**Name of journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO: 20108**

**Manuscript Type:** **ORIGINAL ARTICLE**

***Retrospective Study***

**Negative short-term impact of intraoperative biliary lavage in patients with hepatolithiasis**

Jiang O *et al.* Intraoperative biliary lavage for hepatolithiasis

Ou Jiang, Rong-Xing Zhou, Ke Yang, Chun-Xian Cai, Yu Liu, Nan-Sheng Cheng

**Ou Jiang, Ke Yang, Chun-Xian Cai, Yu Liu,** Department of Surgical Oncology, The Second People’s Hospitalof Neijiang, Neijiang 641100, Sichuan Province, China

**Rong-Xing Zhou, Nan-Sheng Cheng,** Department of Biliary Surgery, West China Medical Center of Sichuan University, Chengdu 610041, Sichuan Province, China

**Author contributions:** Jiang O and Zhou RX contributed same work to this study; Cheng NS was the guarantor and designed research; Jiang O and Zhou RX performed research; Yang K participated in the acquisition; Cai CX and Liu Y performed the analysis, and interpretation of the data; Jiang O and Zhou RX drafted the manuscript; Cheng NS revised the article.

**Supported by** the Science and Technology Support Project of Sichuan Province, No. 2014SZ0002-10 and No. 2015FZ0076.

**Institutional review board** **statement:** This study is retrospective, it was approved by the review board of West China Hospital.

**Informed consent statement:** All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

**Conflict-of-interest statement:** There are no conflicts of interest to report.

**Data sharing statement:** No additional data are available.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Correspondence to:** **Nan-Sheng Cheng, MD,** Department of Biliary Surgery, West China Medical Center of Sichuan University, No. 37 Guo Xue Vally, Chengdu 610041, Sichuan Province, China. zhourongxing@vip.163.com

**Telephone:** +86-28-85422465

**Fax:** +86-28-85422468

**Received:** May 28, 2015

**Peer-review started:** May 31, 2015

**First decision:** June 19, 2015

**Revised:** September 27, 2015

**Accepted:** December 8, 2015

**Article in press:**

**Published online:**

**Abstract**

**AIM:** To evaluate short-term outcomes following intraoperative biliary lavage for hepatolithiasis.

**METHODS:** A total of 932 patients who were admitted to the West China Medical Center of Sichuan University between January 2010 and January 2014 and underwent bile duct exploration and lithotomy were retrospectively included in our study. The patients were divided into the lavage group and the control group. Related pre-, intra-, and postoperative factors were recorded, analyzed and compared between the two groups in order to verify the effects of biliary lavage on the short-term outcome of patients with hepatolithiasis.

**RESULTS:** Amongst the patients who were included, 678 patients with hepatolithiasis were included in the lavage group, the other 254 patients were enrolled in control group. Data analyses revealed that preoperative baseline and related intraoperative variables were not significantly different. However, patients who underwent intraoperative biliary lavage had prolonged postoperative hospital stays (6.67 d *vs* 7.82 d, *P =* 0.024), higher hospitalization fees (RMB 28437.1 *vs* RMB 32264.2, *P =* 0.043), higher positive rates of bacterial cultures from blood (13.3% *vs* 25.8%, *P =* 0.001) and bile (23.6% *vs* 40.7%, *P =* 0.001) samples, and increased usage of advanced antibiotics (26.3% *vs* 38.2%, *P =* 0.001). In addition, in the lavage group, more patients had fever (> 37.5 ºC, 81.4% *vs* 91.1%, *P =* 0.001) and hyperthermia (> 38.5℃，39.7% *vs* 54.9%, *P =* 0.001), and higher white blood cell counts within 7 d after the operation was observed compared to the control group.

**CONCLUSION:** Intraoperative biliary lavage might increase the risk of postoperative infection, while not significantly increasing gallstone removal rate.

**Key words:** Hepatolithiasis; Biliary lavage; Postoperative infection

**© The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Hepatolithiasis remains a prevalent disease in Asia-Pacific regions, the most important treatment procedures are hepatectomy and intraoperative choledochofiberscopy combined with basket stone extraction, and intraoperative biliary lavage is also a commonly used, simple, and effective procedure for the extraction of intrahepatic stones. However, few investigators have noted the potential risks associated with this method. In this study, we collected and analyzed the data and the aim of this retrospective study was to evaluate the risks and short-term patient outcomes following intraoperative biliary lavage.

Jiang O, Zhou RX, Yang K, Cai CX, Liu Y, Cheng NS. Negative short-term impact of intraoperative biliary lavage in patients with hepatolithiasis. *World J Gastroenterol* 2015; In press

**INTRODUCTION**

Despite its rarity in western countries, hepatolithiasis remains a prevalent disease in Asia-Pacific regions[[1-3](file:///C%3A%5CUsers%5Crongxing%5CDesktop%5Cmanuscript.doc#_ENREF_1)]. As an important component of primary stones, intrahepatic stones associated with hepatolithiasis are frequently pigment or mixed stones[[4](file:///C%3A%5CUsers%5Crongxing%5CDesktop%5Cmanuscript.doc#_ENREF_4)]. Intrahepatic stones can cause recurring episodes of localized proliferative cholangitis, possibly leading to ductal wall thickening and biliary stricture or obstruction. This can also be accompanied by irregular distal dilatation, which might influence biliary fluid dynamics. In addition, the role of infections should also be considered[[2](file:///C%3A%5CUsers%5Crongxing%5CDesktop%5Cmanuscript.doc#_ENREF_2),[3](file:///C%3A%5CUsers%5Crongxing%5CDesktop%5Cmanuscript.doc#_ENREF_3),[5](file:///C%3A%5CUsers%5Crongxing%5CDesktop%5Cmanuscript.doc#_ENREF_5)]. Taken together, the proliferation of the stones may result in a vicious cycle, eventually leading to hepatic abscesses, atrophy, cirrhosis, or even cholangiocarcinoma[4-6].

The current treatment principle for hepatolithiasis includes gallstone extraction, removal of affected segments, elimination of strictures, and prevention of recurrence[[3](file:///C%3A%5CUsers%5Crongxing%5CDesktop%5Cmanuscript.doc#_ENREF_3),[4](file:///C%3A%5CUsers%5Crongxing%5CDesktop%5Cmanuscript.doc#_ENREF_4),[7-10](file:///C%3A%5CUsers%5Crongxing%5CDesktop%5Cmanuscript.doc#_ENREF_7)]. In conventional bile duct exploration and lithotomy, the most important treatment procedures are hepatectomy and intraoperative choledochofiberscopy combined with basket stone extraction[[8-10](file:///C%3A%5CUsers%5Crongxing%5CDesktop%5Cmanuscript.doc#_ENREF_8)]. In addition, some other passages to access biliary were also commonly adopted, such as, combined endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy (EST), percutaneous transhepatic cholangioscopy (PTCS) and hepaticocutaneous jejunostomy[2,11-13]. Similarly, biliary lavage is also a commonly used method for stone extraction. Many surgeons or endoscopists perform biliary lavage at a certain pressure in order to remove minuscule or uncaptured stones and to loosen entrapped stones for easier extraction. In contrast, choledochofiberscopy combined with basket stone extraction enables the removal of only one stone at a time; hence, biliary lavage is a more convenient extraction method, and this has led to its widespread application.

Intraoperative biliary lavage is a commonly used, simple, and effective procedure for the extraction of intrahepatic stones. However, few investigators have noted the potential risks associated with this method. Since Jan 2010, our team have noticed and suspected that intraoperative biliary lavage may increase postoperative infective complications. And we avoided employing intraoperative lavage since then while the other surgeons still follow the traditional way. So we collected and analyzed the data and the aim of this retrospective study was to evaluate the risks and short-term patient outcomes following intraoperative biliary lavage.

**MATERIALS AND METHODS**

All patients with hepatolithiasis who were admitted to the West China Hospital of Sichuan University between January 2010 and January 2014 were retrospectively included in the study. This study was approved by the review board of West China Hospital.

Patients were assigned to either the lavage group or control group based on whether or not they had received intraoperative biliary lavage. Patients who had undergone emergency surgery or who had presented with acute preoperative suppurative cholangitis or other infections with evidence of fever (axillary temperature > 37.5 ºC) were excluded.

In our hospital, EST was the primary treatment choice for extrahepatic bile stones, while all intrahepatic bile stones patients were resolved by surgical procedure. PTCS was implemented recently, the patients were performed PTCS were not included in this study. All the surgical procedure were performed by a total of 6 surgeons, though all the surgeons were engaged in hepatobiliary surgery more than 10 years, therefore, there were no significant gap in surgical technique and management among them.

Medical histories were obtained from all patients; in addition, all patients underwent physical examinations, followed by preoperative liver and kidney function tests, routine blood tests, electrocardiography, chest radiography, and other tests. B-mode ultrasound and magnetic resonance cholangiopancreatography or computed tomography, as well as intraoperative choledochofiberscopy, were also performed to comprehensively assess the location of the gallstones and to determine pathological changes in the liver, biliary strictures.

Intraoperative biliary lavage involved inserting an 8–14F catheter into the intrahepatic bile duct besides the stones, attaching a 20 mL hollow needle to the catheter, and rinsing the intrahepatic bile duct by rapid expulsion of physiological saline in about 2 s, and the stones would be discharged with the rapid outflow stream. The pressure of lavage was not detected directly, while it was much higher than the normal pressure of the bile duct (8-10 cm H2O).

Thirty minutes before abdominal incision, 2 g of first-generation or second-generation cephalosporin was routinely administered intravenously. Cephalosporin administration was also repeated every 3 h during the operating time or when blood loss exceeded 1000 mL. All patients were under general anaesthesia and the surgery approach including open or laparoscope which is decided by the chief surgeon according to the condition of each patient. We opened and explored the common bile duct while biliary endoscopy and lithotomy were routinely performed through CBD. The lavage group patients received one or repeated intraoperative biliary lavage while the control group patients not. We would remove all stone intraoperative through common bile duct unless the lithotomy procedure lead hemabilia. Bile samples were collected after opening the bile duct for bacterial culture. For patients with unilateral hepatolithiasis or with accompanying liver atrophy, liver resection was also performed during surgery unless the patients refused. After completing the lithotomy, T-tube and peritoneal drainage catheter placement was performed routinely before closed the abdominal wall. Six week after surgery, we would perform lithotomy repeatedly by T tube sious with choledochoscope for the incompletely stone removed patients.

Cephalosporin administration did not exceed 72 h following surgery, unless the patient had an infection or was clearly at risk of infection. Axillary temperature was measured 2–4 times daily after the operation, and the highest daily temperature was recorded and analyzed. If the patient’s axillary temperature exceeded 38.5 ºC, one or more biological samples, including peripheral venous blood, bile, sputum, and peritoneal fluid, were collected for bacterial culture. Antibiotic administration was then adjusted based on the results of the culture. If antibiotics were ineffective, the medication was adjusted further based on the results of the bacterial culture. Routine blood tests and liver function tests were performed on the first, third, and seventh days after the operation and bile samples for bacterial culture were collected from the T-tube on postoperative days 1–3. Other surgery-related complications were also recorded and analyzed.

Related preoperative, intraoperative, and postoperative factors were recorded, analyzed, and compared between the lavage and control groups; the effects of biliary lavage on postoperative short-term patient outcomes were then analyzed and compared.

***Statistical analysis***

SPSS version 19.0 (SPSS Inc, Chicago, IL) was used for all analyses. Results are presented as mean ± standard error of the mean. The *t* or *U* tests were applied to continuous variable, while binary categorical variable were assessed using the χ2 test. *P* value less than 0.05 with two-sided considered statistically significant.

**RESULTS**

Between January 2010 and January 2014, a total of 1035 patients with hepatolithiasis were included in the study. After applying the exclusion criteria, 932 patients were included in the study, including 261 men and 662 women (Figure 1). As our hospital is a regional center for intensive care, the patients admitted to our hospital were typically in serious conditions. Among the patients included in our study, 44% had histories of single or multiple bile duct exploration or lithotomy, and 10.2% of these patients received partial liver resection. In 298 patients, the stones were located on both the right and left sides of the liver and the extrahepatic bile duct. In 134 patients, the stones were located bilaterally in the liver only. In 275 patients, the stones were located either on the left or right side of the liver, as well as in the extrahepatic bile duct. For the remaining 225 patients, the stones were located either on the left or right side of the liver only.

Two patients in our study died: one due to severe abdominal infection while the other due to hemorrhagic shock.

In all, 678 patients were included in the lavage group and 254 patients in the control group. There were no statistically significant differences between the two groups with regard to age; gender; comorbid diseases; gallstone location; past history of bile duct exploration, liver resection, and cholangioenterostomy; and laboratory serological test results (Table 1).

The intraoperative variables of the two groups are outlined in Table 2. Blood loss, presence of liver atrophy and biliary stricture, addition of liver resection and cholangioenterostomy during surgery, and other related variables were not significantly different between the two groups, while the operation time of control group was slightly longer than lavage group.

Table 3 shows a comparison of postoperative variables between the two groups. Compared to the control group, the lavage group had a longer average length of hospital stay, increased hospitalization fees, and increased risk of postoperative fever and hyperthermia, as well as an increased probability of positive blood and bile bacterial cultures. The number of patients who required stronger antibiotic was also higher in the lavage group. The peak axillary temperature on the first to fourth day after surgery was also significantly higher in the lavage group compared to the control group. In addition, white blood cell counts during the first seven days after surgery were significantly higher in the lavage group compared to the control group (Figure 2). However, the incidence of other surgery-related complications, such as bile leakage and lung infections, was not significantly different between the two groups. Furthermore, although the probability of abdominal infection was higher in the lavage group compared to the control group, this difference was not statistically significant. Moreover, there was no significant difference between the two groups with regard to stone clearance rate, which is an important prognostic factor for hepatolithiasis; this was likely because of the use of choledochofiberscopy intraoperatively and postoperatively.

The results of postoperative bacterial culture using blood and bile samples revealed that 545 colonies of bacteria were cultivated from 438 patients. There were 172 colonies of *Escherichia coli* (*E. coli*)*,* which had the highest count, followed by 141 colonies of *Klebsiella**pneumoniae,* 94 colonies of *Enterobacter cloacae,* 75 colonies of *Pseudomonas aeruginosa,* 43 colonies of *Enterococcus faecalis*, and 87 colonies of other bacteria. In terms of the total bacterial culture count, the lavage group had significantly higher counts for both blood and bile cultures compared to the control group. However, with blood cultures, there were no statistically significant differences in the counts of *Pseudomonas aeruginosa*, *Enterobacter cloacae*,and *Enterococcus faecalis* between the two groups. Similarly, with bile cultures, *Enterococcus faecalis*counts were not significantly different between the two groups (Table 4).

Higher level antibiotic were more frequently required in the lavage group compared to the control group, and this difference was statistically significant. There were significant differences between the two groups in the antibiotic usage of imipenem, moxifloxacin, piperacillin-tazobactam, and cefoperazone-sulbactam. However, there were no significant differences antibiotic usage between the two groups of ceftriaxone, levofloxacin, and ciprofloxacin (Table 5).

**DISCUSSION**

In this study, we found that performing intraoperative biliary lavage during biliary lithotomy might have negative effects on patients with hepatolithiasis, and it may not increase the clearance rate of gallstones. As hepatolithiasis can lead to recurring localized chronic cholangitis, which can cause ductal wall thickening and biliary stricture[[2](file:///C%3A%5CUsers%5Crongxing%5CDesktop%5Cmanuscript.doc#_ENREF_2),[3](file:///C%3A%5CUsers%5Crongxing%5CDesktop%5Cmanuscript.doc#_ENREF_3),[5](file:///C%3A%5CUsers%5Crongxing%5CDesktop%5Cmanuscript.doc#_ENREF_5)], it creates large obstacles against stone removal in the drainage segments of the bile ducts. Furthermore, miniscule and soft stones are not easily removed by choledochofiberscope-guided basket stone extraction; therefore, surgeons commonly apply biliary lavage at a certain pressure to expel the stones. Therefore, unfortunately, according to our investigations, this commonly used method of stone extraction might significantly increase the risk of postoperative infection, fever, and hyperthermia in patients, thereby prolonging the patients’ average length of hospital stay and increasing hospitalization fees. Moreover, the technological advancements and application of choledochofiberscopy and shock wave lithotripsy though may prolong the operation time, as well as increased use of liver resection, are sufficiently able to maintain a high clearance rate of intrahepatic bile duct stones[[2](file:///C%3A%5CUsers%5Crongxing%5CDesktop%5Cmanuscript.doc#_ENREF_2)], and therefore, the relative effectiveness of biliary lavage for stone removal may be decreasing.

The causes of hepatolithiasis are complicated and related to various health conditions. In China, a large proportion of patients have a history of roundworm infection[[14](file:///C%3A%5CUsers%5Crongxing%5CDesktop%5Cmanuscript.doc#_ENREF_11)], while several studies have shown that bacteria play an important role in the occurrence of hepatolithiasis[[15-17](file:///C%3A%5CUsers%5Crongxing%5CDesktop%5Cmanuscript.doc#_ENREF_12)]. Normal bile should be sterile; however, hepatolithiasis will occur due to the involvement of bacteria. For example, *E. coli* can secrete β-glucuronidase which breaks down conjugated bilirubin found in bile into free bilirubin; the free bilirubin will then combine with calcium to form pigment stones, and pigment stones are the main type of gallstone found in hepatolithiasis[[18](file:///C%3A%5CUsers%5Crongxing%5CDesktop%5Cmanuscript.doc#_ENREF_15)]. Other research has also shown that there were remnants of bacterial DNA in a proportion of intrahepatic bile duct stones[[19](file:///C%3A%5CUsers%5Crongxing%5CDesktop%5Cmanuscript.doc#_ENREF_16)]. Therefore, a few scholars believe that chronic bacterial infection may be present even in patients with hepatolithiasis who do not experience acute attacks, and that the bacteria still retain a certain degree of activity[15,17]. Bile duct exploration and lithotomy for hepatolithiasis can easily lead to the occurrence of acute postoperative biliary infection or even sepsis. This might be because patients with hepatolithiasis also present with accompanying biliary strictures and chronic proliferative cholangitis. Firstly, the gallstones might have sharper edges, and the use of bougienage, choledochofiberscopy, and other procedures during surgery might damage the biliary mucosa. Subsequently, bacteria that were already involved in chronic biliary infection may then enter the blood stream and cause sepsis. In addition, in theory, pressurized lavage may cause bacteria to break free from the gallstones, which will exacerbate or increase the risk of retrograde flow of bacteria into the blood. Besides, portions of the hepatolithiasis patients combined with liver cirrhosis which can impair immune system[20]. Our study has shown that acute biliary infection and concurrent blood infection occur frequently in patients with hepatolithiasis, and intraoperative biliary lavage can exacerbate the occurrence and severity of acute infections.

In the absence of intraoperative biliary lavage, patients with hepatolithiasis are already prone to fever and hyperthermia after bile duct exploration and lithotomy, with occurrence rates of 81.4% and 39.7%, respectively. However, the application of biliary lavage increased these occurrence rates to 91.1% and 54.9%, respectively. Our results also demonstrated that bacterial cultures from bile and blood samples of patients with postoperative infection had lower positive rates compared to those without postoperative infection (blood: 13.3% and 25.8%, respectively; bile: 23.6% and 40.7%, respectively). This might be due to the use of prophylactic antibiotics. Bacterial cultures from patients with postoperative infection contained mostly Gram-negative bacteria, of which *E. coli*, *K. pneumoniae, Pseudomonas aeruginosa,* and *Enterobacter cloacae* were the most common types; of note, these bacteria are normal intestinal bacteria. Currently, studies have shown that causative pathogens of biliary infections come mostly from the intestines[[11-13](file:///C%3A%5CUsers%5Crongxing%5CDesktop%5Cmanuscript.doc#_ENREF_12)], which is consistent with our results.

Since hepatolithiasis is usually accompanied by bacterial infection, the generally consensus for treatment is that the intraoperative use of prophylactic antibiotics is beneficial; however, the most effective type of antibiotic for prophylaxis has not been established[21,[22](file:///C%3A%5CUsers%5Crongxing%5CDesktop%5Cmanuscript.doc#_ENREF_18)]. At present, it is believed that first- and second-generation cephalosporins should be used during abdominal surgery as prophylactic antibiotics for surgical site infection[[23](file:///C%3A%5CUsers%5Crongxing%5CDesktop%5Cmanuscript.doc#_ENREF_19)]. In this study, we used first- and second-generation cephalosporins as prophylactic antibiotics for all cases. However, most patients with hepatolithiasis have concurrent Gram-negative bacterial infections, and the antibacterial activity of first- and second-generation cephalosporins is quite poor against these bacteria. Furthermore, most of the patients who were recruited for this study had previously undergone multiple biliary operations and had histories of multiple acute cholangitis; thus, different types of antibiotics were administered to patients, and non-standard antibiotics were used in certain cases. Accordingly, there may be several types of bacteria present with resistance to various drugs. Therefore, for these reasons, there were higher proportions of patients in our study who had fever, cholangitis, and sepsis. In addition, these proportions were even higher in the lavage group. With regard to the treatment of biliary infections, as some patients developed concurrent blood infection, antibiotic selection was based on drug sensitivity, while also taking into account drug concentrations in the blood and bile[[24](file:///C%3A%5CUsers%5Crongxing%5CDesktop%5Cmanuscript.doc#_ENREF_20),[25](file:///C%3A%5CUsers%5Crongxing%5CDesktop%5Cmanuscript.doc#_ENREF_21)]. It is currently believed that piperacillin-tazobactam, cefoperazone-sulbactam, ceftriaxone, and levofloxacin, which have high bile concentrations, are the better choices, and those with additional β-lactamase inhibitor activity might have even better efficacies[[26-30](file:///C%3A%5CUsers%5Crongxing%5CDesktop%5Cmanuscript.doc#_ENREF_22)]. The results of our study have shown that the use of cefoperazone-sulbactam, piperacillin-tazobactam, and moxifloxacin within our medical center is in line with the abovementioned drug selection principle, while the lack of difference between the two groups in terms of drug usage for ceftriaxone, levofloxacin, and ciprofloxacin is likely due to surgeons’ preferences.

In this study, we investigated and clarified the postoperative short-term effects of biliary lavage in a large group of patients with hepatolithiasis. However, there were certain limitations to our study. First, our study was a retrospective analysis; thus, data collection, statistical analyses, and other aspects of the study might be biased, which might influence the results. Second, intraoperative biliary lavage involves manual control of the syringe by the surgeon, and the water pressure is not set automatically by machines; therefore, each surgeon might use different levels of water pressure for each operation, and the pressure gradient might theoretically be positively correlated to the retrograde flow of bacteria into the blood. In reality, the use of choledochofiberscopy during surgery also requires a certain level of water pressure in order to maintain a clear field of vision. Our study showed that intraoperative pressurized biliary lavage correlated with postoperative occurrence of bacteremia and sepsis. However, we were not able to analyze water pressure as one of the factors, and therefore, we were not able to determine what level of water pressure may cause the abovementioned effects. In order to address these issues, our research group has registered a prospective randomized controlled trial on the World Health Organization website (currently under ethical review) in order to further clarify and comprehensively evaluate the effects of different levels of lavage pressure gradients and the addition of antibiotic intervention on patients with hepatolithiasis.

In conclusion, intraoperative biliary lavage is a commonly used method of stone extraction. Although it does not increase the occurrence of severe and fatal complications, our study has shown that it might increase the postoperative risk of infection-related complications in patients with hepatolithiasis. These complications will lead to prolonged hospital stays and increased hospitalization fees, while not significantly increasing the rate of gallstone removal; therefore, we suggest that this procedure should be used with caution.

**COMMENTS**

***Background***

Hepatolithiasis remains a prevalent disease in China. As hepatolithiasis can lead to recurring localized chronic cholangitis, which can cause ductal wall thickening and biliary stricture, it creates large obstacles against stone removal in the drainage segments of the bile ducts. Furthermore, miniscule and soft stones are not easily removed by choledochofiberscope-guided basket stone extraction; therefore, surgeons commonly apply biliary lavage at a certain pressure to expel the stones. However, few investigators have noted the potential risk of biliary lavage.

***Research frontiers***

Intraoperative biliary lavage is commonly used for clear the intrahepatic stone, however, there are very few English literatures could be soured in PubMed concerning the risk of this procedure. This study focus on the short-term impact of biliary lavage for the hepatolithiasis patients.

***Innovations and breakthroughs***

Intraoperative biliary lavage is commonly used, as one of the tradition methods to remove the intrahepatic biliary stones. However, very few experts noticed the risk of this procedure. In this study, the authors research the short-term impact of intraoperative biliary lavage. The result suggested intraoperative biliary lavage may increase the rate of postoperative infection and prolong the hospital stay.

***Applications***

The data in this study suggested intraoperative biliary lavage may negative short –term impact for the hepatolithiasis patients, however, this study was retrospectively designed, further prospective RCT to re-confirm the conclusion.

***Terminology***

Intraoperative biliary lavage is inserting an 8–14F catheter into the intrahepatic bile duct besides the stones, attaching a 20 mL hollow needle to the catheter, and rinsing the intrahepatic bile duct by rapid expulsion of physiological saline in about 2 s. Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa, Enterobacter cloacae, Enterococcus faecalis are various kinds of bacteria. Imipenem, Ceftriaxone, Moxifloxacin, Piperacillin-tazobactam, Cefoperazone-sulbactam, Levofloxacin, Ciprofloxacin are different kinds of antibiotics.

***Peer-review***

This manuscript addresses the necessity and safety of intraoperative biliary lavage for hepaticolithiasis. This paper is interesting and provides information to answer an important clinical question when dealing with recurrent pyogenic cholangitis, *i.e*., sepsis.

**REFERENCES**

1 **Zhang GW**, Lin JH, Qian JP, Zhou J. Identification of risk factors for intraoperative hemobilia and its correlation with early postoperative complications in patients with hepatolithiasis. *Am J Surg* 2015; **209**: 260-267 [PMID: 25190546 DOI: 10.1016/j.amjsurg.2014.05.032]

2 **Tsuyuguchi T**, Miyakawa K, Sugiyama H, Sakai Y, Nishikawa T, Sakamoto D, Nakamura M, Yasui S, Mikata R, Yokosuka O. Ten-year long-term results after non-surgical management of hepatolithiasis, including cases with choledochoenterostomy. *J Hepatobiliary Pancreat Sci* 2014; **21**: 795-800 [PMID: 25070702 DOI: 10.1002/jhbp.134]

3 **Suzuki Y**, Mori T, Yokoyama M, Nakazato T, Abe N, Nakanuma Y, Tsubouchi H, Sugiyama M. Hepatolithiasis: analysis of Japanese nationwide surveys over a period of 40 years. *J Hepatobiliary Pancreat Sci* 2014; **21**: 617-622 [PMID: 24824191 DOI: 10.1002/jhbp.116]

4 **Kim HJ**, Kim JS, Suh SJ, Lee BJ, Park JJ, Lee HS, Kim CD, Bak YT. Cholangiocarcinoma Risk as Long-term Outcome After Hepatic Resection in the Hepatolithiasis Patients. *World J Surg* 2015; **39**: 1537-1542 [PMID: 25648078 DOI: 10.1007/s00268-015-2965-0]

5 **Zhang GW**, Lin JH, Qian JP, Zhou J. Identification of prognostic factors and the impact of palliative resection on survival of patients with stage IV hepatolithiasis-associated intrahepatic cholangiocarcinoma. *J Surg Oncol* 2014; **109**: 494-499 [PMID: 24310342 DOI: 10.1002/jso.23524]

6 **Liu FB**, Yu XJ, Wang GB, Zhao YJ, Xie K, Huang F, Cheng JM, Wu XR, Liang CJ, Geng XP. Preliminary study of a new pathological evolution-based clinical hepatolithiasis classification. *World J Gastroenterol* 2015; **21**: 2169-2177 [PMID: 25717253 DOI: 10.3748/wjg.v21.i7.2169]

7 **Ma WJ**, Zhou Y, Shrestha A, Mao H, Li FY, Cheng NS, Zhang W, Xu RH, Zhang YQ, Jiang T, Feng H, Li W, Han Q. Applying chemical bile duct embolization to achieve chemical hepatectomy in hepatolithiasis: a further experimental study. *J Surg Res* 2014; **187**: 113-121 [PMID: 24290428 DOI: 10.1016/j.jss.2013.10.053]

8 **Li SQ**, Liang LJ, Peng BG, Hua YP, Lv MD, Fu SJ, Chen D. Outcomes of liver resection for intrahepatic stones: a comparative study of unilateral versus bilateral disease. *Ann Surg* 2012; **255**: 946-953 [PMID: 22504194 DOI: 10.1097/SLA.0b013e31824dedc2]

9 **Fang CH**, Liu J, Fan YF, Yang J, Xiang N, Zeng N. Outcomes of hepatectomy for hepatolithiasis based on 3-dimensional reconstruction technique. *J Am Coll Surg* 2013; **217**: 280-288 [PMID: 23870220 DOI: 10.1016/j.jamcollsurg.2013.03.017]

10 **Tian J**, Li JW, Chen J, Fan YD, Bie P, Wang SG, Zheng SG. Laparoscopic hepatectomy with bile duct exploration for the treatment of hepatolithiasis: an experience of 116 cases. *Dig Liver Dis* 2013; **45**: 493-498 [PMID: 23395128 DOI: 10.1016/j.dld.2013.01.003]

11 **Tan J**, Tan Y, Chen F, Zhu Y, Leng J, Dong J. Endoscopic or laparoscopic approach for hepatolithiasis in the era of endoscopy in China. *Surg Endosc* 2015; **29**: 154-162 [PMID: 25027471 DOI: 10.1007/s00464-014-3669-5]

12 **Cheon YK**, Cho YD, Moon JH, Lee JS, Shim CS. Evaluation of long-term results and recurrent factors after operative and nonoperative treatment for hepatolithiasis. *Surgery* 2009; **146**: 843-853 [PMID: 19744434 DOI: 10.1016/j.surg.2009.04.009]

13 **Parlak E**, Disibeyaz S, Oztas E, Cicek B, Ulas M, Ozogul Y, Ozdemir E, Olcer T, Sasmaz N, Sahin B. Endoscopic treatment of biliary disorders in patients with Roux-en-Y hepaticojejunostomy via a permanent access loop. *Endoscopy* 2011; **43**: 73-76 [PMID: 21108177 DOI: 10.1055/s-0030-1255957]

14 **Heimes JK**, Waller S, Olyee M, Schmitt TM. Hepatolithiasis after Hepaticojejunostomy: Ascaris lumbricoides in the biliary tract. *Surg Infect (Larchmt)* 2013; **14**: 470-472 [PMID: 23991626 DOI: 10.1089/sur.2012.115]

15 **Yu JK**, Pan H, Huang SM, Huang NL, Yao CC, Hsiao KM, Wu CW. Calcium content of different compositions of gallstones and pathogenesis of calcium carbonate gallstones. *Asian J Surg* 2013; **36**: 26-35 [PMID: 23270822 DOI: 10.1016/j.asjsur.2012.06.001]

16 **Weerakoon HT**, Ranasinghe S, Navaratne A, Sivakanesan R, Galketiya KB, Rosairo S. Serum lipid concentrations in patients with cholesterol and pigment gallstones. *BMC Res Notes* 2014; **7**: 548 [PMID: 25135323 DOI: 10.1186/1756-0500-7-548]

17 **Katz SC**, Ryan K, Ahmed N, Plitas G, Chaudhry UI, Kingham TP, Naheed S, Nguyen C, Somasundar P, Espat NJ, Junghans RP, Dematteo RP. Obstructive jaundice expands intrahepatic regulatory T cells, which impair liver T lymphocyte function but modulate liver cholestasis and fibrosis. *J Immunol* 2011; **187**: 1150-1156 [PMID: 21697460 DOI: 10.4049/jimmunol.1004077]

18 **Tsui WM**, Lam PW, Lee WK, Chan YK. Primary hepatolithiasis, recurrent pyogenic cholangitis, and oriental cholangiohepatitis: a tale of 3 countries. *Adv Anat Pathol* 2011; **18**: 318-328 [PMID: 21654363 DOI: 10.1097/PAP.0b013e318220fb75]

19 **Wu T**, Zhang Z, Liu B, Hou D, Liang Y, Zhang J, Shi P. Gut microbiota dysbiosis and bacterial community assembly associated with cholesterol gallstones in large-scale study. *BMC Genomics* 2013; **14**: 669 [PMID: 24083370 DOI: 10.1186/1471-2164-14-669]

20 **Acalovschi M**. Gallstones in patients with liver cirrhosis: incidence, etiology, clinical and therapeutical aspects. *World J Gastroenterol* 2014; **20**: 7277-7285 [PMID: 24966598 DOI: 10.3748/wjg.v20.i23.7277]

21 **Kobayashi S**, Gotohda N, Nakagohri T, Takahashi S, Konishi M, Kinoshita T. Risk factors of surgical site infection after hepatectomy for liver cancers. *World J Surg* 2009; **33**: 312-317 [PMID: 19023613 DOI: 10.1007/s00268-008-9831-2]

22 **Kondo K**, Chijiiwa K, Ohuchida J, Kai M, Fujii Y, Otani K, Hiyoshi M, Nagano M, Imamura N. Selection of prophylactic antibiotics according to the microorganisms isolated from surgical site infections (SSIs) in a previous series of surgeries reduces SSI incidence after pancreaticoduodenectomy. *J Hepatobiliary Pancreat Sci* 2013; **20**: 286-293 [PMID: 22481442 DOI: 10.1007/s00534-012-0515-9]

23 **Bergman S**, Deban M, Martelli V, Monette M, Sourial N, Hamadani F, Teasdale D, Holcroft C, Zakrzewski H, Fraser S. Association between quality of care and complications after abdominal surgery. *Surgery* 2014; **156**: 632-639 [PMID: 24656856 DOI: 10.1016/j.surg.2013.12.031]

24 **Westphal JF**, Brogard JM. Biliary tract infections: a guide to drug treatment. *Drugs* 1999; **57**: 81-91 [PMID: 9951953]

25 **Mukaiya M**, Hirata K, Katsuramaki T, Kihara C, Kimura Y, Yamaguchi K, et al. Isolated bacteria and susceptibilities to antimicrobial agents in biliary infections. *Hepatogastroenterology* 2005; 52: 686-960 [PMID: 15966183]

26 **Weickert U**, Wiesend F, Subkowski T, Eickhoff A, Reiss G. Optimizing biliary stent patency by coating with hydrophobin alone or hydrophobin and antibiotics or heparin: an in vitro proof of principle study. *Adv Med Sci* 2011; **56**: 138-144 [PMID: 21940267 DOI: 10.2478/v10039-011-0026-y]

27 **Ortega M**, Marco F, Soriano A, Almela M, Martínez JA, López J, Pitart C, Mensa J. Epidemiology and prognostic determinants of bacteraemic biliary tract infection. *J Antimicrob Chemother* 2012; **67**: 1508-1513 [PMID: 22408140 DOI: 10.1093/jac/dks062]

28 **Darkahi B**, Sandblom G, Liljeholm H, Videhult P, Melhus Å, Rasmussen IC. Biliary microflora in patients undergoing cholecystectomy. *Surg Infect (Larchmt)* 2014; **15**: 262-265 [PMID: 24801654 DOI: 10.1089/sur.2012.125]

29 **Hwang JJ**, Lee DH, Yoon H, Shin CM, Park YS, Kim N. Efficacy of moxifloxacin-based sequential and hybrid therapy for first-line Helicobacter pylori eradication. *World J Gastroenterol* 2015; **21**: 10234-10241 [PMID: 26401089 DOI: 10.3748/wjg.v21.i35.10234]

30 **Ober MC**, Hoppe-Tichy T, Köninger J, Schunter O, Sonntag HG, Weigand MA, Encke J, Gutt C, Swoboda S. Tissue penetration of moxifloxacin into human gallbladder wall in patients with biliary tract infections. *J Antimicrob Chemother* 2009; **64**: 1091-1095 [PMID: 19734170 DOI: 10.1093/jac/dkp318]

**P-Reviewer:** Co M, Tsutsumi K **S-Editor:** Yu J **L-Editor:** **E-Editor:**

**1035 hepatolithiasis patients**

**932 patients enrolled**

**678 patients enrolled in**

 **Lavage group**

**254 patients enrolled in**

**Control group**

**103 patients exclueded**

**Figure 1 Schematic of patient inclusion in the study.**





**Figure 2 Body temperature and white blood cell curves.** WBC: White blood cell.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Control group (254)** | **Lavage group (678)** | ***P* value** |
| Age, years | 55.96 ± 13.48 | 50.81 ± 10.91 | 0.223 |
| Gender (M:F) | 81:173 | 180:498 | 0.119 |
| Pulmonary disease | 45 (17.7) | 154 (22.7) | 0.106 |
| Hypertension | 25 (9.8) | 63 (9.3) | 0.803 |
| Diabetes mellitus | 11 (4.3) | 27 (3.9) | 0.853 |
| Past history of biliary tract surgery | 119 (46.9) | 287 (42.3) | 0.235 |
| Past history of cholangioenterostomy | 11 (4.3) | 15 (2.2) | 0.115 |
| Past history of liver resection | 23 (9.1) | 72 (10.6) | 0.713 |
| Stone location |  |  | 0.892 |
| Right | 159 (62.5) | 395 (58.3) |
| Left | 215 (84.6) | 577 (85.1) |
| Extra | 158 (62.2) | 406 (59.8) |
| Total bilirubin | 15.8 ± 10.42 | 18.3 ± 24.33 | 0.110 |
| ALB (g/L) | 40.31 ± 3.45 | 39.45 ± 6.92 | 0.197 |
| WBC (× 109/L) | 5.61 ± 2.02 | 6.05 ± 4.7 | 0.462 |
| AST (U/L) | 39.6 ± 45.12 | 53.51 ± 61.38 | 0.155 |
| ALT (U/L) | 38.76 ± 54.37 | 64.61 ± 76.79 | 0.306 |

**Table 1 Preoperative variables of patients in the control and lavage groups *n* (%)**

Data for age and levels of total bilirubin, ALB, WBC, AST, and ALT are presented as the mean ± SD. ALB: Albumin; WBC: White blood cells; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

**Table 2 Intraoperative variables of patients in the control and lavage groups *n* (%)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Control group****(*n =* 254)** | **Lavage group****(*n =* 678)** | ***P* value** |
| Operation time (min) | 124.2 ± 48.1 | 100.1 ± 51.9 | 0.036 |
| Surgical approach |  |  | 0.128 |
| Open | 233 (91.4) | 641 (94.5) |
| Laparoscopy | 21 (8.6) | 37 (5.5) |
| Blood loss (mL) | 235.3 ± 358.2 | 241.6 ± 256.9 | 0.918 |
| Combined liver resection | 137 (53.9) | 355 (52.4) | 0.713 |
| Cirrhosis | 71 (27.9) | 229 (33.8) | 0.098 |
| Liver atrophy | 97 (38.2) | 282 (41.6) | 0.369 |
| Biliary stricture | 23 (9.1) | 92 (13.6) | 0.113 |
| Biliary distal dilatation | 118 (46.4) | 294 (43.4) | 0.416 |
| Cholangioenterostomy | 8 (3.1) | 15 (2.2) | 0.491 |
| Complete stone remove | 207 (81.5) | 523 (77.1) | 0.249 |
| Bile bacterial culture positive | 15 (5.9) | 38 (5.6) | 0.874 |

Data for operation time and blood loss are presented as the mean ± SD.

**Table 3 Postoperative variables of patients in the control and lavage groups *n* (%)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Control group****(*n =* 254)** | **Lavage group****(*n =* 678)** | ***P* value** |
| Death | 1 | 1 | 0.471 |
| Cost | RMB 28437.1 ± 8530.5 | RMB 32264.2 ± 11893.2 | 0.043 |
| Postoperative hospital stay (d) | 6.67 ± 3.78 | 7.82 ± 4.34 | 0.024 |
| Fever (> 37.5 °C) | 207 (81.4) | 618 (91.2) | 0.001 |
| High fever(> 38.5 °C) | 101 (39.8) | 372 (54.9) | 0.001 |
| Antibiotic up-regulation | 67 (26.3) | 259 (38.2) | 0.001 |
| Blood bacterial culture positive | 34 (13.4) | 175 (25.8) | 0.001 |
| Bile bacterial culture positive | 60 (23.6) | 276 (40.1) | 0.001 |
| Cholangitis | 51 (20.1) | 238 (35.1) | 0.001 |
| Pulmonary infection | 5 (1.9) | 22 (3.2) | 0.383 |
| Abdominal infection | 12 (4.7) | 59 (8.7) | 0.051 |
| Bile leakage | 8 (3.1) | 33 (4.8) | 0.287 |
| Complications |  |  |  |
| Grade I | 69 (27.1) | 174 (25.7) | 0.250 |
| Grade II | 87 (34.2) | 305 (45.0) |
| Grade III | 7 (2.8) | 16 (2.3) |
| Grade IV | 2 (0.8) | 3 (0.4) |

Data for cost and postoperative hospital stay are presented as the mean ± SD.

**Table 4 Species isolated in postoperative bacterial cultures *n* (%)**

|  |  |  |
| --- | --- | --- |
|  | **Blood** | **Bile** |
|  | **Control group****(*n =* 254)** | **Lavage group****(*n =* 678)** | ***P* value** | **Control group****(*n =* 254)** | **Lavage group****(*n =* 678)** | ***P* value** |
| *Escherichia coli* | 11 (4.3) | 57 (8.4) | 0.034 | 19 (7.4) | 85 (12.5) | 0.035 |
| *Klebsiella pneumoniae* | 9 (3.5) | 48 (7.1) | 0.046 | 15 (5.9) | 69 (27.2) | 0.041 |
| *Pseudomonas aeruginosa* | 8 (3.1) | 18 (2.7) | 0.659 | 7 (2.8) | 42 (6.2) | 0.046 |
| *Enterobacter cloacae* | 5 (2.0) | 22 (3.2) | 0.383 | 11 (4.3) | 56 (8.3) | 0.045 |
| *Enterococcus faecalis* | 2 (0.8) | 13 (1.9) | 0.379 | 7 (2.8) | 21 (3.1) | 0.265 |
| Others | 5 (2.0) | 34 (5.0) | 0.043 | 8 (3.1) | 40 (5.9) | 0.098 |
| Total | 40 (15.7) | 192 (28.3) | 0.001 | 67 (26.4) | 313 (46.2) | 0.001 |

**Table 5 The varieties of the up-regulated antibiotics of the control and lavage groups *n* (%)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Control group****(*n =* 254)** | **Lavage group****(*n =* 678)** | ***P* value** |
| Imipenem | 4 (1.6) | 29 (4.3) | 0.047 |
| Ceftriaxone | 8 (3.1) | 21 (3.1) | 1.000 |
| Moxifloxacin | 11 (4.3) | 57 (8.4) | 0.034 |
| Piperacillin-tazobactam | 15 (5.9) | 69 (10.2) | 0.041 |
| Cefoperazone-sulbactam | 18 (7.1) | 80 (11.8) | 0.041 |
| Levofloxacin | 4 (1.6) | 10 (14.7) | 0.261 |
| Ciprofloxacin | 5 (2.0) | 7 (10.3) | 1.000 |
| Others | 7 (2.8) | 18 (26.5) | 0.439 |
| Total | 72 (28.3) | 291 (42.9) | 0.005 |