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针刺减轻利多卡因慢性毒性的实验
REDUCTION OF LIDOCAINE CHRONIC TOXICITY WITH ACUPUNCTURE IN EXPERIMENT

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注释。本研究旨在研究在针灸实验中，颌面部局部麻醉药 2% 利多卡因盐酸盐反复注射是否有可能降低其毒性。实验在两组白色实验室小鼠上进行，用于确定化学物质的毒性和制剂的标准化，实验对象为 33 只成年雄性小鼠。所有实验动物分为两组，每 3-4 天在颌下区域注射 50 mg/kg 体重的 2% 利多卡因盐酸盐。第一组由 16 只动物组成，作为对照组。第二组由 17 只动物组成，这些动物之前已根据我们的 Su-Jok 疗法方案在动物后爪上接受过电针治疗。在实验的每个阶段，我们都收集了处死的实验动物并取出其实质器官，以进行病理形态学研究。在分析了实验结果后，我们得出结论，针刺作为预防性治疗可以显著减少利多卡因重复注射后的慢性毒性现象。

关键词：慢性毒性，局部麻醉药，利多卡因，形态测量学。

Annotation. *Aim of examination was to study the possibility of the toxicity reducing of the local anesthetic 2% lidocaine hydrochloride during its frequent repeated injections in the maxillofacial region in the experiment with acupuncture. The experiment was performed on two series of white laboratory mice used to determine the toxicity of chemicals, the standardization of preparations, on 33 adult male. All experimental animals were divided into two series which were injected every 3-4 days with 2% lidocaine hydrochloride in dose of 50 mg/kg of body weight in the submandibular region. The first series consisted of 16 animals and served as a control. The second series consisted of 17 animals who had previously received a course of electroacupuncture device on the back paw of the animals according to our scheme of Su-Jok therapy. We collected the parenchymal organs of killed and*

taken out of the experiment animals for pathomorphological study at each stage of the experiment. After having analyzed the results of experimental examinations we conclude that acupuncture as a prophylactic tretment can significantly reduce the phenomenon of chronic toxicity after repeated injection of lidocaine.

Keywords: *chronic toxicity, local anesthetics, lidocaine, morphometry.*

Introduction. The problem of drug safety now can be assigned to one of the most vital in modern medicine and pharmacy. As you know, there is no absolutely safety drugs, especially when the terms of there rational use are violated [4, 13, 14].

Local anesthesia makes an integral part of the daily work of all dentists, but the safe choice of local anesthetic remains the issue of the day.

General toxic reactions to local anesthetics are demonstrated in changes of the central nervous system (CNS) and cardiovascular system (CVS) [3, 4, 11, 13].

Due to the deterioration of the demographic situation and the current tendency towards the population aging («European statistical review for 2010» states that by 2030 the population 65 years old will consist 19% in Belarus and it was 14.1% in 2009) the number of old patients became higher who require repeated injection of local anesthetics during the oral cavity sanation for orthopedic indications. The women in the postpartum period having multiple carious sanation lesions should be included into the same group. Often, these patients want to do all the manipulations quickly and they have double local anesthetic injections, usually every 2-3 days. Old patients have a particular state of the body characterizing by reduction of compensatory and adaptive capacities. This is due to atherosclerotic changes of the coronary, cerebral, hepatic and renal vessels and functional circulation of the blood failure, decreased metabolic rate, respiratory function and the sensitivity of the respiratory center to carbon dioxide reductions appear. Renal function according to research may be reduced to 50%, the inhibition of the function of the liver is fixed which reduces the intensity of the hepatic metabolism. The excretory function of these organs is limited. Respectively, the excretion of drugs decreases, the concentrations of drugs longer circulating in the body becomes higher. Reduction of drugs distribution in the body and blood plasma binding by proteins can lead to a high concentration of drug in the blood due to the old age. It is necessary to take it into consideration when using the local anesthetics of amide type (lidocaine mepivocaine, prilocaine, bupivcaint) that are metabolizing by liver and removing by kidneys. For example, the half-value period of lidocaine is extended from 100 to 120 minutes what must be kept in mind when repeated injections of anesthetics [3, 10, 14].

Maxillofacial region being the object of stomatological treatment has a good innervation and blood supply because of its topographical and functional features,

that's why the invasive surgeries of this area cause response reactions from different parts of body systems [16].

It should be noted that population allergization which tends to rapid growth limiting the ability of the standard methods of prevention, treatment and rehabilitation of disorders is the most frequently fixed in dentistry. Therefore, actual prevention, treatment and rehabilitation methods should include not only the current level of treatment of the disease but also to consider the status of the background of the patient. The above is the basis for wider use of non-drug methods in the dental practice, in particular, acupuncture (A) [9, 15].

Acupuncture can be considered the treatment method corresponding to all requirements of modern medicine. It is effective, harmless can be combined with other methods and replace them, if necessary, such as medicaments and physical therapy treatments, used alone or in combination with preventive and treatment and rehabilitation methods. The successful use of acupuncture in clinical practice is confirmed by a significant number of papers. In 1980 the WHO recognized the acupuncture as scientifically well-grounded and recommended it for use in the world care practice [1].

The mechanism of therapeutic and prophylactic effect of acupuncture is neurohumoral factor that may have an impact on the vasculature and on the activity of reparative processes in tissues. Acupuncture, focusing on the common and local pathogenetic mechanisms of toxic reactions, contributes the recovery of the physiological and morphological homeostasis. The result is the elimination of the pathogenic effects, the normalization of the immune and emotional status of the patient, the stimulation of reparative processes of the body [1, 15].

All this points to an interest of dentists in application of acupuncture in daily practice as an independent method of treatment and in a complex of preventive and rehabilitation treatment.

One of main clinical researches is related to the study of pathological changes in the body during acute and chronic toxic effects of certain drugs and the search for ways to prevent them. Experiments provide substantial help in studying the mechanisms of morphological and functional complications of acute and chronic toxicity of drugs including dental. They allow tracking the dynamics of pathological changes in the body, to understand and describe the development of pathological processes on the system, organ, cell levels which is a main condition for the development of effective methods of prevention. The toxicity of chemicals modeling is often performed in rodents. White laboratory mice, which are home albino gray mouse is usually used to determine the toxicity of chemicals and standardization of pharmaceutical preparations. Preference is given to males in toxicology studies, since they do not show sharp and significant changes in hormone levels.

Most sources of specialized information highlights that during the experimental study of toxicity of caused pathology, special attention should be given to ways of modeling the concentrations of toxic substances, corresponding to the real conditions of clinical practice. In the study of the absolute majority of drugs, including the local anesthetics, we used the method of intraperitoneal injection in preclinical studies. However, it should be noted that all dental procedures performed in the maxillofacial region, have different intensity of vascularization and innervation, as well as proximity of the CNS. Now, 2% lidocaine hydrochloride is one of the most accessible and commonly used local anesthetics in daily dental practice in the Republic of Belarus. In the available domestic and foreign literature found no information on the results of a comparative evaluation of morphological changes in different types of 2% lidocaine hydrochloride injection in experiment [2, 7].

Lidocaine belongs to the amide anesthetics - xylidine (tertiary amines with aromatic moiety containing two methyl groups). Amide anesthetics are metabolized in the liver by two successive reactions: oxidation which leads to the formation of polar metabolites and hydroxylated metabolites conjugation with glucuronic acid or amino acids. Lidocaine is metabolized to form monoethylglicinexylidyne and glicinexylidyne. Monoethylglicinexylidyne and glicinexylidyne remain active partly and can have toxic effects. About 10% of the injecteds dose is excreted in the urine in unchanged form [3, 4, 13].

All these facts confirm the relevance of this work and determine the expediency of studies.

Aim of examination was to study the possibility of the toxicity reducing of the local anesthetic 2% lidocaine hydrochloride during its frequent repeated injections in the maxillofacial region in the experiment with acupuncture.

Objects and methods. The experiment was performed on two series of white laboratory mice used to determine the toxicity of chemicals, the standardization of preparations, on 33 adult male of white mice weighing 22-35 grams. Animals were obtained from the nursery of the Central Research Laboratory of «Belarusian State Medical University». Before the experiment the animals were two-week quarantined and kept on a standard diet. Experimental studies were carried out in accordance with the requirements governing the work with experimental animals [6] and permission of Belarusian State Medical University Committee for Bioethics. The therapeutic dose of lidocaine was calculated per unit of body weight based on the data of clinical pharmacology.

We modeled a subchronic experiment (2 weeks). All experimental animals were divided into two series which were injected every 3-4 days with 2% lidocaine hydrochloride in dose of 50 mg/kg of body weight in the submandibular region (option extraoral mandibular anesthesia access). The first series consisted of 16 animals and served as a control. The second series consisted of 17 animals who

had previously received a course of acupuncture with electroacupuncture device «Vityaz AET-01» (Republic of Belarus) on the back paw of the animals according to our scheme of Su-Jok therapy.

We studied the behavioral responses of animals during the anesthetic injection: we fixed toxic effects on the central nervous system (CNS): convulsive effects, floppiness, hemiparesis or paraparesis phenomenon, hyperactivity. We recorded the breathlessness and fixed facts of mortality.

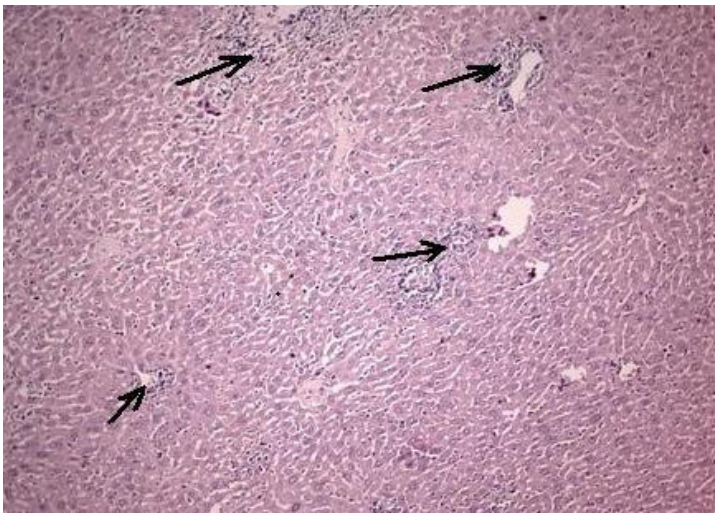
We collected the parenchymal organs of killed and taken out of the experiment animals, including the control series, for pathomorphological study at each stage of the experiment.

Results of the study. We fixed mortality after the drug injection in the 1-series in 37.5%, in the second - 23.5%. Deaths occurred within 5 minutes after injection with pronounced symptoms of hemiparesis on the side of injection, without convulsive manifestations, sometimes during injection. All animals had shortness of breath with the auxiliary muscles participation in breath.

According to the results of pathological studies in the 1-series after five injections, the liver preparations had weak pronounced nuclear polymorphism; a few small focuses of necrosis of hepatocytes with perifocal inflammatory reaction (large number of eosinophils was fixed in the infiltrate); sparse inflammatory infiltration in some portal tracts; not sharply marked, mainly intraduct, cholestasis. In some specimens a more pronounced inflammatory response revealed in the portal tracts, determined in all portal tracts. Inflammatory infiltration was observed around the central vein. Inflammatory infiltrate was primarily represented by lymphocytes mixed with a small number of eosinophils and isolated neutrophils. We stated the more numerous small focuses of necrosis of hepatocytes (pic. 1). Eosinophilic intranuclear inclusions were revealed in some nucleuses.

Mild plethora with single diapedetic bleeding, uneven plethora glomerules, dystrophic changes in the tubular epithelium and a few small roundcells infiltrates in the interstitium were fixed in kidneys during the post mortem examination. In some preparations the number of infiltrates and their size were bigger and glomerular vascular disorders (mucoid and fibrinoid swelling) in isolated glomerules were found.

Animals of the 2nd series also had focuses of necrosis of hepatocytes with perifocal inflammatory infiltration at post mortem examination of the liver. But these changes were mostly small, single.



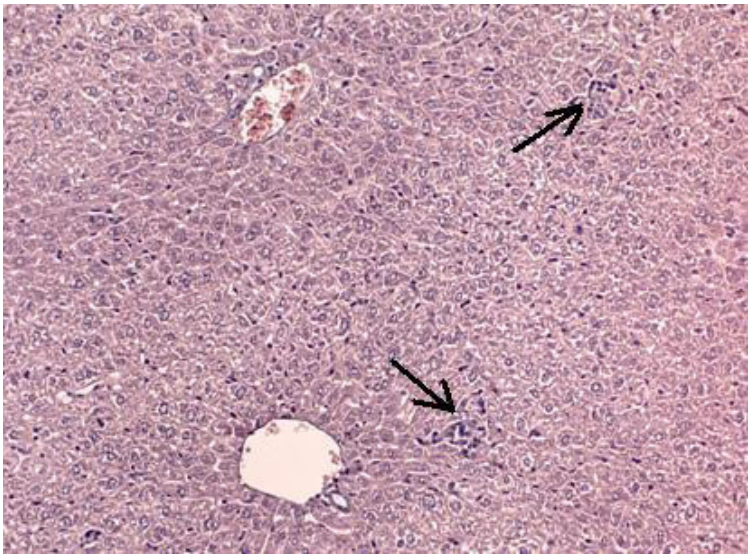
Picture 1. *Focuses of hepatitis necrosis for animals of 1st series (hematoxylin-eosin stain).*
Image magnification. x200

We fixed a moderate plethora, slight inflammatory infiltration of single portal tracts. Periportal cholestasis was slightly developed. Some specimens had weakly expressed albuminous degeneration. Around the small focuses of necrosis of hepatocytes in the perifocal inflammatory infiltration we found an important number of eosinophils and neutrophils (the last were prevalent). We observed groups and short chains of cells of lymphocytes with an admixture of eosinophils and neutrophils in sinuses. Inflammatory infiltration was present in almost all portal tracts, sometimes going outside the boundary of the plate and necrosis of the surrounding tissue of the liver. The inflammatory reaction was observed also around single central veins.

During examination of kidney for the animals of the 2nd series we found focuses of petrification and packed eosinophilic masses into the collecting ducts as well as very small and single, mainly perivascular, roundcellular infiltrates in the intersticium, we fixed weak plethora.

When carrying out the morphometry examinations by method of serial sections, we discovered that the speciments of animals of the 1st series had no necrosis and had inflammatory changes in the portal tracts, cholestasis; lymphoid cells dominated among the cells of inflammatory infiltration, the number of neutrophils and eosinophils was small.

Animals of the 2nd series had less number of necrosis (pic. 2) with smaller in size (up to 1-4 cells), cholestasis was almost not expressed, a lot of eosinophils in the inflammatory infiltration, inflammation in the portal tracts was more weaker.



Picture 2. *Focuses of hepatitis necrosis for animals of 2nd series (hematoxylin-eosin stain). Image magnification x 200*

A quantitative comparison of the results of morphometric studies is presented in the table 1.

Table 1

Quantitative comparison of morphometric examinations results, (p<0,05).

Type of changes	1st series	2nd series
Necrosis focus of hepatocytes cells 1-2 cells	72,5%	44,3%
Necrosis focus of hepatocytes cells 3-4 cells	22,5%	17,2%
Necrosis focus of hepatocytes cells 6-8 cells	7,5%	1,43%
Periportal necrosis 2-3 cells	2,5%	1,43%
Periportal necrosis 6-8 cells	5%	1,43%
Periportal necrosis 10-14 cells	5%	-
Periportal inflammation	55%	15,7%
Periportal cholestasis	52,5%	2,86%

Hepatotoxic action of lidocaine can be explained by pharmacokinetics and pharmacodynamics of the drug. 70% of the injected drug undergoes biotransformation during the first passage through the liver. 90-95% of the lidocaine dose is metabolized in the liver by microsomal oxidases by oxidative M-dealkylation of aminogroup, hydroxylation ring, spliting of the amide bond and conjugation. The resulting metabolites (monoethylglicinexylidyne and glicinexylidyne) partly remain active and are able to have a toxic effect. Monoethylglicinexylidyne can cause convultions and glicinexylidyne – depreses the CNS. In addition, these compounds have ganglion blocking effect, influence on the blood pressure and cardiac function. During the lidocaine injection without vasoconstrictor the blood vessels dilate is rapidly absorbed what provokes the risk of side effects and shorten the drug action [5, 8, 12].

Thus, it is clear that frequent repeated injections of 2% lidocaine solution is not always safe for the body, especially during the plasma choline esterasedeficit that may occur during the involutive changes of the liver. Significant frequency of toxic effects on the central nervous system can be explained by particular features of the drug injection as well as features of innervation and vascularization of the head and neck.

At post mortem examination of the animals liver who received acupuncture treatment before injection of 2% lidocaine hydrochloride, we fixed a significant reduction of necrosis of hepatocytes focuses, reduction of eosinophilic infiltration. It demonstrated the protective effect of acupuncture.

Conclusion. After having analyzed the results of experimental examinations we conclude that acupuncture as a prophylactic tretment can significantly reduce the phenomenon of chronic toxicity after repeated injection of lidocaine.

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