Comparative Study on Nosocomial Biliary Tract Infection Rate Between Biliary Stent Loaded with Radioactive $^{125}$I Seeds and Conventional Biliary Stent in the Treatment of Distal Malignant Biliary Obstruction

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Background: The purpose of this prospective randomized study was to compare the nosocomial biliary tract infection rate of biliary stent implantation with a biliary stent loaded with radioactive $^{125}$I seeds (radioactive biliary stent, RBS) and conventional biliary stent (CBS); additionally, to preliminary discuss the causes of postoperative cholangitis. Moreover, the results will provide clinical evidence for the prevention of postoperative biliary tract infection.

Materials and Methods: We prospectively analyzed the nosocomial infection rate of the distal malignant biliary obstruction (MBO) treatment by stent implantation with RBS and CBS. All MBO patients who initially visited our tertiary hospital between July 2015 and December 2019 (n = 196) were evaluated, enrolled, and randomly divided into 2 groups, RBS (n = 97) and CBS (n = 99) group. $\chi^2$ test was used to evaluate the categorical data, and $t$ test was used to evaluate the numerical data.

Results: Our analysis of the study showed the incidence of postoperative infections of a biliary tract of the RBS group (23.7%) was significantly higher than the CBS group (11.1%). The difference was statistically significant ($\chi^2 = 5.425, P = 0.020$). Our study also showed the most common pathogenic bacteria after surgery was Escherichia coli (26.5%).

Conclusion: Treatment for distal MBO with biliary stent loaded with radioactive $^{125}$I seeds had a higher nosocomial infection rate, and the most common pathogenic bacteria was E.coli.

Key Words: nosocomial infection rate, malignant biliary obstruction, biliary stent, radioactive $^{125}$I seeds, pathogenic bacteria

Malignant biliary obstruction (MBO) is a biliary disease caused by various malignant tumors, such as the primary and secondary malignancies of the liver, bile duct, gallbladder, pancreas, or peripancreatic area. Most patients diagnosed at the late stage of the disease with malignant distal biliary stricture were unresectable. Percutaneous transhepatic insertion of biliary stent (PTIBS) is presented as an option as a palliative treatment for MBO in clinical practice. Although the stent placement can effectively relieve the symptoms of biliary obstruction and improve the quality of life for patients, it has no therapeutic effect on tumors. The stenosis of the biliary stent was increasingly prominent, leading to the recurrence of jaundice after stent obstruction. The blockage of the biliary stent directly affected the long-term effect of PTIBS. The radioactive $^{125}$I combined with a biliary stent may perform as an internal radiotherapy on neoplasm to inhibit the proliferation of vascular endothelial cells and the growth of tumor, greatly prolong the biliary stent patency time and patient’s survival time.

With the increasing number of interventional radiologic procedures for treating MBO with PTIBS, people were increasingly concerned about the causes and avoidance of postoperative complications with this percutaneous intervention. Postoperative infection of the biliary tract was one of the very common and serious postoperative complications. Numerous studies have shown that the infection rate post-biliary stent implantation was high, and severe biliary tract infection was fatal in some cases. Therefore, extensive preventive care to prevent postoperative cholangitis was necessary. On the other hand, combined with biliary stent placement was fairly new, and its postoperative infection of biliary tract incidence was rarely known. A single-center, randomized controlled study showed that the postoperative cholangitis incidence of the radioactive biliary stent group was not significantly different from that of the conventional biliary stent group. However, the postoperative biliary tract infection rate of radioactive biliary stent implantation compared with conventional a radioactive biliary stent is still unknown. This study aims to compare the incidence rate of postoperative cholangitis between radioactive and conventional biliary stent implantation.
Subjects
Two hundred forty-seven distal MBO patients aged from 40 to 90 years admitted to the hospital between July 2015 and December 2019 were evaluated for this study. All patients were admitted to the hospital for the first time due to distal MBO (Bismuth-Corlette I). They had not previously received any antitumor treatment (chemotherapy, radiotherapy, or immunotherapy). Eligible patients were randomly assigned to receive either the biliary stent implantation loaded with radioactive $^{125}\text{I}$ seeds (radioactive biliary stent, RBS) or conventional biliary stent (CBS). Research staff at the study site opened the sequentially numbered opaque envelope that contained the biliary stent assignment. An individual unassociated with the clinical portion of the study prepared the envelopes. Randomization sequence was created using Stata 9.0 (StataCorp., College Station, TX) statistical software. The sample size determination formula was used to calculate the sample size. The outcome was the incidence of biliary tract infection. The infection rate was 20% in the RBS group and 10% in the CBS group.$^{10}$ Two-side test was required, $\alpha = 0.05$, the ratio of sample size was 1:1 (the number of cases was equal), $\beta = 0.1$, the degree of assurance was 1% to 90%, and the minimum sample size required was 193.9. A signed informed consent was obtained from each patient. This study was approved by the Ethics Committee (200901B003).

Inclusion and Exclusion Criteria
Inclusion criteria were MBO with an obstruction site located in the distal common bile duct. These patients had no indication of tumor resection, or these patients refused open surgery; their expected survival period was more than 6 months, they were suitable for and agree to biliary stent implantation. Furthermore, to observe postoperative complications and deal with them in time, postoperative patients should be observed in the hospital for more than 1 week. Exclusion criteria were the patient had undergone surgical, interventional treatment and endoscopic retrograde cholangiopancreatography (ERCP), biliary infection or other infections [fever, white cell counts (WBC) ($\times 1000/\mu\text{L}$) $>$ 10, CRP (mg/dL) $\geq$ 1, the percentage of neutrophils exceeded 70%), used of antibiotics before PTIBS, or discharge from hospital within a week.

A total of 247 MBO patients were evaluated in this study and randomly allocated either to RBS ($n=125$) arm

| TABLE 1. Comparison of Primary Tumor Type and Performance Status Scores Between Two Groups |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| RBS ($n=97$)                | CBS ($n=99$)                | Statistics                  | $P$                          |
| Primary malignancy          | Primary malignancy          |                             |                             |
| Biliary cancer ($n=46$)     | Biliary cancer ($n=47$)     | $t=0.278$                   | 0.782*                      |
| Pancreatic cancer ($n=24$)  | Pancreatic cancer ($n=28$)  |                             |                             |
| Ampullary cancer ($n=17$)   | Ampullary cancer ($n=15$)   |                             |                             |
| Gallbladder carcinoma ($n=10$) | Gallbladder carcinoma ($n=7$) |                             |                             |
| Duodenal cancer ($n=2$)     |                             |                             |                             |
| KPS                         | 62.40 $\pm$ 1.83            | 62.33 $\pm$ 1.70            | 0.782*                      |
| ZPS                         | 2.09 $\pm$ 0.14             | 2.08 $\pm$ 0.13             | 0.605*                      |

$^{*}$ $P$ value was greater than 0.05, showing no statistical difference. CBS indicates conventional biliary stent; RBS, radioactive biliary stent.

FIGURE 1. A shows the X-ray image after the placement of conventional biliary stent, and B shows the X-ray image after the placement of radioactive biliary stent.
or CBS (n = 122) arm. Twenty-eight patients were excluded from the study in the RBS arm. Twenty-three patients were excluded from this study in the CBS arm. Finally, 196 patients diagnosed with MBO with an obstruction site located in the distal bile duct were included in the analysis of this study, where 97 patients were in the RBS arm and 99 patients in the CBS arm. Figure 1A shows the CBS group, and Figure 1B shows the RBS group.

**Measures of Nosocomial Infection of Biliary Tract**

The primary endpoint of the study was the incidence of nosocomial infection of the biliary tract within 1 week after PTIBS, according to the Tokyo Guidelines, and was defined as fever (body temperature ≥ 38°C), WBC (×1000/µL) <4, or >10, CRP (C-reactive protein) (mg/dL) ≥1, positive blood culture. Imaging examination showed continuous dilatation of the biliary tract, total bilirubin ≥34.2 µmol/L, AST (IU) >1.5×STD (upper limit of normal value), ALT (IU) >1.5×STD (upper limit of normal value).

The secondary endpoint was a 50% decrease in the total bilirubin level within 14 days of stent placement, technical success, and procedural complication except for infection.

**PTIBS Process**

The method described by Zhu et al for biliary stent implantation was used and performed by our senior doctors with more than 10 years of experience in interventional surgery. The patient received a conventional biliary stent or radioactive biliary stent, according to the grouping. The operative staff ensured that the procedure was strictly sterile and that prophylactic antibiotics were not used before and after the PTIBS procedure.

Both CBS (Fig. 1A) and RBS (Fig. 1B) were provided by MTN Nanjing Micro Invasive Medical. The CBS was a self-expanding “I” shaped stent with 10 mm in diameter and 80 mm in length. The biliary intraluminal irradiation stent was also a self-expanding “I” shaped stent and had the same diameter and length as a CBS; the difference was the RBS had a few sheaths (6.0 mm in length × 1.3 mm in diameter) which contained 125I radioactive seeds and attached to the outer surface of the stent. The 125I seed has a half-life of 59.4 days with an effective irradiating distance of 17 mm. The principal photon emissions were 27.4–31.4 keV x-ray and 35.5 keV γ-ray. A dose of 125I seeds equivalent to 0.7 mCi ionizing radiation was added to the stent prior to implantation surgery. The dosage was determined according to the treatment planning system.

**Pathogen Cultivation and Identification**

A 1 to 2 ml of blood sample was taken when the patient was febrile and was injected into the culture bottle for cultivation and identification using the VITEK 2 Compact microbial identification system. Stock Escherichia coli (ATCC25922), Pseudomonas aeruginosa (ATCC27853), Klebsiella pneumoniae (ATCC700603), Enterococcus faecium (ATCC51916), Enterococcus faecalis (ATCC29212), Staphylococcus epidermidis (ATCC12228), Bacteroides fragilis (ATCC25285) and other strains were obtained from the Industrial Culture Collection and were used for quality control. The cultivation and identification of pathogenic bacteria were performed by our inspection department according to relevant operating guidelines.

**Statistical Analysis**

SPSS 23.0 statistical software was used to process the data. The numerical data were expressed in X ± S, t test was used to compare means. The categorical data were expressed in rate or composition ratio, and χ² test was used to compare differences between these 2 groups. P < 0.05 was considered statistically significant.

**RESULTS**

**Comparison of Tumor Condition and Performance Status Between the 2 Groups**

The tumor types of the 2 groups of patients are shown in Table 1; they were all admitted for the first time because of jaundice. After admission, they were confirmed by imaging, laboratory examination, or pathologic examination. In addition, the Karnofsky Performance Status (KPS) score of the RBS group was 62.40 ± 1.83, and the ZPS (Zubrod Performance Status) score of the RBS group was 2.09 ± 0.14, while those were 62.33 ± 1.70 and 2.08 ± 0.13, respectively. There was no significant difference between the 2 groups.

**Comparison of Patient Demographics between 2 Groups**

There were no statistical differences between these 2 arms in terms of demographic, as shown in Table 2. The mean age in the RBS group was 65.9 ± 12.3 years, while the mean age in the CBS group was 66.2 ± 12.5 years, the difference can be neglected. In all, 68% of the patients RBS

| TABLE 2. Comparison of Age and Sex Composition Between the Two Groups. |
|-----------------|-----------------|---------------------|---------------------|
|                  | RBS (n = 97)    | CBS (n = 99)        | Statistics        |
| Ages             | 65.9 ± 12.3     | 66.2 ± 12.5         | t = 0.172         |
|                 |                 |                     | 0.864*            |
| Sex (F/M)        | 31/66           | 38/61               | χ² = 0.887         |
|                 |                 |                     | 0.346*            |

*P value was greater than 0.05, showing no statistical difference.

**CBS indicates conventional biliary stent; RBS, radioactive biliary stent.**

**TABLE 3. Comparison of the Number of Successful Surgical Techniques and Postoperative Complications Between the Two Groups.**

|                  | RBS (n = 97) | CBS (n = 99) | χ² Value | P |
|------------------|--------------|--------------|----------|---|
| Success          | 97           | 99           |          |   |
| Adverse event    |              |              |          |   |
| Abdominal pain   | 46           | 39           | 1.286    | 0.257* |
| Pancreatitis     | 1            | 2            | 0.318    | 0.573* |

*P value was greater than 0.05, showing no statistical difference.

**CBS indicates conventional biliary stent; RBS, radioactive biliary stent.**

**TABLE 4. Comparison of Biliary Stent Across the Papilla in Two Groups.**

|                  | RBS (n = 97) | CBS (n = 99) | χ² Value | P |
|------------------|--------------|--------------|----------|---|
| Across the papilla | 25           | 29           | 0.300    | 0.581* |
| Not across the papilla | 72        | 70           |          |   |

*P value was greater than 0.05, showing no statistical difference.
group were male while 61.6% in the CBS group. The statistical difference was insignificant between these 2 groups. The effect of age and gender differences from both arms on the result of this study can be excluded.

Comparison of Success Rate of Stent Implantation and Adverse Events between the 2 Groups

As shown in Table 3, corresponding biliary stents were successfully implanted in the biliary tract of all 196 patients and intraoperative cholangiography was performed to make sure that contrast media could enter the duodenum through the obstruction site. All patients had a significant decrease of more than 50% in total bilirubin within 2 weeks after PTIBS.

The most common adverse reaction after the operation was abdominal pain, which improved after the treatment of analgesia. Postoperative patients with intolerable abdominal pain were treated with tramadol injections. Postoperative pancreatitis was rare in patients, but the patient’s condition improved after antipancreatitis treatment. No other definite complications occurred. There was no significant difference in the incidence of abdominal pain and pancreatitis between the 2 groups.

Comparison of Whether the Stent Across the Papilla between the 2 Groups

Depending on the location of the obstruction, either the stent across the papilla or the stent did not. As shown in Table 4, according to the comparison between the 2 groups of patients according to whether the stent across the papilla, the ratio of the RBS across the papilla was 25.8%, while the ratio of the CBS across the papilla was 29.3%. And there was no statistically significant difference between the 2 groups.

Comparison of Postoperative Biliary Tract Infection Rate Between 2 Groups

As shown in Table 5, a total of 34 had an infection among 196 patients; in the CBS arm, it was 11 (infection rate was 11.1%), and in the RBS group it was 23 (infection rate was 23.7%). The incidence of infection in the RBS group was significantly higher than that in the CBS group. All the infected patients had different degrees of jaundice symptoms; the time of total bilirubin decrease to 50% was significantly longer than that of patients without biliary tract infection (P < 0.0000), see Table 6 for details.

Pathogen Identification Result

As shown in Figure 2, 19 out of 34 patients, or 55.9%, had positive blood culture results. Top 3 gram-negative bacteria were *E coli* (n = 9), *K pneumoniae* (n = 2), *P aeruginosa* (n = 1), top 2 gram-positive bacteria were *E faecium* (n = 4), *E faecalis* (n = 3). All patients diagnosed with biliary tract infection were treated with empirical antibiotics. Piperacillin sodium and tazobactam sodium were applied empirically; after the blood culture results came back, the antibiotics were adjusted according to the results, and the antibiotics stopped after the infection was controlled. Follow-up within 1 month showed all patients without stent restenosis and did not need reinvention Figure 3.

![FIGURE 3. Flow diagram.](image)

**TABLE 5.** Comparison of Postoperative Infection Between Two Groups

|                      | RBS (n = 97) | CBS (n = 99) | χ² Value | P     |
|----------------------|--------------|--------------|----------|-------|
| Number of infections | 23           | 11           | 5.425    | 0.020*|
| Number of not infections | 74             | 88           |  —       | —     |

*P value was less than 0.05, showing statistical difference.

![FIGURE 2. Type of primary pathogens in infected patients.](image)

**TABLE 6.** Comparison of Bilirubin Decrease Time Between Infected and Uninfected Patients After Operation

|                      | Infected Patients (n = 34) | Not Infected Patients (n = 162) | T Value | P     |
|----------------------|---------------------------|---------------------------------|---------|-------|
| The time of bilirubin Decreased to 50% (d) | 9.029 ± 1.527            | 3.944 ± 1.035                    | 23.77   | < 0.0000* |

*P value was less than 0.05, showing statistical difference.
DISCUSSIONS

Biliary tract infection was a serious complication after stent implantation. Numerous studies have shown the incidence of biliary infection was 1.9% to 12%. Infection of biliary tract was a high-risk factor for biliary stent restenosis. Therefore, acute cholangitis after biliary stent placement should be studied. In this study, the infection rate of the CBS group in our study was closely in line with those studies. However, the infection incidence of biliary intraluminal irradiation stent (23.7%) was significantly higher than the CBS group.

Bile duct excretion function was affected after stent implantation. Studies have shown that the continuous elastic expansion of the stent during the early stage of the stent implantation can cause necrosis of the epithelial cells of the bile duct and subcutaneous matrix edema, granulation of the tissue, which can cause bacterial infection. Induced by the siltation of bile mud and chyme, bacteria can be retrograde into the gallbladder or bile duct, causing acute purulent cholangitis, and resulting in biliary tract infection. Continuous releases low-energy radiation, destroys the DNA strand of tumor cells, inhibits the proliferation of tumor cells, reduces angiogenesis, kills or suppresses active tumor cells, and effectively controls local tumors. The surrounding biliary tissue also suffers from different degrees of radiation damage. The biliary tract was not only mechanical damage caused by biliary tract expansion, but also suffers from radioactive damage. Therefore, the degree of cell damage was much higher and it was more likely to cause biliary tract bacterial infection. Studies had shown long-term low dose of ionizing radiation reduces white blood cells and immunoglobulin level. It may also increase the risk of bacterial infection.

Past studies showed that whether or not the biliary stent across the papilla may play a role in biliary tract infection. The traditional view was that stent crossing the duodenal nipple will cause ampulla of Vater contraction dysfunction and intestinal contents regurgitation. Intestinal bacteria enter the biliary system, bacteria breed and chyme siltation of bile mud and chyme, bacteria can be retrograde into the gallbladder or bile duct, causing acute purulent cholangitis, and resulting in biliary tract infection. Continuous releases low-energy radiation, destroys the DNA strand of tumor cells, inhibits the proliferation of tumor cells, reduces angiogenesis, kills or suppresses active tumor cells, and effectively controls local tumors. The surrounding biliary tissue also suffers from different degrees of radiation damage. However, the biliary tract was not only mechanical damage caused by biliary tract expansion, but also suffers from radioactive damage. Therefore, the degree of cell damage was much higher and it was more likely to cause biliary tract bacterial infection. Studies had shown long-term low dose of ionizing radiation reduces white blood cells and immunoglobulin level. It may also increase the risk of bacterial infection.

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Our results suggest that bilirubin decreased over a longer period of time in patients with acute biliary tract infection. The time of bilirubin decreased to 50% in patients with biliary tract infection was more than twice that in patients without biliary tract infection. During the bacterial infection, fibrin formed on the inner surface of the stent will cause the infected bile to deposit and form bile mud, which was the main reason for stent blockage. Therefore, early prevention of biliary tract infection was important to ensure and prolong the patency of the biliary stent.

Our study identified 3 most common bacterial infection of biliary tract after PTIBS; E coli (n = 9), followed by E faecium (n = 4) and E faecalis (n = 3). It is highly recommended patients should use antibiotics to prevent intra-biliary infection within 1 week after surgery. Antibiotics should cover as many strain of bacteria as identified in this study, and the antibiotic application can be modified according to the result of patient’s blood culture.

The main limitation in this study was the sample size, especially in the RBS group, for various reasons patients tend to decline to participate in this study after being randomly allocated to RBS arm. We hope the sample size will be expanding in future studies, making the experimental data more accurate to provide greater guidance for clinical diagnosis and treatment.

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