CO2 Cholangiography Reduce Cholangitis Risk in Patients with Bismuth Type IV Hilar Biliary Obstruction during ERCP

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Abstract

Backgrounds: Endoscopic palliation in hilar obstruction requires endoscopic retrograde cholangiopancreatography (ERCP), whereas cholangitis could be induced by contrast injection. Post ERCP cholangitis risk is particularly high in Bismuth type IV hilar obstruction, and the risk is further increased if the contrast could not be drained. The aim of this study is to evaluate the cholangitis risks associated with contrast agent, air and CO₂ injection in type IV hilar lesions. Methods: The authors retrospectively evaluated the utility of contrast, air and CO₂ cholangiography in consecutive 70 patients with type IV hilar obstruction. The patients were divided into 3 groups based on the agent used: A) contrast (n=22), B) air (n=18), and C) CO₂ (n=30). Prior to ERCP, MRCP was obtained in all patients to guide endoscopic intervention. Results: At baseline, there was no significant difference in patient’s age, gender, symptoms, liver function tests between different groups (p >0.05). The complication rates in group B and C were significantly lower than that in group A (27.8% and 26.7% versus 63.6%, p <0.05). Except cholangitis risk (p >0.05), no significant difference was found in post ERCP pancreatitis and bleeding risks (both p >0.05) between the 3 groups. After ERCP, the mean hospital stay duration was shorter in group B and C compared with group A (p >0.05). However, the difference of one month mortality between 3 groups was not significant (p >0.05). There was no significant difference between group B and C in primary end points. Conclusions: CO₂ cholangiography based ERCP is safer and should be utilized to reduce the risk of post-ERCP cholangitis in type IV hilar obstruction.

Background

In patients with malignant hilar biliary obstruction is associated with a poor prognosis and endoscopic retrograde cholangiopancreatography (ERCP) is a standard approach to
palliative obstructive jaundice\textsuperscript{[1-2]}. Despite routine antibiotic prophylaxis, post ERCP cholangitis risk is particularly high in Bismuth type IV hilar obstruction: stricture extending into the left and right intrahepatic ducts\textsuperscript{[3]}, leading to prolonged hospital stay, increased mortality, repeated endoscopic interventions and percutaneous drainage\textsuperscript{[4-6]}. The cholangitis risk is further increased if the injected contrast cannot be drained during ERCP. Recently, some studies have investigated the safety of air cholangiography and suggest it can reduce the risk of post ERCP cholangitis compared to contrast injection\textsuperscript{[7-9]}. However, air embolism has been reported during ERCP and is a known risk if air is utilized for insufflation during endoscopy. Even more seriously, the mortality of air embolism can reach up to 40\%\textsuperscript{[10-13]} \text{CO}_2 is widely used in gastrointestinal endoscopy for insufflations\textsuperscript{[14-18]}. \text{CO}_2 cholangiography is feasible and cheap. \text{CO}_2 is absorbed by the gut and tissue approximately 160 times faster than nitrogen, the major component of air. Even \text{CO}_2 embolism is common in laparoscopy such as laparoscopic radical prostatectomy. However there is no reported cardiorespiratory instability associated with \text{CO}_2 embolism\textsuperscript{[19,1]}. To the best of our knowledge, \text{CO}_2 embolism related mortality is extremely rare during ERCP. One fatality was recently reported after direct peroral cholangioscopy and this might due to pre-existing biliovenous shunt\textsuperscript{[20]}. The aim of this study is to evaluate cholangitis risks associated with contrast agent, air and \text{CO}_2 injection in patients with type IV hilar lesions.

Methods

Between October 2013 and November 2017, all patients with type IV hilar obstruction who underwent ERCP were included in this study. Prior to ERCP, MRCP was obtained in all patients to assess ductal anatomy and to guide endoscopic intervention. The type of hilar strictures was classified based on Bismuth’s classification\textsuperscript{[3]} and none of these patients
received prior percutaneous drainage. A written informed consent was obtained. In all patients, either biliary stenting or nasobiliary drainage was utilized to drain the intrahepatic duct during ERCP. The primary study outcome was post-ERCP cholangitis 1 week after procedure. The secondary outcomes were other ERCP complications, such as pancreatitis, bleeding, perforation, and cholecystitis, hospital stay after procedure, total serum bilirubin levels one week, and mortality at one month. The study was approved by the Institutional Review Board.

**ERCP procedure**

All patients underwent ERCP under monitored sedation using propofol. Prophylactic broad-spectrum antibiotic was initiated the day before ERCP and continued for 3 days post procedure. After deep biliary cannulation, guided by MRCP, one or two guide wires (JagWire, Boston Scientific, Natik, Mass) were inserted through the hilar strictures into one/two significantly dilated intra hepatic duct (IHD). The endoscopist aspirated the bile using a sphincterotomy (Autotome, Boston Scientific) to confirm the target duct aimed to be drained and to decrease the intra-ductal pressure. During the first study period, the authors used conventional contrast for cholangiography. This practice was changed to air (10-20mL) in the middle study period and finally to CO₂ (10-20 mL) during the last study time frame. Visualized ductal tree was compared with MRCP images. If the selected intra-hepatic duct was confirmed to be the target duct suggested by MRCP, after aspirating the injected agents, one or two 7 French×7-9 cm plastic stents (double-pigtails, Boston Scientific) were placed. If the selected duct was not considered to the target ducts, a 7 French nasobiliary tube (Microinvasive, Nanjing, China) was placed as therapeutic trial. The drainage effect was evaluated after 7 days, if the temporary drainage was effective, then a plastic stent was introduced. Otherwise percutaneous drainage was performed and nasobiliary drain was removed.
Technical success was defined by fluorography and visualized bile flow through the stent. Clinical success was defined as a decrease in serum bilirubin level > 30% within 30 days (usually within 10 days) [1]. After ERCP, complications were documented and managed. Cholangitis was defined as a new onset of fever (temperature ≥ 38°C) without any source of infection outside the biliary system and persisted > 24 hours after procedure. Pancreatitis was defined as new onset of abdominal pain with serum amylase level three times normal after ERCP, requiring new admission or prolongation of planned admission. A hemoglobin level drop of > 3 gm and with/without transfusion indicated bleeding. Perforation was defined as any leak of fluid or contrast that needed further treatment including surgery or percutaneous drainage [21]. The patients were re-evaluated in clinic at one week and again in one month.

Statistics

Baseline characteristics of the patients were expressed as mean (standard deviation, SD). Statistical significance was assessed with the use of one way-ANOVA for normally distributed continuous data (e.g., bilirubin) and least significant difference (LSD) for multiple comparisons. Fisher’s exact test was used for categorical data (e.g., incidence of post-ERCP cholangitis) analysis. Statistical significance of all tests was defined as p ≤ 0.05 by two-tailed tests. All analyses were performed by the SPSS 22.0 statistical software (SPSS, Chicago, Ill, USA).

Results

Between October 2013 and November 2017, a total of 70 patients with Bismuth type IV hilar biliary obstruction were enrolled in this study. Their baseline clinical and biochemical characteristics are shown in Table 1. There was no significant difference in age, gender, symptoms, liver function tests, types of tumor etiology between 3 groups (Table 1, p
0.05). All the procedures were performed by one experienced senior endoscopist (WHZ). Compared to contrast injection, the image quality of air and CO₂ cholangiograms was considered optimal for diagnostic and therapeutic ERCP. Technical success, including stenting and nasobiliary tube insertion, was achieved in all patients. In patients with successful clinical drainage (52/70, 74.3%), obstructive symptoms relieved or improved. No significant difference existed with numbers of stents and nasobiliary drainage tubes used in different groups (p>0.05, Table 2). The risks of post ERCP complications were significantly higher in group A (63.6%), compared with that of Group B (27.8%) and group C (26.6%) (p=0.018, Table 2). The cholangitis risk in group B and group C was significantly lower than that in group A (16.7% and 10.0% versus 50.0% respectively, p=0.004). Between groups B and C, there was no statistical difference in cholangitis risk (Table 2, p=0.658). Between three groups, post-ERCP pancreatitis and bleeding risks were similar. No other ERCP complications developed in all 70 patients. Post ERCP, a significant shorter hospital stay was observed in the groups B and C comparing with group A (Table 2, p=0.004), whereas there was no significant difference between groups B and C (Table 2, p=0.970). During follow-up, ERCP re-intervention was performed on 3 patients in group C for exchange of nasobiliary tubes to biliary stents, while only one patient needed repeat ERCP in groups A and B (p=0.854). No significant difference was observed in one month mortality between all three groups (p=0.238).

Discussion

Hilar tumors carry a poor prognosis while 5 years survival < 10%. Most of these patients are unsuitable or unfit for curative resection[17]. Palliative surgery is difficult and is associated with a high complication risk. Endoscopic biliary drainage has become the preferred method for palliation. Post ERCP cholangitis is a major issue in patients with
hilar obstruction, which occurs in 7%-57% of patients according to different types of obstruction [23-24]. The risk can reoccur between CO2 and air cholangiography. Patients who received stenting for malignant hilar biliary obstruction each up to 75% in type IV obstruction [25]. The most common reason for post ERCP cholangitis is the lack or insufficient drainage of obstructive intrahepatic bile ducts, particularly after contrast injection. It is important for the endoscopist to avoid over injection. MRCP provides useful information about ductal anatomy, can guide endoscopic intervention, and minimizes the usage of contrast injection. However, even a small amount of contrast injection without drainage can lead to cholangitis. In a recent study, no significant difference was found between air cholangiography and contrast injection in regard to technical and clinical success rates, while with a significantly lower cholangitis risk was reported with air cholangiography [26]. In an uncontrolled study performed by De Palma et al., no cholangitis was reported after air cholangiography in patients with infra-hilar obstructions [27]. In patients with type II and III hilar obstructions, Sud et. al. demonstrated similar results [28]. Although air cholangiogram is effective and can decrease post-ERCP cholangitis risk, air embolism is a rare and potentially fatal complication. Though CO2 embolism is very common in laparoscopic hepatectomy due to long operative time and vessels injuries, no clinical consequence has been reported. [29]. Recently, Zhang et. al. introduced CO2 being a contrast medium for cholangiography and studied in a small numbers of patients with Bismuth type II, III and IV lesions. CO2 embolism was not reported in the study, likely due to the extremely low volume of CO2 injected compared with that of direct peroral cholangioscopy [18]. To the best of our knowledge, our current study is the first to demonstrate a significant difference between CO2, air and contrast
cholangiography in type IV hilar obstructions. In the present study, the post ERCP cholangitis risks were 10% in the CO₂ group, 16.7% air group, and 50% in the contrast group (p≤0.05). These differences may be explained by minimal contamination and quicker tissue absorption during and after air and CO₂ injection, compare with contrast injection. Hydrostatics law states that the rate of increased pressure in a vertically downward direction in fluid/liquid is equal to weight density of the liquid. The density of water at room temperature is taken as 1000 kg/m³ (20°C and 1 atmosphere), while that of injected contrast agents is more than that of water. By contrast, the densities of air and CO₂ are 1.205 kg/m³ and 1.842 kg/m³ respectively under the same condition. That means when endoscopist injects the same volume of contrast, air and CO₂, the latter two media only generate < 1/800 to 1/600 pressures of that of contrast. The uses of air or CO₂ results in fewer increase of partial pressure inside the obstructed intrahepatic duct, and then significantly lower the risk of small bowel bacteria migrating into the bile duct or blood. Despite all available measures were performed to prevent post ERCP cholangitis, there were still 17 patients developed cholangitis. At one month follow-up, 7 patients died from sepsis: CO₂ (1), air (2) and contrast (4) groups.

During endoscopic palliation of malignant hilar obstructions, the endoscopists often place the plastic/metal stent in the most dilated bile ducts. Due to various anatomical factors and the level of expertise, no more than two stents are placed in most cases. The current study was not designed to demonstrate whether bilateral stenting is better than unilateral stenting, or metal stenting is superior to plastic stenting. We only utilized plastic stents and nasobiliary drains in all cases. It is known that only 25%-30% of the liver volume needs to be drained in order to improve clinical and biochemical parameters[^30]. Even with MRCP, in some cases, it is challenging to decide if decompressing the selected bile
duct is adequate and can achieve clinical success. Therefore, we recommend temporary nasobiliary drainage as a therapeutic trial. If drainage is successful clinically, the nasobiliary drain can be exchanged into plastic stent. In current study, nasobiliary drainage was utilized in 15 patients: contrast (5), air (4) and CO\(_2\) (6) group respectively. Of these 15 patients, 5 patients: contrast (1), air (1) and CO\(_2\) (3), underwent repeat ERCP and had nasobiliary drains changed to stents. This study demonstrates that both CO\(_2\) and air cholangiography can significantly lower post-ERCP cholangitis risk and there was no significant difference in clinical success (76.6% versus 72.2%), post-ERCP cholangitis (10% versus 16.7%), serum bilirubin levels after one week and one month mortality (3.3 % versus 11.1%). However, air embolism has been reported during ERCP and is a known risk if air is utilized for injection or during endoscopy. We strongly recommend using CO\(_2\) over air in non-contrast or contrast free cholangiography. Limitations of this study include: 1) relatively small sample size and short follow-up; 2) single center study setting; 3) instead of being a prospective study, this is a retrospective review.

Conclusion

In conclusion, ERCP with CO\(_2\)/air cholangiography is feasible and effective in patients with type IV hilar obstructions. Both techniques can significantly reduce cholangitis risk and hospital stay after ERCP. For safety concerns, we strongly recommend CO\(_2\).

Declarations

Compliance with Ethical Standards

Disclosure of potential conflicts of interest

All authors have no conflict of interest to disclose related to this study.

Research involving human participants and/or animals
This study is a retrospective study which focus on the risk factors of post-ERCP cholangitis in type IV hilar obstruction. We collected and analyzed some information of patients.

Informed consent
We have got the informed consents of all the patients.

Ethics approval and consent to participate
The experimental protocol was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the “Human Ethics Committee of Beijing 302 hospital”.

Written informed consents were obtained from all of these individuals or guardian participants.

Consent for publication
We don’t need the consent of others before this article can be published.

Availability of data and material
All data generated or analysed during this study are included in this article.

Competing interests
The authors, WHZ, PPD, LL, YLW, WHL, JJH, JH and HWL have no conflicts of interest or financial ties to disclose.

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Authors' contributions
Wen-hui Zhang performed ERCP procedures and was the major contributor in writing the manuscript.

Peng-peng Ding, Lei Liu, Yan-ling Wang, Wen-hui Lai, Jing-jing Han collected the data of the patients.

Jun Han and Han-wei Li did the statistical analysis.
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List Of Abbreviations

Endoscopic retrograde cholangiopancreatography (ERCP); Alkaline Phosphatase (ALP);
Gamma Glutamyl Transpeptidase (γ-GT); White blood cell (WBC)

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Tables

Table 1. Baseline characteristics of 70 patients with Bismuth IV hilar obstruction.

| Study time frames | Patients | Age | Men:Women | Jaundice | Abdominal pain | Fever | Pruritus | WBC (×10^9/L) | Liver function tests | Serum bilirubin (umol/L) | ALP (IU/L) | γ-GT (IU/L) | p values |
|-------------------|----------|-----|-----------|----------|----------------|-------|----------|---------------|----------------------|------------------------|------------|-----------|---------|
| Oct. 2013 – Feb. | 22       | 57.74±9.34 | 16:6      | 22 (100%) | 6 (27.3%)     | 2(9.1%) | 6 (27.3%) | 7.15±2.65     | Serum bilirubin | 320.39±100.86 | 470.39±215.76 | 408.91±394.23 | 0.99    |
| 2015              |          |             |           |          |               |        |          |               | ALP                  | 407.58±220.87 | 264.23±82.92  | 8.70±3.82 | 0.131   |
| May 2015 – June   | 18       | 58.32±13.66 | 14:4      | 18 (100%) | 3 (16.7%)     | 4 (22.2%) | 3 (16.7%) | 8.70±3.82     | ALP                  | 407.58±220.87 | 264.23±82.92  | 8.70±3.82 | 0.131   |
| 2016              |          |             |           |          |               |        |          |               | γ-GT                 | 403.26±235.30 | 252.89±74.94  | 7.17±3.30 | 0.131   |
| July 2016 – Nov.  | 30       | 58.64±11.52 | 19:11     | 30(100%)  | 5 (16.7%)     | 7 (13.3%) | 5 (16.7%) | 7.17±3.30     | γ-GT                 | 407.58±220.87 | 264.23±82.92  | 7.17±3.30 | 0.131   |
| 2017              |          |             |           |          |               |        |          |               | Liver function tests | 447.09±272.03 | 567.67±304.14 | 567.67±304.14 | 0.164 |

Table 2. Clinical outcomes of study patients

| Technical success | Functional success | Number of stent | One stent (31.8%) | Two stents (45.5%) | Nasobiliary drain (22.7%) | Post-ERCP complications (63.6%) | Cholangitis (50.5%) | Pancreatitis (9.1%) | Bleeding (4.5%) | WBC 2 days post ERCP | Serum bilirubin one week post ERCP | Mean hospital stay time post ERCP | ERCP re-intervention during follow up | One month mortality |
|-------------------|-------------------|-----------------|-------------------|-------------------|--------------------------|-----------------------------|---------------------|-------------------|-----------------|---------------------|-------------------------------|-------------------------------|-------------------------|----------------------|
| contrast          | air               | CO2             | 7 (31.8%)         | 10 (45.5%)        | 5 (22.7%)         | 14 (63.6%)**             | 11 (50.5%)**          | 2 (9.1%)          | 1 (4.5%)        | 8.08±2.89          | 174.46±109.73                | 14.22±8.56**                  | 1 (4.5%)                | 4 (18.2%)            |
| 22/22 (100%)      | 18/18 (100%)      | 30/30 (100%)    | 3 (16.7%)         | 11 (61.1%)        | 4 (22.2%)         | 5 (16.7%)                | 3 (16.7%)            | 2 (11.1%)        | 0               | 9.48±3.79          | 158.77±68.17                | 9.58±5.12                     | 1 (5.6%)                | 2 (11.1%)            |
| 16/22 (72.7%)     | 13/18 (72.2%)     | 23/30 (76.6%)   | 4 (13.3%)         | 19 (63.3%)        | 6 (20%)          | 8 (26.6%)                | 3 (10%)              | 4 (13.3%)        | 0               | 7.81±4.17          | 156.18±85.94                | 9.68±7.11                     | 3 (10%)                | 1 (3.3%)             |
| 7 (31.8%)         | 3 (16.7%)         | 5 (16.7%)       | 4 (22.2%)         | 19 (63.3%)        | 6 (20%)          | 8 (26.6%)                | 3 (10%)              | 4 (13.3%)        | 0               | 7.81±4.17          | 156.18±85.94                | 9.68±7.11                     | 3 (10%)                | 1 (3.3%)             |
| 1 (4.5%)          | 0                 | 1 (3.3%)        | 0                 | 1 (3.3%)          | 0              | 0                        | 0                   | 0                | 0               | 7.81±4.17          | 156.18±85.94                | 9.68±7.11                     | 3 (10%)                | 1 (3.3%)             |
| p values          |                   |                 |                   |                   |               |                          |                      |                  |                 |                   | ** contrast vs. air , p <0.05   |                              |                        |                      |                     |
# contrast vs. CO₂, \( p < 0.05 \)

**Figures**

![Fluoroscopic images during ERCP showing air (A-C) and CO2 (D-F)](image)

Fluoroscopic images during ERCP showing air (A-C) and CO2 (D-F) cholangiograms. A) A selected MRCP image showing type IV hilar obstruction. B) Air cholangiogram on the same patient. C) Bilateral stenting on the same patient. D) A selected MRCP image showing another patient with type IV hilar obstruction. E) CO2 cholangiogram on the same patient showing selective wire cannulation of the right intra-hepatic biliary system. F) CO2 cholangiogram on the same patient showing selective wire cannulation of the left intra-hepatic biliary system.