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Chemotherapy in the Prevention of Recurrence of Echinococcosis of the Liver

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Resume. The aim of the study is to improve the quality of treatment of patients with echinococcosis of the liver by developing effective methods to reduce the recurrence of the disease.
Material and methods of research. The clinical trial consisted of 371 patients with EP. In order to study the effect of albendazole in various dosages on the germinal forms of echinococcosis, by morphological examination of the internal organs of experimental animals (32 sheep) infected with echinococcosis in natural conditions.
Results of the study. Chemotherapy with albendazole was started no later than 1 month after surgical treatment. In the comparison group, postoperative chemotherapy was performed on 112 (43.8%) patients according to the traditional regimen. Against the background of treatment, an increase in the average concentration of AST and ALT after the first course of chemotherapy was noted, respectively, to 0.55±0.05 and 0.88±0.08 mmol / l.
Conclusion. Experimental studies on 32 sheep showed that in areas of the liver remote from the primary echinococcal cyst, the presence of microscopically identifiable germinal microcysts was detected, which can lead to the development of relapse of the disease after removal of large cysts.

Key words: echinococcosis of the liver, chemotherapy, relapse, prevention.

Introduction. According to the World Health Organization, "in the world, echinococcosis affects more than 1 million people, while among various organs and tissues in 44-84% of cases the process is localized in the liver" [5, 6, 7]. Due to the lack of a tendency to reduce the number of patients and the existence of endemic regions, where the incidence rate varies from 1.2 to 9.0 per 100,000 population, this parasitic disease continues to be a serious medical and social problem [4]. At the present stage, the diagnosis of echinococcosis of the liver (EP) does not present significant difficulties, largely due to the emergence of non-invasive imaging methods, the information content of the complex application of which reaches 95-100% [1]. However, the lack of caution regarding echinococcosis contributes to late diagnosis, and, consequently, an increase in complicated forms of the disease [2, 3]. "However, a fairly high incidence of postoperative complications (34-50%) and numerous cases of postoperative relapses of the disease (15-64%) indicate insufficient effectiveness and reliability of common surgical tactics" [7]. In the light of the foregoing, it becomes obvious the need to improve the known and develop new effective measures for the prevention and treatment of this terrible disease.

The aim of the study is to improve the quality of treatment of patients with echinococcosis of the liver by developing effective methods to reduce the recurrence of the disease.

Material and methods of research. The clinical trial consisted of 371 patients with EP. In order to study the effect of albendazole in various dosages on the germinal forms of echinococcosis, by morphological examination of the internal organs of experimental animals (32 sheep) infected with echinococcosis in natural conditions. On the basis of ultrasound, all these animals were diagnosed (with the participation of specialists - veterinarians) echinococcosis of the liver.

To determine the action of albendazole, in the first stage of the experimental study, the liver tissues of sheep that did not receive chemotherapy were studied. Morphological study was carried out on serial sections

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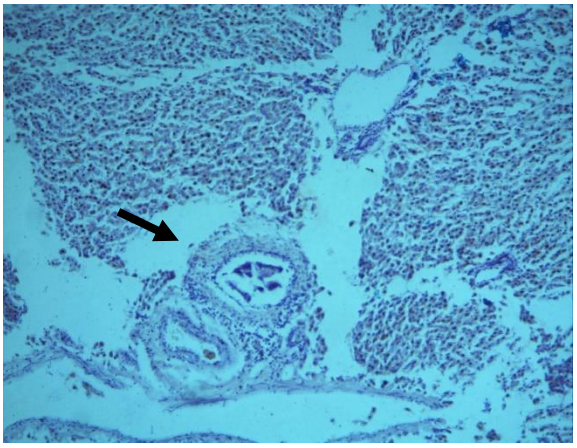
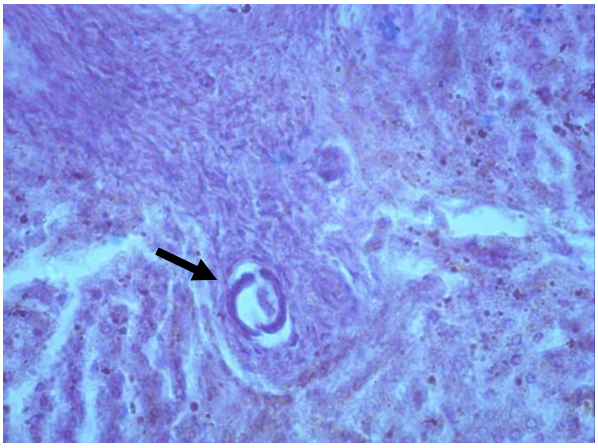
of the liver stained with hematoxylin - eosin (G-E). In all animals, newly formed germinal cysts were found in the liver. The remaining animals were treated with albendazole for 2 and 3 weeks in different dosages of the drug (5, 10, 15 and 20 mg / kg of weight). When studying the liver of animals treated with albendazole at a dose of 5 mg / kg body weight for 3 weeks, the microscopic walls of the germinal cyst were homogeneous, significantly thickened. Along the periphery, a fairly powerful framework of lymphoid-histiocytic cells was formed (Fig. 1). At a dose of 10 mg / kg of weight for 2 weeks, it was determined that among the lobules of the liver, forming germinal blisters of echinococcus are visible, consisting of a layered chitinous membrane filled with amorphous masses. Among them, scolexes are visible. There is a pronounced delamination and swelling of the wall of the chitinous membrane (Fig. 2).

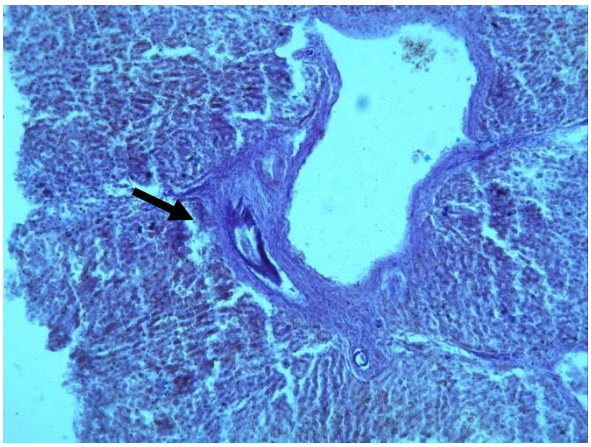


Rice. 1. Liver after applying albendazole at a dose of 5 mg / kg. Coloration G-E. Cv. 10×20.

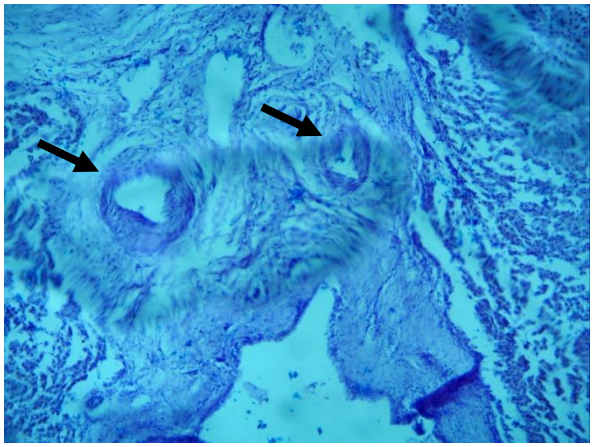


Rice. 2. Liver after the use of albendazole at a dose of 10 mg / kg. Coloration G-E. Cv. 10×10.

With microscopic examination of the liver against the background of taking albendazole at a dose of 15 mg / kg of animal weight for 2 weeks, it was revealed that the newly formed germ capsule of the echinococcal bladder is edematous and the walls are loosened. Along the periphery of the bladder wall, lymphoid-histocytic infiltrates appear, which were not noted at a dose of 10 mg / kg (Fig. 3). When studying the liver of sheep treated with albendazole at a dose of 20 mg / kg of animal weight for 2 weeks, it was microscopically revealed that the peripheral zones of the embryonic capsule of echinococcus are significantly enriched with lymphoid cell infiltrates. The cavity forming the cyst is gaping, it contains an amorphous mass. The walls of the capsule are homogeneous, homogeneous (Fig. 4).



Rice. 3. Liver after the use of albendazole at a dose of 15 mg / kg. Coloration G-E. Cv. 10×10.



Rice. 4. Liver after applying albendazole at a dose of 20 mg / kg. Coloration G×E. Uv. 10x19.

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Before the start of chemotherapy, during and at the end of the course of chemotherapy, a complete blood count, biochemical parameters and a coagulogram were examined. In sheep treated with albendazole at a dose of 5 mg / kg, pathological changes were not observed in the blood test. In sheep treated with albendazole at a dose of 10 and 15 mg / kg, there were slight changes in biochemical parameters of blood. At a dose of 20 mg / kg, blood enzymes at the end of the first week were moderately elevated, and at the end of the second week they increased significantly.

Studies have shown that in distant areas of the liver from the primary echinococcal bladder, microscopically identifiable germinal echinococcal microcysts were found. They were represented by formed or forming chitinous membranes without signs of a macrophage-cellular reaction around the embryonic formation, or with the presence of a pronounced cellular reaction. Treatment with albendazole in a high dose - 10 mg / kg body weight for 2 weeks and a lower dose - 5 mg / kg body weight for 3 weeks helped to stimulate a proliferative - productive cellular reaction around the germinal cyst of the parasite and depressed on the scolexes of the echinococcus.

Results of the study. The vast majority of echinococcectomies performed (99.8%) were organ-preserving in nature, and only 1 (0.2%) of the patient had to resort to resection of the left lobe of the liver. In suitable situations, the opportunity to perform an ideal echinococcectomy was not missed - 2 (0.3%) parasitic cysts were removed by peeling off the whole chitinous membrane. In our observations, 412 (77.6%) residual cavities were treated according to the type of closed echinococcectomy and only 116 (21.8%) fibrous capsules were sutured semi-closed method on drainage.

Chemotherapy with albendazole was started no later than 1 month after surgical treatment. In the comparison group, postoperative chemotherapy was performed on 112 (43.8%) patients according to the traditional scheme. Against the background of treatment, an increase in the average concentration of AST and ALT after the first course of chemotherapy was noted, respectively, to 0.55±0.05 and 0.88±0.08 mmol / L. Parenchymal jaundice was observed in 3 (2.7%) patients, dyspeptic symptoms were noted in 41 (36.6%) patients and 2 (1.8%) patients developed reversible alopecia, while in 16 (14.3%) cases it was necessary to cancel preventive treatment. It should be emphasized that the increase in transaminases was characteristic of patients suffering or previously suffering from liver disease. Of the 112 in 54 (48.2%) patients, the presence of concomitant chronic diffuse liver pathology was detected. Taking into account this fact, the dose of albendazole was adjusted in the main group, taking into account the initial functional state of the liver. In cirrhosis of the liver, as well as in cases with the initial (before surgery) increase in liver enzymes, albendazole was used at a dose of 5 mg / kg / day. In turn, with the development of changes in the biochemical parameters of the blood or clinical manifestations of the toxic effect against the background of a standard dose of albendazole, patients were also changed the treatment regimen to 5 mg / kg / day. In the main group, chronic diffuse liver diseases were detected in 51.3% of cases. Initially, reduced doses of albendazole were used in 11 (9.6%) patients, and another 21 (18.3%) patients required a reduction in the traditional dose against the background of biochemical changes. In general, 32 (27.8%) patients of the main group received chemotherapy according to the proposed scheme.

Studies have shown that the probability of adverse reactions on the background of chemotherapy with albendazole in clinical and laboratory indicators was 52.7% (59 patients in the comparison group), which is due to the toxic effect of the drug and the presence of concomitant chronic diffuse liver pathology, while in 14.3% treatment was noted, in turn, the possibility of dose adjustment allowed to reduce this value to 18.3% (21 patients in the main group) and accordingly to ensure a full course of antiparasitic therapy (criterion χ^2 = 26.703; $p<0.001$). Monitoring of hepatic aminotransferases also showed a significant difference in these indicators in the comparison groups. So the level of ALT in the comparison group was 0.88±0.08 mmol / l versus 0.51±0.04 mmol / l in the main group ($p<0.001$), AST indicators did not differ significantly, while among patients with concomitant chronic liver pathology, the ALT value was - 1.14±0.11 against 0.62±0.05 mmol / l ($p<0, 001$) and AST - 0.72±0.07 against 0.52±0.04 mmol / l ($p<0.05$).

Of the 236 patients examined in the long term, a relapse of echinococcosis was noted in 21 (8.9%) patients, while in the group of patients operated on in 2005-2008, this figure reached 16.3%, which was due to the lack of preventive chemotherapy.

Subsequently, thanks to the use of measures to prevent the disease, the frequency of relapse of the disease was reduced in the 2nd subgroup of the comparison group to 5.9%, and in the main group to 2.6%.

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Thus, the developed method of prophylactic chemotherapy improved the quality of care by reducing the frequency of nearby postoperative complications from 12.5% (32 patients in the comparison group) to 4.3% (5 patients in the main group) (criterion $\chi 2 = 4.954$; Df=1; p=0.027) and recurrence of the disease from 11.9% (19 patients in the comparison group) to 2.6% (in 2 patients in the main group) (criterion $\chi 2 = 4.692$; Df=1; p=0,031).

Conclusion. Experimental studies on 32 sheep showed that in areas of the liver remote from the primary echinococcal cyst, the presence of microscopically identifiable germinal microcysts was detected, which can lead to the development of relapse of the disease after removal of large cysts.

Stimulation of the proliferative-productive cellular reaction around the germinal cyst of the parasite with a depressing effect when using albendazole at a dose of 20 mg / kg occurs within 2 weeks, whereas at a dose of 10-15 and 5-7 mg / kg, the effect occurred by 3-4 weeks of observation, which makes it possible to adjust the recommended dose of albendazole (10-12 mg / kg) in cases of possible risk of developing toxic reactions (diffuse liver disease), taking into account the prolongation of course treatment.

Clinically justified dose adjustment of albendazole for the prevention of recurrence of liver echinococcosis in patients with concomitant chronic diffuse liver pathology made it possible to reduce the likelihood of adverse reactions from 52.7% to 18.3% ($\chi 2 = 26.703$; $p<0.001$), and, accordingly, the indicators of hepatic aminotransferases: ALT in the comparison group from 1.14±0.11 to 0.62±0.05 mmol / l ($p<0.001$) in the main group and AST from 0.72±0.07 to 0.52±0.04 mmol / l ($p<0.05$).

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