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Albendazole associated to surgery or minimally invasive procedures for hydatid disease – how much and how long

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Rezumat

Albendazolul asociat chirurgiei sau procedurilor minim invazive în boala hidatică - dozaj și durată

Chistul hidatic este o boală parazitară dată de localizarea formei larvare a parazitului în ficat (80%), plămân, rinichi, splină, cord etc. Omul este gazdă intermediară accidentală. Diagnosticul se stabileşte pe baza investigațiilor de laborator şi imagistice. Tratamentul este multimodal, chirurgical şi medical. Prezintă risc de complicații periculoase şi recidivă. Se impun măsuri adecvate de urmărire. Albendazolul joacă un rol central în tratamentul medical al bolii.

Cuvinte cheie: chist hidatic, tratament chirurgical, albendazol

Abstract

Cystic echinococcosis represents a parasitic disease due to the development of larval stage of metacestode Echinococcus granulosus in the liver (80%), lungs, kidneys, spleen, myocardium etc. Human is an accidental intermediate host. Diagnosis is done on base of laboratory and imaging investigations. Treatment is multimodal, surgical and medical. Risks for dangerous complications and relapses are quite common. It is needed an adequate follow-up regimen. Albendazole is playing a central role in the medical therapy of the disease.

Key words: hydatid cyst, surgical treatment, albendazole

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Introduction

Cystic echinococcosis, due to the development of larval stage of metacestode Echinococcus granulosus, is common in many parts of the world, including Balkan region and Central and eastern Europe. In spite of the incomplete notification of the cases, Romania is considered highly endemic territory. The disease is more common in pastoral regions, in geographic areas where the transhumance is common, but the possible "urbanization" of the disease is present in urban areas where the stray dogs are common. The disease is salient for many years, but, when complications occurs it become an emergency. Early diagnosis and appropriate treatment are important, saving the life of the patients. CE treatment should be chosen according to several factors related to the cyst and to the host as well.

According to WHO recommendations and other authors (1,2,3,4,5,6), regarding the medical attitude and therapeutic strategy in CE, the appropriate decision should take into account one of the following methods, evaluating carefully the indications, contraindications, risks and limits for the patient's benefit:

- Surgery;
- PAIR and other mini invasive techniques;
- Medical treatment;
- Watch and wait.

During the last period, the "watch and wait" approach has been adopted (7).

Surgical methods

The success of the surgical treatment, followed by the lowest recurrence rate, depends on:

a) Surgical technique: radical – complete removal of the cyst (segmentectomy, lobectomy) or conservative – sterilization and evacuation of the cyst contents, including membranes. It should be reserved for complicated (rupture, infection) and refractory to the medical treatment, or PAIR cases (3,4).

b) Using the best protoscolicidal agent (effective and safe): 70-95% ethanol, 15-20% hypertonic saline, 5% cetrimide solution (1). Other authors (8) evaluated different agents able to melt hydatid cyst membranes without harming the host tissue, but the results are under discussion (9).

c) Host reactivity to the presence of the parasite: it was demonstrated that eosinophyl cationic protein (ECP) can damage protoscolices and prevent secondary hydatidosis (10).

d) Using preoperative medication:
   - Albendazole is able to destroy the protoscolices and the germinal layer as well (11): using albendazole 10 mg/kilo/day for four days prior surgery (7), protoscolices viability remains about 60% (12), but the results can be improved if administration is prolonged, up to one month (13,14). Cyst viability estimated by measuring the internal cyst pressure is much lower in patients receiving preoperative albendazole for 3 weeks (15). Nevertheless, albendazole efficacy is better correlated with the duration of the therapy, than with the serum or cyst levels achieved (16).
   - When albendazole is used in combination with praziquantel, which has a protoscolicidal activity (17,18,19) the bioavailability of albendazole is increased 4,5 fold and intracystic level of albendazole sulphoxide, albendazole's active metabolite, shows a 3 fold better cystic concentration than in sera (17). However, intracystic concentration of albendazole is also related to the parasitic strain and age of the cyst, young cysts allowing a better penetration of the drug.
   - Albendazole absorption depends on duration of treatment and pharmacokinetic of the drug. Better absorption is influenced by: (i) fatty meals, up to 4-9 fold (20); (ii) co-administration with grapefruit juice meal can increase its bioavailability up to 3,2 fold (5, 6,21); (iii) cyclodextrin associated to albendazole (22), or (iiii) liposomized forms (23,24). A perspective could be the association of albendazole with propolis (25).

Surgical procedures are indicated for the following situations (4):

a) Large cysts, type CE2-CE3b, with multiple daughter cysts;
b) Single liver cysts, superficially located, that may rupture spontaneously, or, as the result of trauma, when percutaneous treatment is not available;
c) Infected cysts, when percutaneous treatment is not available;
d) Cysts communicating with the biliary tree, as alternative to percutaneous treatment;
e) Cysts exerting pressure on adjacent vital organs.

Contraindications for surgery:

a) In patients to whom general contraindications for surgery apply;
b) Inactive asymptomatic cysts;
c) Difficult to access cysts,;
d) Very small cysts.

Surgical treatment of hepatic hydatidosis

Surgical treatment of hepatic hydatidosis has the following objectives: the hepatic time (represented by removal of the cyst followed by treatment of the residual cavity) and biliary time (represented by treatment of biliary complications) (26).

Hepatic time consists of one of the following surgical interventions:

a) Radical operations:
   - regulated hepatectomy;
   - total (ideal) pericystectomy;

b) Conservative operations (they remove the parasitic cyst, but leave back a remnant cavity), presuming the following sequence of therapeutic gestures:
   - neutralization of the parasite;
   - removal of the parasite;
   - treatment of the remnant hepatic cavity (pericystic attitude): it represents the delicate moment of the operation, almost 25% of the reinterventions after operated hepatic hydatid cyst being due to complications of the remnant cavity (external biliary fistula, subphrenic abscess, hepatic abscess, choleperitoneum etc); it is using one of the following conservative surgical techniques:
     - external drainage of the remnant cavity;
     - partial pericystectomy (Lagrot);
   - pericystic digestive anastomosis: it is reserved for marginal cysts situated in anterior hepatic segments in patients who could not support an radical more ample intervention; it is done with stomach or jejunum (on Y type Roux loop or Ω loop).

Biliary time: if there are no clinical or echographic signs of a hydatid biliary obstacle in the choledochus, the surgical intervention assumes no other biliary gestures excepting for cholecystectomy which is by principle done regarding the vesicle pathology frequently associated (90% of the cysts are communicating with the biliary tree). One recommends consecutive transcystic cholangiography with goal to make evidence of eventual biliary-cystic fistula and visualisation of the status of the extrahepatic biliary channels. If there are any evident signs of choledochus involvement (jaundice, angiocholitis, acute cholecystitis), biliary time is continued with choledochus dislodgement (choledochotomy completed by instrumental gestures or even choledochoscopy to make sure about oddian status) and reestablishment of a good biliodigestive flow (external biliary drainage of Kehr type, oddian sphincterotomy or biliodigestive anastomosis). Digestive endoscopy can solve by mean of endoscopic sphincterotomy proceeded 8-10 days later after operation the problem of the significant biliary drainage of the remnant cavity.

Medical treatment

Albendazole used before and after surgery, or only after surgery seems to be efficient, as the appearance of the recurrences is absent (27), or near to 0. Pre-operative therapy, applied in order to decrease protoscolices viability, intracystic pressure and to facilitate the removal of the cyst, should begin at least four days before surgery (1,5,6,28,29) and has to be continued for three or more months after surgery (30).

In liver hydatidosis it is advisable to initiate the treatment one month before surgery (31) and it should continue between two to six months or more after surgery (32), according to the surgical procedure (radical procedures are followed by fewer relapses and complications), to eventual cyst rupture (33), when antiparasitic medication is mandatory, being more important than the scolicidal agent in terms of prognosis (34), or until the serology become negative (35). Longer peri-operative administration, for three months is also recommended (36) and should be continued one month or more after surgery, according to the viability of protoscolices. Used peri- and post-operative, albendazole is also very good in children (37), the response being better than in adults (38).

Lung hydatidosis, more common in children than in adults (39) also requires albendazole therapy, mostly post surgery (40, 41), as it is considered that long-term preoperative treatment increases the number of complications, mostly perforations. More than that, some authors consider useless the medical treatment (42), being recommended only for cysts less than 6 cm diameter (43) and for disseminated infections, even if the pleural complications occur (44). It seems that in lung cystic echinococcosis, albendazole is accelerating the rupture of the cyst.

In cardiac hydatidosis, a quite rare condition, albendazole associated to surgery, used for several months, is also followed by very good results (45,46) and is also useful, mostly in case of intracardiac rupture of the cyst (47).

Regarding kidney hydatidosis some studies recommend medical treatment pre-and post surgery (48) in order to avoid the spillage of protoscolices, while other authors do not mention this alternative in their papers (49). The integrity of the cyst and the type of surgery (radical or conservative) as well, will indicate the opportunity and duration of the treatment.

Cerebral and spinal hydatidosis (50) requires concomitant and post surgical albendazole for six months, up to 1 year, but some authors sustain controversial results (51).

To cure muscle hydatidosis, albendazole should start 1 month before and to be continued up to 1 year post surgery (52), or its efficacy can be increased adding praziquantel.

Laparoscopic surgery is an alternative to opened surgery, useful even in central and posterior cysts, or infected cysts, followed by low complications and recurrence rate (5,6,53). Albendazole prophylaxis is recommended at least 2-4 weeks or more than 2 months before surgery (54) and should continue for 1 month, up to six, or more, in case of cystic complications (rupture). The procedure was applied successfully in Venezuela, in echinococcosis due to E. vogeli.

Our study

According to our experience, in surgical cases albendazole 10-15 mg/kilo should be recommended differentiated, according to the location and cyst's characteristics. Association with fatty meals and silimarine is advisable. During the follow up a strict hematological, biochemical, serological and imagery monitorization is required. When radical procedures are applied, the duration of the treatment can be shortened; when conservative procedures are applied, according to the local situation of the cyst (complications), the treatment can be prolonged. The mean follow up period is 5 years.

Liver cysts:

- Intact, viable, serologically confirmed, Albendazole should start at least one month before surgery, administered including the day of the surgical intervention, 4 hours prior surgery, followed by 2-3 months continuously post-surgery; treatment can be prolonged with 1-2 months, if the cyst contains viable protoscolices at the examination and a certain resistance to albendazole is suspected. Re-administration of albendazole should start as soon as possible during the post-operative period.
- Complicated, rupted/infected cysts, when surgical intervention is mandatory, urgently, albendazole should be administrated at least 4-7 days before surgery, including the day of intervention, and continued for up to six months post surgery, under hematological, biochemical, serological and imagery surveillance.
- Intact cysts, serologically negative (ELISA, HA and WB confirmation), albendazole should start 1 week before surgery, in the same dosage and continued post surgery, if the parasitic origin of the cyst is confirmed during surgery, usually for 2-3 months in conservative surgical procedures and prolonged if necessary (if complications occurred). During the follow up, in certain cases, the serology, initial negative, can become positive post

surgery, so that the serological monitorization is necessary for 3-5 years. In case of total removal of an intact cyst, antiparasitic medication should be restricted to the preoperative period.

Lung cysts:

- Large cysts, with positive serology, requires albendazole before surgery for at least 1 week, and continued for 1-3 months according to the cyst intra-operative status (2-4 weeks if the cyst is intact)
- Rupted cysts, neglected hydatid cysts, with positive serology, albendazole should be recommended during the follow up for up to 6 months, or even more, in case of any residual small cyst, under a strict serological (if positive) and imagery monitorizing.
- Intact cysts, with negative serology (screening and confirmation tests), when the diagnosis of CE remains under discussion, can start albendazole therapy 4 days before, during the day of intervention and continued for 1-3 months according to the cyst status during the surgical intervention.

Cysts with other locations:

- Albendazole at least one month before surgery and continued for 3-6 months post surgery, according to the situation of the cyst during the surgical intervention
- In case of unexpected situations, when the diagnosis of CE is established during surgery, albendazole should start as soon as possible during the postoperative period, and continued for 3-6 months, according to the cyst's status during the surgery (intact, rupted, infected, etc.).

In children:

- The same regimes of albendazole are recommended and the same attitude, but the results are better as the tolerance and the cure rate are better in children than in adults.

In endemic areas, developing countries, where cases with previous surgical interventions are followed by chronic hepatitis consequent to blood transfusion is quite common and patients can not receive albendazole in the recommended dosage, or as long as necessary, praziquantel either alone, or in association with albendazole, reduced dosage, can be an alternative. Praziquantel 25-40 mg/kylo/day, divided into three equal doses, in cycles of 14-30 days, 1 week before surgery, during and post surgery for 1-3 months. In association with albendazole, it allows to reduce its dosage and duration; finally the total quantity of albendazole intake is reduced.

PAIR (Punction-Aspiration-Injection-Respiration) and related minimally invasive methods

Innitially applied by a Tunisian Group in 1986, PAIR (using either 95% alcohol, 30% hypertonic solution or 0,5% cetrimide solution), rapidly imposed as a new, save, successful, non-invasive and with very few complications technique. Moghadam (55) in his systematic review emphasizes the superiority of PAIR compared with opened surgery, for uncomplicated cysts. Different regimes of albendazole are used by different authors, so that the harmonizing of the protocols seems to be necessary. Albendazole is recommended to be associated to the punctures as follows: (i) at least 4 hours before puncture and to be continue for 2-4 weeks (3,56,57), (ii) one week before puncture, followed by 3-4 weeks after (1,5,58); (iii) 3 days before, followed by 3-8 weeks after the procedure in uncomplicated cases and up to 3-6 months in complicated cases (53,59), (iv) 10 days before and 2 months after (60), (v) 2 days before and 2 months after (61), or (vi) 14-20 days before puncture, followed by 2 months or more (62).

According to Khuroo (60) and Kabaaliolu (63), PAIR plus albendazole is by far superior to albendazole alone or opened surgery in terms of complications, recurrences, hospitalization costs. It is recommended either as initial treatment option or in patients whose illness fails to respond to drug therapy alone (7), but in intact, univesicular cysts, or cysts with few, large and accessible daughter cysts over 5cm diameter and multiple cysts in different liver segments (64). PAIR can be associated to laparoscopic interventions for concomitant diseases (65). Vuitton (66) is also mentioning the significant differences between various regimes of albendazole therapy and emphasizes the necessity of harmonizing the protocols. Aribas (67) recommends medical therapy only after surgery, for an unspecified period, Chalupa (68), only before PAIR, discontinued, for three months, Genetzakis (69), only 28 days before procedure and Gulalp (70), six months only after surgery. So that, percutaneous treatment is the method of choice, with albendazole at least one month post-intervention, in CE I, CE II, some CE III, while ERCP in the preoperative treatment and radical surgical procedures, when possible, remain to complete the treatment (71) because surgery remains for symptomatic patients, who are not good candidates for percutaneous therapy (72).

The technique is also useful and safe in children (73,74) recommended pre- and post- intervention (one week before puncture and two months after) and for other cystic locations: pancreas (75), kidney (67,73), lung and pleural locations (76, 77), soft tissues (78) or in pregnancy (79).

An alternative to PAIR, double puncture-aspiration-injection (D-PA), without reaspiration, initiated by Giorgio et al in 1992 is applied with good results by Ormeci (80).

Another therapeutic approach consists in direct intracystic injection, on experimental models, of albendazole sulfoxide as scolicidal agent (81) or benzimidazole derivates (82), followed by human use of albendazole direct intracystic injection (10% albendazole with 20% hypertonic saline), US-guided, covered with systemic albendazole, starting 48 hours before intervention and continuing 2 months after (83). Polat (84) is using an albendazole solution of 1,7 μ/ml intracystic, associated with systemic albendazole, starting between 2-28 days before intervention and continuing for 5 months.

Indications of PAIR (4):

- inoperable patients;
- those who refuse surgery;
- relapses after surgery;
- failure to the medical treatment with benzimidazoles carbamates;
- is highly recommended in CE1 and CE3a cysts, or in cysts with the size smaller than 5 cm;
- pregnant woman;

- children less than 3 years old.

Counter indications of PAIR:

- CE2 and CE3b
- CE4 and CE5
- Lung cysts;
- When biliary fistula exists, the instillation of protoscolicidal agent is forbidden.

The best protoscolicidal agents are: 20% NaCl solution and 95% ethanol.

PEVAC: The method, variant of PAIR (PEVAC - percutaneous evacuation of cyst content) is recommended in multivesicular and/or infected cysts, or in cases with spontaneous rupture of the cyst (cysto-biliary fistula). It allows the evacuation of cyst's content, using a large bore catheter, under albendazole protection, 10mg/kg/day, before (median of 11 weeks) and six months after intervention (85).

When percutaneous treatment (PT) and minimally invasive procedures are applied, Albendazole is recommended in the same schedule, before and after intervention. Periodically hematological and biochemical evaluation completed with imagery and serology (according to the case), are required.

- For abdominal cysts, treatment should start 10-30 days before the procedure, no less than 4 days and to be continued for 2-4 months after. The day of the procedure Albendazole has to be administered 4 hours before the procedure, in order to get the optimal serum concentration. The minimum follow up period is 4-5 years.
- When PEVAC is required, a longer administration of albendazole is advisable (pre-interventional, about 2-3 months and post-interventional, 6 months).
- In children, albendazole is recommended in the same dosage, starting 14-30 days before and to be continued 1-3 months after.

In cases with limited tolerance to albendazole, or counter indications for the drug, praziquantel in the same regimes as it was recommended for surgery can be useful.

Conclusion

The follow up of CE should be confined to a parasitologist or infection diseases specialist, with experience in the field, able to adapt the appropriate treatment for each case. More than that, more comprehensive and accurate data regarding the evolution, treatment options, results, prognosis, epidemiologic aspects and surveillance are available from each country, having into account that in many countries CE is not a reportable disease. In each country, some reffered specialized centres (where parasitologists, biologists, surgeons, imaging specialists, etc are working together and cooperate) for the patient's diagnosis, reatment. The correct notification of all the cases, the surveillance of the disease and follow up of the patients are necessary.

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