Nitazoxanide – A New Option in Biliary Ascariasis

DR. HASINA NASREEN, MD1*
PROF. DR. MAHTABUDDIN HASSAN, MRCP (UK), FCPS 2

1 Deputy Director, Planning and Development, Chattogram Medical University, Bangladesh
2 Internal Medicine, Chittagong Medical College and Hospital, Chittagong, Bangladesh

*(hasinanasreen2018@gmail.com)

Abstract

This prospective study was conducted in the in-patient department of medicine, Chittagong Medical College Hospital (CMCH), Chittagong, Bangladesh from February 2016 to September 2016. The study included 70 patients admitted to emergency department of medicine. Clinical assessment was performed in all the cases. Detailed history was taken as per site, severity and nature of pain. Nitazoxanide is a newly recommended antihelminthic agent elicits its activity by interfering with pyruvate: ferredoxin oxidoreductase (PFOR) enzyme dependent electron transfer reaction, which is essential for anaerobic energy metabolism. It is given by the oral route with good bioavailability and is well tolerated, with primarily mild gastrointestinal side effects. Nitazoxanide (500mg) tablet was given twelve hourly for 3 days. Relief of pain after taking antihelminthic was observed and serial ultrasonogram was performed to determine the worm present or absent in biliary tree. In this study majority of the patients presenting biliary ascariasis were females (74.3%) and the most common age group affected was within 18 to 35 years of age. Among the total respondents, 88.57% were cured, while only 11.43% were not cured off their diseases.

Keywords
Helminth infections; biliary ascariasis; nitazoxanide.

INTRODUCTION

Ascariasis is infestation of humans by nematode, ascaris lumbricoides and is a common in the endemic zones of tropics and subtropics especially in developing countries where it usually affects people of lower socio-economic groups living in unhygienic conditions (Agarwal, 2014). Warm and humid soil, poor sanitation and unhygienic conditions favour presence, development and survival of Ascaris lumbricoides. It is more prevalent and its course more serious in children than in adults (Hussain, 2010). It is the commonest helminthic infection worldwide effecting about 1.4 billion people (Shoff, 2008; Dr. Ali, 2003). Humans are infected with A. lumbricoides when they ingest its eggs, often in food contaminated by human feces. Infection can also occur when hands or fingers with contaminated dirt on them are put in the mouth. In Bangladesh 82% of the population are affected (Shah, 2006; Khuroo, 1996). Most
of the people of this country are poor and live in an inadequate hygienic condition and sanitation facilities which are in favors of helminthic infection. The number of cases of biliary ascariasis has been found to be increasing day by day.

Biliary ascariasis is a common and severe complication of ascariasis. It is one of the most common causes of acute abdominal pain among the hospitalized patients in our country. The most common symptoms are acute upper abdominal pain, nausea, vomiting, occasional fever and jaundice simulating acute cholecystitis. Common complications of biliary ascariasis are acute cholecystitis, acute cholangitis, acute pancreatitis, liver abscess and hepatobiliary lithiasis is a remote complication. Ascarial invasion of the biliary tree is a well known entity. It accounts for 10% - 19% of ascaris related hospital admissions (Shah, 2006). Prevalence of biliary ascariasis in Bangladesh is 0.45% in male patients & 0.55% in female patients (Akhter, 2008). Female of third decade are more likely to be affected. Pregnant females are also more prone probably because of the relaxing effect of hormones on the biliary smooth muscles. It often presents as abdominal colic, cholecystitis, cholangitis, pancreatitis etc. Gallbladder ascariasis is less commonly seen due to a narrow and tortuous cystic duct. About 95% of patients respond well to medical management. Medical management fails if there is a distal stone or stricture in the common bile duct. Surgical intervention in the form of endoscopic removal, laparoscopy or open surgery may be required in such cases (Ramzan, 2014; Keating, 2012; Jethwani, 2012).

CT scan is another highly sensitive non invasive method of identification of biliary ascariasis, but it is only indicated when USG report is negative or confusing. The role of Endoscopic Retrograde Cholangio Pancreatography (ERCP) is not only diagnostic but also therapeutic in case of biliary ascariasis. It is technically demanding procedure and costly. Not easily available in our hospital setting (Dr. Ali, 2003). Other investigations are routine blood test, liver function test like SGPT, AlPO4, prothombin time, serum bilirubin, serum amylase, urinary amylase. Different modalities of treatment are available for biliary ascariasis such as conservative, endoscopic and surgical. In our study we deal with conservative treatment. Conservative treatment in the form of nothing by mouth, nasogastric suction, intravenous fluid, analgesic, antispasmodics and antihelminthics applied to all patients. Reported success rate varies from 14.24%-97% (Dr. Ali, 2003).

Conservative management along with oral antihelminthic medication was found to be effective in treating biliary ascariasis in the majority of patients and can avoid surgical intervention or invasive endoscopic extraction (Das, 2008). Commonly used antihelminthics are Albendazole, Mebendazole, Pyrantel Pamoate. Commonly used drug with highest efficacy in ascariasis is Albendazole(95%) (Cambridge university press, 2001; Haburchak, 2008) which is widely used in Bangladesh for the treatment of biliary ascariasis. It works by decreasing ATP production in worm causing energy depletion, immobilization and finally death.

Nitazoxanite is a newly recommended antihelminthic agent elicits its activity by interfering with pyruvate: ferredoxin oxidoreductase (PFOR) enzyme dependent electron transfer reaction, which is essential for anaerobic energy metabolism. Adult dose 500mg PO bid for 3 days. Contraindication - documented hypersensitivity. Side effects – Abdominal discomfort, diarrhoea, vomiting, headache. Nitazoxanide is a drug used primarily for protozoal infection was shown to have 89% clinical efficacy in the treatment of ascariasis in rural mexico and may offer a future alternative to other medications in ascaris lumbricoids infection (Chak, 2008; Helminthol, 2007; Ritz, 2002). We want to open a new door for conservative treatment of
biliary ascariasis with Nitazoxanide. It was a clinical trial conducted in medicine ward of Chittagong Medical College Hospital to evaluate the efficacy of Nitazoxanide in case of biliary ascariasis.

Nitazoxanide (NTZ), a nitrothiazolyl-salicylamide compound first described by Rossignol and Cavier (J. F. Rossignol and R. Cavier, Chem. Abstr. 83:28216n, 1975), has a broad spectrum of activity against microaerobic and anaerobic bacteria, anaerobic protozoa, and helminths (Arya, 2002; Dubreuil, 1996). It is the first antiparasitic agent reported to be effective against both protozoa and helminths, particularly in the treatment of intestinal parasitic infections (Gilles, 2002; Romero, 1997). The pharmacokinetics and metabolism of NTZ have been studied after the administration of single oral doses to healthy subjects (Stockis, 1996), as well as after administration of radiocarbon-labeled NTZ (Broekhuysen, 2000). The main circulating metabolites have been identified as deacetyl-NTZ or tizoxanide (TIZ) and the corresponding acyl-glucuronide. Since 1996, nitazoxanide has been marketed in most of Latin America and has been studied worldwide. The US Food and Drug Administration (FDA) approved oral suspension nitazoxanide in December of 2002 for the treatment of diarrhea caused by Cryptosporidium species and Giardia intestinalis in pediatric patients 1–11 years of age, and in July 2004, nitazoxanide was approved for treatment of diarrhea caused by G. intestinalis in adults. It is the first and only US FDA-approved drug for treatment of Cryptosporidium infection and is the first new drug approved for treatment of Giardia infection in 140 years.

MATERIALS AND METHODS

This prospective study was conducted in the in-patient department of medicine, Chittagong Medical College Hospital (CMCH), Chittagong, Bangladesh from February 2016 to September 2016. The study included 70 patients admitted to emergency department of medicine. Clinical assessment was performed in all the cases. Detailed history was taken as per site, severity and nature of pain. In addition nausea, vomiting, history of passage of worms in the stool or vomitus and recurrent abdominal pain, with or without jaundice, was taken in each case. Previous history of surgery or endoscopy to the gastrointestinal tract was noted. Complete blood cell count, liver function test, kidney function tests, serum amylase and lipase, X-ray of the chest and abdomen and ultrasound of the abdomen was performed in all the patients at the time of admission and repeated when required. The mainstay of the diagnostic tool was ultrasound of the abdomen. All the patients were initially managed conservatively with IV fluids, analgesics, IV antibiotics and IV/IM antispasmodics and nothing per oral. All patients were dewormed with three repeated doses 500 mg nitazoxanide during first three days of admission. Response to conservative treatment was assessed by improvement in symptoms, and serial ultrasounds were done to know about the presence of worms in bile ducts. Patients who failed to respond to conservative lines for five days were subjected to endoscopic retrograde cholangiopancreatography (ERCP) for removal of worms. Surgical exploration was done in patients where ERCP was failure or not possible. All patients were followed monthly up to six months and Serial ultrasonography was performed to check for recurrence. The patients were dewormed at 3-monthly intervals.

Relieve of pain after taking antihelminthic was observed and serial USG was done to see the worm present or absent in biliary tree. Patient those USG shows no worm in biliary tree counted as cured by conservative treatment and discharged with advice to maintain personal hygiene and sanitation and taking regular antihelminthic to prevent recurrence of infection. Patient those pain relieved but follow up USG shows worm in biliary tree was also discharged and
advised to come with another follow up USG after 10 days. Patients those shows no worm in biliary tree after 10 days follow up USG were counted as cured by conservative treatment and those USG shows worm in biliary tree were counted as not cured by conservative treatment and advised for endoscopic (ERCP) or surgical treatment. During treatment all patients were observed for adverse effects of drugs. Some complaints nausea, anorexia, headache but none of the patient complaints of any major adverse effects. After giving antihelminthic maximum time were taken to see relieve of pain were five days. After that if pain not relieved, patients were advised to endoscopic treatment, ERCP or surgery.

**Institutional Approval**

Proper permission was taken for this study from the department of medicine and ethical clearance from ethical review committee (ERC) of Chittagong Medical College Hospital.

**DATA COLLECTION PROCEDURE**

Study population was selected after fulfilling the selection criteria on the basis of history and physical examination and USG findings of worm in the biliary tree. Me, self in collaboration with trained, briefed and oriented research associates from IMo’s/HMO’s /Interns of all three Medicine units recruited for monitoring of the patients. All patients & attendants were informed about the treatment options and written witnessed consent was taken from them. Treatment outcome was observed by regular monitoring and serial USG of HBS of the patient.

**VARIABLE OF THE STUDY**

**Markers used to assess clinically improved**

1. Pain -relieve
2. Vomiting-stop
3. Body temperature - <98.4°F (If previously febrile)
4. Non ecteric

**Outcome markers**

Complete recovery –

Clinically – pain relieved

symptom improved

Serial USG – no worm in biliary tree

Not recovered –

Clinically - pain not relieved within five days of taking antihelminthic

symptom not improved

Serial USG – worm in biliary tree

**Statistical Analysis**

Sample size estimates were based upon an expected prevalence rate of 30%. Prevalence values were calculated as a percentage, while quantitative variables were determined by means and standard deviation (SD). Nominal data were described using percentage and frequency. Associations among positives and socio-demographic variables or risk factors were estimated
by using an odds ratio, with 95% confidence intervals. Statistically significant differences were calculated utilizing chi-square or Fisher’s exact tests, using SPSS 18.0 software (SPSS Inc., Chicago, Illinois, USA).

**Rationale**

It is expected that the result of this study will help the physician to make early diagnosis and prompt treatment of biliary ascariasis with result of decrease morbidity and mortality, shortening hospital stay and also can prevent recurrences of this disease. We can create awareness to the patient and attendant about the serious side effects of ascariasis and teach them how to prevent ascariasis.

**RESULTS AND DISCUSSION**

**Results**

The objective of this study was the use of Nitazoxanide in the Management of Biliary ascariasis in terms of efficacy and safety and to see the effectiveness of Nitazoxanide in Biliary ascariasis. Distribution of treated cases with Nitazoxanide is shown in tabulated form.

Biliary ascariasis was found to more in females in our study. Out of 70 patients, 52 were females (74.3%) and 18 were males (25.7%) (Table 1). In this study young patients below thirty five years comprised the bulk 80% (56 patients), while as there were only 14 patients (20%) who were above 35 years (Table 2).

| Sex   | Study Population |
|-------|------------------|
|       | Number | %   |
| Male  | 18     | 25.7|
| Female| 52     | 74.3|
| Total | 70     | 100.0|

Table 1. Distribution of sex among study population

| Age Groups | Study Population |
|------------|------------------|
|            | Number | %   |
| < 18 Years | 08     | 11.4|
| 18 to 35 Years | 48 | 68.6|
| > 35 Years | 14     | 20.0|
| Total      | 70     | 100.0|

Table 2. Distribution of age in study population (n=70)

It was seen that, vomiting was present in 77.1% of the respondents, while emesis of worm and fever were present among 22.9% and 24.3% of the total respectively. Only 10% of the total has got diarrhea as a symptom (Table 3).
Table 3. Distribution of presenting symptoms among the study population

| Presenting Symptoms | Study Population |
|---------------------|------------------|
|                     | Number | %    |
| Vomiting            | 54     | 77.1 |
| Fever               | 17     | 24.3 |
| Emesis of Worm      | 16     | 22.9 |
| Diarrhea            | 07     | 10   |

It was noted that, epigastric tenderness was present in cent percent respondents, while right rectus abdominis muscle tenderness was found among 87.1% of the total and Jaundice was detected 44.3% (Table 4).

Table 4. Distribution of presenting signs among study population

| Presenting Signs                          | Study Population |
|-------------------------------------------|------------------|
|                                           | Number | %    |
| Epigastric Tenderness                     | 70     | 100  |
| Tenderness of Right Rectus Abdominis Muscle | 61     | 87.1 |
| Murphy’s Sign                             | 18     | 25.7 |
| Jaundice                                  | 31     | 44.3 |

It was observed that, biliary colic was the most common presentation among the total respondents (48.6%), while acute cholangitis, cholecystitis and pancreatitis were found in 27.1%, 17.1% and 7.2% patients, respectively (Table 5).

Table 5. Distribution of distinct clinical presentations among study population

| Clinical Presentations | Study Population |
|------------------------|------------------|
|                        | N   | %    |
| Biliary Colic          | 34  | 48.6 |
| Acute Cholangitis      | 19  | 27.1 |
| Acute Cholecystitis    | 12  | 17.1 |
| Acute Pancreatitis     | 05  | 7.2  |
| Total                  | 70  | 100.0|

The mean total WBC, neutrophil and eosinophil counts were $8987 \pm 2573.07$ per cu mm SD, $67.79 \pm 10.97$ % SD and $5.03 \pm 2.18$ % SD, respectively, among the total respondents. The mean ESR was $45.78 \pm 30.45$ mm SD among the total (Table 6).
The mean serum alkaline phosphatase and SGPT were 71.16 ± 32.64 U/L SD and 47.18 ± 28.67 U/L SD respectively, while the mean serum bilirubin and prothrombin time were 2.34 ± 2.56 mg/dl SD and 12.53 ± 3.27 minutes SD respectively, among the total respondents (Table 7).

| Biochemical Investigations                | Number | Mean   | ± Sd   | Median | Range   |
|-----------------------------------------|--------|--------|--------|--------|---------|
| Serum Alkaline Phosphates (U/L)         | 70     | 71.16  | 32.64  | 66.00  | 38 – 225 |
| SGPT (U/L)                              | 70     | 47.18  | 28.67  | 40.00  | 28 – 210 |
| Serum Bilirubin (mg/dl)                 | 70     | 2.34   | 2.56   | 2.10   | 0.4 – 5.0 |
| Prothrombin (Minutes)                   |        | 12.53  | 3.27   | 12.00  | 8 – 17   |
| Serum Amylase (U/L)                     | 70     | 192.40 | 227.71 | 97.00  | 52 – 1026 |

Table 7. Statistics of biochemical investigations among study population

It was seen that, among the total respondents, 97.14% patients were relieved from their pain, while in only 2.86% cases pain were not relieved (Table 8).

| Pain Relief           | Study Population |
|-----------------------|------------------|
| Number | % |
| Relieved | 68 | 97.14 |
| Not Relieved | 02 | 2.86 |
| Total   | 70 | 100.0 |

Table 8. Distribution of pain relief among study population (n = 70)

It was seen that, among the respondents who has been relieved off their pain (n = 68), 72.06% has got no worm in their biliary tract, while in 27.94% worm was found within the biliary tract (Table 9).
Table 9. Distribution of first follow-up USG findings among study population (n = 68)

| First Follow-Up USG Findings | Study Population |
|------------------------------|------------------|
| Worm in Biliary Tract       | 19               |
| No Worm in Biliary Tract    | 49               |
| Total                       | 68               |
| Number                      |                  |
| %                           |                  |

It was seen that, among the respondents who has been found with worm in biliary tract in first follow-up ultrasonography (n = 19), 84.21% has got alive worm within (Table 10).

Table 10. Distribution of first follow-up USG comments among study population (n = 19)

| First Follow-Up USG Comments | Study Population |
|------------------------------|------------------|
| Worm Alive                   | 16               |
| Worm Dead                    | 03               |
| Total                        | 19               |
| N                            |                  |
| %                            |                  |

It was seen that, among the respondents who has been found with alive worm in biliary tract in first follow-up ultrasonography (n = 16), only 12.5% has got worm remaining within (Table 11).

Table 11. Distribution of second follow-up USG findings among study population (n = 16)

| Second Follow-Up USG Findings | Study Population |
|-------------------------------|------------------|
| Worm in Biliary Tract        | 02               |
| No Worm in Biliary Tract     | 14               |
| Total                        | 16               |
| Number                       |                  |
| %                            |                  |

Table 12. Distribution of treatment outcome among study groups (n = 70)

| Treatment Outcome | Study Population |
|-------------------|------------------|
| Cured             | 62               |
| Not Cured         | 08               |
| Total             | 70               |
| n                 |                  |
| %                 |                  |
DISCUSSION

Albendazole is a commonly used antihelminthic in patient of biliary ascariasis coming with acute abdominal pain. The present study was done Nitazoxanide in the treatment of biliary ascariasis and the effectiveness of Nitazoxanide in the treatment of biliary ascariasis. Among patients enrolled in the study majority were aged between 18-35 years (68.6%) (Table 2), majority were female (74.3%) (Table 1). Nasima Akhter (2008) shows overall prevalence of biliary ascariasis was 0.45% in male patients and 0.55% in female patients. This translates into susceptibility of young female to biliary ascariasis. Our study shows that biliary ascariasis is more prone to develop in young female patients, but it is also a commonest cause of acute abdominal pain in young male in our country which is (25.7%) in our study (Table 1).

Distinct clinical presentations among study population were biliary colic found in 34(48.6%) patients, acute cholangitis found in 19(27.1%) patients, acute cholecystitis present in 12 patients (17.1%), acute pancreatitis present in 5(7.2%) patients (Table 5). However, cholelithiasis and hepatic abscess were not found in study population. Alam Shahinul (2007), Department of Hepatology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, conducted a study which shows, 97.4% presented with biliary colic, 15.6% with acute cholangitis, 9.1% with obstructive Jaundice, 6.5% with acute pancreatitis, 6.5% with cholelithiasis, 6.5% presented with acute cholecystitis and 2.6% presented with liver abscess. In our study data among clinical presentations were different from previous studies. Here acute pancreatitis prevalence is higher than previous study. So in our setting if any young patient comes with acute pancreatitis one important differential diagnosis will be biliary ascariasis. In a study done by Mukhopadhyay (2009) the result was 28.56% come with obstructive jaundice, 16.7% came with cholangitis, 2.4% came with acute pancreatitis, 2.4% came with hepatic abscess.

In our study presenting symptoms were vomiting present in 77.1% patients, fever present in 24.3% patient, emesis of worm present in 22.9% of patients and diarrhoea present in 10% of patients (Table 3). In Mukhopadhyay (2009) data vomiting was present in 76.2% patients, fever present in 16.7% patients, emesis of worm in 38.1% patients and no patients present with diarrhoea. In a study conducted by Das (2008) shows 83.72% patient presented with vomiting, 13% with fever. In our study presenting symptoms among study population were different from previous studies. Abdominal pain was present in 100% of patients signs among study population were epigastric tenderness present in 100% of patients. Tenderness of right rectus abdominis muscle presents in 87.1% of cases. Murphy’s sign positive in 25.7% cases, jaundice present in 44.3% cases (Table 4). Tenderness of right rectus Abdominis muscle is a common presenting sign in biliary ascariasis patients. In 61(87.1%) cases out of 70, it was present. There was no previous data about this sign. So this will be a new diagnostic sign in biliary ascariasis. When we suspect any patient as biliary ascariasis we must examine for this sign.

Haemotological investigations among study population show that total count of WBC were mean 8987.82, ±SD 2573.07, (range 5000-18000), Nutrophill count were mean 67.79, ±SD 10.97, (range 35-89), Eosinophill count mean 5.03, ±SD 2.18, (range 1-12), ESR mean 45.78, ±SD 30.45, range (18-124) (Table 6). Haematological investigations were variable and total count of WBC & Nutrophil count was raised in patients presents with fever, acute cholecystitis and other complications. Antibiotics were given to those patients and 17 patients (24.3%) (Table 3) of this study received antibiotics with other conservative treatment. Serum Alkaline
phosphates was mean 71.16, ±SD 32.64, median 66 (range 38-225), SGPT mean 47.18, ±SD 28.67, median 40.00 (range 28-210). Serum bilimbin mean 2.34, ± 2.56, median 2.10 (range 0.4-5). Prothrombin time mean 12.53, ±SD 3.27, median 12, (range 8-17) (Table 7).

Our first parameter to see conservative treatment outcome was pain, 68 patients (97.14%) pain relived (Table 8) by conservative management. Maximum time we wait for pain relieve were 5 days after that time we advised them for other interventional treatment like Endoscopy, ERCP or surgery. Pains of 2 patients were not relieved within 5 days and we advised them for endoscopy. Pain relieved time was recorded, also examined the patients for other symptomatic improvement. After that we advised for another USG as follow up to observe the worm. Among them 49 (72.06%) patients USG showed no worm in biliary tree (Table 9). We discharged them with proper advice to take regular antihelminthic and proper education about personal hygiene to prevent recurrence. In 19(27.94%) patients USG showed worm present in biliary tree. Among this 19 patients worm was alive in 16 patients and 3 patients having dead worm in their biliary tree (Table 10). We also discharged 16 patients and advised them to come with another follow up USG after 10 days to see the worm as spontaneous migration of worm is also occurs. Those 3 patients presented with dead worm in their biliary tree were advised for Endoscopy or ERCP. In second follow up USG in 14 patients USG showed no worm in biliary tree and in 2 patients USG showed worm in biliary tree (Table 11) and they were advised for endoscopic treatment.

Among 70 patients 62 patients (88.57%) were cured by conservative treatment. 8 patients (11.43%) were not cured (Table 12) by conservative treatment and needs endoscopic management & ERCP or surgery.

Our parameters observed treatment outcome with conservative treatment were pain relieved by conservative treatment along with antihelminthic drugs and worm removed after pain relieved in follow up USG. The results essentially translate into the superiority of Nitazoxanide in pain relieve and worm removal in follow up USG. In light of present study findings it can be assumed that Nitazoxanide will be a new option antihelmentihic in the treatment of biliary ascariasis.

**CONCLUSION**

Present study was conducted with a view to observe the efficacy and effectiveness of Nitazoxanide in biliary ascariasis. Although Albendazole is an effective antihelminthic in treatment of biliary ascariasis but Nitazoxanide can be a newer option for treatment of biliary ascariasis. Ultrasonography is a non-invasive and effective initial investigation for diagnosis of biliary ascariasis but follow up USG is also necessary to see the worm-whether it is present or removed from the biliary tree and can take decision about further management.

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