was diluted in 20 ml of 0.9 sodium chloride solution; 0,5 ml of ready solution was injected intramuscularly every 24 hours, №10), and essentiale N (in a dose of 0.03 ml, intraperitoneally every 24 hours, №10).

The experimental animals were divided into the groups according to the following criteria:

Group 1 – experimental moderate AP without treatment;
Group 2 – experimental severe AP without treatment;
Group 3 – experimental moderate AP with treatment according to scheme №1;
Group 4 – experimental moderate AP with treatment according to scheme №2;
Group 5 – experimental severe AP with treatment according to scheme №1;
Group 6 – experimental severe AP with treatment according to the scheme № 2.

The drugs were administered for 10 days. Modeling of AP was performed 5 days before the withdrawal of the animals from the experiment by an over dose of ethyl ether.

Laboratory tests

The functions of peripheral blood neutrophils in the modeling of the hypertension model of AP were assessed

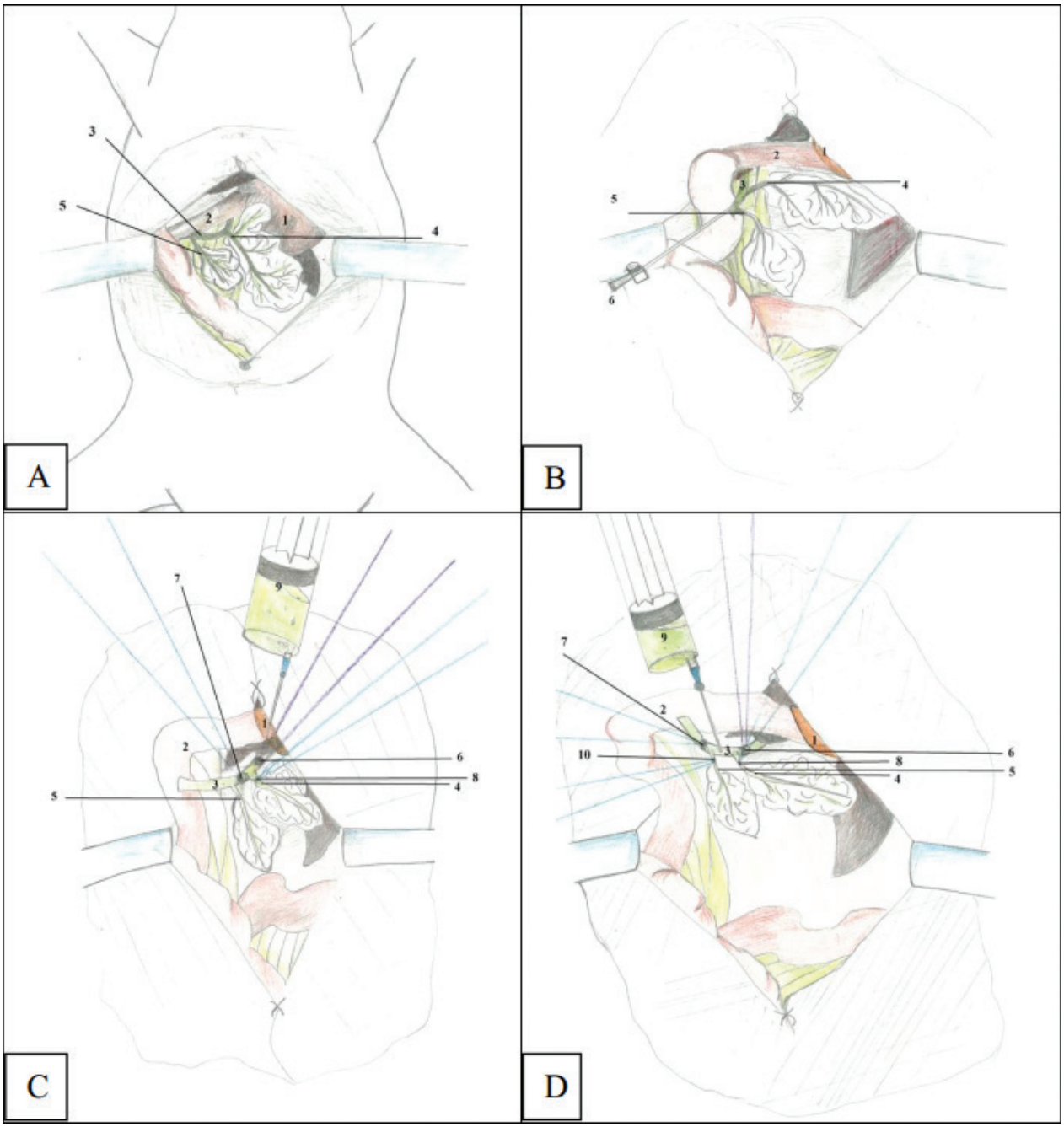

Figure 1. Stages of modeling acute pancreatitis of various severity. **A** – Medial laparotomy, cannulating the common bile duct with pancreatic lobes; **B** – sampling bile from the common bile duct; **C** – modeling moderately severe AP; **D** – modeling severe AP. **Note:** 1 – stomach; 2 – duodenal loop; 3 – common bile duct; 4 – distal pancreatic duct; 5 – accessory duct of the pancreatic lobe; 6 and 7 – tourniquets; 8 – main duct ligature; 9 – introduction of 50% bile solution through the catheter; 10 – accessory duct ligature.

by the phagocytosis index (PhI), the number of particles absorbed by one phagocyte (PhN), and the phagocytosis activity index (PhAI).

Oxygen dependent activity was investigated with the use of photometrical technique in reaction of nitroblue tetrazole restoration, according to the optical density index (mOD) in NBT-test spontaneous, NBT-test stimulated by non-opsonized zymozan (NBTn/o) and NBT-test stimulated by opsonized zymozan (NBTo) and the functional reserve ratio was calculated – CAo (the ratio of opsonized NBT-test to the spontaneous reaction), CAn/o (the ratio of non-opsonized NBT-test to the spontaneous reaction) and (CO) (the ratio of the opsonized and non-opsonized NBT-test).

Intensity of lipids peroxidation was assessed according to the contents of acylhydroperoxides (AHPs) and malonic dehyldehyde (MDA) in blood plasma. Catalase activity was assessed with use of spectrophotometry technique which revealed the contents of stable nitrogen oxide metabolites (NOm). The result was calculated on the curve with the use of standard solutions of sodium nitrite (Schmidt et al. 2017, Nazarenko et al. 2019).

Statistical analysis

Statistical processing of the obtained results was carried out using conventional statistics methods by means of BioStat software for Microsoft Windows.

Results and discussion

The histological study of the pancreas samples of the rats with experimentally modeled AP revealed the loci of destroyed pancreatic tissue in the form of extensive structureless eosinophilic necrosis foci with perifocal inflammatory infiltration composed predominantly of polymorphonuclear leucocytes. Necrotic changes spread over not only the tissue of the pancreatic gland, but also over the adjacent adipose tissue, with the signs of its inflammatory infiltration. Profound plethora of the blood vessels and interstitial edema developed in the intact pancreatic tissue, especially in the regions of necrosis.

There was a decrease in the indices characteristic of the absorption phase of phagocytosis (PhI, PhN, PhAI) up to 50% of its norm and an increase of oxygen-dependent metabolism of granulocyte cells up to 2.5 times compared with the norm. Besides, there was a mixed response of the cellular reserves, especially an increase in one of the indices – CAn/o, alongside with a concomitant decrease in the opsonization coefficient (CO) and no changes in the normal level of the functional reserve index on opsonized zimozan – CAo. The metabolite indices – AHP and MDA – turned out to have increased 19 times compared with the norm, whereas the catalase activity decreased 3 times, and the general antioxidant activity (GAA) of the blood plasma decreased 2.2 times. An increase in the concentration of nitrogen oxide stable metabolites was observed (1.5 times) (Table 1).

Table 1. Effects of Combination of Polyoxidonium, Emoxipin and Essentiale N on Immunoreactivity Indices in Experimental Moderate Acute Pancreatitis.

Index	Units of measurement	1	2	3	4
		Control group	Experimentally modeled AP of moderate severity		
			Without medicines	Ferrovir, Mexidol, Phosphogliv	Polyoxidonium Emoxpin Essentiale N
PhI	%	77.5±2.6	60.1±1.8*1	67.1±2.2*1,2	75.3±4.1*2,3
PhN	abs.	2.18±0.03	1.4±0.18*1	1.85±0.11*1,2	2.35±0.21*2,3
PhAI	–	1.62±0.09	0.84±0.03*1	1.24±0.02*1,2	1.77±0.06*2,3
NBT-test sp.	mOD	0.85±0.04	2.1±0.04*1	2.13±0.15*1	1.13±0.15*1-3
NBTn/o	mOD	1.31±0.03	3.74±0.06*1	3.22±0.16*1	2.18±0.13*1-3
NBTo	mOD	1.6±0.07	3.87±0.02*1	3.77±0.06*1	2.23±0.15*1-3
CAn/o	–	1.54±0.02	1.78±0.02*1	1.51±0.02*2	1.92±0.03*1,3
CAo	–	1.88±0.01	1.84±0.04	1.77±0.06	1.97±0.07*1-3
CO	–	1.22±0.03	1.03±0.06*1	1.17±0.05*2	1.02±0.02*1,3
AHP	conv. units	0.37±0.03	7.20±0.07*1	5.44±0.04*1,2	1.32±0.08*1-3
MDA	mcmole/l	1.76±0.07	19.11±1.93*1	15.4±1.33*1,2	11.14±1.79*1-3
Catalase	mccat/l	12.1±0.31	4.0±1.8*1	6.5±0.2*1,2	18.5±1.2*1-3
GAA	%	47.9±0.55	21.1±1.5*1	24.2±0.22*1,2	34.12±0.12*1-3
NOm	mcmole/l	1.75±0.09	2.5±0.1*1	3.02±0.03*1,2	3.81±0.01*1-3

Note: * – reliability of differences of indicators ($p<0.05$); [1] – indicator significantly different from that in the group of intact animals; [2] –indicator reliable different from that in the group of animals with experimentally modeled AP who were not treated with drugs; [3] – indicator significantly different from that in the group of animals with experimentally modeled AP treated with a combination of ferrovir, mexidol and phosphogliv.

The combination of ferrovir, mexidol and phosphogliv increased the indicators of the absorption phase of phagocytosis, GAA from the initially reduced level, and reduced the level of metabolites (MDA and AHP) in blood plasma by no more than 10%, and returned the coefficients of oxygen-dependent granulocyte reserves to normal (CAn/o, CO). In the case of NOm, the parameter almost doubled (Table 1).

The combination of polyoxydonium, emoxipin and essentiale N increased the phagocytosis indices from the initial level up to the norm and corrected at the most the level of oxygen dependent neutrophil activity of the peripheral blood in rats, as well as the reserves of the granulocytes functional activity, the contents of intermediate and final products of the lipids peroxidation in the blood plasma, and GAA. When using this scheme in rats with experimental moderate-severity AP, the maximum increase in the antioxidant potential (catalase activity, GAA), the level of stable nitric oxide metabolites was observed in comparison with the other groups (Table 1).

Postoperative mortality in the group of animals which had not received the medicines was 14.7%; postoperative mortality in the group of animals which had received the combination of polyoxydonium, emoxipin and essentiale N was 12.9%; the introduction of the combination of polyoxydonium, emoxipin and essentiale N resulted in the mortality rate of 11.8%. There was no statistically significant difference in the mortality rate in the groups of the experimental animals with AP, having received treatment with the combination of the above mentioned medicines.

In the experimentally induced severe AP compared with the experimental model of the moderately severe AP, there were decreased phagocytosis indices (PhI, PhN, PhAI), antioxidant activity of catalase and GAA with a simultaneous increase in neutrophil-produced oxygen active forms and, as a result, an increase in the intensity of lipid peroxidation processes (increase in MDA and AHP). At the same time, out of all the reserves of blood granulocyte functional activity, the only index which turned out to be increased was CAo (Table 2).

The combination of ferrovir, mexidol, phosphogliv and the combination of polyoxydonium, emoxipin, essentiale N were comparable in efficacy (with a difference of no more than 10%) and stimulated phagocytosis processes from the initially lowered level and also slowed down oxygen dependent metabolism of the neutrophils of peripheral blood (Table 2).

At the same time, the comparative analysis of the antioxidant effects of the schemes under investigation made it evident that the combination of polyoxydonium, emoxipin and essential N corrected both the contents of lipid peroxidation products in the blood plasma and the activity of antioxidant ferments, stable metabolites of nitrogen oxide (Table 2).

The post-operative mortality rate was 22.4% in the group of rats which had not received the medicines, and it was 19.8% in the groups which had received the combination of ferrovir, mexidol, and phosphogliv. The morta-

Table 2. Effects of Combination of Polyoxidonium, Emoxipin and Essentiale N on Iimmunoreactivity Indices in Experimental Severe Acute Pancreatitis.

Index	Units of measurement	1	2	3	4
		Control group	Experimentally modeled severe AP		
			Without medicines	Ferrovir, Mexidol, Phosphogliv	Polyoxidonium Emoxipin Essentiale N
PhI	%	77.5±2.6	50.3±2.8*1	59.2±1.2*1,2	63.3±2.1*1,2
PhN	abs.	2.18±0.03	1.1±0.08*1	1.8±0.11*1,2	1.7±0.21*1,2
PhAI	–	1.62±0.09	0.55±0.02*1	1.06±0.09*1,2	1.07±0.11*1,2
NBT-test sp.	mOD	0.85±0.04	3.5±0.08*1	2.53±0.12*1,2	2.13±0.15*1-3
NBTn/o	mOD	1.31±0.03	5.74±0.16*1	4.13±0.11*1,2	3.23±0.31*1-3
NBTo	mOD	1.6±0.07	7.82±0.17*1	6.87±0.12*1,2	5.54±0.28*1-3
CAn/o	–	1.54±0.02	1.64±0.01*1	1.63±0.01*1	1.51±0.01*1,2
CAo	–	1.88±0.01	2.23±0.08*1	2.72±0.03*1,2	2.6±0.05*1,2
CO	–	1.22±0.03	1.36±0.04	1.67±0.05*1,2	1.7±0.03*1,2
AHP	conv. units	0.37±0.03	17.40±0.04*1	16.99±0.23*1	4.51±0.03*1-3
MDA	mcmole/l	1.76±0.07	29.1±2.91*1	30.1±2.54*1	17.14±1.99*1-3
Catalase	mccat/l	12.1±0.31	2.0±1.4*1	2.6±1.0*1,2	8.5±1.0*1-3
GAA	%	47.9±0.55	10.0±1.2*1	11.1±0.13*1	17.22±0.14*1,2
NOm	mcmole/l	1.75±0.09	0.5±0.3*1	0.76±0.03*1,2	0.81±0.05*1,2

Note: * – reliability of differences of indicators ($p<0.05$); [1] – indicator significantly different from that in the group of intact animals; [2] –indicator reliable different from that in the group of animals with experimentally modeled AP who were not treated with drugs; [3] – indicator significantly different from that in the group of animals with experimentally modeled AP treated with a combination of ferrovir, mexidol and phosphogliv.

lity rate was 19.6% if the combination of polyoxydonium, emoxipin and essential N was injected, i.e. like with the previous group with AP, no significant differences were revealed in the mortality rates.

The suggested experimental model of AP allows modeling different severity degrees of the disease, which was clearly demonstrated by the laboratory indicators of the functional activity of phagocytosis and oxidant status. Various immune and oxidant disorders with anti-inflammatory characteristics were revealed in severe and moderately severe forms of experimental AP.

The combinations of medicines selected for the present work were determined by the idea that pathogenetically based correction of immunometabolic disorders in AP can be obtained by a separate or combined use of pharmacological and non-pharmacological techniques, which require solution of several tasks, among which affecting the cells of the damaged tissues in order to prevent appearance of immunosuppressive metabolic combinations in blood and, finally, direct stimulating the effector immune-competent cells.

The suggested combinations of medicines correct to various extent the modified laboratory indices in the rats with experimental model of acute biliary dependent pancreatitis. Different intensity effects of the used schemes on the laboratory indices were caused by the active ingredients, which made it possible to suppose various degrees of synergy within the matched combinations of the pharmacological agents. The obtained experimental findings made it possible to assert that combined immune rehabilitation in AP could exert differently expressed synergetic effects on several pathogenic links, regardless a degree of the disease severity, which will produce a favorable effect on the disease course, its complications and outcomes (Thoeni 2012; Korokin et al. 2015; Lankisch et al. 2015; Skutova et al. 2016; Mikaelyan et al. 2019).

Unfortunately no statistically significant difference was revealed in the number of fatal outcomes when injecting the medicinal combinations to the rats when modeling both moderately severe and severe AP, but it can be supposed that even clinically insignificant influence of the medication used on the immunoreactivity indices will help prevent development of AP purulent complications in the remote future.

Conclusions

According to the obtained data, the following conclusions were made:

Modeling of acute pancreatitis in rats according to the suggested technique (Patent for invention № 2709220): ligation of one or two pancreatic ducts followed by intra-ductal injection of 50% bile solution with pH = 6 in a dose of 0.2 mg/kg makes it possible to model the disease of various degrees of severity, which is confirmed by different indices of immunoreactivity in the experimental animals.

When using the combination of ferrovir, mexidol, and phosphogliv in the rats with moderately severe experimental AP, the mortality rate in the group of experimental animals decreased from 14.7% to 12.9% and in case of severe AP – from 22.4% to 19.8%.

When using polyoxidonium, emoxipine, and essentiale H in the moderate form AP, the mortality rate decreased from 14.7% to 11.8%, and in the severe – from 22.4% to 19.8%.

Conflict of interests

The authors declare no conflict of interests.

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