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# TO ASSESS & COMPARE CLINICAL EFFICACY AND TOLERABILITY OF NITAZOXANIDE AND METRONIDAZOLE IN PATIENTS WITH UNCOMPLICATED AMOEBIC LIVER ABSCESS: AN OBSERVATIONAL STUDY.

Pharmacology

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## ABSTRACT

**Introduction:** Amoebiasis is a widespread parasitic disease caused by Entamoeba histolytica. Amebic liver abscess (ALA) is the most common manifestation of extra intestinal disease.

Present study was done to compare the efficacy of nitazoxanide with metronidazole in patients with uncomplicated ALA in tertiary care hospital.

**Methodology:** In this prospective, observational study; 60 patients of ALA (> 12 years) were included and randomized into two treatment groups for 10 days therapy. Detailed history, clinical examination, U.S.G. and serology were done in all patients at day1, 5, 10 and 40. Clinical improvement and sonographic assessments were done and compared with baseline values. Descriptive statistics were used to summarize the data.

**Results:** ALA was more common in males (21-40 years) and in low socioeconomic status. Most common symptoms were abdomen pain and fever and signs were tenderness, hepatomegaly and jaundice. After day 40; mean volume of liver abscess reduced from 233.53 ml to 81.03 ml in group A & 214.27 ml to 97.22 ml in group B. After 6 month cavity resolved in all patients.

**Conclusion:** Both groups achieved the end points of pain free and afbrile with equal rapidity. Total adverse events were less in group A versus group B (7 & 50). There was significant difference in metallic taste (0&19), nausea (1&18) and headache (1&6) in group A&B respectively.

In conclusion both nitazoxanide & metronidazole were similar in efficacy and safety in treating small ALA. Nitazoxanide is having better patient tolerability.

## KEYWORDS

### Introduction

Amoebiasis is a widespread parasitic disease caused by Entamoeba histolytica. Entamoeba histolytica infection presents in a variety of forms; 90% of infections presents asymptomatic colonisation of intestinal tract. Symptomatic disease ranges from transient colitis to fulminant colitis with an array of manifestations that may include dysentery, toxic megacolon and peritonitis to extra intestinal disease. Liver abscess or hepatic amoebiasis is the most common manifestation of extra intestinal disease. ALA is an inflammatory space- occupying lesion of the liver caused by Entamoeba histolytica. The incidence of ALA has been reported to vary between 3% and 9% of all cases of amoebiasis [1]. In India ALA is endemic [2].

### Pathogenesis [3]

Entamoeba histolytica exists in the trophozoite or cyst form. After oral ingestion the amoebic cyst passes through the gastrointestinal tract and becomes a trophozoite in the colon where it invades the mucosa by the release of protease, degrading extracellular matrix components. Subsequent lateral spread with overlying epithelium results in typical flask shaped ulcer. Trophozoites gain access to liver through entry into the portal venous system and rarely by direct extension.

Liver is usually enlarged. The common site involved is postero-superior surface of the right lobe of the liver. Characteristic appearance of liver abscess is roughly circular abscess containing a large necrotic center, resembling anchovy souce paste that is surrounded by a narrow ring of few inflammatory cells, fibrosis and occasionally few amoebic trophozoites.

Most patients present with an acute illness and duration of symptoms less than 2 weeks. The main presenting features include abdominal pain, fever, and anorexia. Tender hepatomegaly was detected in 80% of patients.

Most of amoebic liver abscess presented as solitary, round cavity 80.4% and located to right lobe of liver 85%. Ultrasound is very useful for diagnosis of ALA. The classic appearance is a non-homogeneous, hypoechoic, round or oval mass with well defined borders. Serum antibodies to entamoebae develop only during Entamoeba histolytica infection and are detected in 85-95% of all patients who present with invasive amoebiasis or liver abscess.

### Medical therapy

Symptomatic intestinal or extraintestinal amoebiasis is treated successfully with metronidazole or another nitroimidazole drug followed by luminal amoebicidal such as diloxanide furoate, iodoquinol or paramomycin [4].

Amoebicides effective in both tissues and the intestinal lumen include nitroimidazole derivatives- Metronidazole, Tinidazole, Ornidazole and thiozolyl derivative Nitazoxanide [5].

Single-agent therapy with metronidazole yields excellent results. Metronidazole is the standard treatment for ALA since 1966 when, powell et al [6] first described its efficacy. Other nitroimidazole have also been studied for their efficacy in ALA. Tinidazole [7] and secnidazole [8] have been used for the treatment of ALA. Both these drugs were found to have no advantage over metronidazole with regard to their efficacy, except for a lower dosing schedule and better tolerability required for secnidazole.

Oral or intravenous metronidazole or tinidazole leads to rapid clinical improvement of ALA. The response to anti-amoebic drugs is usually evident within 48-72 hours with the subsidence of toxaemia, abdominal pain, guarding and tenderness in the right hypochondrium. Therapy should be continued for at least 10 days. Relapses have been reported with this duration of therapy and the drug may be administered for up to 3 weeks.

Additionally, metronidazole resistance has been documented in clinical isolates of Giardia intestinalis and Trichomonas vaginalis and has been artificially induced in a laboratory strain of E. Histolytica [9]. Furthermore, transmission of metronidazole-refractory amoebiasis has been reported.

Metronidazole has a black box warning (carcinogenic in rats and mice), problems with drug interaction (warfarin, phenobarbitone, and lithium) and significant side effects like nausea, metallic taste, seizure, antabuse like effects etc. Because of side effects few patients do not tolerate metronidazole [10].

Nitazoxanide, a nitrothiozolyl-salicylamide derivative [11] is a broad

spectrum antimicrobial agent with activity against protozoa (mainly Giardia Lambia and Entamoeba histolytica), nematode, cestoda, trematoda and anaerobic infections [12].

There is no comparative study to test the efficacy, tolerability and adverse effect of nitazoxanide with metronidazole in ALA hence this study was planned.

**AIMS AND OBJECTIVES**

The main objective of the comparative study is to know the efficacy, tolerability and safety profile of nitazoxanide with metronidazole in patients with uncomplicated ALA.

**MATERIAL & METHOD:**

Patients of more than 12 years of age presented with ALA (<500 ml) without comorbid conditions and showing positive serology were included after getting the consent. Patient not fulfilling the inclusion criteria, pregnant and lactating women were excluded. Study was conducted in accordance to GCP guidelines.

**Study design:**

This prospective and comparative study was conducted in a total of 60 patients attending OPD/IPD of Gastroenterology department, JLN Medical College Ajmer after getting approval from the institutional ethical committee (letter no. 729/Acad-III/MCA/2016, dated 5.5.16)

**Methodology**

A detailed history including age sex, socioeconomic status, smoking and alcohol intake, duration and severity of presenting symptoms and previous history of allergy to any study drug was taken. Height and weight were measured. Thorough clinical examination was done.

Stool examination and amoebic serology were done only at baseline to confirm the causative agent. After diagnosis, study patients were randomized into two groups having 30 patients in each group as follows:–

- Group A - Nitazoxanide 500 mg BD orally for 10 days.
- Group B- Metronidazole 800 mg TDS orally for 10 days.

The patients were followed regularly at day 1, 5, 10 and 40. Clinical examination was done on follow up visits. USG was done at baseline and day 10, 40 and 180 to assess the radiological status of ALA.

**Study outcome**

The primary outcome measures were clinical improvement in signs (tenderness, hepatomegely, fever) and symptoms (pain abdomen, distension, jaundice, anorexia) from baseline to day 5 and 10. Secondary outcomes parameter was USG resolution of abscess volume from baseline to that of day 10, 40 and 180.

The safety outcomes were adverse events recorded during therapy.

**Statistical analysis**

Sample size of 30 patients in each group was determined. Continuous data were presented as mean ± standard deviation and categorical data was presented as frequency and percentage. Clinical improvement in sign and symptoms (duration and intensity) and resolution of USG abscess volume were compared from baseline and day 5,10 and 40 values and paired 't' test at 5% level of significance. Adverse events were compared using chi square test.

**Results**

Most of the patients of liver abscess were in the age group of 21-40 years with male predominance (83% in group A and 86% in group B). 86.67% & 90% patients were of average nutrition in group A and group B respectively (Table-1).

All patients were positive for amoebic serology done by ELISA. Clinical response was evident after 3-5 days of therapy.

Mean time for pain relief was 4.1 ± 0.96 days and 4.20 ± 1.0 days for group A and B respectively (p value<0.6936). Mean duration of fever subsidence was 3.93 ± 0.84 days and 3.76 ± 0.64 days in group A and B respectively (P value <0.3826). Hepatomegely subsided with a mean duration of 17.12 ± 8.12 days and 16.05 ± 16.05 days (P value <0.6023) and tenderness disappeared in mean duration of 4.03± 0.89 days and 3.77 ± 0.43 day (P value <0.1449). Abdominal distension disappeared with a mean duration of 5.93 ± 1.54 days and 5.59 ± 1.66 days (P value <0.7148). Jaundice disappeared with a mean duration of 9.5 ± 3.7 days and 11.2 ± 4.49 days in group A and B respectively (P value <0.5627) (Table-2).

Mean volume of liver abscess 233.53 ± 113.04 ml & 214.27 ± 91.05 ml reduced to 173.37 ± 84.91 ml & 196.27 ± 89.44 ml in group A& B respectively at day 10. The reduction in abscess was continued and on day 40 the mean volume further reduced to 81.03 ± 37.47 ml and 91.02 ± 39.51 ml in group A and B respectively. At 6 month cavity resolved completely in both groups (Table-3).

It is evident from table-4 that observed adverse effects were non-serious and did not warrant discontinuation of treatment. Total adverse effects were more with metronidazole as compared to nitazoxanide (50 v/s 7).

With nitazoxanide, yellow urine (10%) was the most common adverse effect followed by nausea (3.33%), abdominal pain (3.33%), headache ( 3.33%) and insomnia (3.33%) whereas in metronidazole group, matallic taste (63.34%) was most common followed by nausea (60%) headache (20%) insomnia (10%) and yellow discoloration of urine (3.33%).

**Discussion:**

ALA is the most common manifestation of extra intestinal disease. If left untreated it may lead to further liver damage and development of compression lesion and perforation in pleural cavity, peritoneum and neighbouring organs. With early diagnosis and therapy, mortality rates from uncomplicated ALA are <1%.

**Demography:** In the present study, out of 60 patients, most of the patients were in age group 21-40. Mean age in group A was 42.67 years. & in group B was 38.77 years.

The cause of increased incidence in adult age group as compare to younger age group is probably because of more active life in adults and more chances of their exposure to infective agents and to predisposing factors like alcohol.

Above results were in accordance with Katzenstein, D et al [13].

Males were predominantly affected. Similar findings were also observed in previous study carried by O.P. Kapoor [14]. The higher incidence in males still unexplained but may be due to heavy alcohol consumption in men, hormonal effect on premenopausal women that may modulate infection and possible protective role of iron deficiency anaemia in menstruating women.

In our study, patients of poor and average nutrition were present in 13.33% and 86.67% in group A & B.

**Clinical efficacy:** Abdominal pain was most common followed by fever (in 96.67% in both groups), abdominal distension (60% v/s 56.67%), loss of appetite (50% v/s 46.67%) jaundice (13.3 v/s 18.6%) and vomiting (10% v/s 6.67%) in both groups respectively. Pain & tenderness is due to the abscess reaching the surface of liver and involving the glisson's capsule, which is supplied by pain fibres.

In some previous studies abdominal pain was reported most common symptom in patients of amoebic liver abscess [15].

Fever was present in 96.67% in both groups with short duration <10 days, it was the second most common presenting symptom after abdominal pain. These findings are similar to Mondragon Sanchez et al 1995 [16].

On systemic examination tenderness in right hypochondrium was present in 100% patients in both groups. Hepatomegaly was present in 83.33 % & 73.33% in group A & B respectively. Spleenomegaly was present in 13.33%& 16.66% patients in group A& B respectively. In the present study jaundice was present in 13.33% & 16.67% patient in group A & group B respectively. Mean time for temperature to settle was 3.80 days & 3.63 days in group A and B respectively which is statistical insignificant (P value 0.5274).

Mean time for pain abdomen to disappear after starting the treatment was 4.10 days & 4.20 days in group A and B respectively. (P value 0.6936 not significant). Mean time for jaundice resolution after

treatment is 9.5 days & 11.20 days in group A & B respectively (P value 0.5627).

Mean time for abdominal distension to disappear after treatment is 5.93 days & 5.59 days in group A and B respectively (P value 0.7148). Mean time for hepatomegaly to disappear after treatment is 17.12 days & 16.05 days in group A & B respectively (P value 0.6023).

Mean time for tenderness to disappear after treatment was 4.03 days & 3.77 days in group A and B respectively (P value 0.1449).

These findings are consistent with Seeto RK, et al [17]. Mean time for pain abdomen to disappear was 4.24 ± 1.88 & 5.22 ± 2.31 days. Temperature to settle 5.20 ± 3.80, 5.2 3 ± 3.17 days and time to disappearance of tenderness was 7.96 ± 4.23 days and 7.94 ± 3.19 days. Rossignol et al found similar clinical response with nitazoxanide in patients of ALA[18].

Nitazoxanide is an effective amoebicidal drug for amoebic liver abscess and invasive amoebiasis but comparative trials with metronidazole are lacking.

Nitazoxanide is used for giardiasis and cryptosporidiosis. In a study, Oritz JJ et al compared nitazoxanide with metronidazol for giardiasis [19]. Both drugs were found equally effective but nitazoxanide showed better tolerability.

When adverse effect were compared in both groups there was significant difference in metallic taste (0 v/s 19), nausea (1 v/s 18), headache (1 v/s 6), in nitazoxanide & metranidazole group respectively, difference was statistically significant. There was no significant difference in adverse effects like insomania (1 v/s 3), abdominal Pain (1v/s 2) & yellow urine (3v/s 2). All the adverse effects were nonserious and therapy was not discontinued. Adverse effects due to metronidazole found in the study were consistent with adverse effects reported in previous studies.

In a study by Abaza H et al, nitazoxanide was found effective in patients with intestinal protozoa and helminthic infections [20].

Our study revealed that nitazoxanide is as effective as metronidazole in treating ALA but patients' compliance was better with nitazoxanide.

Strength of the study includes the comparison with the standard drug metronidazole. Serological and radiological confirmed diagnosis of Entamoeba histolytica infection and periodic follow up to detect recurrence and adverse effects. Nitazoxanide is the agent that has broad spectrum of activity against both common intestinal parasitic protozoa and helminths. This offers the single drug therapy of both types of infections.

The comparative studies for the treatment of ALA with nitazoxanide and other standard drugs are lacking so our study is one of its kind done in Indian population suffering from ALA.

Further studies in patients with hepatic amoebiasis will be required to assess the effectiveness of nitazoxanide.

## Conclusion

Nitazoxanide was found to be effective, safe and well tolerated in the treatment of small ALA and efficacy is comparable to that of metronidazole. Response evaluated by disappearance of fever, pain abdomen, jaundice, hepatomegely and tenderness.Adverse effect profile in nitazoxanide group was found to be lesser in number, tolerable and less troublesome as compare to metronidazole group. Nitazoxanide can be used in patients who are intolerant or allergic to nitroimidazole drugs. Nitazoxanide is a noteworthy addition to antiamoebic drugs.

Overall, we found that nitazoxanide is better than metonidazole. Due to lacking of data on such type of study; further research studies are recommended to obtain more data to assess the effectiveness of nitazoxanide.

**Table 1**

| Sex | Group A (Nitazoxanide) | | Group B (Metronidazole) | |
|---|---|---|---|---|
| | No. of Patients | % | No. of Patients | % |
| Male | 25 | 83.33 | 26 | 86.66 |
| Female | 05 | 16.67 | 04 | 13.34 |
| **Age distribution(years)** | | | | |
| <20 | 01 | 3.33 | 03 | 10 |
| 21-40 | 15 | 50 | 14 | 46.66 |
| 41-60 | 09 | 30 | 12 | 40 |
| 61-80 | 05 | 16.66 | 01 | 3.33 |
| | Mean ± SD 42.67 ± 12.76 | | Mean ± SD 42.67 ± 13.11 | |
| **Nutrition** | | | | |
| Poor | 4 | 13.33 | 03 | 10 |
| Average | 26 | 86.67 | 27 | 90 |
| Overweight | 0 | 0 | 0 | 0 |

**Table:2- Clinical Efficacy**

| Symptoms | Group A (Nitazoxanide) | Group B (Metronidazole ) | P value |
|---|---|---|---|
| | Days | Days | |
| Pain Relief | 4.10± 0.96 | 4.20± 1.0 | 0.6936 |
| Subsidence of fever | 3.93± 0.84(29) | 3.76± 0.64(29) | 0.3826 |
| Abdominal Distension | 5.93± 1.54(n=18) | 5.59± 1.66(n=17) | 0.7148 |
| Jaundice | 9.5± 3.7(n=4) | 11.20± 4.49(n=5) | 0.5627 |
| Hepatomegaly | 17.12± 8.12(n=25) | 16.05± 5.48(n=22) | 0.6023 |
| Tenderness | 4.03± 0.89 | 3.77± 0.43 | 0.1449 |

**Table:3- Effect of drug on abscess volume of ALA patients**

| | Group A (Nitazoxanide) | Group B (Metronidazole ) | P Value |
|---|---|---|---|
| | Mean± SD | Mean± SD | |
| Day1 | 233.53± 113.04 | 214.27± 91.05 | 0.4701 |
| Day10 | 173.37± 84.91 | 196.27± 89.44 | 0.3133 |
| Day 40 | 81.03± 37.47 | 91.20± 39.51 | 0.1093 |
| 6 month | Resolved | Resolved | |
| P value b/w Day1 & Day10 | 0.0001 | 0.0001 | |
| P value b/w Day10 & Day40 | 0.0001 | 0.0001 | |

**Table 4 - Side effects observed in patients of liver abscess**

| Adverse effect | Group A (Nitazoxanide) | Group B (Metronidazole) | P value |
|---|---|---|---|
| Metallic taste | 0 | 19 | <0.00001 (S) |
| Nausea | 1 | 18 | <0.00001 (S) |
| Abdominal Pain | 1 | 2 | <0.553812 (NS) |
| Headache | 1 | 6 | <0.044352 (S) |
| Insomnia | 1 | 3 | <0.3006 (NS) |
| Yellow Urine | 3 | 2 | <0.640429 (NS) |
| Total Adverse Effects | 07 | 50 | |

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