Author’s response to reviews

Title: Intrahepatic bile duct exploration lithotomy is a useful adjunctive hepatectomy method for bilateral primary hepatolithiasis: An eight-year experience at a single centre

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Author’s response to reviews:

Dear Tobias Hermann Zingg and Reviewers,

Thank you for your letter and the reviewers’ comments concerning our manuscript. These comments are all valuable and very helpful for revising and improving our manuscript. We have studied the comments carefully and have made corrections that we hope meet with approval. The revised portions are marked in bold in the manuscript. The main corrections in the paper and the responses to the reviewers’ comments are as follows:

Elena Arabadzhieva, M.D., Ph.D.

(Reviewer 1):

The manuscript is very promising. It is discussing a rare disease in Western countries, so the number of studied patients is substantial, even if the condition is endemic in the Asia-Pacific
region. The used surgical technique is very interesting, too. However, I have several concerns about this article:

1/ There are several discrepancies in reported numbers. For example, in the abstract, it is written that 14 patients (25%) developed complications, but in the Result section and Table 2, it is mentioned that complication rate is 26.8% (15 cases). In the text - 7 of 52 patients have recurrent disease, but in Table 3 they are 7 of 51 cases.

Response: We appreciate your careful observations to this study. We have re-evaluated our clinical data and the data included in this article. This problem is mainly because one patient died of postoperative hepatic failure in this study, so this patient was not included in the abstract. The abstract has been revised to describe 15 complications. In addition, we have been modified Table 3 to describe 7/52 cases.

Revisions:

Page 2:

(1) Abstract: Postoperative complications occurred in 15 patients (26.8%), 14 patients responded to conservative management, and there was 1 case of postoperative mortality because of hepatic failure.

(2) Table 3. Outcomes of Stone Clearance

Recurrent stone 7/52 (13.5%)

2/ The design of the study is not clear to me. It is written that it is retrospective, but how is it possible a retrospective study to be funded; it is mentioned "at the end of the study" - how is the end of follow-up determined? Maybe the study has a prospective collection of the patients and a retrospective analysis of the data.

Response: Thank you for this excellent suggestion. This study is concerned about patients with multiple liver segment stones and complex conditions. It was difficult to ensure that the residual liver volume was sufficient and to remove stones with conventional surgical methods. We developed this surgical plan based on a precise preoperative assessment. We also formulated a detailed study and follow-up plan, and the programme was also approved by the ethics committee and consented to by the patients. The follow-up period lasted until December 2015. Postoperative follow-up began 1 month after surgery, followed by once every 3 months or as needed if the patients presented with cholangitis or were suspected of having stone recurrence. Patients who failed to attend follow-up visits were contacted by telephone. In addition, in order to assess the effectiveness and safety of the procedure, we retrospectively collected and analysed
clinical patient data. Therefore, I strongly agree with your point of view, which involves prospective patient collection and retrospective data analysis.

Revisions:

Page 1: Methods

A study was conducted involving 56 patients with complicated bilateral primary hepatolithiasis who underwent IHBDIL combined with hepatectomy at our hospital from January 2006 to December 2014. The perioperative and long-term outcomes that were retrospectively analysed included the stone clearance rate, operative morbidity and mortality, and stone recurrence rate. Patients with a preoperative diagnosis of cholangiocarcinoma were excluded.

3/ The inclusion and exclusion criteria are not clear. It is mentioned only that the patients with concomitant cholangiocarcinoma are excluded.

Response: Thank you for your advice. We have added detailed inclusion and exclusion criteria to the “Patients” subsection of the “Methods” section.

Revisions:

Page 3–4: Patients

The inclusion criteria for this study were as follows: (1) the stones were located in multiple segments of the liver; (2) the patients could not tolerate multiple segmental resection; (3) the distal bile duct where the stones were located was dilated, and the proximal bile duct did not have severe stricture; and (4) patients had Child-Pugh class A or B disease. The exclusion criteria for this study were as follows: (1) the stones could be removed by routine hepatectomy and CBD exploration; (2) the patients were highly suspected of having cholangiocarcinoma; (3) the patients could not tolerate surgery due to poor general conditions; or (4) the patients refused surgery.

4/ The description of the whole procedure should be improved. For example, what happens with the traction sutures after IHBDIL, how deep are they placed?

Response: Thank you for your helpful suggestions.

We have described the procedure in detail and added content to the “Methods” section of the article. There are various degrees of dilatation in the distal aspect of the diseased intrahepatic bile duct. We incised the dilated bile duct approximately one centimetre. After the stones were removed, we sutured the bile duct in a continuous pattern with Prolene and sutured the liver
parenchyma in an interrupted pattern. We often use traction sutures on both sides of the diseased bile duct on the surface of the liver parenchyma. The traction lines were placed approximately 1 cm deep and had the effect of fully exposing the intrahepatic bile duct and reducing bleeding. After the stones were removed and suturing completed, we removed the traction sutures.

Revisions:

The revised portions are marked in bold on pages 3-4 (Surgical Procedure).

5/ The postoperative results and follow-up could be presented more precisely. There is no information about the liver function; what happened with the treated with IHBDIL liver segments - % of atrophy, for example?

Response: According to your suggestion, we have improved the description of postoperative and follow-up results. We have included postoperative liver function parameters including albumin, ALT, and bilirubin in Supplementary Table 2. The postoperative follow-up results showed that there were 7 patients with different degrees of liver atrophy at the site of IHBDIL liver segments, but their liver function was normal.

Revisions:

(1) Page 5: Follow-up

The follow-up period lasted until December 2015, and the postoperative follow-up began 1 month after surgery. All patients were followed for routine liver function tests and recurrence of the stones by US or CT monitoring every 3 months.

(2) Page 6: Perioperative Outcome

Patients' liver function parameters gradually returned to normal serum concentrations during hospitalization (Supplemental Table 2). However, 2 patients with grade IIIa bile leakage had two times the normal level of alanine aminotransferase (ALT) discharge, without fever or jaundice. These two patients were treated with hepatoprotective drugs after discharge, and their ALT levels returned to normal after one month of follow-up.

Seven patients had different degrees of liver atrophy at the site of the IHBDIL liver segments, but their liver function was normal.

6/ The English should be improved.

Response: We have chosen your recommended professional English language editing company to improve our English.
Emmanuel Melloul (Reviewer 2):

This study by Li et al. includes many shortcomings in the method and interpretation of the results that render the conclusions questionable. One of the major limitations of the study is the small study group. The technique described is novel but the design of the study lacks a control group to draw any conclusions. Many patients were already at the stage of secondary biliary cirrhosis which raise some concern about the selection criteria of the patients. In addition, the number of transfused patients seems very high (please clarify). Finally, the manuscript needs more language editing.

Response: Thank you very much for your comments. We must admit that there are still some limitations of this study. Each year, our team collected large numbers of patients with intrahepatic and extrahepatic bile duct stones, most of whom could be treated with hepatectomy. However, the patients involved in this study had some unique characteristics: most of them had complicated conditions, a long course of disease, and multiple liver segments with stones. These patients could not tolerate hepatectomy of multiple hepatic segments, and the limited surgical treatment options for these patients led to the relatively small number of cases for an effective case-control study. Based on your suggestion, we will increase the sample size by conducting a multicentre controlled study to confirm the conclusions of this study.

However, the aim of this study was to evaluate complicated hepatolithiasis. Although it is difficult to perform a controlled study, the results of this study, such as the stone clearance rate, stone recurrence rate, and postoperative complications, revealed similar clinical outcomes compared to other clinical studies in the literature[1,2]. Due to the long course of disease and long-term biliary obstruction, some patients developed secondary biliary cirrhosis. In this study, 13 patients with secondary biliary cirrhosis were treated with preoperative hepatoprotective drugs, and their liver function reached Child-Pugh A. We analysed the data and considered that there are several reasons for the increased blood transfusion rate in this study. First, all the patients had stones located in multiple liver sections and had to undergo both IHBDIL and hepatectomy. Second, due to long-term biliary obstruction and inflammation, the diseased liver bleeds more readily than the normal liver. Third, in order to ensure patient safety, we administered blood transfusions when a patient’s intraoperative haemoglobin level was 70-80 g/L. By reviewing the relevant literature, we found that the transfusion rate in this study was similar to that in other studies of intrahepatic duct stones treated with laparoscopic hepatectomy[3].
