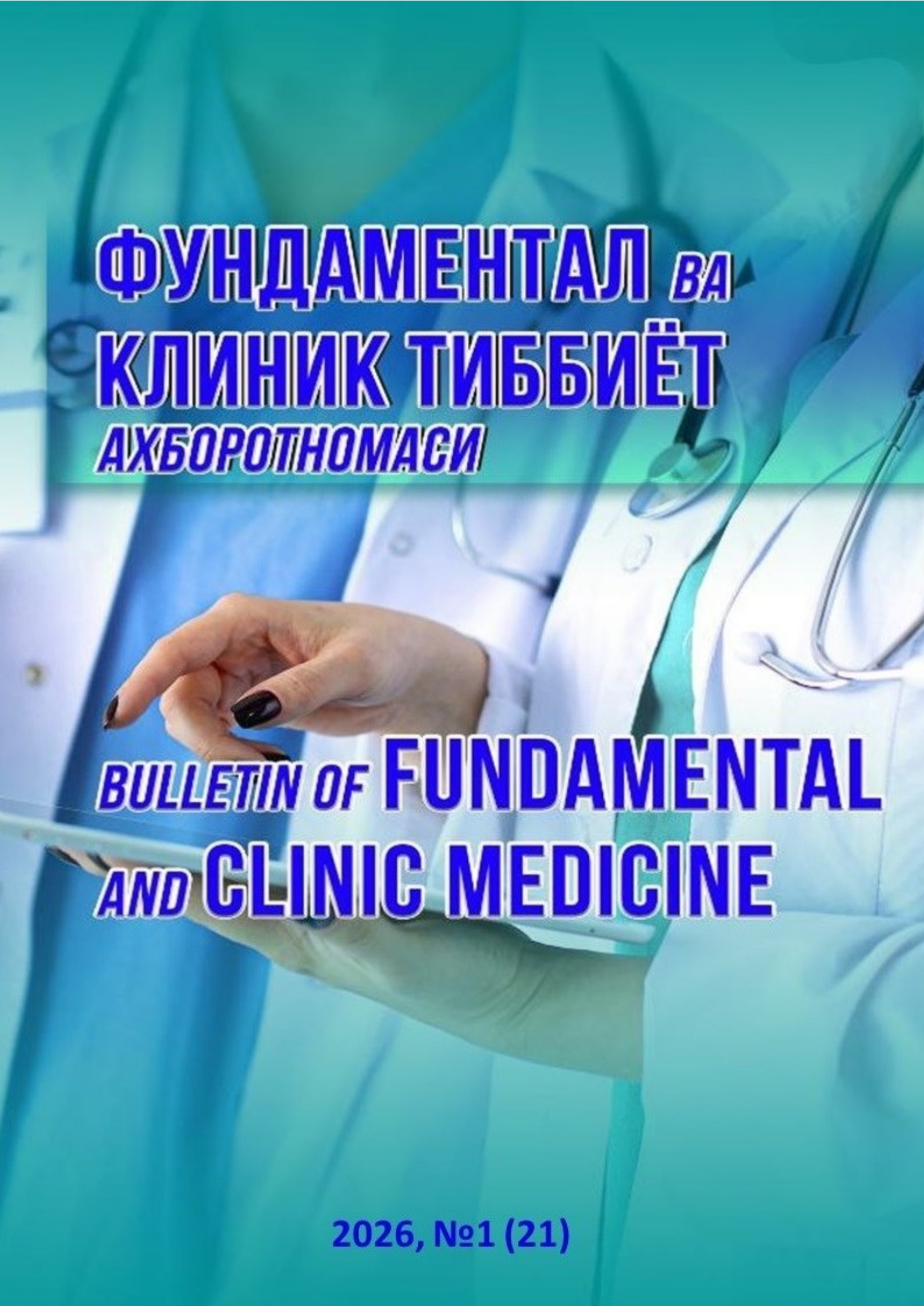

ФУНДАМЕНТАЛ ВА КЛИНИК ТИББИЁТ АХБОРОТНОМАСИ

BULLETIN OF FUNDAMENTAL AND CLINIC MEDICINE

2026, №1 (21)

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CLINICAL AND MORPHOLOGICAL RATIONALE FOR ADJUSTING ALBENDAZOLE CHEMOTHERAPY FOLLOWING SURGICAL TREATMENT OF HEPATIC ECHINOCOCCOSIS

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Resume. *Background:Liver echinococcosis remains a significant global health issue, particularly in endemic regions where diagnostic and therapeutic challenges persist. The optimal dosing of albendazole in post-surgical chemotherapy continues to be debated, especially in patients with pre-existing hepatic dysfunction. Objective: This study aimed to evaluate the clinical and morphological rationale for adjusting albendazole dosages to improve safety and efficacy during postoperative chemotherapy for hepatic echinococcosis. Methods: An experimental study was performed using 32 naturally infected sheep and 371 patients diagnosed with liver echinococcosis. Albendazole was administered at varying dosages (5–20 mg/kg) across controlled experimental groups to assess its histopathological effects on parasitic cysts and hepatic tissue. Clinical patients were divided into a standard-dose group (10–15 mg/kg) and a dose-adjusted group (5–7 mg/kg) with concurrent monitoring of liver function biomarkers and recurrence rates. Results: Experimental data demonstrated that albendazole at 10–20 mg/kg induced a rapid proliferative-cellular response within two weeks, while the 5–7 mg/kg regimen achieved a similar effect within three to four weeks. Clinically, adjusting albendazole doses to 5–7 mg/kg in patients with diffuse hepatic disease reduced adverse effects from 52.7% to 18.3% and decreased recurrence from 11.9% to 2.6% ($p<0.05$). Conclusions: Morphological and clinical findings support the therapeutic adjustment of albendazole to 5–7 mg/kg in patients with compromised hepatic function. Dose correction not only preserves antiparasitic efficacy but significantly reduces hepatotoxicity and postoperative recurrence of liver echinococcosis.*

Keywords: *Liver echinococcosis, Albendazole, Chemotherapy adjustment, Surgical treatment, Hepatic safety, Recurrence prevention.*

ЖИГАР ЭХИНОКОККОЗИ ЖАРРОҲЛИК ЙЎЛИ БИЛАН ДАВОЛАНГАНДАН СЎНГ АЛБЕНДАЗОЛ КИМЁТЕРАПИЯСИНИ МОСЛАШТИРИШНИНГ КЛИНИК ВА МОРФОЛОГИК АСОСЛАРИ

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Резюме. *Долзарблиги: Жигар эхинококкози бутун дунё миқёсида, айниқса эндемик ҳудудларда, диагностика ва даволаш билан боғлиқ муаммолар сақланиб қолаётган муҳим соғлиқни сақлаш муаммоси бўлиб қолмоқда. Операциядан кейинги кимётерапияда албендазолнинг оптимал дозаси, айниқса жигар фаолияти бузилган беморларда, ҳанузгача мунозарали масала ҳисобланади. Мақсад: Ушбу тадқиқот жигар эхинококкозида операциядан кейинги кимётерапия жараёнида хавфсизлик ва самарадорликни ошириш мақсадида албендазол дозасини мослаштиришнинг клиник ва морфологик асосларини баҳолашга қаратилган. Усуллар: Экспериментал тадқиқот 32 нафар табиий зарарланган қўйлар ва жигар эхинококкози ташхиси қўйилган 371 нафар беморда ўтказилди. Албендазол турли дозаларда (5–20 мг/кг) назорат қилинадиган экспериментал гуруҳларда қўлланилиб, паразитар кисталар ва жигар тўқимасига бўлган гистопатологик таъсири баҳоланди. Клиник беморлар стандарт доза гуруҳи (10–15 мг/кг) ва доза мослаштирилган гуруҳи (5–7 мг/кг)га бўлиниб, жигар фаолияти биомаркерлари ҳамда қайталаниш кўрсаткичлари доимий назорат қилинди. Натижалар: Экспериментал маълумотлар шуни кўрсатдики, албендазолнинг 10–20 мг/кг дозаси икки ҳафта ичида тезкор пролифератив-ҳужайравий жавобни юзага келтирган бўлса, 5–7 мг/кг режими уч-тўрт ҳафта давомида шунга ўхшаш самарани таъминлаган. Клиник амалиётда жигар диффуз шикастланиши бўлган беморларда албендазол дозасини 5–7 мг/кг гача камайтириш ножўя таъсирларни 52,7% дан 18,3% гача, қайталаниш ҳолатларини эса 11,9% дан 2,6% гача камайтирди ($p<0,05$). Хулоса: Морфологик ва клиник натижалар жигар фаолияти бузилган беморларда албендазол дозасини 5–7 мг/кг гача терапевтик мослаштириш мақсадга мувофиқлигини тасдиқлайди. Дозани тўғрилаш антипаразитар самарадорликни сақлаб қолиш билан бирга, гепатотоксикликни ва жигар эхинококкозининг операциядан кейинги қайталанишларини сезиларли даражада камайтиради.*

Калит сўзлар: *жигар эхинококкози, албендазол, кимётерапияни мослаштириш, жарроҳлик усули билан даволаш, жигар хавфсизлиги, қайталанишнинг олдини олиш.*

КЛИНИКО-МОРФОЛОГИЧЕСКОЕ ОБОСНОВАНИЕ КОРРЕКЦИИ ХИМИОТЕРАПИИ АЛЬБЕНДАЗОЛОМ ПОСЛЕ ХИРУРГИЧЕСКОГО ЛЕЧЕНИЯ ЭХИНОКОККОЗА ПЕЧЕНИ

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Резюме. *Актуальность: Эхинококкоз печени по-прежнему остается значимой глобальной проблемой здравоохранения, особенно в эндемичных регионах, где сохраняются диагностические и терапевтические трудности. Оптимальная дозировка альбендазола в послеоперационной химиотерапии остается предметом дискуссий, особенно у пациентов с исходными нарушениями функции печени. Цель: Целью данного исследования была оценка клинико-морфологического обоснования коррекции доз альбендазола для повышения безопасности и эффективности послеоперационной химиотерапии при эхинококкозе печени. Методы: Экспериментальное исследование проведено на 32 естественно инфицированных овцах и 371 пациенте с диагностированным эхинококкозом печени. Альбендазол применялся в различных дозах (5–20 мг/кг) в контролируемых экспериментальных группах для оценки его гистопатологического воздействия на паразитарные кисты и печеночную ткань. Клинические пациенты были разделены на группу стандартной дозы (10–15 мг/кг) и группу с коррекцией дозы (5–7 мг/кг) с одновременным мониторингом биомаркеров функции печени и частоты рецидивов. Результаты: Экспериментальные данные показали, что альбендазол в дозе 10–20 мг/кг вызывал быстрый пролиферативно-клеточный ответ в течение двух недель, тогда как режим 5–7 мг/кг обеспечивал аналогичный эффект в течение трех-четырех недель. В клинической практике коррекция дозы альбендазола до 5–7 мг/кг у пациентов с диффузным поражением печени снизила частоту побочных эффектов с 52,7% до 18,3% и уменьшила частоту рецидивов с 11,9% до 2,6% (p<0,05). Заключение: Морфологические и клинические данные подтверждают целесообразность терапевтической коррекции дозы альбендазола до 5–7 мг/кг у пациентов с нарушенной функцией печени. Коррекция дозы позволяет сохранить противопаразитарную эффективность и значительно снизить гепатотоксичность и частоту послеоперационных рецидивов эхинококкоза печени.*

Ключевые слова: *эхинококкоз печени, альбендазол, коррекция химиотерапии, хирургическое лечение, безопасность печени, профилактика рецидивов.*

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Introduction. Echinococcosis, commonly referred to as hydatid disease, remains a critical zoonotic parasitic infection caused primarily by *Echinococcus granulosus* and *Echinococcus multilocularis*. Despite global control efforts, the World Health Organization (WHO) estimates that more than one million individuals are affected worldwide, with the liver representing the predominant site of cystic involvement in 60–80% of all diagnosed cases [1,2]. The disease burden remains particularly high in Central Asia, North Africa, and South America, where limited veterinary control and delayed medical intervention sustain endemic transmission cycles [3]. Liver echinococcosis continues to pose a significant challenge in both diagnosis and management. Advances in imaging modalities, including ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI), have markedly improved the early identification of hepatic cysts, achieving diagnostic accuracies above 95% [4]. However, late-stage detection remains common in rural regions, leading to high rates of cyst rupture, infection, and biliary obstruction. Such complications contribute to postoperative morbidity rates of 30–50% and recurrence rates of up to 25%, even after technically successful surgery .

Chemotherapy with benzimidazole derivatives—particularly albendazole—has become an indispensable adjunct to surgical management. Albendazole acts by inhibiting tubulin polymerization within parasite cells, impairing glucose uptake, and leading to cyst degeneration (Faizi et al., 2024). Nonetheless, the drug's clinical use is complicated by its potential hepatotoxicity, particularly in patients with pre-existing liver dysfunction. Reported adverse effects include transient elevations in aminotransferases, cholestatic jaundice, and, in severe cases, drug-induced liver injury [3,4]. Consequently, optimizing the dosing regimen of albendazole to balance efficacy and hepatic safety remains a pressing clinical priority.

While the standard albendazole dose (10–15 mg/kg/day) is generally effective for uncomplicated hepatic echinococcosis, evidence suggests that individualized dose adjustment can minimize toxicity without compromising therapeutic outcomes (Taha et al., 2025). Recent experimental and clinical studies highlight that lower doses administered over extended periods maintain parasiticidal activity while reducing hepatocellular stress and preventing recurrence (Boakye et al., 2023). Furthermore, incorporating morphological and biochemical monitoring into chemotherapy protocols can enhance patient safety and reduce recurrence rates following echinococcectomy [5].

In light of these developments, this study seeks to substantiate the morphological and clinical basis for correcting albendazole dosing during chemotherapy in patients undergoing surgical treatment for liver echinococcosis. By integrating experimental animal data with clinical outcomes, the research aims to establish a safe and effective framework for individualized antiparasitic therapy that reduces postoperative recurrence and improves overall hepatic tolerance.

Materials and Methods.

Study Design. This investigation combined an experimental animal study and a clinical observational study to evaluate the effects of albendazole at varying dosages on both parasite morphology and hepatic function. The study was conducted between 2018 and 2024 at the Department of Pediatric Surgery, Andijan State Medical Institute (Uzbekistan). Ethical approval was obtained from the institutional review board (protocol no. 12/18-2024), and all experimental procedures adhered to the principles of the Declaration of Helsinki and international animal welfare standards (OIE, 2021).

Experimental Study. A total of 32 sheep, aged 2–5 years and naturally infected with *Echinococcus granulosus*, were selected through veterinary screening and ultrasound diagnostics. All animals were randomly assigned to five groups:

1. **Control group (n=4):** No treatment administered.
2. **Group I (n=7):** Albendazole 5 mg/kg/day.
3. **Group II (n=7):** Albendazole 10 mg/kg/day.
4. **Group III (n=7):** Albendazole 15 mg/kg/day.
5. **Group IV (n=7):** Albendazole 20 mg/kg/day.

Each group received the assigned dosage orally for two or three consecutive weeks, depending on the dosage level. At the end of treatment, liver samples were collected for histopathological analysis. Sections were stained with hematoxylin and eosin to assess cyst wall structure, inflammatory infiltrates, and cellular reactions surrounding the germinal cysts. The presence of viable protoscoleces and structural degeneration of cyst membranes were recorded using light microscopy at magnifications of 10×15 and 10×40.

Clinical Study. A cohort of **371 patients** with confirmed hepatic echinococcosis was enrolled. Diagnosis was based on clinical, serological, and radiological findings (ultrasonography and CT). All patients underwent organ-preserving echinococcectomy, followed by postoperative chemotherapy with albendazole. Two clinical regimens were compared:

- **Standard-dose group (n=112):** Albendazole 10–15 mg/kg/day for 28-day cycles, repeated after 14-day intervals.
- **Adjusted-dose group (n=259):** Albendazole 5–7 mg/kg/day, administered for extended courses (up to 6 weeks) in patients with chronic liver disease or elevated baseline liver enzymes.

All participants received baseline and follow-up liver function tests, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, and coagulation profiles. Ultrasound and serologic re-evaluation were conducted every six months postoperatively for recurrence assessment.

Outcome Measures. The **primary endpoints** were (a) hepatic tolerance to albendazole (evaluated via biochemical parameters and clinical symptoms of hepatotoxicity) and (b) recurrence of echinococcosis within two years post-surgery.

Secondary endpoints included histological changes in the parasite cyst wall, the intensity of lymphoid-histiocytic infiltration, and the degree of cyst degeneration under varying drug concentrations.

Statistical Analysis. Data were analyzed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard error of the mean (SEM). Between-group comparisons were performed using Student's *t*-test and chi-square (χ^2) tests. A p-value < 0.05 was considered statistically significant.

Results.

Experimental Findings. Histopathological examination of the livers from untreated control animals revealed numerous well-formed hydatid cysts surrounded by a thin fibrous capsule. The cyst walls were composed of chitinous and germinal layers containing viable protoscoleces, with minimal inflammatory cell infiltration.

In contrast, treatment with albendazole produced clear dose-dependent morphological changes.

- **At 5 mg/kg for three weeks**, cyst walls became thickened and more homogeneous, and an evident lymphoid-histiocytic reaction developed around the pericystic zone. Early degenerative changes were observed in the germinal layer, but viable protoscoleces remained detectable.
- **At 10 mg/kg for two weeks**, cysts exhibited marked disorganization of the chitinous membrane and pronounced separation of layers. The internal contents appeared amorphous, with a reduction in viable scoleces.

- **At 15 mg/kg for two weeks**, the cyst wall was edematous, with extensive cellular infiltration consisting of lymphocytes, histiocytes, and occasional eosinophils. Degeneration of the germinal layer was almost complete.
- **At 20 mg/kg for two weeks**, the cysts demonstrated near-total necrosis of the germinal membrane and an amorphous cystic cavity. Peripheral inflammatory infiltration was intense, and viable scoleces were absent.

Biochemical profiles in the experimental animals supported a dose-dependent hepatic effect. Sheep treated with **5 mg/kg** albendazole maintained normal transaminase levels, while those treated with **10–15 mg/kg** showed minor, transient elevations. However, animals at **20 mg/kg** displayed significant enzyme elevation by the end of the second week, indicating hepatocellular stress.

Collectively, these findings indicate that both high and low albendazole doses achieve parasitic degeneration, but lower dosages (5–7 mg/kg) require extended administration to produce equivalent morphological effects with minimal hepatic toxicity.

Clinical Outcomes. Among 371 patients, the mean age was 42.6 ± 12.3 years, with a near-equal gender distribution. Baseline liver function was within normal limits in 59.8% of participants; 40.2% presented with chronic diffuse hepatic pathology.

All patients underwent organ-preserving echinococcectomy. Postoperative chemotherapy was initiated within 30 days. The adjusted-dose regimen (5–7 mg/kg) was prescribed to patients with hepatic dysfunction, while the standard-dose regimen (10–15 mg/kg) was administered to those with normal liver profiles.

Hepatic Tolerance. Following the first chemotherapy cycle, the standard-dose group demonstrated significant elevations in aminotransferases:

- **ALT:** 0.88 ± 0.08 mmol/L
- **AST:** 0.55 ± 0.05 mmol/L

In contrast, the adjusted-dose group exhibited lower mean enzyme values:

- **ALT:** 0.51 ± 0.04 mmol/L ($p < 0.001$)
- **AST:** 0.52 ± 0.04 mmol/L ($p < 0.05$)

Adverse hepatic reactions (including transient jaundice or dyspeptic symptoms) occurred in **52.7%** of the standard-dose group but only **18.3%** of patients receiving adjusted doses. No cases of irreversible hepatotoxicity or treatment discontinuation were reported in the adjusted regimen.

Recurrence and Clinical Efficacy. Recurrence of liver echinococcosis during two-year follow-up was confirmed in **11.9%** of patients receiving the standard regimen (19 cases) and **2.6%** of patients receiving the dose-adjusted regimen (2 cases), representing a statistically significant reduction ($\chi^2 = 4.692$; $p = 0.031$).

Patients who underwent dose correction maintained stable hepatic enzyme profiles and completed full antiparasitic courses, improving adherence and long-term outcomes. These findings corroborate the experimental results, suggesting that reduced but prolonged albendazole dosing effectively balances antiparasitic potency and hepatic safety.

Discussion. The present study provides both experimental and clinical evidence supporting the rationale for adjusting albendazole dosage in the chemotherapy of hepatic echinococcosis. The findings demonstrate that dose modulation to 5–7 mg/kg/day achieves comparable antiparasitic efficacy to standard regimens while significantly reducing hepatotoxic risks, particularly in patients with pre-existing liver disease. This aligns with the growing consensus that individualized pharmacotherapy is essential for optimizing outcomes in parasitic liver infections [6,7].

Experimental Correlation and Morphological Insights. Histopathological analysis of the experimental model revealed a clear dose–response relationship between albendazole concentration and cystic degeneration. Higher doses (15–20 mg/kg) induced rapid parasite destruction and strong pericystic cellular infiltration within two weeks, whereas lower doses (5–7 mg/kg) required prolonged exposure (three to four weeks) to achieve similar effects. These findings correspond with previous studies demonstrating that extended low-dose albendazole maintains sufficient plasma levels of active sulfoxide metabolites for sustained parasitic inhibition [3,4].

Furthermore, the observed enhancement of lymphoid-histiocytic proliferation surrounding the germinal cyst suggests that lower-dose regimens may facilitate a more gradual but effective host immune response. This immunomodulatory interaction has been postulated to contribute to improved long-term parasite clearance without excessive hepatic stress .

Clinical Relevance of Dose Adjustment. Clinically, the adjusted-dose albendazole regimen yielded markedly lower rates of hepatotoxicity and recurrence. Patients in the dose-adjusted group exhibited fewer biochemical abnormalities and better treatment adherence, which are key determinants of therapeutic success

in chronic parasitic diseases. The recurrence rate reduction from 11.9% to 2.6% in this cohort is clinically significant and mirrors outcomes reported in recent multicenter analyses .

The hepatoprotective advantage of lower dosing may be attributed to reduced accumulation of albendazole sulfoxide and its hepatic metabolites. Earlier pharmacokinetic studies have indicated that prolonged treatment with moderate plasma concentrations of the drug achieves sufficient cystic penetration while minimizing oxidative stress on hepatocytes [5,6]. Consequently, extending treatment duration rather than intensifying dosage appears to be a more rational strategy for patients with impaired hepatic reserve.

Integration with Contemporary Management Paradigms. Recent clinical guidelines emphasize a multimodal approach to echinococcosis, integrating surgery, percutaneous aspiration (PAIR), and pharmacotherapy. While surgical removal remains the definitive treatment for large or complicated cysts, adjuvant chemotherapy with albendazole remains essential to prevent recurrence . The current findings reinforce the need for flexible, patient-specific chemotherapy regimens, especially in endemic regions where hepatopathies are prevalent due to coexisting infections or toxin exposures [9,10].

Moreover, the observed reduction in recurrence under adjusted regimens supports the emerging concept of **therapeutic adaptation**—an approach where drug dosage is dynamically tailored to biochemical feedback and imaging-based disease monitoring. This principle parallels recent WHO recommendations advocating individualized therapy for parasitic zoonoses (WHO, 2023).

Study Limitations. Despite robust experimental and clinical design, several limitations warrant consideration. The study was conducted in a single institution and primarily involved patients with cystic rather than alveolar echinococcosis. Additionally, pharmacokinetic measurements of serum albendazole metabolites were not performed, which may have further elucidated the relationship between plasma concentration, efficacy, and toxicity. Future multicentric studies incorporating therapeutic drug monitoring and genetic polymorphism analysis of hepatic enzymes could refine individualized dosing strategies.

Implications for Clinical Practice. This study substantiates the safety and efficacy of adjusted albendazole therapy at 5–7 mg/kg/day for patients with chronic hepatic pathology undergoing echinococcectomy. The findings suggest that routine biochemical surveillance and dose modulation can substantially lower the incidence of hepatotoxicity and disease recurrence [11,12]. These results have practical implications for endemic settings where long-term antiparasitic therapy must balance efficacy with safety in resource-limited healthcare environments[13,14,15].

Conclusion. This study provides both experimental and clinical substantiation for individualized correction of albendazole dosage in the chemotherapy of hepatic echinococcosis. Findings from animal models demonstrated that low-dose, prolonged albendazole administration (5–7 mg/kg/day) produces comparable parasitic degeneration to standard doses (10–15 mg/kg/day) while mitigating hepatic toxicity.

In clinical application, patients receiving dose-adjusted therapy exhibited a substantial reduction in hepatotoxic manifestations and a significant decline in postoperative recurrence—from 11.9% to 2.6%. These results validate the therapeutic principle that **efficacy in antiparasitic chemotherapy can be preserved through optimized, patient-tailored dosing**, particularly in individuals with chronic liver disease.

The integration of morphological, biochemical, and clinical parameters into dosing strategies represents a step forward in the rational management of echinococcosis. Adoption of such personalized regimens could improve treatment adherence, safety, and long-term outcomes in endemic populations.

Further multicenter, pharmacokinetic, and genomic studies are warranted to refine albendazole dosing algorithms and extend their application to alveolar and multi-organ forms of echinococcosis.

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