

Albendazole Therapy in Postoperative Spinal Cystic Echinococcosis: Evaluating Recurrence and Survival Outcomes Between Short and Long-Term Protocols

Traitement post-opératoire par Albendazole dans l'échinococcose kystique rachidienne: évaluation de la récurrence et de la survie entre les protocoles à court et à long terme

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ABSTRACT

Introduction: The spine is a rare location in cystic echinococcosis even in endemic regions. Surgery is the treatment of choice. There are still uncertainties regarding anthelmintic treatment protocol and duration.

Aim: To evaluate the impact of Albendazole therapy duration on the functional outcome, overall survival and recurrence-free survival in patients operated for spinal cystic echinococcosis (SCE)

Methods: We retrospectively selected patients operated for SCE and collected their epidemiological, clinical, imaging, surgical, and outcomes data. These patients were categorized into two groups: a 6-month Albendazole therapy after surgery group and an indefinite treatment group. Statistical tests were applied to compare the outcomes.

Results: Thirty-two patients were included, predominantly male (68%) with a mean age of 40 years. The thoracic level was involved in 56%, lumbar in 31% and cervical in 13% of cases. According to Dew/Braithwaite and Lees, 69% of our patients had dumbbell formation, 22% had type 2 and 9% had type 4 lesions. Complete resection was achieved in 50% of cases. 18 patients received a 6-month Albendazole therapy while 14 patients received an indefinite treatment. All patients had a recurrence in a mean delay of 17.7 months. The only statistical difference between the two groups was the recurrence-free survival with a mean of 11.4 months for 6-month therapy patients and 27 months for long-term therapy patients ($p=0.047$).

Conclusion: Post-operative SCE Albendazole treatment duration might not affect neither the functional outcome nor the overall survival. Otherwise, our findings suggest indefinite Albendazole therapy following SCE surgery could not prevent local recurrence but might delay it compared with 6-month therapy.

Keywords: Echinococcosis, Spine, Surgery, Albendazole, Recurrence, Survival.

RÉSUMÉ

Introduction : Le rachis est une localisation rare de l'échinococcose kystique même dans les régions endémiques. La chirurgie est le traitement de choix. Il existe encore des incertitudes concernant le protocole et la durée du traitement anthelminthique.

Objectif : Évaluer l'impact de la durée du traitement par Albendazole sur le résultat fonctionnel, la survie globale et la survie sans récurrence chez les patients opérés pour échinococcose kystique rachidienne (EKR).

Méthodes : Nous avons sélectionné rétrospectivement des patients opérés pour EKR et recueilli leurs données épidémiologiques, cliniques, d'imagerie, chirurgicales et de suivi. Ces patients ont été classés en deux groupes : un groupe de traitement par Albendazole de 6 mois après la chirurgie et un groupe de traitement indéfini. Des tests statistiques ont été appliqués pour comparer les résultats.

Résultats : Trente-deux patients ont été inclus, majoritairement de sexe masculin (68 %) avec un âge moyen de 40 ans. Le niveau thoracique était atteint dans 56 %, lombaire dans 31 % et cervical dans 13 % des cas. Selon Dew/Braithwaite et Lees, 69 % de nos patients avaient des lésions en "dumbbell formation", 22 % des lésions de type 2 et 9 % des lésions de type 4. Une résection complète a été obtenue dans 50 % des cas. 18 patients ont reçu un traitement à l'albendazole pendant 6 mois tandis que 14 patients ont reçu un traitement à vie. Tous les patients ont eu une récurrence dans un délai moyen de 17,7 mois. La seule différence statistique entre les deux groupes était la survie sans récurrence avec une moyenne de 11,4 mois pour les patients sous traitement de 6 mois et de 27 mois pour les patients sous traitement à long terme ($p = 0,047$).

Conclusion : La durée du traitement postopératoire à l'albendazole après une chirurgie EKR pourrait n'avoir aucune incidence sur les résultats fonctionnels ni sur la survie globale. Par ailleurs, nos résultats suggèrent qu'un traitement à l'albendazole à durée indéterminée après une chirurgie EKR ne permettrait pas de prévenir la récurrence locale, mais pourrait la retarder comparativement à un traitement de 6 mois.

Mots clés : Echinococcose, Rachis, Chirurgie, Albendazole, Récurrence, Survie.

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INTRODUCTION

Spinal cystic echinococcosis (SCE) is a rare but serious manifestation of hydatid disease, an anthroponozoonosis endemic in Tunisia and other regions (1). Although bone involvement is uncommon, representing only 0.5–4% of cases, spinal involvement accounts for up to 50% of these (2). Surgical resection remains the cornerstone of treatment. However, postoperative recurrence rates remain high, ranging from 40% to 90%, with an associated mortality rate exceeding 50% within 5 years (3,4). Postoperative management, particularly with anthelmintic therapies like Albendazole, is consensual, yet there is considerable debate regarding the optimal duration and dosage of such treatments (5). In our institutions patients were treated with Albendazole 10-15 mg/kg/day for 6 months but the tendency has changed towards long-term treatment following recent data of the literature. This study aims to assess the impact of two distinct postoperative Albendazole protocols on recurrence intervals, survival, and quality of life for patients with SCE. By comparing a six-month course of Albendazole with a lifelong regimen, we aim to clarify which approach provides superior clinical outcomes.

METHODS

We conducted a 10-year retrospective, multicenter, comparative study from January 2013 to December 2023, gathering data from 32 patients treated at the Neurosurgery Department of the Trauma and Burns Center (Ben Arous) and the Orthopedic Surgery Department at Mongi Slim Hospital (La Marsa). We included in our study adult patients who underwent surgical treatment for SCE and received postoperative Albendazole therapy. Exclusion criteria were non-operated cases of vertebral echinococcosis, early treatment discontinuation, and patients lost to follow-up. Our patients were categorized into two groups based on the postoperative Albendazole followed protocol:

- **Group 1:** Patients receiving 10-15mg/kg/day of Albendazole orally in two doses for six months.
- **Group 2:** Patients receiving 10-15mg/kg/day of Albendazole orally in two doses for life.

Data were retrospectively collected from patient medical records, including: demographic and clinical characteristics (age, gender, symptoms at diagnosis, and medical history), surgical details (surgical approach, extent of resection: complete or incomplete), treatment protocols (duration of Albendazole treatment) and follow-up evaluations (serological and MRI follow-ups for monitoring recurrence, with clinical evaluations to assess any new or progressing lesions). The primary outcome measure was recurrence, defined as the appearance of new lesions or enlargement of existing lesions, with or without associated clinical symptoms. Secondary outcome measures included survival rates and quality of life. We also went through statistical analysis. Firstly with descriptive analysis: we evaluated basic characteristics of the study population using means for continuous

variables and frequencies for categorical variables. Followed by comparative analysis: the mean recurrence interval between the two groups was compared using Student's t-test. Differences in survival and recurrence rates between groups were evaluated through Kaplan-Meier survival analysis and compared using the log-rank test. Statistical significance was set at $p < 0.05$. Finally, multivariate analysis was performed using binary logistic regression test to determine the odds ratio (OR) and 95% confidence interval (CI95%).

RESULTS

The mean age of our patients was 40 years, ranging from 25 to 72 years. A male predominance was observed, with 22 men versus 10 women and a male-to-female ratio of 2.2. None of the patients had diabetes, although 6 had previously been treated for pulmonary hydatid cysts, and 15 had been treated for hepatic hydatid cysts, with an average delay of 12 years between treatment and the onset of spinal symptoms. Most patients originated from rural areas with a history of contact with dogs. The diagnostic delay, defined as the time from the onset of symptoms to diagnosis, averaged 6 months, ranging from 3 to 12 months. Clinically, the patients reported spine-related pain (dorsal pain in 19, lumbar pain in 10, and cervical pain in 3) with pain intensity on the VAS scale between 3 and 8 (mean 5.8). Radicular pain was reported by 12 patients, presenting as sciatic pain in 9 (with 6 reporting multi-root pain) and intercostal neuralgia in 3, with pain scores ranging from 4 to 8 (mean 6.5). Twenty-five patients presented with motor deficits, including paraparesis in 17, paraplegia in 6, and isolated right L5 segmental deficit in 2. Sensory disturbances were noted in 15 patients, corresponding to the level of spinal involvement in 12 and saddle anesthesia in 3. Sphincter disorders included urinary incontinence in 12 patients, overflow urinary retention in 5, constipation in 4, and anal incontinence in 10. Additionally, 5 patients reported erectile dysfunction. Imaging studies included radiography in 7 patients, showing lytic lesions in 4 and L4-L5 spondylolisthesis in 3 other patients. CT was performed in 14 patients, revealing osteolytic involvement of vertebral bodies in 10 and the posterior arch in 4 (Figure 1).

Spinal misalignment (anterolisthesis or scoliosis) was observed in 5 cases (Figure 2).

All patients had spinal MRI, identifying multivesicular masses that were hypointense on T1-weighted images (WI) and hyperintense on T2-WI without enhancement after Gadolinium administration. MRI also assessed lesion's location and impact on spinal cord and nerve roots. Lesions were primarily in the thoracic spine in 18 patients, lumbar in 10, and cervico-dorsal in 4. Lesions were contiguous, involving an average of 2.4 vertebrae (range: 2-5) (Figures 3, 4).

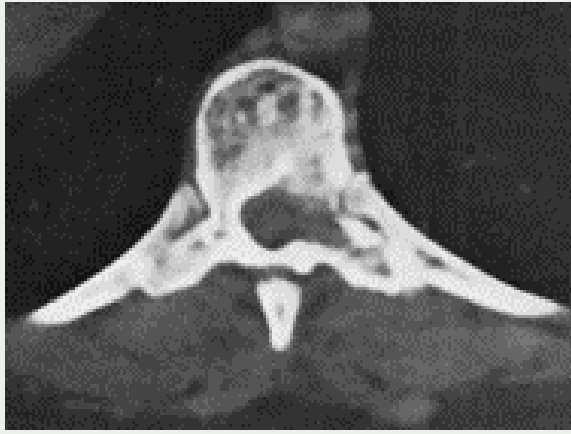


Figure 1. Echinococcosis of the thoracic spine: Axial CT scan of T11 vertebra showing an osteolytic lesion centered on the left pedicle with central canal extension



Figure 2. Lateral X-ray of the lumbar spine showing an osteolytic lesion of the vertebral body and the superior vertebral endplate of L3 causing vertebral collapse and obliteration of the overlying disc space.



Figure 3. Axial T2-weighted MRI image of a thoracic vertebra showing type 6 Dew Braithwaite vertebral hydatidosis, containing vesicles that are hyperintense. Involvement of the vertebral body, the left posterior vertebral and costal arches with extension to the paravertebral soft tissues and central canal spaces in contact with the spinal cord.



Figure 4. Sagittal T2-weighted MRI image of the dorsal spine showing vertebral hydatidosis extending to the central canal and causing significant compression and signal abnormality (hyperintensity) of the spinal cord.

According to the Dew/Braithwaite and Lees classification (Figure 5) (6), 22 patients had type 6 lesions, 7 had type 2, and 3 had type 4. Patients with type 6 “Dumbbell” lesions demonstrated spinal cord compression in 16 cases, with T2 hyperintensity adjacent to the lesion in 9 and cauda equina compression in 7 others. Among patients with type 2 lesions, 3 showed spinal cord T2 hyperintensity at T3-T4 level.

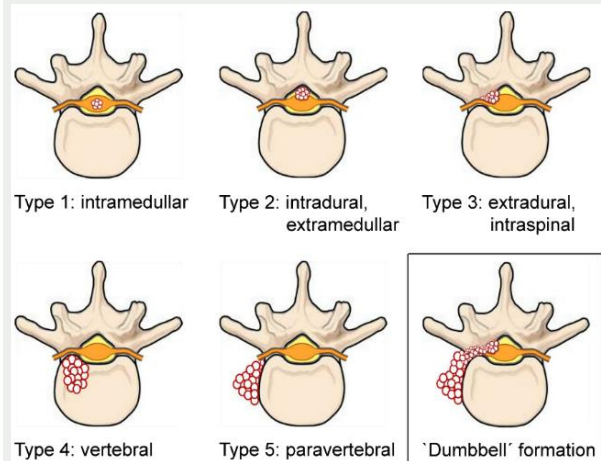


Figure 5. Classification of spinal cystic echinococcosis according to the Dew/Braithwaite & Lees classification (type 1–5) and ‘dumbbell’ formation (3)

Preoperative management included analgesics and corticosteroids in 8 patients with rapid-onset paraplegia due to spinal cord compression. All patients received urinary catheterization for urinary dysfunction. Surgically, posterior decompression was performed in 28 patients, with laminectomy in 17 dorsal cases and 10 lumbar cases. Four patients underwent combined anterior and posterior approaches. Complete resection was achieved in 16 patients, while incomplete resection occurred in 16 (4 lumbar, 12 thoracic with intrathoracic extension). Stabilization with osteosynthesis was necessary in 25 cases.

Intraoperative scolical treatment included hypertonic saline irrigation to minimize dissemination risk. Blood loss was substantial, averaging one liter for posterior-only approaches and over two liters for combined approaches. Fifteen patients required transfusions. Postoperative medical treatment varied by group: group 1 with 18 patients who received Albendazole 10-15mg/kg/day for 6 months, and group 2 with 14 patients who received 10-15mg/kg/day indefinitely. Six months after surgery and treatment, motor improvement was seen in 21 patients (6 with complete recovery, 15 with partial improvement), while 4 patients deteriorated to paraplegia, and 7 kept the same status. Sensory disturbances persisted in 20 patients, with 12 showing improvement. Sphincter function improved in 7 patients but remained impaired in others. On another note, all patients in both groups exhibited high levels of adherence to the treatment protocol, and no cases of non-compliance were observed. Regarding the adverse effects of albendazole, two patients in group 1 experienced headaches with dizziness and one patient had diarrhea. In group 2, one patient had abdominal pain with diarrhea and another had a transient elevation of liver enzymes less than twice the normal level after 30 months of treatment. The difference between the two groups was not statistically significant. Over the long term, all patients experienced recurrence, with a mean interval of 17.7 months (range: 3-36 months). Recurrence averaged 17.5 months for thoracic lesions, 18 months for lumbar, and 18 months for cervico-dorsal. Complete resection cases had an average recurrence time of 19.2 months (range: 6-36 months), while incomplete resection cases averaged 16.2 months (range: 3-24 months). Patients receiving the first protocol had an average recurrence time of 11.4 months, while those on the second had a mean of 27 months. Thus, the two groups were statistically comparable in terms of epidemiological data. The duration of treatment had no statistically significant influence on functional results neither on survival outcomes. Only the recurrence delay between the two groups was statistically significant, with a $p=0.047$. Moreover, multivariate analysis confirmed the only impact of treatment duration in delaying recurrence ($OR=2.5$; $CI_{95\%}:1.6-2.9$), whereas recurrence was not statistically influenced by initial radiological stage ($OR=3.4$; $CI_{95\%}:0.8-3.7$) or type of surgery ($OR=2.1$; $CI_{95\%}:0.6-2.6$). Concerning clinical progression in terms of motor function: among the seven patients with residual motor deficits, one showed improvement, regaining independent walking after motor rehabilitation. Three experienced worsening due to hydatid cyst recurrence, while two retained the same level of motor deficit. However, in terms of genitourinary and sphincter disorders, recovery was rather limited. Only one patient regained urinary continence, while three required either permanent or intermittent catheterization. No improvement in fecal incontinence was observed in three patients, one of whom ultimately required a colostomy. Erectile dysfunction persisted without improvement in both affected patients. Four patients died within a few years following surgery, at 10, 18, 36, and 40 months, respectively. Causes of death included: acute

renal failure associated with neurogenic bladder in one patient, septic shock originating from a pressure ulcer in another, massive pulmonary embolism in the remaining two. Of the deceased patients, three were from Group 1, having received the shorter Albendazole protocol, while one belonged to Group 2 on the extended protocol. One patient was lost to follow-up 20 months post-surgery.

DISCUSSION

Cystic echinococcosis also known as cystic hydatidosis is a cosmopolitan parasitic zoonosis caused by the larval stage of *Echinococcus granulosus* cestode. Endemic regions include the Mediterranean basin, Middle East, South America, Australia, Central Asia, and China (1). Although surgical treatment is widely accepted, the optimal duration of postoperative medical Albendazole treatment remains a subject of controversy. Therefore, our study aimed to compare long-term treatment with limited-duration treatment and concluded that long-term protocol after SCE surgery might not influence neither postoperative functional outcomes nor overall survival. It also might not prevent recurrence but could delay it compared with limited 6 months Albendazole treatment protocol. All patients in our study had postoperative recurrence. However, patients receiving a 6-month treatment had a recurrence delay of 11.4 months, while those on indefinite medication had a recurrence delay of 27 months ($p=0.04$). Our study has certain limitations, namely its retrospective nature and the potential biases this may entail, the small sample size given the rarity of the disease, and the fact that patients were operated on and followed up by different surgical teams, which could be a potential source of bias. In Tunisia, the surgical incidence is 15 per 100,000 inhabitants corresponding to approximately 10% of the activity of Tunisian surgical departments, and the prevalence varies from 1.5 to 4% depending on the regions (7–9). Risk factors include livestock (sheep) farming, living with dogs and living in areas with poor hygienic conditions and deficient water quality (10). Most of our patients were indeed from rural regions with contact with sheep and dogs. Wile, the liver (70%) and lungs (20%) are the most commonly affected (11), bone is affected in only 0.5-4% of cases, about 50% of which involve the spine (2). SCE is rarely observed in children and is more common in middle aged adults (mean 35 years), frequently men (56-66%) (2,12), Similar to the literature, we found a male predominance (68%) and a mean age of 40 years. In fact, it remains a highly disabling condition for young active population affecting not only quality of life (progressive physical disability and major psychologic effects) but also had important socio-economic impact with high health care costs (imaging, surgery, long term treatment and heavy chronic complications) and loss of productivity with social disintegration in young adults (2,9,13). The clinical presentation of SCE is non-specific and depends on the level of spinal involvement and the degree of cord/nerve roots compression. Back pain remains the most common

symptom, which was found in 100% of our patients. Other symptoms include limb weakness, radicular pain, para/tetra paresis, para/tetraplegia and anal sphincter, bowel or bladder dysfunction (13,14). Since the disease is slow-progressing, the diagnosis delay can be long ranging from several months to years (2,14). In our study, the mean diagnosis delay was 6 months. Radiography is the first-line imaging modality for such symptoms. It shows non-specific osteolysis of the vertebral body with possible extension to the posterior vertebral elements. Paravertebral soft tissues extension is frequent and presents as paraspinal opacities with well-defined rounded or poly cyclical, sometimes calcified contours. CT assesses bone destruction and shows vertebral hypodense multivesicular cystic masses. MRI is the best imaging modality for diagnosis confirmation: It depicts a multi vesicular mass that is hypointense on T1-WI and hyperintense on T2-WI without enhancement after Gadolinium administration (15). MRI is also the modality of choice for assessment of precise levels involvement, local extension to the spinal canal and the relationship with spinal cord and nerve roots, thereby establishing the status according to the Dew/Braithwaite and Lees classification (6). SCE occurs in about 50% of the 0.5–4% of cases affecting bones and is most commonly located in thoracic (50%), followed by lumbar (21%), cervical and sacral level (2). These literature data are consistent with our results: Thoracic level was involved in 56%, lumbar in 31% and cervical in 13% of cases. According to Dew/Braithwaite and Lees, SCE is classified into type 1 (intramedullary); type 2 (intradural extramedullary); type 3 (extradural intraspinal); type 4 (vertebral); type 5 (paravertebral) and “dumbbell formation” (a combination of type 3 and type 5 +/- additional vertebral /intradural structures) (2,6). Type 1 is very rare. Extradural, vertebral and dumbbell formation lesions are frequently reported (2). Sixty nine percent of our patients had dumbbell formation, 22% had type 2 and 9% had type 4 lesions. Serology is an additional tool for diagnostic confirmation and for subsequent monitoring under or after treatment. Among serology methods, Indirect Hemagglutination (IHA) has the highest specificity and Enzyme-linked Immunosorbent Assay (ELISA) has the highest sensitivity (16). Both techniques are widely used and recommended as screening tests (5). Since serological tests may remain elevated even after successful removal of the cyst, recurrence is defined by the patients’ clinical and radiological imaging findings (5). Surgery remains the cornerstone for curative treatment, although complete removal of unruptured cysts is difficult in the spine, achievable in about 16-38% of cases, due to the infiltrative nature of the disease and advanced stage at presentation (14,17). The other aims of surgery are decompression of the spinal cord and stabilization of a compromised spinal segment depending on the location and extent of disease. Variable and combined surgical approaches have been reported and posterior decompression by laminectomy is performed in over 90% of cases (3). Intraoperative cyst rupture and fluid spillage is a major problem associated with high recurrence. Therefore, thorough irrigation of the operative field with scolicalid agents, mainly 20%

hypertonic saline is widely used and recommended (3,13,18). Medical treatment with benzimidazoles, especially Albendazole, in visceral cystic echinococcosis is effective (18), depending on cyst stage and size (19). In the osseous location, including vertebrae, data on the efficacy of Albendazole is scarce and debated (20). However, it is used in almost 100% of cases in the literature (3), and surgery without adjunct medical treatment is no longer considered except in rare cases of complete resection without cyst rupture (21). Since the pharmacokinetic features of benzimidazoles in spinal bone or soft tissue are unknown, the doses recommended for visceral cystic echinococcosis (albendazole 10-15 mg/kg/day in two doses orally) are usually applied (5,18,22). Albendazole should be initiated at least 4 hours before surgery to reach scolicalid blood levels. Monthly treatment interruptions, previously required based on limited available long-term toxicity data, are no longer recommended (5,23). In fact, albendazole side effects such as headache, dizziness, gastrointestinal disorders and elevated liver enzymes, remain fairly rare, even with long-term treatment protocols and with no proven risk of toxicity after long duration therapy (23). The optimal duration of medical treatment has not been formally assessed. Most authors prefer 6 months of treatment, but there is a tendency towards indefinite treatment especially in case of extensive disease (3). Despite use of different postoperative anthelmintic medical protocols, several authors claim that the most common complication remains symptomatic recurrence within two years after the surgery, occurring in 40–90% of cases (13,14,24). Thus, there is still a need for further research aiming to compare, adjust and improve postoperative anthelmintic protocols. To the best of our knowledge, this is the first study to retrospectively compare the outcome of limited (6 months) versus long-term medical treatment duration for operated SCE. In fact, even if some authors have examined case series, the majority had conduct only simple descriptive analysis without well-structured comparison of duration impact of different anthelmintic treatment protocols on postoperative functional outcomes, overall survival, and place particular emphasis on local recurrence effect (3,4,19,24).

CONCLUSIONS

Post-operative SCE Albendazole treatment duration might not affect neither the functional outcome nor the overall survival. Otherwise, our findings suggest indefinite Albendazole therapy following SCE surgery could not prevent local recurrence but might delay it compared with 6-month therapy. Further prospective, randomized, multicenter studies remain essential in order to better evaluate outcomes of long-term compared with limited duration anthelmintic medical treatment for operated SCE.

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