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**Лаптиёва А.Ю., Глухов А.А., Андреев А.А., Остроушко А.П.
ОЦЕНКА ИНДЕКСА ПРОЛИФЕРАЦИИ КИ-67 ПРИ
ВНУТРИПЕЧЕНОЧНОМ ВВЕДЕНИИ ЦИАНОКОБАЛАМИНА**

Кафедра общей хирургии

Воронежский государственный медицинский университет им. Н.Н. Бурденко
Воронеж, Российская Федерация

**Laptieva A. Yu., Glukhov A. A., Andreev A. A., Ostroushko A. P.
EVALUATION OF THE KI-67 PROLIFERATION INDEX IN
INTRALIVER CYANOCOBALAMIN ADMINISTRATION**

Department of General Surgery

N. N. Burdenko Voronezh State Medical University
Voronezh, Russian Federation

E-mail: laptievaa@mail.ru

Аннотация. В статье рассмотрены особенности репаративной регенерации печени после субтотальной резекции при интраоперационном введении цианокобаламина. Выявлено влияние введения цианокобаламина на метилирование ДНК гепатоцитов и повышение их индекса пролиферации.

Annotation. The article discusses the features of reparative regeneration of the liver after subtotal resection with intraoperative administration of cyanocobalamin.

The effect of cyanocobalamin administration on the methylation of hepatocyte DNA and an increase in their proliferation index was revealed.

Ключевые слова: резекция, печень, регенерация, индекс пролиферации.

Key words: resection, liver, regeneration, proliferation index.

Introduction

Liver resection, in most cases, remains the method of choice, allowing to achieve a radical cure and long-term survival of patients with focal liver formations [4]. The liver is capable of rapid regeneration in response to various stimuli, due to a sufficient functional reserve that is susceptible to activation, but the frequency of post-resection liver failure varies from 0.7 to 9.1% [5,8]. In clinical practice, in order to improve the metabolic processes of the liver, hepatoprotectors are often used, most of which include cyanocobalamin [7]. Active form of vitamin B12 (methylcobalamin) it is able to stimulate the proliferative activity of hepatocytes by participating in the methylation of their DNA [2, 3].

The purpose of the study - to evaluate the hepatocyte proliferation index during intraoperative cyanocobalamin administration during liver resection.

Materials and methods

The experiment was performed on 54 male white rats of the Wistar line. The animals were divided into 3 experimental groups and all animals were resected in a volume of 70% according to the model of G. Higgins, R. Anderson, in the 1st experimental group, prevention of post-resection liver failure was not carried out, in the 2nd experimental group, intraoperatively after resection, 0.9% sodium chloride solution in a volume of 1 ml was injected into the preserved liver lobes, in the 3rd experimental group, vitamin B12 (concentration of 200 mcg/ml) in a volume of 1 ml. The animals were removed from the experiment on the 1st, 7th and 14th day after the operation. In all groups, liver fragments were taken for immunohistochemical analysis. The biomaterial was fixed in 10% neutral formalin. The proliferative activity of hepatocytes was evaluated by immunohistochemical detection in compliance with the necessary protocol procedures [1, 6], primary rabbit antibodies (dilution 1: 200). As secondary antibodies, goat anti-rabbit antibodies #AS-R1-HRP were used, the visualization of which was carried out with the ImmPACTTM DAB Peroxidase Substrate Kit (#SK-4105) according to the manufacturer's instructions. The nuclei were contrasted with Mayer's hematoxylin, and the colored sections were enclosed in a permanent mounting medium. Liver sections were examined using a ZEISS Axio Imager microscope.A2 with an image documentation system that includes a color digital camera Camera AxioCam 506 color. The obtained photos were processed using the ZEN 2.3 program (Carl Zeiss, Germany). The proliferation index was calculated by determining the Ki-67-positive nuclei in mononuclear and binuclear hepatocytes. The ratio of the number of hepatocyte nuclei containing the Ki-67 protein to their total number in the visual field was calculated. At least 4,500 hepatocytes were evaluated for each micropreparation.

Statistical processing was performed using the "Descriptive Statistics" package of the Excel program. To assess the reliability of the differences, the Student comparison criterion was used. The differences were considered significant when the significance level was $p < 0.05$.

Results and discussion

In the immunohistochemical study of the liver in all experimental groups of animals, the greatest proliferative activity of hepatocytes is observed on the 7th day after liver resection, and is in the 1st experimental- $2.78\% \pm 0.21\%$, in the 2nd experimental- $2.64\% \pm 0.58\%$, in the 3rd experimental- $6.54\% \pm 0.71\%$. On the 14th day after the operation, there were no significant differences in the proliferation index in the 1st and 2nd experimental groups (the 1st experimental group- $2.54\% \pm 0.29\%$, the 2nd experimental group- $2.56\% \pm 0.45\%$). The maximum proliferative activity of hepatocytes was observed in the 3rd experimental group (proliferation index- $6.22\% \pm 0.54\%$), which is associated with DNA methylation with the participation of methylcobalamin, the intensification of transcription processes and the rate of proliferation of hepatocytes. Slight differences in the results obtained in the 1st and 2nd experimental groups on both the 7th and 14th day of the study allow us to exclude the influence of mechanical action (parenchyma injection) on the increase in the proliferative activity of regenerating liver cells.

When assessing the number of Ki-67-positive nuclei in binucleated hepatocytes, a similar trend is observed – an increase in the proliferation index after liver resection in all experimental groups. The highest indicators were observed on the 7th day after the operation: The 1st experimental group - $0.038\% \pm 0.027\%$, the 2nd experimental group- $0.021\% \pm 0.017\%$, the 3rd experimental group- $0.089\% \pm 0.051\%$. By the 14th day of the experiment, the proliferation index was $0.038\% \pm 0.027\%$ in the 1st experimental group, $0.021\% \pm 0.017\%$ in the 2nd experimental group, and $0.069\% \pm 0.024\%$ in the 3rd experimental group.

Conclusion

The proposed method of intrahepatic intraoperative administration of cyanocobalamin can significantly increase the proliferative activity of both mononuclear and binuclear hepatocytes. Intraoperative administration of cyanocobalamin is involved in the reactions of DNA methylation, stimulating mitotic activity and ensuring the restoration of the structural organization of the liver.

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**Омурбеков Т.О., Орозоев У.Д., Сапарбеков А.А., Порощай В.Н,
Самсалиев М.Ж.**

**ДИНАМИКА РОСТА АППЕНДИКУЛЯРНОГО ПЕРИТОНИТА У ДЕТЕЙ
И РЕЗУЛЬТАТЫ ЕГО ЛЕЧЕНИЯ**

Кыргызская Государственная Медицинская академия им. И.К. Ахунбаева
Кыргызско-Российский Славянский университет им. Б.Н. Ельцина
Городская детская клиническая больница скорой медицинской помощи
г. Бишкек, Кыргызская Республика

**Omurbekov T.O., Orozoev U.D., Saparbekov A.A., Sprout V.N.,
Samsaliev M.Zh.**

**DYNAMICS OF GROWTH OF APPENDICULAR PERITONITIS AT
CHILDREN AND THE RESULTS OF HIS TREATMENT**

Kyrgyz State Medical Academy named after I.K. Akhunbaeva
Kyrgyz-Russian Slavic University named after B.N. Yeltsin
City Children's Clinical Emergency Hospital
Bishkek, Kyrgyz Republic

E-mail: saparbekovaman142@gmail.com

Анатоция. В статье проведен анализ частоты оперативных вмешательств по поводу острого аппендицита и его осложнённых форм. Применение перчаточного дренажа в комплексном лечении аппендикулярного перитонита улучшает конечные результаты в раннем и позднем послеоперационном периоде у детей.