

The value of endoscopic duodenal papilloplasty with titanium clip in improving post-operative complications of choledocholithiasis

El valor de la papiloplastia duodenal endoscópica con clip de titanio en la mejora de las complicaciones postoperatorias de la coledocolitiasis

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Abstract

Objective: To investigate the value of endoscopic duodenal papillary sphincterotomy combined with balloon dilatation in the treatment of duodenal papilloplasty with titanium clip after choledocholithiasis in post-operative complications. **Materials and methods:** One hundred and twenty-five patients (69 males and 56 females) with a median age of 65 (32-81) years were included. The treatment plan was randomly divided into Group A (n = 59) and Group B (n = 66) according to the random number table. Patients in Group A were treated with endoscopic sphincterotomy (EST) combined with endoscopic papillary large balloon dilation (EPLBD), followed by a titanium clip for duodenal papilloplasty and then indwelling nasobiliary drainage, whereas those in Group B were treated with EST combined EPLBD to remove stones and then indwelling nasobiliary drainage. **Results:** In patients with choledocholithiasis or with anatomical changes that make stone extraction difficult, this prospective study attempted to perform duodenal papilloplasty with titanium clips after EST and EPLBD lithotripsy to compare and observe post-operative papillary healing, biliary reflux, and complication rates. **Conclusions:** The use of endoscopic duodenal papilloplasty with a titanium clip can improve biliary reflux after lithotripsy and reduce the incidence of post-operative cholangitis complications.

Keywords: Titanium clip. Plastic surgery of duodenal papilla. Common bile duct stones. Complication. Cholangitis. Biliary tract reflux.

Resumen

Objetivo: Investigar el valor de la esfinterotomía papilar duodenal endoscópica combinada con dilatación con balón en el tratamiento de la papiloplastia duodenal con clip de titanio después de coledocolitiasis en complicaciones postoperatorias. **Materiales y métodos:** Se incluyeron un total de 125 pacientes (69 hombres y 56 mujeres) con una mediana de edad de 65 (32-81) años. Los pacientes del Grupo A se trataron con esfinterotomía endoscópica (EST) combinada con dilatación papilar endoscópica con balón grande (EPLBD), seguida de clip de titanio para papiloplastia duodenal y luego drenaje nasobiliar permanente, mientras que los del Grupo B se trataron con EPLBD combinado con EST para eliminar cálculos y luego drenaje nasobiliar permanente. **Resultados:** En pacientes con coledocolitiasis o con cambios anatómicos que dificultan la extracción de cálculos, este estudio prospectivo intentó realizar papiloplastia duodenal con clips de titanio después de litotricia EST y EPLBD para comparar y observar la cicatrización papilar postoperatoria, el reflujo biliar y las tasas de complicaciones.

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Conclusión: *El uso de papiloplastia duodenal endoscópica con clips de titanio puede mejorar el reflujo biliar después de la litotricia y reducir la incidencia de complicaciones de colangitis postoperatorias.*

Palabras clave: *Clip de titanio. Cirugía plástica de la papila duodenal. Cálculos del conducto biliar común. Complicación. Colangitis. Reflujo del tracto biliar.*

Introduction

Endoscopic sphincterotomy (EST) is an important endoscopic treatment modality based on the diagnostic endoscopic retrograde cholangiopancreatography (ERCP) technique and is widely used for the treatment of choledocholithiasis¹, and its clinical safety and efficacy are widely recognized^{2,3}. However, EST requires a full or partial incision of the sphincter of Oddi, which damages its structure and function to a certain extent, and post-operative complications such as cholangitis, pancreatitis, and bleeding can occur⁴. The endoscopic papillary balloon dilation (EPBD) procedure allows for greater preservation of Oddi sphincter function. Many studies^{5,6} have shown that EST combined with endoscopic papillary large balloon dilation (EPLBD) is effective in the treatment of choledocholithiasis and has the advantage of preserving papillary sphincter function to a greater extent and reducing the incidence of complications. However, post-operative complications, such as enterobiliary reflux, pancreaticobiliary reflux, infection, and bleeding were still present in patients who underwent EST combined with EPLBD for choledocholithiasis. Therefore, how to effectively improve the function of the sphincter of Oddi and further reduce the incidence of post-operative complications still needs to be studied and discussed in depth. In this study, we used EST combined with EPLBD lithotripsy to treat choledocholithiasis and applied titanium clips to perform duodenal papilloplasty to observe the success rate of lithotripsy, post-operative papilla healing, X-ray dilute barium to detect biliary reflux, and analyze the incidence and extent of complications such as cholangitis, pancreatitis, bleeding, and perforation in patients.

Materials and methods

General information

Patients who underwent ERCP lithotripsy at the Second Hospital of Nanjing Medical University and the Second Hospital of Xuzhou Medical University Gastrointestinal Endoscopy Center from June 2015 to June 2020 were screened. A total of 125 patients were

included, 69 men and 56 women, with a median age of 65 (32-81) years. Among them, 27 had combined gallbladder stones and 38 had combined parapapillary diverticula. The inclusion criteria were as follows: (1) Pre-operative diagnosis of choledocholithiasis by computed tomography (CT) or magnetic resonance cholangiopancreatography (MRCP); (2) stone diameter $\geq$ 1.4 cm. The exclusion criteria were as follows: (1) Combination of intrahepatic bile duct stones; (2) upper gastrointestinal stenosis or lower common bile duct stenosis; (3) combination of acute cholangitis; (4) poor cardiopulmonary function unable to tolerate ERCP procedure; (5) severe allergy to iodine contrast agent or multiple drugs; (6) previous history of combined ERCP operation; (7) previous history of combined PTCD operation; (8) significant abnormalities in coagulation function; (9) combination of other contraindications to endoscopic treatment. The criteria of surgeons were as follows⁷: (1) Experienced with 4-5 years of experience and at least 200 ERCP procedures per year; (2) standard ERCP conforming to normal anatomy with $\geq$ 95% successful intubation rate. This study was approved by the Hospital Ethics Committee of The Second Affiliated Hospital of Xuzhou Medical University, this study was registered in the Chinese Clinical Trial Registry (ChiCTR) under number ChiCTR1900027465, and the patients or their family members signed an informed consent form.

Instruments and materials

Olympus TJF-260V electronic duodenoscope and STO725 contrast catheter were used. The contrast agent was Hengrui iodofol (50 mL). GEC 9900Elite X-ray machine, barium, 14 mm*40 mm dilatation balloon (balloon length 40 mm, maximum diameter after filling 14 mm), 16 mm*60 mm dilatation balloon (balloon length 60 mm, maximum diameter after filling 16 mm), 18 mm*60 mm dilatation balloon (balloon length 60 mm, maximum diameter after filling 18 mm), stent, and titanium clip (Angelus) were used.

Treatments and groups

Pre-operative preparation: Patients underwent a complete blood routine test, coagulation function

test, hepatitis immunity test, virus test, and ECG. An imaging scan (CT/MRCP) was also performed to further clarify the patient's condition. Anticoagulation and antiplatelet drugs were discontinued 1 week before surgery. Patients fasted 6-8 h before surgery.

Grouping: Patients who met the selection criteria were randomly divided into two groups: Group A and Group B, using the random number table method by numbering them according to the order of the time they were admitted.

Group A (study group): Duodenal papilloplasty was applied. Patients were placed in the left lateral position and were monitored for ECG, blood pressure, pulse rate, and oxygen saturation.

After sedation with diazepam and pethidine hydrochloride, enter the scope to find the papilla in the descending duodenum, selective intubation and contrast (iophorol) under the guidance of a zebra guidewire, confirm successful intubation, then place the guidewire and perform duodenal papillotomy. The papillary sphincter was dilated with a combined large balloon, followed by lithotripsy basket or balloon extraction, re-imaging to confirm the removal of the stone, leaving the guidewire in place, and then applying a titanium clip to close the incised duodenal papilla along the edge of the incision for shaping. According to the size and location of the incision, combined with the surrounding tissue damage, bleeding, and other conditions to determine the number of titanium clips applied. A nasobiliary tube was routinely placed for drainage, the drainage of the nasobiliary tube after surgery was observed, the amount of bile drained, and the color and properties of the drainage fluid were recorded. The nasobiliary drainage time was about 3-5 days. When the patient's clinical symptoms improved, the relevant indexes were normal, and no obvious stone shadow was observed on the imaging, the drainage tube was then removed. Patients fasted for 24 h after surgery and were observed for clinical symptoms and vital signs. Blood routine test and blood amylase analysis were performed at 3 h after surgery. Blood routine, blood amylase, bilirubin, transaminase, and C-reactive protein were measured at 24 h after surgery.

Group B (control group): After the stone was removed by EST combined with EPLBD, a nasobiliary drain was routinely left in place. After surgery, the nasobiliary drainage was observed, the amount of bile drained, and the color and properties of the drainage fluid were observed. The drainage tube was then removed according to the condition of the patient.

Patients fasted for 24 h after surgery. The observation index and examination were the same as those in Group A.

Data collection

- Blood routine test, analysis of blood amylase, C-reactive protein, and liver function were performed before, 3 h after surgery, and 24 h after surgery.
- The clinical symptoms included abdominal pain, bloating, nausea, vomiting, black stool, fever, jaundice, itchy skin, etc.
- The success rate of lithotripsy, number of days in hospital, and cost.
- The incidence and extent of intraoperative (bleeding) and post-operative complications (bleeding, perforation, biliary ductitis, pancreatitis, and stone recurrence) at 1 week, 1 month, and 12 months.
- Post-operative follow-up 1 week, 1 month, and 1 year, X-ray detection of titanium clip detachment
- Post-operative follow-up at 1 week, 1 month, and 1 year, X-ray dilute barium meal to detect gas and barium reflux to the biliary tract, which assisted in determining post-operative changes in duodenal papillary sphincter function.
- Endoscopy 1 month and 1 year after surgery to observe the healing of the post-operative duodenal papilla incision and the length of the opening.

Complications

- **Gastrointestinal bleeding:** intraoperative bleeding refers to active bleeding seen intraoperatively under the endoscope, with a large amount that cannot be stopped by itself and requires the application of electrocoagulation, titanium clips, or drugs to stop bleeding; post-operative bleeding refers to bleeding that occurs hours to weeks after the operation and can be as late as more than 2 weeks after the operation, and the patient can be accompanied by blood in the stool, black stool, vomiting blood. and other manifestations of gastrointestinal bleeding, which can be accompanied by a progressive decrease in hemoglobin, or confirmed by endoscopy.
- **Post-operative cholangitis:** clinical signs and symptoms of new or worsening abdominal

pain, fever, jaundice, systemic toxic symptoms or infectious shock, combined with abnormal liver function, elevated bilirubin, bile duct dilatation, and other tests, and excluding cholecystitis and other infections.

- Post-operative pancreatitis: new or worsening abdominal pain with more than 3-fold elevation of serum amylase, or higher than the upper limit of normal for 24 h, supported by imaging.
- Cholecystitis: fever, abdominal pain, elevated inflammatory markers, and imaging suggestive of an enlarged gallbladder or with effusion of the gallbladder fossa.
- Gastrointestinal perforation: imaging reveals the presence of free gas or subcutaneous emphysema under the diaphragm or retroperitoneum.

Follow-up

Outpatient or telephone follow-up was used, with a follow-up period of 12 months.

Statistical analysis

SPSS 16.0 statistical software was used for data analysis. Data were expressed as median or mean $\pm$ standard deviation. The t-test was used for measurement data. The χ^2 test was used for count data. $p < 0.05$ was considered a statistically significant difference.

Results

General information

The differences in age, stone size, number, white blood cell count, total bilirubin, C-reactive protein, and operation time for stone extraction between the two groups were not statistically significant ($p > 0.05$) (Table 1).

Lithotripsy success rate

The success rates of lithotripsy in Group A and Group B were 88.14% (52/59) and 86.36% (57/66), respectively, with no statistically significant difference ($p > 0.05$). For patients in both groups who were unsuccessful in stone extraction, biliary stenting or surgical transfer was performed according to the wishes of the patients and their families after communication about their conditions, with no statistically significant differences ($p > 0.05$).

Symptom remission rate

Patients showed better symptom relief within 1 week postoperatively. The symptom remission rates of abdominal pain, bloating, nausea, and vomiting in both groups (86.44% [51/59] in Group A vs. 81.82% [54/66] in Group B) were not statistically significant ($p > 0.05$); the symptom remission rates of jaundice in both groups (83.05% [49/59] in Group A vs. 81.82% [54/66] in Group B) were not statistically significant ($p > 0.05$).

Hospitalization time and cost

The hospitalization costs of patients in Group A and Group B were $21,576.59 \pm 2217.76$ and 22016.29 ± 2552.57 (CNY), respectively. The hospitalization cost of Group A was slightly lower than that of Group B, the difference was not statistically significant ($p > 0.05$). The hospitalization time of patients in Groups A and B was 6.5 days and 7.6 days, respectively, and the difference was not statistically significant ($p > 0.05$).

X-ray detection of titanium clip detachment at 1 week, 1 month, and 1 year after surgery

In Group A, 59 patients with a total of 120 titanium clips were applied, 51 patients (with a total of 103 clips) were X-rayed 1 week after surgery, and 7.77% (8/103 clips) were dislodged. A total of 45 patients (with a total of 89 clips) were X-rayed 1 month after surgery and 80.90% (72/89 clips) were dislodged; 22 patients (with a total of 45 clips) were X-rayed 1 year after surgery in 22 patients (45 titanium clips), all titanium clips were dislodged.

Biliary gas/barium reflux detected by X-ray dilute barium meal at 1 week, 1 month, and 1 year after surgery

At 1 week, 1 month, and 1 year postoperatively, Group A showed gas reflux of 15.69% (8/51), 8.89% (4/45), and 4.55% (1/22) and barium reflux of 5.88% (3/51), 2.22% (1/45), and 0% (0/22), respectively; Group B showed gas reflux of 19.23% (10/52), 17.78% (8/45), and 13.64% (3/22) and barium reflux of 13.46% (7/52), 13.33% (6/45), and 9.09% (2/22), respectively, during the same period. The incidence of gas and barium reflux in Group B was higher than that in Group A in the same post-operative period.

Table 1. General data of two patients

Groups	n	Gender (male/ female)	Medium age (range, years)	Stone diameter (mm)	Number of stones (n)	Diverticulum (n)	Gallbladder stones (n)	TBIL (umol/L)	WBC (10 ⁹ /L)	CRP (mg/L)	Operation time (min)
Group A	59	32/27	66 (36-81)	18 (14-30)	3.15 ± 1.57	18	14	125.57 ± 61.79	9.57 ± 5.98	56.57 ± 30.59	30.55 ± 17.69
Group B	66	37/29	63 (32-79)	16 (14-28)	3.03 ± 1.05	20	13	113.61 ± 59.57	9.29 ± 5.77	54.42 ± 31.57	30.67 ± 19.65
p-value		0.838	0.319	0.257	0.375	0.980	0.584	0.451	0.395	0.417	0.597

TBIL: total bilirubin; WBC: white blood cell count; CRP: C-reactive protein.

Table 2. Comparison of the incidence of post-operative complications between the two groups of patients

Groups	n	Early complications (within 1 month)					Long-term complications (12 months of follow-up)			
		Cholangitis	Hyperamylasemia	Pancreatitis (mild)	Intraoperative bleeding	Post-operative bleeding	Cholangitis	Cholangitis	Pancreatitis	Stone recurrence
Group A	59	0 (0%)	8 (13.56%)	2 (3.39%)	7 (11.86%)	0 (0%)	0 (0%)	1 (1.69%)	0 (0%)	7 (11.86%)
Group B	66	6 (9.09%)	11 (16.67%)	3 (4.55%)	9 (13.64%)	3 (4.55%)	1 (1.52%)	0 (0%)	1 (1.52%)	12 (18.18%)
p-value		0.029	0.629	1.000	0.767	0.246	1.000	0.472	1.000	0.326

Duodenoscopy at 1 month or 1 year after surgery

In Group A, the healing of the duodenal papilla incision was observed at 1-month and 1-year post-operative review, and the post-operative incision was healed, and the opening was not narrower than before. In Group B, the length of the duodenal papilla incision was observed to be slightly shorter than after surgery, the post-operative incision was slightly shortened, and the opening was larger than before. In Group B, the improvement of the incision length and opening was not obvious at 1-year post-operative review.

Comparison of post-operative complications

- Early complications: 0 cases (0%) of cholangitis, 8 cases (13.56%) of hyperamylasemia, 2 cases (3.39%) of mild pancreatitis, 7 cases (11.86%) of intraoperative bleeding and 0 cases (0%) of post-operative bleeding in Group A; 6 cases (9.09%) of cholangitis, including three cases of

combined parapapillary diverticulum, in Group B. Post-operative patients presented with elevated body temperature and abdominal pain, combined with examination. In Group B, 6 cases (9.09%) had post-operative cholangitis, of which three cases had combined parapapillary diverticulum, postoperative temperature rise, and abdominal pain, combined with the examination, and the symptoms improved after treatment with intravenous application of sensitive antibiotics and unobstructed drainage; 11 cases (16.67%) had hyperamylasemia, 3 cases (4.55%) had mild pancreatitis, 9 cases (13.64%) had intraoperative bleeding, and 3 cases (4.55%) had post-operative bleeding, all of which improved after conservative medical treatment without complications such as perforation and severe pancreatitis.

The incidence of post-operative cholangitis complications in Group A was lower than that in Group B, and the difference was statistically significant ($p < 0.05$); the incidence of post-operative bleeding complications in Group A was lower than that in Group B, but the difference was not statistically significant ($p > 0.05$);

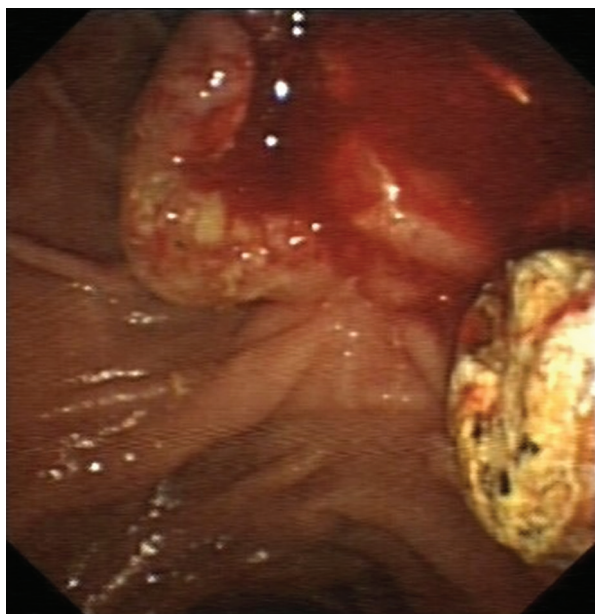


Figure 1. Endoscopic sphincterotomy combined with endoscopic papillary large balloon dilation for stone removal.

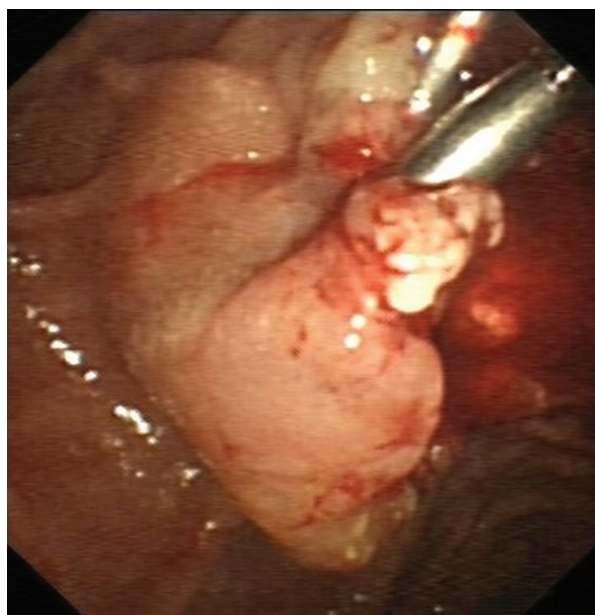


Figure 2. Titanium clip for duodenal papilloplasty.

the differences in the incidence of post-operative hyperamylasemia and pancreatitis (mild) in both groups were not statistically significant ($p > 0.05$), and the differences in the incidence of intraoperative bleeding complications in both groups were not statistically ($p > 0.05$) (Table 2).

- Long-term complications: 1 case (1.69 %) of biliary tract infection (cholecystitis); 0 cases (0%) of pancreatitis; 7 cases (11.86%) of stone recurrence,

including 6 patients with combined gallbladder stones in Group A. 1 case (1.52%) of biliary tract infection (cholangitis) and 1 case (1.52%) of pancreatitis in Group B, all of which improved after conservative medical treatment; 12 cases (18.18%) of stone recurrence and eight of them were combined with gallbladder stones. Three patients in Group B had recurrent post-operative post-prandial abdominal pain with nausea and vomiting, which was diagnosed as bile reflux gastritis by gastroscopy. The differences in the incidence of post-operative biliary tract infection, pancreatitis, and stone recurrence between the two groups were not statistically significant ($p > 0.05$) (Table 2).

Discussion

With the development of medical technology, EST has become the main treatment option for common bile duct stones, but EST requires incision of the sphincter of Oddi, which damages its structure and function to a certain extent, and a variety of post-operative complications can occur. Compared with EST, EPBD can preserve the function of the Oddi sphincter to a greater extent and reduce the risk of complications such as bleeding⁸. However, it was reported that EPBD is more suitable for the application of smaller-diameter stones^{9,10}. Previous studies^{5,6} have shown the efficacy of EST combined with EPLBD in large-diameter common bile duct stones. However, as the balloon diameter increases in EPLBD, the sphincter of Oddi expands further and the deformability of the muscle fibers exceeds the load, which also causes complications of papillary dysfunction. Both papillary sphincterotomy and balloon dilation disrupt the function of the Oddi sphincter to varying degrees, and how to effectively improve the function of the Oddi sphincter after surgery and reduce the complication rate is the focus of this study. In patients with choledocholithiasis or with anatomical changes that make stone extraction difficult, this prospective study attempted to perform duodenal papilloplasty with titanium clips after EST and EPLBD lithotripsy to compare and observe post-operative papillary healing, biliary reflux, and complication rates.

The sphincter of Oddi usually surrounds the jugular abdomen of the common bile duct and the end of the pancreaticobiliary duct to maintain the pressure in the bile duct and pancreatic duct. After ERCP, the pressure gradient between the sphincter

of Oddi and the bile duct duodenum decreases or disappears, triggering the risk of enterobiliary reflux and pancreaticobiliary reflux, and the degree of reflux is influenced by the length of the incision and the function of the papilla. A previous study¹¹ has shown a strong relationship between reflux and cholangitis, biliary bacterial colonization/infection, and recurrence of biliary stones. In this study, through post-operative follow-up duodenoscopy and X-ray dilute barium examination, it was found that without statistical difference in incision length, the duodenal papilloyplasty group had better incision healing than the control group, and the incidence of gas and barium biliary reflux was significantly decreased, analyzing that the application of titanium clip duodenal papilloyplasty could reduce biliary reflux to some extent, and the possible mechanism was that duodenal papilloyplasty could improve the coordinated movement of pylorus and duodenum to some extent.

The incidence of cholangitis, a common complication after EST, has been reported to be about 1-5%^{12,13}, mostly caused by reflux, poor drainage, and other factors. Stone diameter, number of stones, advanced age, combined gallbladder stones, and anatomical changes are also important risk factors for cholangitis after lithotripsy. With the increase of these factors, the incidence of biliary tract infection complications can reach 10.5%¹⁴. Therefore, effective prevention and treatment is also a key research direction for gastrointestinal endoscopists. The results of this study showed that no acute cholangitis occurred in the group with titanium clips for papilloyplasty after surgery, and the incidence of cholangitis was reduced compared with the control group, with statistically significant differences. In this study, we compared two groups of patients who received ERCP again for the recurrence of stones and found that the incisions in the papilloyplasty group had healed without significant stenosis and were well drained; the incisions in the control group were relatively larger compared to the papilloyplasty group. These findings showed that duodenal papilloyplasty promoted the healing of Oddi sphincter incision, improved the function of muscle fibers, promoted the recovery of its anti-reflux barrier function, effectively reduced post-operative biliary reflux, and reduced the incidence of post-operative cholangitis to a certain extent, suggesting that papilloyplasty may have important application value in reducing the incidence of cholangitis after choledocholithiasis extraction of large stones.

Post-operative complications of cholangitis not only prolong the course of the disease, but also increase the pain, increase the economic burden, and the need for timely application of antibacterial drugs to control the disease; in recent years, with the widespread use of antibacterial drugs, bacterial resistance, and adverse reactions are increasing. The incidence of cholangitis in the control group in this study was slightly higher than the literature average and was analyzed in relation to factors such as large stone diameter, some combined gallbladder stones, and advanced age. No complications of acute cholangitis occurred in the study group after surgery, which not only effectively shortened the number of days of hospitalization, reduced the patients' pain, and promoted their early recovery, but also reduced the adverse drug reactions and the occurrence of secondary infections to a certain extent.

The smaller the incision, the lower the efficiency of the stone extraction operation and the success rate of stone extraction, but the larger the incision, the higher the risk of complications such as bleeding and perforation, for EST surgery for large bile duct stones. In this study, no patients with post-operative bleeding or perforation were seen in the duodenal papilloyplasty group, suggesting that the use of titanium clips for duodenal papilloyplasty can not only ensure the degree of papillary expansion but also reduce the risk of bleeding and perforation to a certain extent. We also found that when titanium clips are applied to perform papilloyplasty, the clips can mostly fall off on their own after the wound heals, and even if the clips do not fall off for a long time in some patients, there are no obvious clinical symptoms and no special treatment is needed.

Previous studies^{15,16} have shown that biliary tract infection, sphincter of Oddi dysfunction, cholestasis, abnormal bile composition, diverticula, and gallbladder stones are all high-risk factors for the recurrence of distant stones. Both EST and EPLBD can cause post-operative enterobiliary reflux, pancreaticobiliary reflux, or bacterial contamination of bile to some extent, increasing the risk of recurrent bile duct stones, reflux cholangitis, and even bile duct cancer.

Compared to EST, balloon dilation has the function of protecting the sphincter of Oddi and has some advantages in preventing stone recurrence¹⁷. In this study, the incision healing was better in the titanium-clamped duodenal papilloyplasty group, and the post-operative stone recurrence rate was relatively slightly lower, but the difference in the post-operative stone recurrence rate between the two groups was not statistically significant.

The application of titanium clips for papiloplasty can restore the integrity of the sphincter structure to some extent, reduce the biliopancreatic duct complications secondary to sphincter function damage, reduce the incidence of bile duct reflux and cholangitis, and prevent stone recurrence to some extent.

Conclusion

The application of titanium clips for duodenal papiloplasty can promote papilla healing, reduce post-operative bile duct reflux and the incidence of post-operative cholangitis complications to a certain extent, and did not increase the recurrence rate of post-operative stones. The present study was limited by a small sample with a maximum follow-up of 1 year, and further validation in more prospective controlled studies is still needed for our analysis of whether there is an advantage in the rate of distant stone recurrence.

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Conflicts of interest

All authors have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the

patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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