의학석사 학위논문

간흡충증 감염으로 진단 받은 환자들의 임상경과에 대한 분석

Clinical outcomes of patients who were diagnosed as an infection of *Clonorchis sinensis*

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의 학 과

김광운

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국문요약

연구배경: 간흡충(*Clonorchis sinensis)*은 사람에게 감염되는 기생충으로 한국을 포함한 동아시아에서 호발하고 있다. 간흡충에 의한 만성 감염은 담관의 염증성 질환과 함께 담도암을 유발할 수 있으며, 발암요인으로 분류되고 있다. 1980 년대 간흡충에 대한 약물치료 방법으로서 Praziquantel 이 소개 되었으며, 약물치료에 의한 완치율이 90% 이상으로 알려져 있다. Praziquantel 에 의해 간흡충의 완치가 이루어지면 담도암을 유발하는 것으로 추정되는 여러 기전이 해소되어 담도암 발생의 위험이 감소할 것으로 추정된다. 이 연구에서는 간흡충 감염증에 대하여 Praziquantel 을 이용한 약물 치료 이후 담도암 발생 빈도와 위험인자를 분석하고자 한다.

연구방법: 2000 년 1 월부터 2010 년 12 월까지 간흡충 감염증을 진단받은 환자들의 의무기록을 후향적으로 분석하였다. 1020 명의 환자가 포함되었으며, 이중 간흡충증 진단 당시 담도암을 함께 진단 받은 경우나 추적관찰 자료가 없는 경우 연구 대상에서 제외 되었다.

연구결과: 최종적으로 602 명의 환자가 연구에 포함되었다. 346 명 (57.4%)의 환자가 추적 대변 검사를 시행하였으며, 간흡충증 감염의 재발 여부를 확인하였다. 이들 중 한

명의 환자가 첫 진단 및 치료 5 년 이후 재발을 보였다. 나머지 345 명의 환자는 중위 85 개월 동안 재발이 관찰되지 않았다. CA 19-9 는 460 명 (76.4%)의 환자에서 확인되었으며, 중위 추적기간은 77 개월이었다. 4 명의 환자에서 CA 19-9 의 상승이 관찰되었으며, 이들 중 담도암이 발생한 환자는 없었다. CEA 는 435 명 (72.2%)에서 확인되었으며, 중위 추적기간은 82 개월 이었다. CEA 가 상승하였던 환자는 없었다. 영상검사의 추적기간은 중위 81 개월이었으며, 추적 기간동안 담도암이 발생하였던 환자는 없었다.

결론: 간흡충증 치료 이후 담도암의 발생 위험은 높지 않으며, 간흡충증의 조기 발견 및 치료를 통해 담도암 발생을 예방할 수 있다.

중심단어: 간흡충증, 담도암, Praziquantel

차 례

INTRODUCTION

Clonorchis sinensis is a parasite that infects humans and is endemic in East Asia, mainly in China, Taiwan, Vietnam, Japan, and Korea.[1] More than 200 million people are estimated to be at risk of infection, and 20 million people are infected worldwide.[2]

The adult form of *C. sinensis*, the liver fluke, moves from the common bile duct to the peripheral intrahepatic bile ducts and survives there for 20~30 years.[3] Chronic infection can cause various hepatobiliary diseases, including biliary obstruction, cholangitis, hepatolithiasis, and cholangiocarcionoma.[3] *C. sinensis* has been classified as a group 1 biological carcinogen by the International Agency For Research on Cancer.[4] There are thought to be 3 main mechanisms involved in *C. sinensis* carcinogenesis, as follows: (i) chronic irritation and mechanical damage related to parasite activity, (ii) toxic effects of parasite excretory/secretory (ES) molecules, and (iii) immunopathogenesis due to infection-related inflammation.[5]

In the 1980s, praziquantel was introduced as a treatment for clonorchiasis and

provided a greater than 90% cure rate.[6] The removal of *C. sinensis* that chronically reside in the biliary tract might lead to a decrease in the carcinogenesis associated with this parasite. Therefore, the eradication of *C. sinensis* by praziquantel has been hypothesized to lead to a decreased risk of cholangiocarcinoma. Although many reports have described the carcinogenic effects of *C. sinensis*, few previous studies have examined the clinical outcomes of patients after eradication of *C. sinensis*. Moreover, there are no definitive guidelines on monitoring patients after they are treated for infection by *C. sinensis*. In this study, we aimed to assess the incidence and risk factors of cholangiocarcinoma after treatment for *C. sinensis* infection.

PATIENTS AND METHODS

Patients

We retrospectively reviewed the medical records of all patients who received a diagnosis of clonorchiasis between January 2000 and December 2010 at the Asan Medical Center, Seoul, Korea.

We initially included 1020 patients with clonorchiasis. Patients were subsequently excluded if cholangiocarcinoma was simultaneously diagnosed along with clonorchiasis or if follow-up data after the diagnosis of clonorchiasis were missing from the medical records. Thus, 418 patients were excluded, and a total of 602 patients were eventually examined in this study.

The study protocol followed the ethical guidelines of the Declaration of Helsinki, and was approved by our institutional review board.

Diagnosis and treatment of *Clonorchis sinensis* infection

A stool examination was used in most cases to diagnose *C. sinensis* infection. In addition, cases were included in the study based on findings suggestive of *C. sinensis* infection on radiological imaging modalities such as abdominal ultrasonography (US) and abdominopelvic computed tomography (CT). Cases of infection based on the identification of eggs in bile specimens obtained by endoscopic retrograde cholangiopancreatography were also included in the study.

All patients with the diagnosis of *C. sinensis* infection were treated by praziquantel (25 mg/kg orally TID for 2 days).

Examination following treatment

Patient medical records were reviewed to determine the clinical outcomes. Cure or recurrence of *C. sinensis* infection were determined by follow-up stool examination. All enrolled patients underwent a minimum of 1 follow-up radiological examination such as abdominal US or CT. We reviewed the results of radiological imaging studies and testing for tumor markers (CA19-9, CEA) after treatment of *C. sinensis* infection

to identify the occurrence of cholangiocarcinoma.

RESULTS

Patient characteristics

Of 1020 patients who were diagnosed with clonorchiasis, 64 were excluded because they were diagnosed with cholangiocarcinoma at the same time, and 354 were excluded because follow-up data were missing from their medical records. A total of 602 patients (male, 509 [84.6%]; median patient age, 53 years [range, 30–83 years]) were finally enrolled.

The initial diagnosis of clonorchiasis was obtained by stool examinations for 443 (73.6%) patients, radiological modalities for 127 (21.1%) patients (abdominal US 16, abdominal CT 111), and examination of bile specimens for 32 (5.3%) patients. All the patients were treated by praziquantel shortly after diagnosis.

Follow-up and clinical outcomes

Of 602 patients, 346 (57.4%) underwent follow-up stool examinations to identify the recurrence of clonorchiasis. One of these patients showed a recurrence of

clonorchiasis 5 years after the initial diagnosis. Before the identification of recurrence in that patient, 2 previous stool examinations were negative for *C. sinensis* eggs. The other 345 patients were not found to develop recurrence over a median period of 82 (range 11–189) months.

Serum CA 19-9 was checked in 460 of 602 patients (76.4%) after treatment for clonorchiasis. The median follow-up period for presence of CA 19-9 was 77 (range 5–196) months. Increased serum CA 19-9 was found in 4 of 460 patients. These patients were negative for cholangiocarcinoma on radiological imaging (US, CT) for a median of 88 (range 76–117).

CEA was checked in 435 of 602 patients (72.2%). The median follow-up period for the presence of CEA was 82 (range 5–196) months. None of the patients showed an increase CEA level.

Every patient underwent a radiological examination such as abdominal US and CT. Abdominal US was used for 557 (92.5%) cases and abdominal CT was used for 436 (72.4%) cases. Both US and CT were used for 391 (64.9%) cases. The median

follow-up period for radiological testing was 81 (range 2–196) months. None of the cases showed a radiological occurrence of cholangiocarcinoma during the follow-up period.

DISCUSSION

This study found that the risk of cholangiocarcinoma after treatment for clonorchiasis was low. Most of the patients who were treated by praziquantel remained free of infection for a long time. One case showed a recurrence of clonorchiasis, which we believe was probably a case of reinfection and not a sign of treatment failure. A previous study found that the cure rate of praziquantel was > 90%.[6] The prevention of recurrence requires appropriate education and appropriate treatment by praziquantel and avoiding the consumption of raw fish.[2]

Among cases checked for presence of a tumor marker, 4 cases showed an increase in CA 19-9 levels. All 4 patients with increased CA 19-9 level underwent upper and lower endoscopy, chest x-ray, and abdominal US or CT. None of the examinations revealed evidence of malignancy, and the causes of elevated CA 19-9 levels remained undetermined. Previous studies found that patients with clonorchiasis may have a 15-fold increased risk of cholangiocarcinoma.[7,8] The 1999-2005 Korean National Cancer Incidence Database showed that patients with

clonorchiasis had a relative risk of cholangiocarcinoma of 4.7 (95% confidence interval 2.8-8.4) and estimated that about 10% of cholangiocarcinoma cases in Korea were caused by clonorchiasis.[9] This study found that the risk of cholangiocarcinoma after treatment for clonorchiasis was low. Infected bile ducts undergo pathological changes that include adenomatous hyperplasia of the epithelium, mucin-secreting metaplasia, ductal dilatation, periductal inflammation, and dysplasia or neoplasia.[10,11] We presume that these local pathological changes in bile duct tissue disappeared after praziquantel treatment.

In the author's clinical experience, patients who developed cholangiocarcinoma after clonorchiasis treatment were rarely found. Periodic follow-up examinations may be necessary, because cancer does occur, albeit rarely. Because the risk of cancer after praziquantel treatment is low, we think that frequent examinations are unnecessary.

This study has limitations. It was a retrospective single-center study with a limited number of cases. Because guidelines for follow-up after treatment have not

yet been established for patients with clonorchiasis, the intervals between follow-up examinations and the durations of follow-up varied. And considering the high prevalence of clonorchiasis, the sample size was too small to allow a generalized conclusion. A large-scale, multicenter epidemiologic study may be warranted to overcome this limitation and to confirm our conclusions. Notably, a study that includes a control group that does not receive praziquantel treatment could provide more convincing evidence to support our results.

To the best of our knowledge, this is the first study to assess the clinical outcomes of patients who were treated for clonorchiasis. Based on this study, a well-designed multicenter study or nationwide epidemiological study should reveal the chemopreventive effect of praziquantel in relation to clonorchiasis.

In conclusion, the risk of cholangiocarcinoma in a patient with clonorchiasis after treatment was low, and screening and treatment for clonorchiasis can prevent the occurrence of cholangiocarcinoma. If the treated patient stops consuming raw fish, we think that a follow-up stool examination will not be required, and presume

that a rigorous follow-up screening protocol for cholangiocarcinoma after treatment of clonorchiasis is unnecessary.

REFERENCES

1. Lai DH, Hong XK, Su BX, et al. Current status of Clonorchis sinensis and clonorchiasis in China. Trans R Soc Trop Med Hyg 2016;110:21-27.
2. Hong ST, Fang Y. Clonorchis sinensis and clonorchiasis, an update. Parasitol Int 2012;61:17-24.
3. Kim HG, Han J, Kim MH, et al. Prevalence of clonorchiasis in patients with gastrointestinal disease: a Korean nationwide multicenter survey. World J Gastroenterol 2009;15:86-94.
4. Bouvard V, Baan R, Straif K, et al. A review of human carcinogens--Part B: biological agents. Lancet Oncol 2009;10:321-322.
5. Sripa B, Brindley PJ, Mulvenna J, et al. The tumorigenic liver fluke Opisthorchis viverrini--multiple pathways to cancer. Trends Parasitol 2012;28:395-407.
6. Jong EC, Wasserheit JN, Johnson RJ, et al. Praziquantel for the treatment of Clonorchis/Opisthorchis infections: report of a double-blind, placebo-controlled trial. J Infect Dis 1985;152:637-640.
7. Chaiyadet S, Sotillo J, Smout M, et al. Carcinogenic Liver Fluke Secretes Extracellular Vesicles That Promote Cholangiocytes to Adopt a Tumorigenic Phenotype. J Infect Dis 2015;212:1636-1645.
8. Keiser J, Utzinger J. Food-borne trematodiases. Clin Microbiol Rev 2009;22:466-483.
9. Shin HR, Oh JK, Lim MK, et al. Descriptive epidemiology of cholangiocarcinoma and clonorchiasis in Korea. J Korean Med Sci 2010;25:1011-1016.
10. Rim HJ. The current pathobiology and chemotherapy of clonorchiasis. Kisaengchunghak Chapchi 1986;24 Suppl:1-141.
11. Hong ST. Clonorchis sinensis. International handbook of foodborne pathogens. New York, Basel: Marcel Dekker, Inc. 2003:p. 581-592.