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Retrospective Study

Removal of intrahepatic bile duct stone could reduce the risk of cholangiocarcinoma: A single-center retrospective study in South Korea

Kim TI *et al*. A retrospective study between IHD stone and CCC

Abstract

BACKGROUND

Intrahepatic duct (IHD) stones are among the most important risk factors for adenocarcinoma (CC). However, approximately 10% of patients with IHD stones develop CC, and there are limited studies regarding the effect of IHD stone removal on CC development.

AIM

To investigate the association between IHD stone removal and CC development.

METHODS

We retrospectively analyzed 397 patients with IHD stones at a tertiary referral center between January 2011 and December 2020.

RESULTS

CC occurred in 36 of the 397 enrolled patients. In univariate analysis, chronic hepatitis B infection (11.1% *vs* 3.0%, $P = 0.03$), carbohydrate antigen 19-9 (CA19-9, 176.00 *vs* 11.96 II/mL, $P = 0.010$), stone located in left or both lobes (86.1% *vs* 70.1%, $P = 0.042$), focal atrophy (52.8% *vs* 26.9%, $P = 0.001$), duct stricture (47.2% *vs* 24.9%, $P = 0.004$), and removal status of IHD stone (33.3% *vs* 63.2%, $P < 0.001$) were significantly different between IHD stone patients with and without CC. In the multivariate analysis, CA19-9 > upper normal limit, CA > upper normal limit, stones located in the left or both lobes, focal atrophy, and complete removal of IHD stones without recurrence were independent factors influencing CC development. However, the type of removal method was not associated with the risk of CC.

CONCLUSION

Complete removal of IHD stones without recurrence could reduce the risk of CC.

Key Words: Intrahepatic bile duct stone; Cholangiocarcinoma; Percutaneous transhepatic cholangioscopy; Endoscopic retrograde cholangiopancreatography; Carbohydrate antigen 19-9

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Core Tip: It is well known that intrahepatic duct (IHD) stones are the most important risk factors for cholangiocarcinoma (CCC), but there are limited studies regarding the effect of IHD stone removal on CCC development. It has been reported that remnant stones after percutaneous transhepatic cholangioscopy could be a risk factor for CCC, but the effect of recurrence after complete removal of stones on CCC is unclear. Based on this, we hope to investigate the association of IHD stone removal and CCC development.

INTRODUCTION

Cholangiocarcinoma (CCC) has a poor prognosis, and its incidence is increasing worldwide, especially in East Asia[1]. Surgical resection is the optimal method for curing cancer, but only about 10%-40% of patients are diagnosed as suitable for operation at the time of diagnosis[2]. Research on the use of immune checkpoint inhibitor to treat local advanced or metastatic CCC is rapidly progressing[2]. A recent study found that adding durvalumab to gemcitabine and cisplatin, the standard first-line treatment for advanced CCC, can extend patients' overall survival[3], however, the 5-year survival rate for advanced CCC that is not amenable to surgery does not exceed 5% until now. Therefore, one of the main approaches to increasing the survival rate of CCC is to identify and eliminate risk factors of that.

While the most common risk factor is primary biliary cirrhosis in Western countries, parasitic infections, intrahepatic duct (IHD) stones, and viral hepatitis are more

common causes of CCC in Eastern countries[4]. IHD stones cause repetitive inflammation of the liver parenchyma and structural changes, and 10% of these result in CCC[5]. Therefore, it is important to manage IHD stones consistently. Hence, most patients undergo operative or endoscopic removal of stones. While operative treatment is known to be more effective in managing IHD stones, the endoscopic method can be an option in cases of bilateral IHD stones without structural change, considering severe comorbidity.

Depending on the method, the removal rate in surgical treatment is 95%-100%, with a recurrence rate of 5.7%-13.9%. The non-surgical treatments such as percutaneous transhepatic cholangioscopy (PTCS) and endoscopic retrograde cholangiopancreatography (ERCP) have a removal rate of approximately 80% and a recurrence rate of 35%-63.2%[6,7]. It has been reported that remnant stones after non-surgical treatment could be a risk factor for CCC[8]; however, research on the risk of CCC development after IHD stone removal is still lacking. Therefore, this study aimed to investigate the relationship between IHD stone removal and the risk of CCC development.

MATERIALS AND METHODS

Patients

From January 2011 to December 2020, we retrospectively analyzed the medical records of patients diagnosed with IHD stones who underwent imaging tests such as computed tomography (CT) or magnetic resonance (MR) and had a follow-up record of more than 6 mo. We excluded the patients who have a possibility of malignancy on diagnosis of IHD stones. We reviewed age, sex, past medical history, medication, laboratory findings, imaging tests, and pathologic results. 397 patients with IHD stones were enrolled, and 36 were diagnosed with CCC. This study was performed in accordance with the ethical principles of the Declaration of Helsinki (2013) and was approved by the institutional review board of Pusan National University Hospital (IRB No. 2103-010-101).

Medical record review

We checked for remnants and recurrence after IHD stone removal. A remnant stone was defined as a stone confirmed by CT or MR within 6 months after IHD stone removal, while a recurrent stone was confirmed after 6 mo from treatment. We then investigated the occurrence rate of CCC in accordance with the remnant or not from pathologic data.

We analyzed sex, age, height, body weight, and body mass index (BMI) and the presence of liver cirrhosis, viral hepatitis, diabetes mellitus, and hypertension for past medical history. As serologic markers, carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) were analyzed for their minimal value in consecutive tests during the follow-up period. For medication history, aspirin, ursodeoxycholic acid (UDCA), and statin use for 6 mo or more were considered. In imaging tests, we analyzed the location, size, number of stones, and the presence of stricture of the bile duct or atrophy of the liver parenchyma and distinguished stones larger than the duct by comparing the size of the stone with the duct diameter. Regardless of treatment, we defined recurrent cholangitis as taking antibiotics in outpatient or hospital administration two times or more.

Statistical analysis

We used the SPSS statistical software (version 26.0, IBM, Armonk, NY) for statistical analysis. Qualitative data, including differences between the two groups, were summarized and expressed as frequencies and percentile using the χ^2 test. For continuous variables, we analyzed the difference between the two groups and expressed it as the median with or without standard deviation using an independent two-sample *t*-test. The effect of independent variables on response variable was analyzed using the multivariate logistic regression, and the statistically significant variables were included in the univariate logistic regression with 0.05 alpha level.

RESULTS

Patient data

The data of the 397 patients enrolled in this study are summarized in Table 1. CCC occurred in 36 patients. The two groups' mean follow-up period was approximately 7 years (96.3 *vs* 83.9 mo). In the two groups, 33.3% and 39.6% were male, and the median age at the diagnosis of IHD stone was 60.75 and 61.31 years old. There was no significant difference in BMI and underlying viral hepatitis between the two groups. The number of patients with diabetes mellitus and hypertension was similar between the group (13.9% and 14.7%, 13.9% and 18.4%, respectively). In serologic tests, the minimum value of CA19-9 showed statistically significant differences [CA19-9 (176.00 *vs* 11.96, $P = 0.010$)] and the number of patients who had results exceeding the reference showed significant differences in CA19-9 (19.4% *vs* 1.9%, $P < 0.001$) and CEA (13.9% *vs* 1.9%, $P = 0.002$). On imaging, there was no statistical difference in the occurrence of multiple stones or stones bigger than the duct diameter. IHD stones on the left or both sides of the liver showed a higher rate of accompanying CCC than stones only on the right side (86.1% *vs* 70.1%, $P = 0.042$). Furthermore, the coexistence of atrophy of the liver parenchyma (52.8% *vs* 26.9%, $P = 0.001$) and bile duct stricture (47.2% *vs* 24.9%, $P = 0.004$) showed a statistically significant difference in the rate of CCC.

Although the number of patients who underwent IHD stones removal was lower in those with CCC (33.3% *vs* 63.2%, $P < 0.001$), there was no statistical difference in the method of stone removal, recurrence rate (5.6% *vs* 8.0%) and the incomplete stone removal rate (5.6% *vs* 9.4%). Medication history also showed no difference in the use of aspirin (0% *vs* 3.9%), UDCA (77.8% *vs* 73.4%), metformin (8.3% *vs* 5.3%), and statins (5.6% *vs* 6.4%). There was no difference in the occurrence of recurrent cholangitis (55.6% *vs* 51.2%).

The risk analysis of CCC in patients with IHD

We calculated the odds ratio (OR) of each factors and conducted a multivariate regression analysis of seven factors that showed statistical importance (Table 2): the

number of patients who exceeded the reference for CA19-9 ($P < 0.001$) and CEA ($P = 0.001$), IHD stone on the left side ($P = 0.049$), atrophy of the liver parenchyma ($P = 0.002$), bile duct stricture ($P = 0.005$), complete removal without recurrence ($P = 0.009$), and non-surgical removal method ($P = 0.004$) (Table 2). Of these, the frequency of bile duct stricture and the removal method of non-surgery showed a *P*-value of 0.061 and 0.141, respectively indicating that there were not a significant risk factor for CCC. We verified that the OR of CA19-9 ($P < 0.001$) or CEA (0.005), left-sided and both IHD stone (0.013). In the case of complete removal without recurrence, the OR of CCC showed a statistically significant decrease to 0.21 ($P < 0.001$).

Result analysis according to the removal method

Table 1 also shows the occurrence rate of CCC according to the state of IHD stones. Of 157 patients who did not undergo IHD stone removal, 24 were diagnosed with CCC, resulting in an occurrence rate of 15.3%. Conversely, 12 of the 240 patients who underwent IHD stone removal treatment were diagnosed with CCC, with an occurrence rate of 5.0%. Among the 173 patients with complete removal of IHD stone without recurrence, eight were diagnosed with CCC showing an occurrence rate of 4.6% and a statistically significant difference ($P = 0.007$). Complete removal with recurrent (6.4%) and incomplete removal with remnant (5.6%) stone groups showed a tendency of decreased risk of CCC (OR = 0.57-0.67) in univariate analysis, however, could not derive a statistical significance (Table 2).

Regardless of removal methods, surgical (ERCP and PTCS) or non-surgical (hepatectomy), all patients who underwent removal of IHD stones showed the decreased risk of CCC and there was no difference between two group in CCC development ($P = 0.676$) (Table 3). But, the rates of remnant or recurrent stone, and recurrent cholangitis were more higher in non-surgically treated patients.

DISCUSSION

In the current study, we identified that the occurrence rate of CCC was lower in patients who underwent IHD stone removal than in those who did not. The occurrence rate of CCC (9%) was similar to that of another study (1.3%-13%)[5,9]. In multivariate analysis, the factors affecting CCC were elevation of CA19-9 (OR = 15.85, $P < 0.001$) and CEA (OR = 8.12, $P = 0.005$) above the reference value, left-sided or bilateral IHD stones (OR = 4.37, $P = 0.013$), and atrophy of the liver parenchyma (OR = 2.59, $P = 0.025$). Complete removal of IHD stones without recurrence was identified as a factor decreasing the risk of CCC to 79% (OR = 0.21, $P = 0.001$). Although not in CCC development, there was a difference in the rate of remnant and recurrence between surgically and non-surgically treated group including the rate of recurrent cholangitis. These results could be an evidence that surgical treatment can be more optimal to patients who are young or have a higher risk of CCC like *Cordyceps sinensis* or viral hepatitis infection and primary sclerosing cholangitis, *etc.*

The stone removal rate was 91.5% and 79.9% in surgically treated groups and the others, respectively. This was similar in another study; in the case of recurrence rate, there was no significant difference with other studies (5.7%-13.9%, 35%-63.2%) compared to 11.5% in operation and 45.5% in the PTCS group[6,7]. Although the number of patients who underwent ERCP was too small to compare with other groups directly, the removal rate was high, and the recurrence rate was low in this study because it was applied to patients with relatively small stones in the hilum.

It is well known that structural changes, such as atrophy of the parenchyma and bile duct stricture, are risk factors for CCC; therefore, hepatectomy, including resection, could lower the risk of CCC. In the multivariate analysis, atrophy of the liver parenchyma was identified as a risk factor; however, focal bile duct stricture did not affect CCC. This may be due to the relief of congestion by balloon dilatation during PTCS could influence the development of cancer. In this study, we expect that PTCS can be preferentially applied to patients with IHD stones since PTCS does not increase the risk of CCC if there are no structural changes, such as atrophy or stricture.

The risk factors for CCC were elevated tumor markers, atrophy of the liver parenchyma, and left-sided IHD stones. In one cohort study in Japan, it was reported that bile duct stricture and age above 65 years were risk factors for CCC[9], and in Korea, there was a study that remnant stone increased the risk[10]. These factors were all related to chronic inflammation, which was reported as a major factor of CCC. This was thought to be related to the increased risk in the remnant stone group from another study and the group with remnant or recurrent stone in this study[11]. Also in our study, remnant or recurrent stone showed a tendency of decreasing the risk of CCC, but could not derive a statistically significant difference. This result emphasized the importance of not only attempt to reduce stones to relieve the obstruction but also complete removal and long-term surveillance after treatment. Additionally, there is a possibility that the effect of remnant or recurrent stones on the risk of CCC could not be fully evaluated because of the short follow-up period. In one study about IHD stones in Korea, the average period of occurrence of CCC was approximately 10 years; therefore, the 7-year follow-up period in this study could be too short to verify the effect of remnant stones on CCC[9,10,12].

Recently, there have been reports that drugs such as aspirin, metformin, and statins reduce cancer risk[13-15]. Some studies suggested that aspirin may help prevent cancer, and researches about how metabolic factors like diabetes, hypertension, obesity and *etc.* affect the malignancies are undergoing[16]. In a study of 2395 CCC patients and 4769 controls in 2016, Choi *et al*[17] reported that aspirin reduced the risk of bile duct cancer to 65%-71%, specifically 65% in intrahepatic CCC. However, they simultaneously reported that patients with bile duct disease had a risk of CCC 12.1 times higher; thus, we expect that the higher risk of CCC could offset aspirin use in patients with IHD stones. Although there were a small number of aspirin users in this study, none were diagnosed with CCC. Tseng[18] reported that the risk of CCC was lower in metformin users than in non-users by approximately 50%-60%. However, in this study, metformin users had a higher proportion of CCC without statistical significance. Liu *et al*[19] revealed that statins could reduce the risk of CCC by approximately 12% in a big-data

study of 3118 CCC patients and 15519 controls. These studies about drugs decreasing the risk of cancers were big data research generally conducted on a large number of people, so our small study on approximately 400 patients could not prove the efficacy of drugs. In the future, there is a possibility that large-scale studies will be conducted to investigate the effects of drugs or metabolic factors on the occurrence of CCC. In the long term, we need to actively implement education and campaigns targeting the general population to identify and address these risk factors.

Our study had some limitations. First, this was a single-center study with a small number of patients, approximately 400. Because IHD stone is more common among East Asian countries than in Western world[20], there might be some limitation to generalize the conclusion of a retrospective study conducted at a single center study in South Korea. Second, some patients' medications could not be investigated precisely due to dropout. Third, this was a retrospective study, so it requires attention for interpretation because of defective data. This study has no information about *Clonorchis sinensis* infection as an important risk factor for CCC. Finally, this study's relatively short average follow-up period of 7 years could have affected the risk evaluation for CCC.

CONCLUSION

In conclusion, patients who underwent removal of IHD stones showed a decreased risk of CCC regardless of the methods, specially, in the absence of remnant stone after treatment. Therefore, it is meaningful to remove IHD stones as much as possible. Medications such as statins, metformin, and aspirin[13-15] are not expected to affect the occurrence of CCC. Further studies are warranted to verify these results.

ARTICLE HIGHLIGHTS

Research background

Cholangiocarcinoma (CCC) is a type of gastrointestinal malignancy that has a poor prognosis and a difficulty of treatment. It has a low possibility of operative resection for

cure at the time of diagnosis, so research for systemic chemotherapy is being underway including immune check point inhibitor. In East Asia, the incidence of CCC is increasing, but there are few ways to early diagnosis. Therefore, it is very important to recognize and estimate the risk factor of CCC.

Research motivation

In East Asia, intrahepatic duct (IHD) stone has been recognized as one of the risk factors for developing CCC. It blocks the outflow of normal outflow of bile, resulting repetitive inflammation of liver parenchyma. Chronic inflammation of biliary tract and liver parenchyma known as contributing to malignant change, so it is important to relieve the obstruction. There have been several studies about IHD stone and CCC, but most of them had a small number of subject and few studies identified the correlation between removal of IHD stones and developing of CCC.

Research objectives

We wanted to carry out a large cohort study about the effect of removal of IHD stone for CCC development, including the optimal method for removal. Also, we analyzed the effect of medication for metabolic disease like diabetes mellitus, dyslipidemia, hypertension.

Research methods

We retrospectively analyzed patients who were diagnosed IHD stone with imaging test and underwent removal of them in Pusan National University Hospital from January 2011 to December 2020. Based on medical records, we investigated the occurrence of CCC and factors affecting the development of CCC statistically.

Research results

CCC occurred in 36 of the 397 enrolled patients. In the multivariate analysis, carbohydrate antigen 19-9 > upper normal limit, carcinoembryonic antigen > upper

normal limit, stones located in the left or both lobes, focal atrophy, and complete removal of IHD stones without recurrence were independent factors influencing CCC development. But, the type of removal method or medication for metabolic disease were not confirmed to affect the development of CCC.

Research conclusions

Regardless of methods, the complete removal of IHD stones without recurrence could reduce the development of CCC. So, it is important to choose the optimal method for removal depending on the patient and follow up carefully. Repetitive test or procedure can be needed.

Research perspectives

In the future, optimal method for removal of IHD stone regarding patient's age, sex, social or economic factors and underlying disease should be studied. In addition to this, systemic treatment for CCC including cytotoxic or immune-targeted chemotherapy specific to CCC should be developed.

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PRIMARY SOURCES

1	T. Kim, S. Han, J. Lee, G. Song, S. Park, D. Kim. "P-246 Removal of intrahepatic bile duct stone could reduce the risk of cholangiocarcinoma, regardless of recurrence of stone", Annals of Oncology, 2023 Crossref	17 words — < 1%

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