Vol. 15, No. 2
ORIGINAL PAPER

HEC No. 1428

ISSN No. 1681-5491

MEDICINE

MEDICAL CHANNEL
APRIL - JUNE 2009

"TREATMENT OF AMEBIC LIVER ABSCESS WITH METRONIDAZOLE ALONE OR IN COMBINATION WITH ULTRASOUND GUIDED ASPIRATION, A COMPARATIVE, PROSPECTIVE & RANDOMIZED STUDY"

1. **HAJI KHAN KHOHARO**
MBBS, FCPS
2. **SHUAIB ANSARI**
MBBS, FCPS
3. **SHAHNAWAZ JAMALI**
MBBS, M.Phil
4. **FATIMA QURESHI**
MBBS

1. ***Assistant Professor***
Department of Medicine.
MUHAMMAD MEDICAL COLLEGE HOSPITAL
MIRPURKHAS
2. ***Senior Registrar***
DEPARTMENT OF MEDICINE
LIAQUAT UNIVERSITY HOSPITAL
HYD/ JAMSHORO
3. ***Assistant Professor***
Department of Pharmacolgy
HAMDARD UNIVERSITY,
KARACHI
4. ***Medical officer***
MUHAMMAD MEDICAL COLLEGE HOSPITAL
MIRPURKHAS

Address for Correspondence
DR HAJI KHAN KHOHARO
MBBS, FCPS
Assistant Professor
Department of Medicine.
MUHAMMAD MEDICAL COLLEGE HOSPITAL MIRPURKHAS
Tel: 0321-3010577
022-2908972
E-mail: drhajikhan786@yahoo.com

ABSTRACT (SUMMARY)

AIM: *Treatment of amoebic liver abscess (ALA) with metronidazole alone or in combination with ultrasound-guided needle aspiration, a comparative, prospective and randomized study*
SUBJECTS & METHODS: *A total of 50 patients with ALA were enrolled and randomized into two groups. Twenty five patients randomized into group A were treated with metronidazole, while 25 patients of group B received metronidazole with ultrasound-guided needle aspiration. Bacterial abscesses were excluded by microbiological examination of abscess fluid in all patients.*
RESULTS: *During the first 3 days only one patient of group A while ten patients of group B showed an improvement in pain, fever, liver tenderness, which was significantly faster in the aspiration group ($p < 0.001$), whilst other parameters also showed gross differences between the two groups. On day 30, all patients of group A showed a decrease in the size of abscess, & showed reducing symptoms; while group B patients were normal at this time, having no problem.*
CONCLUSIONS: *It is concluded that both regimens are equally effective & ALA of as much as =10 cm in size may be treated conservatively with metronidazole therapy alone.*

KEYWORDS: Amebic liver abscess Metronidazole Ultrasound-guided aspiration

INTRODUCTION

Amebic liver abscess (ALA) is 10 times as common in men as in women and is a rare disease in children[1]. Approximately 80 percent of patients with ALA present with symptoms that develop relatively quickly (typically within two to four weeks), including fever, cough, and a constant, dull, aching abdominal pain in the right upper quadrant or epigastrium. Involvement of the diaphragmatic surface of the liver may lead to right-sided pleural pain or referred shoulder pain. Associated gastrointestinal symptoms, which occur in 10 to 35 percent of patients, include nausea, vomiting, abdominal cramping, abdominal distention, diarrhea, and constipation. Hepatomegaly with point tenderness over the liver, below the ribs, or in the intercostals spaces is a typical finding**.** ALA develops in less than 1% of patients infected with E histolytica, but this still represents a large number of patients[2]. The cornerstones of ALA treatment are nitroimidazole antibiotics such as metronidazole or tinidazole. In combination with drug treatment, three invasive therapeutic procedures, ultrasound guided needle aspiration; percutaneous catheter drainage and open surgical abscess drainage are effective. The treatment of ALA with or without aspiration in addition to amoebicidal drugs is discussed controversially and therefore the therapeutic approach differs widely. Some authors advocate rare use of aspiration, indicating that less than 10% of all abscesses require this additional invasive treatment. Others report good results with needle aspiration in addition to amoebicidal drugs and recommend treating about 80% of amoebic liver abscesses by this approach [3]. There are only a few randomized, prospective studies comparing metronidazole treatment alone with the combined treatment of needle or catheter aspiration and amoebicidal drugs. Sharma and co-workers performed such a study in Delhi (India) with 39 ALA patients and did not find any difference between the two groups[4]. However, in this study, sizes of abscesses were significantly smaller in the aspiration group. In a similar study performed in Varanasi (India), patients in the combined treatment group became afebrile more rapidly and pain and abdominal tenderness subsided earlier, whereas biochemical parameters improved similarly in both groups[5]. In a third study comprising 41 patients, which were performed in a non-endemic setting; no significant differences were reported [6]. Thus, further studies are required to assess which therapeutic regimen is better

suited for the treatment of amoebic liver abscess. We report on a prospective and randomized study comparing metronidazole treatment alone or with the combined treatment of metronidazole and ultrasound-guided needle aspiration.

MATERIALS & METHODS

This study was a prospective and randomized trial, performed at Department of Medicine, Muhammad Medical College Hospital Mirpurkhas & Liaquat University Hospital Hyderabad/Jamshoro from July 2007 and May 2008. A total of 50 patients with ALA were enrolled and randomized into two groups. Patients randomized into group A were treated with metronidazole, 30 mg/kg daily in three divided doses for 10 days. A puncture with a fine needle (0.95 mm × 120 mm) was performed in order to obtain a small amount of abscess fluid (0.5–1.0 ml) for microbiological examination. Abscess fluids were examined for aerobic and anaerobic bacteria by inoculation on culture media. Patients in group A were closely monitored for first 5 days for any aggravation of the symptoms, if aggravation observed they were excluded from the study. Patients randomized into group B received metronidazole treatment as subjects in group A but, in addition, as much abscess fluid as possible was removed by ultrasound-guided needle aspiration (needle size: 1.5–2 mm × 120 mm) within the first 24 h after hospital admission. On the day of admission, body temperature, pain and tenderness in the right upper abdomen were documented as part of a thorough clinical examination. Blood examinations were performed for white blood cells (WBC), hemoglobin, erythrocyte sedimentation rate (ESR). Chest X-ray was done in all patients at the time of admission. Sonographic findings of focal round or oval hypoechoic liver lesions were noted. Ultrasound examinations were performed using a 4.5 MH sector transducer and the abscess diameter was measured in two planes and abscess volume was estimated using the formula: $4/3\partial\ (a/2 \times b/2)^3$. Patients included in the study had to fulfill the following criteria: abscess with a diameter of >6 cm but = 10 cm; abscess localization in the right liver lobe, except the caudate lobe; age >18 years. Exclusion criteria comprised of: treatment with amoebicidal drugs before hospital admission, pregnancy, or presence of aerobic or anaerobic bacteria in the abscess fluid. Patients were followed as inpatients during therapy for 10 days and re-examined 20 days after discharge (day 30). Body temperature, pain and tenderness of the right upper abdomen were followed daily from day 1 to 10 and on day 30. ESR, WBC and hemoglobin were measured on day 1,

Table I.
General clinical data, signs & symptoms,

Parameter	Group A (*n* = 25)	Group B (*n* = 25)
Gender	Male 15 (60%) Male 16 (64%)	Females10 (40%) Females 9 (36%)
Age (years)	37 (22–56)*	38.5 (23-57)*
Pain in right upper abdomen	23 (92%)	24 (96%)
Fever (°C)†	38.0 (0.8)†	37.9 (0.7)†
Hepatomegaly	7(28%)	11(44%)
Liver tenderness	22 (88%)	23 (92%)
Weight loss	16(64%)	15(60%)
Anorexia	20(80%)	21(84%)
Diarrhea	3(12%)	4(16%)
Jaundice	2(8%)	1(4%)

* Median (range).

Table II.
Laboratory results in the two treatment groups at admission

Parameter	Group A (*n* = 25)	Group B (*n* = 25)
ESR (mm after 1 h)	32 (19)†	28 (23)†
WBC (number/μl)	18132 (4389)†	19865 (5136)†
Hemoglobin (g/dl)	11.6	12.9
Abscess volume (ccm)	300(650)†	330 (750)†

* Median (range).
† Mean value (standard deviation).

Table III:
Follow-up and comparison of right upper abdominal pain, liver tenderness and abscess volume

	Pain in right upper abdomen			Liver tenderness			Abscess volume		
	No. (%)			No. (%)			Millilitre		
	Group A	Group B	*P*-value*	Group A	Group B	*P*-value*	Group A	Group B	*P*-value†
Day 1	23 (92%)	24 (96%)	0.05	20 (80%)	23 (92%)	0.05	650	750	
Day 3	19 (76%)	10 (40%)	0.05	19 (76%)	9 (36%)	0.05	650	50	
Day 5	17 (68%)	8 (32%)	0.05	17 (68%)	4 (16%)	0.05	500	30	0.05
Day 10	15 (60%)	0 (0%)	0.05	10 (40%)	0 (0%)	0.05	500	0	
Day 30	9 (36%)	0 (0%)	0.05	7 (28%)	0 (0%)	0.05	300	0	

* *P*-values were determined by Fisher's exact test.
† *P*-value was determined by Mann–Whitney *U*-test.
P-values <0.05 were considered significant.

10 and 30. Written consent was obtained from all subjects, and clearance was obtained from the ethics committee

Statistical evaluation

The Mann–Whitney *U*-test was used to compare differences in body temperature, WBC, ESR, hemoglobin, and abscess size. Fisher's exact test was used to compare pain and liver tenderness rates during follow-up on day 3, 5, 10 and 30. p-values <0.05 were considered significant.

RESULTS

Fifty patients were included in this study according to the inclusion criteria. Twenty five patients, randomized in group A, were treated by oral application of metronidazole for 10 days, whereas the 25 patients, randomized in group B, were punctured with evacuation of abscess fluid, in addition to a 10 days metronidazole therapy. The male/female ratio was 1.5:1 in group A and 1.6:1 in group B. Despite randomization, the median age was significantly equal in both groups. The most frequent clinical findings on the day of admission were pain in right upper abdomen (96%), liver tenderness (92%), and fever (70%) Elevated values for ESR, and leukocyte counts were present in 100% & 97% of the patients respectively. In addition, 45% of the study subjects had reduced hemoglobin values of less than 12 g/dl. There were no differences for the various clinical findings and laboratory parameters between the two groups. Ultrasound examinations revealed a total of 66 abscesses in the 60 patients examined, as there were two patients in group A and four patients in group B with two abscesses. The mean abscess volume was 650ml and 750ml respectively, corresponding to a mean abscess diameter of =10cm in both groups. Chest X-ray abnormalities, seen on average in 7 (28%), included an elevated hemidiaphragm in all patients 7 (28%), right pleural effusion in 5 (20%) and atelectasis in 2 (8%). Follow-up after initiation of therapy revealed normalization of body temperature in all patients of group B within 5 days, & 2/3 of patients belonging to treatment group A were running low grade fever. Likewise, abdominal pain disappeared in 32% of group B patients within 5 days, & 2/3 of patients belonging to treatment group A were having mild abdominal pain. Follow-up of pain & tenderness revealed minor significant difference between the two groups. During the first 3 days only one patient from group A while ten patients from group B reported disappearance of pain during liver palpation (p< 0.001). On day 30, mild pain & liver tenderness in group A were observed in 9 (36%), & 7(28%) patients respectively, and a mean abscess volume of 300ml, while group B patients having no such findings at this day. The laboratory parameters improved in both groups, but group A patients exhibited some mild abnormalities in laboratory values which were much better compared with day 1. This reveals minor differences between the two treatment groups. The mean quantity of liver fluid that was aspirated in group B patients comprised of 200–400 ml resulting in an immediate decrease of the abscess volumes by about 50%, as determined by ultrasound on day 2. In contrast, there was no reduction in the size of abscesses in group A patients at this time point. Statistical evaluation revealed significant difference in abscess resolution over the whole observation in the aspiration group from day 1 to day 30 (p< 0.001). On day 30, all of subjects of group A revealed decrease in the size of abscess. Mortality was not observed in our study.

Table IV:
Follow-up and comparison of laboratory results

		Day 1	Day 30	*P*-value*
ESR (mm 1 h)	Group A	29 (20)†	20 (15)	0.05
	Group B	30 (21)	6 (4)	
WBC (number/μl)	Group A	14 132	12613	1.000
	Group B	14 865	6800	
Hemoglobin (g/dl)	Group A	11.3 (1.5)	13.0 (1.6)	0.092
	Group B	12.5 (1.4)	13(0.9)	
Abscess volume	Group A	650	300	0.014
	Group B	750	0	

* *P*-values were determined by Mann–Whitney *U*-test.
† Mean value (standard deviation).

DISCUSSION

To compare the clinical outcome of two most widely used regimens for the treatment of ALA; a prospective and randomized study was performed. This comprised ALA patients treated either only with metronidazole or with a combination of metronidazole and abscess puncture, in order to initially remove most of the abscess fluid. At enrollment there were no differences between the two treatment groups with regard to laboratory or clinical findings as well as gender distribution. The patients of group A (non-aspiration) showed much improvement during the observation period, & on day 30th having mild symptoms. Liver tenderness disappeared significantly faster in the aspiration group B during the first 3 days (p < 0.001). Based on the results of this study, it is proved that both therapeutic regimens are equally effective.. No major complication occurred in non-aspiration group. Resolution patterns for the various laboratory and clinical parameters revealed no major differences, except for the liver pain & tenderness which disappeared significantly faster in the aspiration group (p < 0.001). However, benefit from pain relief is likely not to be sufficient to justify the needle aspiration, because of possible fatal complication[7]. The results presented here are in full agreement with two studies performed in Delhi, India by Sharma *et al.*[4] and Los Angeles, USA by Van Allan *et al.* [6] , both of which concluded to recommend drug treatment only. One study performed in Varanasi (India), recommended aspiration of abscess fluid[5]. However, this recommendation was based solely on differences in normalization of body temperature and improvement of pain and tenderness in the right upper abdomen during the first 4 days of treatment. The study conducted by Blessman et al [3] also recommeded to treat at least those ALA with a diameter if =10cm conservatively with the metronidazole as the first line drug. The effect of metronidazole on ALA is striking, as body temperature returned to normal and pain disappeared in most of patients within 5–6 days. This fast improvement of clinical symptoms after initiation of nitroimidazole therapy was also observed in other studies of Sharma et al [8], Weinke et al [9], Ralls et al [10] & Guerin et al [11]. Thus the results presented here confirm that puncture and removal of abscess fluid may not be indicated for those ALA having diameter of =10cm located in the right liver lobe, as they respond very well with

metronidazole therapy.

CONCLUSIONS

It is concluded that both regimens are equally effective & ALA of as much as =10 cm in size may be treated conservatively with metronidazole therapy alone.

REFRENCES:

1. Haque R, Ali IKM, Akther S, Petri WA Jr. Comparison of PCR, isoenzyme analysis, and antigen detection for diagnosis of Entamoeba histolytica infection. J Clin Microbiol 1998; 36:449-452.
2. Haque R, Huston CD, Hughes M, Houpt E, Petri AW. Amebiasis. N Engl J Med 2003; 348:1565-1573.
3. Blessmann J, Binh HD, Hung DM, Tannich E, Burchard G. Treatment of amoebic liver abscess with metronidazole alone or in combination with ultrasound-guided needle aspiration: a comparative, prospective and randomized study. Tropical medicine & International health 2003; 8 Issue 11:1030-1034.
4. Sharma MP, Rai PR, Acharya SK, Samant Ray JC & Tandon BN. Needle aspiration of amoebic liver abscess. British Medical Journal1989; 299: 1308– 1309.
5. Tandom A, Jain AK, Dixit VK, Agarwal AK & Gupta JP. Needle aspiration in large amoebic liver abscess. Tropical Gastroenterology1997; 18: 19– 21.
6. Van Allan RJ, Katz MD, Johnson MD, Laine LA, Liu Y & Ralls PW. Uncomplicated amebic liver abscess: prospective evaluation of therapeutic aspiration. Radiology 1992; 183: 827– 830.
7. Piccinino F, Sagnelli E, Pasquale G & Giusti G. Complications following percutaneous liver biopsy. A multicentre retrospective study on 68,276 biopsies. Journal of Hepatology1986; 2: 165– 173.
8. Sharma M P & Abuja V. Management of amebic and pyogenic liver abscess. Indian Journal of Gastroenterology 2001; 20(Suppl. 1): C33– C36.
9. Weinke T, Grobusch MP & Güthoff W. Amebic liver abscess – rare need for percutaneous treatment modalities. European Journal of Medical Research 2002; 7: 25– 29.
10. Ralls PW, Barnes PF, Johnson MB, De Cock KM, Randall Radin D & Halls J (1987). Medical treatment of hepatic amebic abscess: rare need for percutaneous drainage. Radiology 165, 805– 807. Medline, ISI, Chemport
11. Guérin B, L'Her P, Lenegre-Thourin I et al. (1995) Aspects cliniques et therapeutiques de l'amibiase hepatique au Cambodge. Medicine Tropicale 55, 37– 40.Medline, Chemport.