Repeated Minocycline Hydrochloride Injections for Symptomatic Polycystic Liver Disease

Hiroshi Yoshida, Hiroshi Makino, Tadashi Yokoyama, Hiroshi Maruyama, Atsushi Hirakata, Junji Ueda, Toshimitsu Miyasaka, Yasuhiro Mamada, Nobuhiko Taniai, Eiji Uchida

ABSTRACT

AIM: The present study evaluated the safety and effectiveness of repeated injections of minocycline hydrochloride (MINO) for symptomatic polycystic liver disease (PLD).

METHODS: We retrospectively studied patients who received percutaneous MINO injections for symptomatic PLD and were followed up for at least 2 years between 2002 and 2015. Huge hepatic cysts (diameter > 10 cm) were treated by continuous drainage and multiple MINO injections. Small hepatic cysts underwent one-step drainage followed by a single injection of MINO. Only several cysts that caused complications were treated by percutaneous injection of MINO. Patients were discharged 1 day after treatment.

RESULTS: Ten patients, (4men and 6 women; mean age, 57.8 years) were studied. All patients had Type 2 PLD according to Gigot’s classification. The chief complaints were abdominal distension (n = 10), abdominal pain (n = 6), back pain (n = 4), and appetite loss (n = 8). Four patients had mild liver dysfunction. One patient complained of moderate right subcapular pain immediately after the injection, and another had pain at the site of catheter insertion. Liver dysfunction did not develop in any patient after treatment. The mean follow-up was 63.4 months. The interval from the first to last admission for MINO injection therapy was 14 to 148 months (mean, 40.8 months). The number of admissions for MINO injection therapy ranged from 2 to 12 times (mean, 4.0 times). The average interval for MINO injection therapy was 8.3 to 19 months (mean, 14.8 months). The hepatic cysts shrank in all patients after treatment. Complications improved consistently, and all patients were satisfied with the outcome of treatment.

CONCLUSIONS: Symptomatic PLD was controllable by 14.8 months of repeated MINO injections on average. Repeated MINO injections are a safe, definitive treatment for symptomatic PLD.

Key words: Minocycline hydrochloride; Polycystic liver disease

INTRODUCTION

Polycystic liver disease (PLD) is a rare genetic disorder. Typically, disconnected biliary structures are present in very-early-stage disease\(^1\). Because the hepatic cyst epithelium shows the immunohistochemical, structural, and functional features of cholangiocytes, a hepatic cyst can be described as a fluid-filled cavity lined with cholangiocytes\(^2,3\). Most patients with PLD remain asymptomatic, but 2% to 5% of patients will have symptomatic hepatomegaly caused by a continuous increase in the volumes.
and numbers of hepatic cysts\(^{48-51}\). Documented complications of nonparasitic hepatic cysts include obstructive jaundice\(^{52,109}\), rupture\(^{51-53}\), intracystic hemorrhage\(^{51-56}\), and infection\(^{57-59}\). In PLD, the polycystic liver annually grows by 0.9% to 3.2%\(^{60,26,28,24}\). As polycystic livers grow up to 10 times their normal size, they compress adjacent abdominal and thoracic organs. Symptoms typically caused by massive enlargement of the liver include abdominal distension, abdominal pain, back pain, and appetite loss, which will induce severe malnutrition in some patients. Liver dysfunction, portal hypertension, ascites, or Budd-Chiari Syndrome will develop in some of these patients\(^{6,22,23}\).

A number of treatments for symptomatic hepatic cyst have been developed\(^{66-67}\). We have previously shown that minocycline hydrochloride (MINO) effectively promotes the regression of symptomatic simple hepatic cyst acutely\(^{26,27}\). In symptomatic PLD, radical treatment is difficult, with the exception of liver transplantation. We therefore inject MINO into only several cysts that cause complications. MINO injection is then repeated when complications recur.

In the present study, we evaluated the safety and effectiveness of repeated injections of MINO in patients with symptomatic PLD.

**METHODS**

We obtained approval from our hospital ethics committee to perform a study evaluating the safety and effectiveness of MINO injections for the treatment of symptomatic PLD. Informed consent was obtained from the patients or their guardians before treatment.

We retrospectively reviewed the database on patients who received percutaneous MINO injection in our department from January 2002 through September 2015. All patients were referred from other hospitals because of symptomatic PLD. Patients included in this study had to have received percutaneous MINO injection for symptomatic PLD with clinical, biological, and imaging follow-up for at least 2 years. Hemorrhagic or infected cysts were excluded from this study. Exclusion criteria were contraindications to percutaneous treatment (a platelet count less than 50,000/mm\(^3\)) and the concomitant presence of hepatobiliary malignancy, hemorrhagic cyst, or infected cyst. Percutaneous fluid sampling was performed as required for cytological and chemical analysis.

**Imaging analysis**

The diagnosis of PLD was based on ultrasonography (US), computed tomography (CT), or magnetic resonance imaging (MRI) without or with intravenous contrast material, and follow-up studies were performed using US, CT, or MRI. A travel history was also obtained, especially concerning areas where echinococcosis is endemic. All patients were considered to have PLD. We interviewed the patients regarding potential complications and performed imaging studies to detect cysts responsible for complications.

**Gigot’s classification**

PLD was classified into three types according to Gigot’s classification on the basis of the number, size, and location of cysts within the liver\(^{490}\). Type 1 (mild form) included patients with a limited number (< 10) of large (> 10 cm) cysts. Type 2 (moderate form) included patients with diffuse involvement of the liver parenchyma by multiple medium-sized cysts, with remaining large areas of non cystic liver parenchyma. Type 3 (severe form) included patients with massive, diffuse involvement of the liver parenchyma by small and medium-sized hepatic cysts, with small areas of liver parenchyma between cysts.

**Percutaneous MINO injection protocol**

Large hepatic cysts (diameter > 10 cm) were treated by continuous drainage and multiple MINO injections. Smaller hepatic cysts were treated by one-step drainage and a single injection of MINO. Percutaneous MINO injections were used to treat only cysts that caused complications.

Before treatment, all patients were informed of the details of the procedure. Following premedication with an intravenous injection of pentazocine (15 mg), hydroxyzine (25 mg), and/or diazepam (5 mg), MINO (Lederle, Ltd., Tokyo, Japan) was injected under local anesthesia.

**Multiple MINO injection therapy:** In patients who underwent continuous drainage, the target cyst was punctured with a needle, and an 8-Fr pigtail catheter (Ultrasonic Guided One-step Drainage Set type S, Hakko Shoji, Co., Ltd., Tokyo, Japan) was inserted under US guidance. The cyst fluid was then aspirated from the intraluminal needle under fluoroscopic control. After approximately 50 mL of fluid was removed for cytological examination and chemical analysis, contrast medium was injected. The needle was then removed, and the pigtail catheter was inserted into the cyst without the use of a guide wire. After catheter insertion, another 50 mL of contrast medium was injected into the cyst to confirm the absence of leakage into the peritoneal cavity. After complete aspiration of the cyst fluid, 200 mg of MINO dissolved in 5 mL of saline was injected, and the catheter was flushed with 5 mL of saline, for a total of 10 mL of saline. The catheter was then clamped for 30 min. Improvement was checked by palpating the patient’s distended abdominal region. MINO was injected daily for 7 to 8 days, and the catheter was removed. After clinical checks, patients were discharged 1 day after treatment.

**Single MINO injection therapy:** In patients who underwent one-step drainage, only several cysts that caused complications were punctured with an 18-gauge needle under US guidance. The cyst fluid was aspirated for cytologic examination and chemical analysis. After complete aspiration of the cyst fluid, 1 or 2 mL of MINO (200 mg dissolved in 5 mL of saline) was injected into each cyst without resumption. Improvement was checked by palpating the distended abdominal region. After clinical checks, patients were discharged 1 day after treatment (2 days' admission).

The effectiveness of treatment was evaluated on the basis of the patient’s complications and laboratory test results 1 month after treatment.

**RESULTS**

Ten patients (4 men and 6 women; mean age, 57.8 years; range, 35 to 71) who received percutaneous MINO injection for symptomatic PLD were studied. The baseline characteristics of the patients are presented in Table 1. All patients had Type 2 PLD according to Gigot’s classification. PLD was associated with autosomal dominant polycystic kidney disease in 5 patients (50%). No patient had underlying cirrhosis. The results of all cytologic examinations and cultures were negative.

The chief complaint was abdominal distension in all patients. Other symptoms included abdominal pain (n = 6.60%), back pain (n = 4.40%), and appetite loss (n = 8.80%). On initial laboratory tests, including assessment of liver function, 4 patients (40%) had mild liver dysfunction with slightly elevated levels of serum aspartate transaminase (AST), aspartate aminotransferase (ALT), and gamma-glutamyl transpeptidase (y-GTP). No patient had a hemorrhagic
diathesis, fever, or signs of infection. One patient had received ethanol injection therapy 10 months previously, and another had received transarterial embolization 8 months previously for the treatment of PLD in other hospitals.

One patient complained of moderate right subscapular pain immediately after the injection, and another had pain at the site of catheter insertion. Pain was controlled with non-steroidal anti-inflammatory suppositories in both cases. No patient had liver dysfunction after treatment. Serum AST, ALT, and γ-GTP levels decreased after treatment in all 4 patients who had liver dysfunction before treatment.

Follow-up ranged from 26 to 157 months (mean, 63.4 months). The interval from the first to the last admission for MINO injection therapy was 14 to 148 months (mean, 40.8 months). The number of admissions for MINO injection therapy ranged from 2 to 12 times (mean, 4.0 times). The average interval for MINO injection therapy was 8.3 to 19 months (mean, 14.8 months). Multiple and single MINO injection therapy was given an average of 0.5 times and 3.5 times, respectively.

The size of the hepatic cysts decreased in all patients after treatment. Complications improved consistently, and all patients were satisfied with the outcome of treatment (Table 2).

Case 1 (Figures 1 and 2)
A 43-year-old woman with PLD was admitted with abdominal distension, abdominal pain, back pain, appetite loss, and liver dysfunction. She had received ethanol injection therapy 10 months previously in another hospital. First, multiple MINO injection therapy was performed 3 times. Single MINO injection therapy was then performed a total of 9 times when the patient complained of abdominal distension. The follow-up time was 157 months. The interval from the first to last admission was 148 months. MINO injection therapy was performed 12 times. The interval of MINO injection therapy was 13.5 months. The interval of multiple single MINO injection therapy was 16.0 months and 12.5 months, respectively. Abdominal distension improved with no recurrence during the past 9 months.

Table 1. Baseline characteristics

| Case | Age  | Sex | Gigot’s classification | Poly cystic kidney complications | Abdominal pain | Abdominal distension | Back pain | Appetite loss | Liver dysfunction | Complications after treatment | Past treatment |
|------|------|-----|------------------------|---------------------------------|----------------|---------------------|-----------|---------------|------------------|-------------------------------|----------------|
| 1    | 43   | F   | Type 2                 | +                              | +              | +                   | +         | +             | +                | Ethanol injection therapy      |                |
| 2    | 35   | F   | Type 2                 | -                              | +              | +                   | -         | +             | -                | Moderate right subscapular pain|                |
| 3    | 60   | F   | Type 2                 | +                              | +              | +                   | +         | -             | +                | Transarterial embolization      |                |
| 4    | 71   | F   | Type 2                 | +                              | -              | +                   | -         | -             | +                | Pain at the site of catheter insertion |                |
| 5    | 70   | M   | Type 2                 | -                              | +              | +                   | +         | -             | -                |                              |                |
| 6    | 52   | M   | Type 2                 | +                              | -              | +                   | -         | +             | +                |                              |                |
| 7    | 56   | M   | Type 2                 | -                              | -              | +                   | -         | +             | +                |                              |                |
| 8    | 61   | M   | Type 2                 | -                              | -              | +                   | -         | -             | -                |                              |                |
| 9    | 65   | F   | Type 2                 | +                              | +              | +                   | -         | +             | +                |                              |                |
| 10   | 65   | F   | Type 2                 | -                              | +              | +                   | +         | -             | -                |                              |                |
| Ave  | 57.8 |      |                       |                                |                |                     |           |               |                  |                               |                |
| SD   | 11.6 |      |                       |                                |                |                     |           |               |                  |                               |                |

Liver dysfunction: elevation of serum AST, ALT, or γ-GTP levels

Table 2. Clinical data

| Case | Follow-up time (months) | Interval from first to last admission (months) | Number of admissions | Average interval of admission (months) | Times of multiple MINO injection | Times of single MINO injection |
|------|-------------------------|-----------------------------------------------|----------------------|----------------------------------------|--------------------------------|-------------------------------|
| 1    | 157                     | 148                                           | 12                   | 13.5                                   | 3                             | 9                             |
| 2    | 108                     | 108                                           | 9                    | 13.5                                   | 0                             | 9                             |
| 3    | 26                      | 25                                            | 4                    | 8.3                                    | 0                             | 4                             |
| 4    | 135                     | 28                                            | 3                    | 14.0                                   | 1                             | 2                             |
| 5    | 39                      | 18                                            | 2                    | 18.0                                   | 0                             | 2                             |
| 6    | 36                      | 15                                            | 2                    | 15.0                                   | 1                             | 1                             |
| 7    | 34                      | 15                                            | 2                    | 15.0                                   | 0                             | 2                             |
| 8    | 34                      | 14                                            | 2                    | 14.0                                   | 0                             | 2                             |
| 9    | 33                      | 19                                            | 2                    | 19.0                                   | 0                             | 2                             |
| 10   | 32                      | 18                                            | 2                    | 18.0                                   | 0                             | 2                             |
| Mean | 63.4                    | 40.8                                          | 4.0                  | 14.8                                   | 0.5                           | 3.5                           |
| SD   | 49.7                    | 47.1                                          | 3.6                  | 3.1                                    | 1.0                           | 3.0                           |
DISCUSSION

We repeatedly injected MINO to treat symptomatic PLD. Symptomatic PLD was controlled by repeated MINO injections given over the course of 14.8 months on average.

PLD is a collection of rare human disorders that result from structural changes in biliary tree development\(^{[48-50]}\). The biliary tree emerges from the endodermal hepatic diverticulum\(^{[49]}\). Development of the biliary system starts from the 8th week of gestation by formation of a single layer of hepatoblasts around the portal vein (ductal plate). The ductal plate is the anatomical template for the development of the intrahepatic bile ducts. The PLD results from a ductal-plate malformation during embryonic liver development\(^{[51]}\). In PLD, complexes of disconnected intralobular bile ductules are retained, which explains the non communicating nature of the cysts in PLD. The multiple cysts then arise from progressive dilatation of these abnormal ductules from biliary hamartoma (von Meyenburg complexes)\(^{[52-54]}\).

PLD shows two main clinical presentations: (1) PLD associated with autosomal dominant polycystic kidney disease; and (2) isolated PLD. Both of these forms of PLD have an autosomal dominant pattern of inheritance\(^{[55]}\).

There are various treatments for symptomatic hepatic cysts, such as cyst aspiration sclerotherapy\(^{[26,27,30,35-45]}\), cyst fenestration (deroofing)\(^{[28,46]}\), liver resection\(^{[32-34,47]}\), hepatic arterial embolization\(^{[29]}\), and transplantation\(^{[31]}\). These treatments do not alter the natural course of the disease.

Surgery has been the traditional treatment for symptomatic hepatic cysts, but is quite invasive and has a relatively high incidence of complications\(^{[32-34,40]}\). The recurrence rate after liver resection has been reported to be 3% to 33%\(^{[50-53]}\). In Japan, postoperative complications of liver resection include ascites, bile leakage, and intra abdominal abscess, with an incidence of 31.8%\(^{[59]}\). Cyst fenestration, i.e., surgical de roofing of a cyst, is a minimally invasive surgical treatment, but the recurrence rate has been reported to range from 20% to 72%, with large differences among previous studies\(^{[60-63]}\). The most commonly reported postoperative complication is ascites, with an incidence of 33% to 69%. Liver transplantation is the only radical treatment option for PLD, but carries high risks of postoperative morbidity and mortality\(^{[23,56,64]}\). Among nonsurgical treatments, a 100% recurrence rate has been reported after cyst aspiration alone; an alternative method of treatment is thus required\(^{[59]}\). The instillation of various sclerosing agents has been used to obliterate symptomatic congenital hepatic cysts\(^{[26,27,30,35-45]}\). Aspiration sclerotherapy involves cyst aspiration followed by the injection of a sclerosing agent, which destroys the epithelial cells lining the cyst cavity. However, aspiration sclerotherapy for PLD was reported to be impractical because of its high recurrence rate, ranging from 50% to 78%\(^{[16,39]}\). The most commonly used sclerosing agent is ethanol or MINO. Ethanol injection therapy for the treatment of hepatic cysts has been associated with pain, hyperthermia, hypotension, and intoxication\(^{[33,37,44]}\).

MINO is the antibiotic most widely used to treat cysts. A low concentration of MINO (1 to 2 mg/mL) is usually injected
intravenously. MINO injection has been used to treat renal cysts, splenic cysts, thyroid cysts, and hepatic cysts. Mino 100 mg/mL was injected to treat thyroid cysts, and Mino 10 mg/mL was instilled into renal cysts. Concentrations of Mino that have been used to manage hepatic cysts range from 5 to 50 mg/mL.

The efficacy of MINO injection is related to the extremely low pH of the tetracycline in solution, which destroys the mesothelial cells secreting the effusion, leading to involution of the cyst. Furthermore, Rubinson et al. have suggested that the antibiotic effect of tetracycline provides some protection against infection after instillation.

In Mino injection therapy, pain occurs when Mino leaks into the abdominal cavity. Burette et al. reported that Mino had hepatotoxic effects in one patient. Unlike the usual histologic features of tetracycline-induced hepatic injury, fatty metamorphosis was predominantly macrovesicular. The patient recovered after drug therapy was discontinued. Close monitoring of liver function is recommended in patients who receive high-dose parenteral Mino, particularly if they are pregnant or have renal disease. Mino injection is contraindicated in patients who have a hemorrhagic diathesis, echinococcal cyst, protrusion of the hepatic vein into the cyst, communication with the biliary tree, or extravasation into the peritoneal cavity. The side effects in our study included moderate right sub scapular pain immediately after the injection of Mino in one patient and pain at the catheter insertion site in another patient. Pain was controllable with non-steroidal anti-inflammatory suppositories in both patients. In our series, serum AST, ALT, and γ-GTP levels decreased after treatment in all patients who had liver dysfunction before treatment.

There are two methods for treating hepatic cysts by Mino injection: multiple injection therapy and single injection therapy. In our series, continuous drainage and multiple Mino injections were performed in patients with huge hepatic cysts measuring >10 cm in diameter. We previously reported that multiple Mino injection therapy was effective with no recurrence when used to treat huge symptomatic solitary hepatic cysts. After multiple Mino injections, complications improved because huge cysts decreased in size. However, it was difficult to control complications caused by small hepatic cysts in PLD. The goals of treatment for PLD are to alleviate abdominal symptoms and prevent their recurrence by decreasing liver volume. Symptom recurrence is caused by the growth of new cysts or the re-growth of treated cysts. We therefore treated only several cysts that caused complications and repeated treatment on the recurrence of complications. In case 1, the interval of multiple and single Mino injection therapy was 16.0 months and 12.5 months, respectively. In single Mino injection therapy, only a few days of hospitalization are required for treatment per year.

The Gigot classification of PLD is based on the number, size, and location of cysts within the liver. It reflects disease severity and is useful when choosing treatment options. Recently, several reports on PLD treatment have recommended aspiration sclerotherapy, cyst fenestration, and liver resection for Gigot type 1 or 2 PLD and liver transplantation for type 3 PLD; however, no standardized criteria for the selection of treatment exist. In our series, all patients had Gigot type 2 PLD.

In our series, the duration of hospitalization for Mino injection therapy ranged from 8.3 to 19 months (mean, 14.8 months). The hepatic cysts shrank after treatment in all patients. PLD-related complications improved consistently, and all patients were satisfied with the treatment response. Symptomatic PLD could thus be controlled by 14.8 months of Mino injection therapy on average. The effectiveness of the treatments continued beyond 1 year. Because liver transplantation is the only radical treatment option for all cysts in PLD, the duration of treatment effect in our study is considered satisfactory.

In conclusion, symptomatic PLD was controllable by 14.8 months of repeated Mino injections on average. Repeated Mino injection is a safe, definitive treatment for symptomatic PLD.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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**Peer reviewer:** Yutao Zhan, MD, Associate Professor, Department of Gastroenterology and Hepatology, Beijing Tongren Hospital, Capital Medical University, NO.1 Dongjiao minxiang Dongcheng District, Beijing 100730, China.