

# Intrahepatic Stones: The UKM Experience

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## Summary

Intrahepatic stones remain a major source of morbidity and mortality. With improving techniques in hepatobiliary surgery, the management and the outcome of intrahepatic calculi is reviewed. Forty-nine cases referred from all over Malaysia between January 1993 to June 1996 were analyzed retrospectively. There were thirty-two females and seventeen males. The median age was 46 years. Biliary diseases encountered in association with intrahepatic calculi included benign strictures (n=14), ascariasis (n=3), cholangiocarcinoma (n=1), Caroli's disease (n=1), and thalassaemia, (n=1), fifty-six percent of stones were located in both the intrahepatic ducts while 34% were found in the left intrahepatic duct. Thirty-one patients underwent common bile duct exploration either alone or in combination with liver resection or bilioenteric anastomosis. Despite the various combinations of surgical and non-surgical intervention 28 (57.1%) patients had residual stones. Despite the availability of newer techniques in hepatobiliary surgery, residual stones were common, resulting in higher treatment costs.

**Key Words:** Intrahepatic Stones

## Introduction

Intrahepatic calculi or hepatolithiasis have been described since the 16th century<sup>1</sup>. Intrahepatic calculi are common in the Far East and uncommon in the USA and Europe<sup>2,3</sup>. Miyake in 1913, found 20 cases of intrahepatic stones and 257 cases of cholelithiasis in 8,406 routine autopsies in Japan<sup>4</sup>. Intrahepatic stones are the third commonest abdominal surgical emergency in Hong Kong<sup>5</sup>. Intrahepatic stones have generated a lot of interest due to the high incidence and recurrences which necessitate multiple procedures, be it operative or non operative which may prove to be expensive. Patients usually succumb to hepatic damage caused by long standing intermittent obstructive jaundice, cholangitis, liver abscess and septicaemia<sup>3</sup>. The incidence of intrahepatic stones in Malaysia has previously been documented by Marshal and by Balasengaram<sup>6,7</sup>. In this study we review the more recent experience at Kuala Lumpur Hospital in managing intrahepatic stones.

## Materials and Methods

Intrahepatic stones are defined as stones located within the left and right hepatic ducts and their branches proximal to their junction at the hepatic hilum<sup>8</sup>. Kuala Lumpur Hospital is the national referral center for Malaysia. Forty-nine patients with a diagnosis of intrahepatic stones seen between January 1993 to June 1996 were included in this study. We retrospectively analyzed the case records of all these patients. Details analyzed included age, sex, race, duration of symptoms, liver function tests at presentation and modes of investigations. We also analyzed the sites of the stones and the association with common bile duct stones and gallbladder stones. Associated hepatobiliary diseases present were also documented. The different approaches in the management of intrahepatic stones were scrutinized.

## Results

During the period of study there were six hundred and forty seven cases of cholelithiasis managed by cholecystectomy in the same hospital. Of these patients, a total of 19 cases were noted to have intrahepatic stones, giving a frequency of 2.9% for intrahepatic stones. The additional 30 patients with intrahepatic stones were referred from various part of Malaysia. The overall mean age was 46 years (range 19 to 75 year). Females (n= 32) outnumbered males (n=17) by 1.9:1. Intrahepatic stones were commonest in the Malays (59%) followed by the Chinese (27%). However, when population race mix is taken into account, race does not appear to be a predisposing factor.

The most common presenting symptoms were upper abdominal pain (88%), jaundice (68%) and fever (50%). The presenting symptoms are listed in Table I. Two patients presented with acute pancreatitis. The duration of symptoms ranged from two days to three years. The commonest signs included, jaundice found in 63% of patients and hepatomegaly in 27% of patients. The commonest abnormalities in liver function tests were an elevated serum alkaline phosphatase in 43 patients (89.8%), and elevated alanine transaminase in 32 patients (65.6%). Ultrasonography (48%) was the most common initial mode of radioimaging in diagnosing intrahepatic stones followed by ERCP (32%). Subsequently, ERCP was performed in all patients. In 20% of patients the diagnosis was made using on table cholangiography and T-tube cholangiography.

In 27 patients (55.1%), the intrahepatic calculi were located in both left and right hepatic ducts. Seventeen patients (34.7%) had calculi localized in the left intrahepatic duct and in another 5 patients (10.2%) the calculi was located in the right intrahepatic duct. In 70% of patients, stones were also found within the common bile duct. Strictures were found in the left hepatic duct (n=4), common bile duct (n=3), common hepatic duct (n=3) and right hepatic duct (n=1). In the majority of patients (n=29) there was no associated biliary disease. Benign strictures were found in 14 patients. Other associated biliary diseases included *Ascaris* infestation (n=3), cholangiocarcinoma (n=1), Caroli's disease (n=1) and Thalassaemia (n=1). All 49 patients had undergone cholecystectomy. Of these, one

**Table I**  
**List of presenting symptoms in patients with intrahepatic stones**

Symptom	n
Upper abdominal pain	42 (88 %)
Jaundice	32 (65 %)
Fever	25 (50 %)
Vomiting	15 (31 %)
Pruritus	2 (4 %)
Acute pancreatitis	2 (4 %)

patient defaulted follow-up. In 31 of the patients, cholecystectomy was performed before a diagnosis of intrahepatic stones was made. Post operatively, the diagnosis of intrahepatic stone was made from immediate post-op period (via on table cholangiography or T-tube cholangiography) to 20 years after cholecystectomy.

Non-operative methods used in the management of these intrahepatic stones included choledoscopic extraction (n=31), ERCP extraction (n=9), ERCP balloon dilatation (n=2), extracorporeal shock wave lithotripsy (n=5), contact electrohydropoltripsy (n=3), nasobiliary drainage (n=3), percutaneous transhepatic biliary drainage (n=4), stent placement (n=3) and chemical dissolution (methyl-tert-butyl-ethylene) (n=2). Thirty patients had bile duct explorations and T tube insertion. Five patients had left lateral segmentectomy. Seven patients had choledochoduodenostomy and another seven patients had Roux-en-Y hepaticojejunostomy with three of these patients having an internal biliary access.

In patients undergoing ESWL, 2 patients defaulted while the remaining three patients, were free of recurrent stones at 3-12 months follow-up. The use of methyl-tert-butyl-ethylene (MTBE) via a T-tube over a period of 4 weeks was unsuccessful, and both patients required subsequent choledoscopic extraction. At the end of the study period, 13 patients had defaulted treatment and five were known to have residual stones. Of thirty-six patients under follow up twenty-three (63.9%) patients still have residual stones. However, within this group of 23 patients, only 10 were

symptomatic. Follow-up liver function tests were abnormal in 14 patients.

## Discussion

In Asia the rate of intrahepatic stones varies between countries. In Japan the relative rate was 4.1%, in Taiwan the rates were much higher at 47.3 % and 51.6 % and in Malaysia it has been reported as 10.2%-11.7 %<sup>6,7,9-11</sup>. Within the same country the rate also varies according to the region, these differences being largely attributed to the environmental factors<sup>8</sup>. During the study period the rate of intrahepatic stone in Kuala Lumpur hospital hepatobiliary unit was 2.9 %, a reduction in the frequency when compared to twenty five years ago.

Intrahepatic stones can result from migration of gall bladder stones into the intrahepatic duct (secondary intrahepatic stones), or they can develop proximal to a stricture or within multiple cystic dilatation in Caroli's disease (primary intrahepatic stones)<sup>9,12-13</sup>. The pathogenesis and chemical composition of the stones between the two types are different. The primary intrahepatic stones are primarily calcium bilirubinate stones composed of bilirubin, calcium and cholesterol. These stones are soft, friable and brown in colour. Their formation results from two main factors, bile stasis and bacterial infection. Beta-glucuronidase from bacteria such as *Escherichia Coli* present in intrahepatic ducts hydrolyzes bilirubin diglucuronide to bilirubin. The bilirubin then combines with the calcium in bile to form calcium bilirubinate<sup>8,14</sup>.

The presence of parasites or ova would act as a nidus that promote the stone formation. The two most common parasites are *Clonorchis sinensis* and *Ascaris lumbricoides*<sup>8,14</sup>. In China, stone analysis has revealed that in 38 % of patients the stone showed the presence of ova or the cuticle from *Ascaris*<sup>15</sup>. In Philippines, of 82 patients with biliary ascariasis, 70% of them showed an association with bile duct stones<sup>16</sup>. These parasites were previously thought to have an important role in stone development but more recent studies in Japan have shown that despite eradication of *Clonorchis* the presence of intrahepatic stones has continued<sup>17,18</sup>. In our series, we identified the presence of *Ascaris* in only three patients. Other biliary diseases such as post operative strictures,

sclerosing cholangitis, choledochal cyst, tumour and choledocholithiasis have also been identified to be strongly associated with intrahepatic stones<sup>15,19</sup>. In Hong Kong, there has been a gradual decline in the incidence of intrahepatic stones thought to be due to improvement in hygiene and nutritional status<sup>20</sup>. It had been postulated that poor hygiene predisposes to enteric infection, and in addition, high carbohydrate, low protein, and low saturated fat diet predisposes to malnutrition and possibly spasm of the sphincter of Oddi. In animal and human studies, a low protein diet is responsible for decreased levels of glucaro 1:4- lactone which is the leading inhibitor of bacterial beta-glucuronidase, the enzyme responsible for the splitting of bilirubin diglucuronide into insoluble unconjugated bilirubin, thereby forming calcium bilirubinate stones<sup>20</sup>.

In western series, benign strictures account for 50-80 % of patients with intrahepatic stone<sup>19,21</sup>. In this analysis, the incidence of benign strictures was appreciably less at 29%. Strictures at the liver hilum frequently involve the left hepatic and common hepatic duct<sup>14</sup>. Similar findings are observed in this series. If the strictures are confined to a segmental duct it usually involved the left lateral segmental ducts and right anterior and posterior segmental duct and their branches<sup>14</sup>. Malignant strictures are usually the result of cholangiocarcinoma. In East Asia, the association between cholangiocarcinoma and hepatolithiasis is well recognized<sup>19</sup>. In China 16 out of 20 patients with peripheral intrahepatic cholangiocarcinoma had intrahepatic stones<sup>19</sup>. Similarly in Japan, eight out of 109 cases of intrahepatic stone developed cholangiocarcinoma<sup>17</sup>. We had one patient with cholangiocarcinoma. One patient had an association with thalassaemia. His liver biopsy confirmed secondary biliary cirrhosis.

Most patients have stones located in both intrahepatic ducts<sup>22</sup> as seen in this series. However when only one side is involved, the left lobe of the liver is more commonly affected<sup>22</sup>. The distribution of stones in our patients generally coincided with many studies in the far East<sup>14,22</sup>. In a multiracial and heterogenous society like Malaysia, one would expect the incidence to be high among the Chinese. However this was true only in the late sixties when the ratio of intrahepatic stones for the Chinese to the Malays was 15:1<sup>6</sup>. But our figures show

that the ratio has now reversed to 1:2.1. The changes over the decades can be attributed to progressive changes in the population attitudes. Two decades ago the Malays, due to their customs did not utilize hospital facilities as did the Chinese<sup>6</sup>. The present distribution reflects the actual racial distribution in Malaysia.

Previous studies have indicated that there are no appreciable gender differences<sup>23,24</sup>. In the late sixties intrahepatic stones in Malaya commonly affected males, the ratio then was 1.8:1<sup>6</sup>. However in our current series the females are more commonly affected with a ratio of 1.9:1. These changes can again be attributed to traditional customs at the time. Some authors have shown that ethnic origin does not play a major role in intrahepatic stones as compared to the environmental factors<sup>15</sup>. The peak incidence of gall bladder stone disease is in the fifth or the sixth decades of life. This is in contrast to intrahepatic stones, which are most common in the third and fourth decade of life<sup>23-25</sup>. This finding has led some investigators to speculate that perhaps congenital factors may lead to stone formation at an earlier age<sup>18,24</sup>.

Laboratory results did not offer much additional diagnostic information and served only to indicate the severity of infection and degree of biliary obstruction<sup>25</sup>. Ultrasound has remained the commonest imaging technique employed for the investigation of right hypocondrium pain and jaundice in this hospital. Ultrasound is readily available in most hospitals in Malaysia unlike ERCP. The diagnostic accuracy of ultrasound can reach 70% and some investigators have placed ultrasound as the diagnostic procedure of choice<sup>14</sup>. All patients eventually underwent ERCP, which although invasive, remains the gold standard.

The treatment of hepatolithiasis is often difficult and repeated operative and non-operative interventions are often necessary. Satisfactory results can be obtained by accurate preoperative localization of the pathological site of strictures and stones. In Kuala Lumpur Hospital, a combined approach employing both surgical and non surgical techniques have been used. External access such as via the T-tube tract and hepaticocutaneous jejunostomy with internal access via a duodenojejunostomy have been described to provide

long term access for repeat postoperative choledochoscopic stricture dilatation and stones extraction. Newer approaches such as percutaneous transhepatic cholangioscopic lithotomy and hepaticocutaneous jejunostomy have provided more options to access the retained or residual stones. Hepaticocutaneous jejunostomy provides a more comfortable method of extraction compared to internal access and extraction via the T tube tract<sup>26</sup>. Hepatic resection is increasingly used in hepatolithiasis<sup>7,27</sup>. Partial hepatectomy would be indicated for liver segments that are destroyed by recurrent infection. It is the ideal procedure as strictures, stones and sources of infection are eradicated<sup>20</sup> if the stones and strictures are confined to a single hepatic lobe. However, cases without liver segment atrophy are not suitable for partial hepatectomy and it should be the aim of the surgeon to preserve the liver parenchyma as the disease may recur in the contralateral lobe. Five patients in this series had a left lateral segmentectomy and two of these patients continue to have residual stones.

Despite attempts to remove all stones during surgical intervention there is a high frequency of retained stones<sup>28</sup>. The more common factors responsible for the failure were angular deformity, stricture of bile ducts and impacted stones<sup>28</sup>. Intrahepatic stones have a tendency to recur at a later date even if all the stones are removed. With intra and post-operative choledochoscopic dilatation of strictures and extraction of stones the incidence of retained stones has been reduced to 10%-30.2%<sup>29</sup>. This figure is expected to further diminish with the availability of smaller diameter choledochoscopes. Extracorporeal shock wave lithotripsy (ESWL) and electrohydrolythotripsy (EHL) were indicated in patients where conventional methods failed either due to inaccessibility or where the stones was impacted in the duct. In some centres, ESWL and EHL can achieve an overall clearance of 98% with moderate morbidity and minimal mortality rate<sup>30</sup>. Twenty-three patients (63.9%) out of 36 at follow-up continue to have residual stones. Recurrence of intrahepatic stones is not unusual. Management usually involves prolonged hospitalization and multiple procedures.

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