ORIGINAL ARTICLE — CLINICAL TRIAL PROTOCOL

Albendazole as Sole Treatment for Cystic Echinococcosis (Hydatid Disease) Genotype 6 in Central Sudan: A Randomized Controlled Trial Protocol

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Abstract

Cystic echinococcosis (CE), caused by Echinococcus granulosus, is a neglected zoonotic disease with an estimated global economic burden of 3 billion US dollars annually and a documented prevalence of 1.04% among adults in central Sudan, where Genotype 6—the camel strain—predominates. The established standard of care pairs surgical or percutaneous intervention (PAIR) with six months of adjuvant albendazole, a regimen that is expensive, technically demanding, and carries hepatotoxic risk requiring serial liver-function monitoring. A pilot study by our group in which six patients with hepatic CE were treated with albendazole monotherapy achieved a 100% cure rate at two-year follow-up, providing the rationale for a controlled trial. We present the protocol for the first randomized, double-blind, placebo-controlled trial of albendazole as sole therapy for hepatic CE Genotype 6. Ninety patients will be identified through a mobile-ultrasound survey of 12,000 adults in central Sudan and randomized 1:1 to albendazole or placebo for twelve weeks. The trial pursues three aims: establishing the efficacy and optimal duration of albendazole monotherapy for uncomplicated hepatic CE; characterizing the molecular genotype of Sudanese CE isolates through NADH1 sequencing with GenBank deposition; and evaluating mobile clinic and portable ultrasound models for community-based early detection. If the expected cure rate above 80% is confirmed, this trial would provide the first randomized evidence base for surgery-free management of uncomplicated hepatic CE in an endemic low-resource setting.

1. Introduction

Echinococcosis is a parasitic zoonosis caused by larval-stage tapeworms of the genus Echinococcus, classified by the World Health Organization as a neglected tropical disease and estimated to cost the global economy approximately 3 billion US dollars annually. While sporadic cases occur in Scandinavia, Central Europe, and North America, the disease is highly endemic across sub-Saharan Africa. In endemic European regions such as Spain and southern Italy, incidence reaches 4 to 8 per 100,000 inhabitants.

Two major clinical forms of echinococcosis exist. Cystic echinococcosis (CE)—the form relevant to Sudan—causes large cysts in the viscera of infected individuals, most commonly in the liver and lung, though any organ from head to toe may be affected. Alveolar echinococcosis, caused by E. multilocularis, produces multiple small cysts with an infiltrative, almost malignant growth pattern; it predominates in northern Europe and China and is distinct in both biology and management.

CE is transmitted through a cycle involving domestic dogs as the definitive host and livestock as intermediate hosts. Infected dogs contaminate the environment with tapeworm eggs in their feces; these eggs gain access to intermediate hosts—and incidentally to humans—through contaminated soil, water, vegetation, or direct contact with infected animals. Humans are not a part of the natural transmission cycle but become infected through the fecal-oral route, most often by handling dogs or consuming contaminated food.

Ten genotypes of E. granulosus are recognized (G1 through G10), each associated with a predominant animal host. In Sudan and much of East Africa, the predominant form is Genotype 6 (G6), the camel strain. A community ultrasound survey conducted by our group in central Sudan confirmed a prevalence of 1.04% among adults—a figure consistent with earlier estimates and sufficient to power a randomized trial in a defined study area.

2. Background and Literature Review

Once established, CE may remain clinically silent for months or years. Symptoms, when they appear, arise from mechanical complications: cyst growth compresses adjacent structures, and less commonly, rupture produces acute hypersensitivity reactions. The liver and lungs bear the greatest burden of disease, but the differential diagnosis of any cystic mass anywhere in the body should include CE in endemic regions.

Diagnosis is established by ultrasound for solid-organ involvement —liver, spleen, kidney, heart, mesentery—which enables classification by the WHO five-stage scheme: Stage 1 (active, simple cyst), Stage 2 (active, thickened wall), Stage 3 (inactive, detached membrane), Stage 4 (heterogeneous, calcifying), and Stage 5 (solid, calcified scar). CT scanning and MRI are required for pulmonary, cerebral, and osseous forms.

The current international standard of care consists of PAIR (percutaneous aspiration, injection of scolicidal agent, re-aspiration) followed by six months of high-dose adjuvant albendazole. Albendazole and mebendazole are the only anthelmintic drugs with demonstrated activity against CE, and albendazole is preferred because its systemic absorption and penetration into hydatid cysts substantially exceeds that of mebendazole. Pre-surgical albendazole also reduces intra-cystic pressure and lowers recurrence risk when operative management cannot be avoided.

The limitations of this standard approach are well recognized. PAIR requires specialized sonographic expertise that is unavailable in most primary care and community settings in endemic regions. Six months of high-dose albendazole is expensive, demands serial liver-function monitoring due to hepatotoxic risk, and challenges patient compliance. Whether albendazole alone—without procedural intervention and at a

shorter treatment duration—can achieve comparable efficacy in uncomplicated hepatic CE has never been tested in a randomized trial. A pilot study by our group, in which six patients with hepatic CE Genotype 6 received albendazole monotherapy without PAIR or surgery, achieved a 100% cure rate at two years with no recurrences. These results motivate the present protocol.

3. Study Aims

This trial pursues three aims, each addressing a distinct gap in the management of cystic echinococcosis in Sudan.

Aim 1: To evaluate the efficacy of albendazole as sole treatment for hepatic CE, comparing three months versus six months as the treatment duration. If a three-month course proves equivalent in cure rate, it would reduce drug exposure, cost, and monitoring burden substantially—and would remove the main barrier to albendazole-only management by the non-specialist physician in primary care.

Aim 2: To characterize the predominant CE genotype in central Sudan through DNA sequencing with GenBank deposition, enabling construction of a phylogenetic tree and providing accessible reference sequences for future meta-analyses and global genotype mapping.

Aim 3: To evaluate the feasibility and potential efficacy of mobile clinic and portable ultrasound strategies for early community-based diagnosis of CE. If validated, this model would allow detection before cysts become symptomatic or complicate, and would be transferable to other endemic regions with limited specialist infrastructure.

4. Methods

4.1. Patient Population

Eligible participants are all adults aged 18 years or older with asymptomatic hepatic CE identified by mobile ultrasound survey of approximately 12,000 individuals in central and east-central Sudan. Based on a documented community prevalence of 1.02%, approximately 120 cases are expected from this survey. Patients are excluded if they have elevated liver function tests at baseline, are in early pregnancy, or develop moderate to severe symptoms during the study period.

4.2. Study Design

The study is a prospective, randomized, double-blind, placebo-controlled trial. Randomization will be performed using REDCap. Albendazole tablets (10 mg/kg body weight, twice daily) and matching placebo tablets will be manufactured by Ami Pharma (Khartoum, Sudan) to be visually and physically identical in all respects, identifiable only by barcode accessible to the hospital pharmacy. The biostatistician was involved in study design before the start of enrollment and will remain involved through analysis.

The primary outcome—cure rate by ultrasound criteria—will be analyzed by Chi-square test on an intention-to-treat basis. Ultrasound assessment agreement between readers will be measured by Cohen's Kappa statistic.

4.3. Sample Size

The study is powered at 80% with a two-sided significance level of 0.05, based on an expected cure rate greater than 80% with albendazole and allowing for a 20% dropout rate. This yields a required sample of 90 patients: 45 randomized to albendazole and 45 to placebo. With dropout adjustment (18 additional patients), the enrollment target is 108 patients; the evaluable-participant target is 72.

4.4. Follow-up Schedule

After randomization, all participants are assessed weekly for the first four weeks and fortnightly (every two weeks) for the subsequent eight weeks, with portable ultrasound performed by a trained, certified assessor at each visit. Medication compliance is reviewed at every clinic contact.

4.5. Interventions at Week 12

At 12 weeks, all patients undergo ultrasound assessment and tissue sampling. For cysts remaining active on ultrasound, PAIR is performed with concurrent aspiration for microscopy and molecular testing, followed by a further 12-week course of albendazole. For cysts that have become inactive or calcified, a liver biopsy puncture is performed for laboratory and molecular confirmation. Primary data are released to the analyst at week 12; complete data for all participants are released at week 24.

4.6. Laboratory Procedures

Cyst material aspirated at PAIR or biopsy is examined by direct microscopy to confirm cyst identity and detect protoscolices, which confirm fertility. Genomic DNA is extracted from sediment positive for protoscolices using the GF-1 Blood DNA Extraction Kit (Vivantis) according to the manufacturer's protocol.

Genotyping targets the mitochondrial NADH dehydrogenase subunit 1 (NADH1) gene using nested PCR with validated primers described by Bowles and McManus (1993). Outer primers JBl1 (5'-AGATTCGTAAGGGGCCTAATA-3') and JB12 (5'-ACCACTAACTAATTCACTTTC-3') amplify a 530 bp primary product; nested internal primers JB11.5 (5'-TTATGGTAGATATTATAG-3') and JB12.5 (5'-CACACACATAAAACAAGC-3') produce a 471 bp confirmatory product. Real-time loop-mediated isothermal amplification (LAMP) PCR—developed and validated in our molecular laboratory—is run in parallel as an independent confirmation.

PCR products are purified using the QIAquick PCR Purification Kit (QIAGEN) and submitted for Sanger sequencing at Macrogen (Seoul, South Korea). Sequences are aligned against GenBank reference sequences for E. granulosus-complex NADH1 and deposited with open accession numbers to facilitate future phylogenetic analysis and international meta-analyses.

5. Study Timeline

Weeks 1–6 are devoted to the mobile ultrasound survey of 12,000 adults, with identification of approximately 120 CE-positive individuals. Informed consent and REDCap randomization for 90 participants are completed in weeks 6 through 8. The 12-week treatment period runs from week 8 through week 20, with weekly clinic follow-up during weeks 8–12 and fortnightly assessments from weeks 12 through 20. At week 20 (study week 12), PAIR is performed for participants with active cysts and liver biopsy puncture for those with inactive cysts; primary data are released to the analyst at this point. Participants who underwent PAIR receive a further 12-week course of albendazole, completing treatment at week 32 (study week 24), when complete data for all participants are released and final analysis begins.

6. Expected Results

Based on the pilot data and the biological properties of G6 CE—a strain known to have a slower natural history than the G1 sheep

strain—we expect a cure rate exceeding 80% with albendazole monotherapy in uncomplicated hepatic cases. If this is confirmed in the randomized setting, albendazole alone would become a viable, evidence-based first-line alternative to PAIR for this indication. The implications are substantial: uncomplicated CE could be managed in primary care by a non-specialist physician with access to albendazole and portable ultrasound, without referral for procedural intervention. Treatment cost and duration would fall, compliance challenges would diminish, and the approach would be scalable to resource-limited endemic settings.

The molecular genotyping arm will produce a series of fully sequenced, GenBank-deposited CE isolates from Sudan—the first such dataset from central Sudan at this scale. These sequences will enable a phylogenetic tree of Sudanese G6 CE and provide reference material for future global meta-analyses examining genotype-specific treatment responses.

The mobile ultrasound model, if shown to be operationally feasible and capable of identifying asymptomatic CE at community prevalence, would establish a blueprint for population-based CE surveillance in sub-Saharan Africa. Earlier diagnosis—before cysts enlarge, complicate, or rupture—would increase the proportion of patients eligible for non-surgical management and reduce the burden on tertiary-care centers.

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