

Original Article

Clinical research for delayed hemorrhage after endoscopic sphincterotomy

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Abstract: To analyze the effect of delayed hemorrhage after endoscopic sphincterotomy (EST) and compare the efficacy in improving complication between medicine treatment alone and medicine combined with endoscopic treatment. 1741 patients with EST admitted in Yijishan hospital of Wannan medical college from September 2009 to May 2014 were enrolled in this study. 32 cases suffered from delayed hemorrhage. The patients with delayed hemorrhage were evaluated through incision length of duodenal papilla, clinical manifestation, stool occult blood test and the difference of hemoglobin concentration between pre and post operation. 32 patients were divided into mild bleeding group, mild serious group and serious group through the speed and amount of bleeding. All cases in mild group accepted medicine treatment. Mild serious group were divided into medicine therapy group and medicine combined with endoscopic therapy group randomly. Serious group accepted vascular intervention therapy even traditional operation. The different treatments for delayed hemorrhage were judged by efficiency. The dates were analyzed by t-test or chi-square test. Nobody endured delayed hemorrhage who accepted small incision. Delayed hemorrhage was found in 7 patients out of 627 cases who accepted medium-large incision, 25 patients of 920 cases who accepted large incision. The patients who accepted larger EST were more dangerous than small EST ($\chi^2=4.718$, $P=0.030$) concerning delayed hemorrhage. 32 cases in 1741 patients suffered from delayed hemorrhage. 14 patients only have passed black stool after EST. Among 14 cases, 13 patients stop bleeding after medical therapy, and 1 case received endoscopic hemostasis. 15 cases with hematemesis or melena after EST, 7 patients who received combination therapy stop bleeding. 3 patients from 8 cases stop bleeding after single chemical treatment, 5 cases had to receive endoscopic hemostasis after ineffectual medical therapy. There are significant difference for concerning effect between combination therapy group and medical therapy group ($P=0.026$). 3 patients repeatedly vomited blood and develop to peripheral circulatory failure. Those patients all received vascular intervention therapy, 2 patients stop bleeding, 1 patient failed in vascular intervention therapy and given up emergency rescue and died. Large EST has more risks than small EST in concerning delayed hemorrhage. Delayed bleeding after EST should be treated by different levels. Adapted therapy should be recommend for patients with different levels bleeding.

Keywords: Endoscopic sphincterotomy, delayedhemorrhage, treatment

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is a technique that combines the use of endoscopy and fluoroscopy to diagnose and treat for the diseases concerning the biliary or pancreatic ductal systems. It can be divided into diagnostic ERCP and therapeutic ERCP, with the developments of MRCP and the other imaging examination, especially MRCP become a comparable diagnostic method in comparison to ERCP for diagnosing biliary disease [1-3]. Thus, therapeutic ERCP is an impor-

tant treatment for removal of stones form bile duct, insertion of stents to alleviate obstructive jaundice or pancreatic duct disease. Endoscopic sphincterotomy (EST) is the first step for the therapeutic ERCP, which was introduced in 1974, and had initiated into therapeutic ERCP times [4]. The application of therapeutic ERCP alleviated part injure and decreased the burden of health-care costs for the patients compared with surgery [5]. Meanwhile, it may occasionally lead to complications, such as acute pancreatitis, perforation and hemorrhage, especially delayed hemorrhage.

Delayed hemorrhage will be happened after EST more than 24 hours [6]. It is difficult to be found immediately because it not appearing in operation time and compensatory mechanisms of the body for bleeding, and then the patients with delayed hemorrhage can't accept early treatment. So, the result of the seirous delayed hemorrhage is very dangerous, even directly leads patients to death. It also increases the medical costs, prolongs the time of hospitalization. Delayed bleeding is very harder to avoid than the others complications in the therapeutic ERCP. So, how to reduce the rate of delayed bleeding after EST and how to deal with this complication are very urgent and important for clinicians.

Thus, we had designed this study and enrolled the patients who accepted EST from Sep, 2009 to May, 2014 and analysis the characteristics of patient and EST methods. We chose different treatments including medical therapy, endoscopic combined with medical therapy, interventional and laparotomy therapy for varying degrees of delayed hemorrhage and had evaluated the best treatment for the special case with delayed bleeding.

Materials and methods

Patients

Between Sep, 2009 to May, 2014 who received EST in Yijishan hospital of Wannan medical college were enrolled in our study. Exclusion criteria including the patient with the other complications of EST such as perforation, acute pancreatitis and uncontrolled bleeding during operation; the patients with serious organ dysfunction; the patients with anti-platelet or anti-coagulant therapy; the patient with Patients with thrombocytopenia (defined as platelet count $< 80000/\mu\text{L}$), coagulopathy (defined as prolonged prothrombin time > 3 s of the control value); the patients with pre-cut in EST operation.

Materials

Duodenal endoscopy (ED-3470TK, PENTAX); High frequency electricity (ERBE ICC 200, ERBE ICC 200B + APC2);

EST treatment

Every EST which takes part in this study was operated or conducted by the endoscopists

who have taken more than 300 cases before this study. The location of the sphincterotomy was performed between the 11 and 12 o'clock position. Approximately one-half to two-thirds of the wire be visible in the duodenum, and then incision was done with pure cutting current set at 45 watts. The incision directed along the longitudinal axis of the intramural segment of the common bile duct. Incision is divided into large incision, medium-large incision and small incision by the length. The incision was never continued beyond the junction of the intramural segment of the common bile duct and the duodenal wall.

Clinical observation indices

Stool occult blood testing was checked though colloidal gold method. Blood routine examination was tested by automatic hematology analyzer. Melena and haematemesis were taken as clinical indexes. Amount of bleeding was measured by the hemoglobin concentration difference between before EST and before treatment.

Classification and treatment for the delayed hemorrhage

The patients without melena, haematemesis or hemoglobin drop during the period of monitoring were defined as non-hemorrhage. The hemoglobin concentration drop less than 10 g/l during the watch were defined as mild hemorrhage, those cases accepted medicine treatments. The patients whose hemoglobin concentrations drop more than 10 g/l in 24 hour but without hemorrhagic shock were accepted medicine treatment or medicine treatment combined with endoscopic therapy in different treatment groups randomly. The patients with hemorrhagic shock or continuous bleeding were accepted emergency interventional operation to stop bleeding after fluid resuscitation and anti-shock. Surgical operation was taken to stop bleeding after the above treatments fail. Medical treatment includes esomeprazole sodium, 40 mg, BID; hemocoagulase, 1 unit, q8 h.

Medical treatment for the delayed hemorrhage with different classification

The patients without melena, haematemesis or hemoglobin drop during the period of monitoring were defined as non-hemorrhage. The hemoglobin concentration drop less than 10

Table 1. The characteristics of patients with EST and delayed hemorrhage

Item		EST (n)	delayed hemorrhage (n)
Sex	Male	776	17
	Female	965	15
Age	< 20	16	
	21-30	36	
	31-40	105	2
	41-50	258	8
	51-60	283	8
	61-70	485	12
	71-80	427	2
	>81	131	
Incision size	Small incision	194	0
	Medium-large incision	627	7
	Large incision	920	25
Delayed bleeding	2nd day after EST		13
	3rd day after EST		11
	4th day after EST		6
	5th day after EST		2

uous bleeding were accepted emergency interventional operation to stop bleeding after fluid resuscitation and anti-shock. Surgical operation was taken to stop bleeding after the above treatments fail.

Endoscopic homeostasis techniques

Endoscopic sprays: All patients who accepted endoscopic therapy will accept hemostyptic sprays. 1/10000 noradrenalin solution to rinse the bleeding point through endoscopic injector, then affirmed the exact position of hemorrhage, hemorrhage and speed. **Thermo-coagulation:** It was divided into two kinds of treatment: first, single pure coagulation current which set at 30 watts, second, endoscopic argon plasma coagulation (APC) with pure coagulation current set at 30 watts.

Statistical analysis

SPSS16.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. All continuous values are expressed as the mean $\pm$ SD. Difference of measurement data was compared with analysis of variance, the chi-square test or Fisher's exact test for categorical variables. $P < 0.05$ was considered a statistically significant difference.

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Results

A total of 1741 patients were enrolled from Sep, 2009 to May, 2014 in this study. Delayed hemorrhage was happened in 32 cases from 1741 individuals. The delayed hemorrhage rate after EST was 2.55% (32/1741). **Table 1** reveals the characteristics of the study population who accepted EST and delayed hemorrhage after EST.

Results of hemostasis

There are 14 patients with mild late bleeding (hemoglobin drop less than 10 g/l in the observed time). The bleeding of 13 cases was stopped by medicine treatments. 1 case accepted Thermo-coagulation and got hemostasis. 15 patients with mild serious bleeding

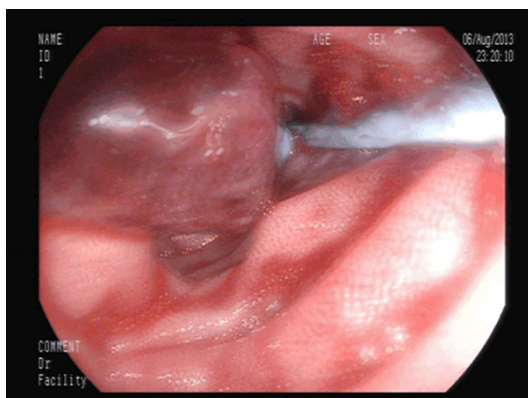


Figure 1. Before endoscopic treatment (blood clot from duodenal papilla).

g/l during the watch were defined as mild hemorrhage, those cases accepted medicine treatments. The patients whose hemoglobin concentration drops more than 10 g/l in 24 hour but without hemorrhagic shock were accepted medicine treatment or medicine treatment combined with endoscopic therapy randomly. The patients with hemorrhagic shock or contin-

Table 2. The efficacy of different therapies for the patients with delayed hemorrhage

Treatment	Success	Failure
Mild delayed hemorrhage	13	1
Medicine treatment	13	1
Mild serious delayed hemorrhage		
Medicine treatment	3	5
Combined treatment	7	0
Serious hemorrhage		
Interventional therapy	2	1

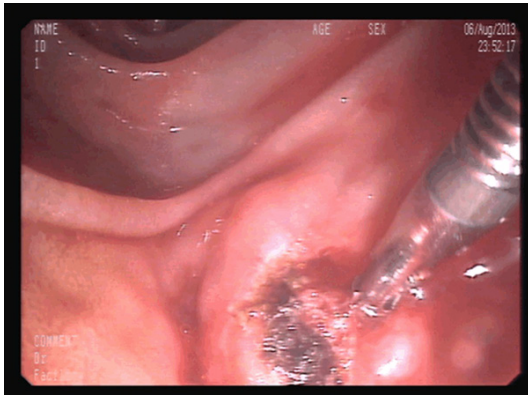


Figure 2. Thermo-coagulation treatment.

(hemoglobin drop more than 10 g/l in the observed time) were divided to medicine treatment group and medicine combined endoscopic treatment group by random number table. 3 cases stopped bleeding in single medicine treatment group which including 8 cases, the other 5 cases were still bleeding and stopped bleeding after medicine combined endoscopic therapy. 7 patients in medicine combined endoscopic treatment group all got hemostasis. There are 13 cases accepted endoscopic therapy as hemostyptic sprays and high-frequency electric coagulation. There were 3 cases with serious de-layed hemorrhage and shock, they were all accepted interventional operation and 2 patients stopped bleeding, 1 case given up treatment (**Figure 1**) and died because of rebleeding after intervention operation 4 days. **Table 2** and **Figures 2, 3** reveals the efficacy of different therapies for the patients with delayed hemorrhage.

For the patients with mild delayed hemorrhage, the ratio of hemostasis through medicine treatment was 92.86% (13/14). For the patients with mild serious delayed hemorrhage, the ratio

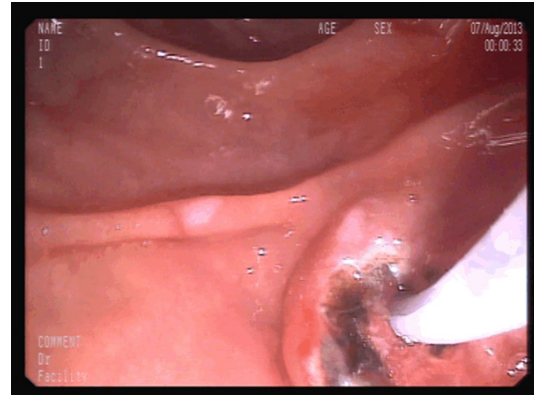


Figure 3. After thermo-coagulation treatment.

of hemostasis through medicine treatment was 37.50% (3/8), the ratio of hemostasis through medicine treatment combined endoscopic therapy was 100% (7/7), There were significant difference between the two kinds of treatments ($P=0.026$).

The relationship between incision size and delayed bleeding

There was no patient with delayed hemorrhage in 194 patients with small incision, 7 cases with delayed bleeding in 627 patients with medium-large incision, 25 cases with delayed bleeding in 920 patients with large incision. The ratio of delayed bleeding in medium -large group and large group were 1.12% and 2.72%. There were significant difference in delayed bleeding rate between medium-large group and large group ($\chi^2=4.718$, $P=0.030$).

Discussion

The characteristics and reasons of delayed bleeding

The complications of EST include bleeding, acute pancreatitis, perforation, biliary tract infection and so on. Hemorrhage not only happened in operation but also after EST even after several days [7]. For immediate bleeding in EST operation, the delayed bleeding has such features as unobvious and undetectable. So, the treatment for delayed hemorrhage is often late, especially mild and mild serious hemorrhage, and late treatment leads to serious consequences.

There are two kinds of reasons leading to delayed hemorrhage after EST. Firstly, the sys-

temic factors includes clotting factor defect, taking antiplatelet medications or blood-thinning drugs [6]. Secondly, the local factors includes inflammation of duodenal papilla, mold and power of incision current, direction and speed of incision, the other operation (ballon dilation, basket removal of biliary tract stone) after EST. For the systemic factors, local factors are more difficult to predict and control.

Without regard of systemic factors, the delayed hemorrhage can be divided into arterial bleeding, venous bleeding and errhysis. The clinical types divided into serious hemorrhage, mild serious hemorrhage and mild hemorrhage. Sometimes, mild bleeding which show as errhysis and small venous are managed successfully by conservative measures without endoscopic therapy [7]. But, for venous and arterial bleeding, endoscopic homeostasis even interventional operation or surgery should be taken to stop bleeding.

From this study, the result revealed that larger incision is more easily lead to delayed bleeding than small incision and medium-large incision. There are several reasons for this phenomenon. First, larger incision means more likely to damage the blood vessels. Second, deep incision will easy to damage the artery.

In this study, there are 14 patients with mild late bleeding, and 13 patients hemorrhage stop after single medical therapy. But for mild serious hemorrhage, only 3 cases bleeding stop in 8 cases after single medical therapy, at the same time 7 cases all bleeding stop after medical combine with endoscopic therapy. For the serious delayed bleeding, endoscopic treatment is not suitable, because it is impossible to get clean vision and operation. So 3 cases with serious accepted interventional operation directly. From this study, we can find that the delayed hemorrhage should be divided into different classes and given different therapy.

Endoscopic treatments for delayed hemorrhage after EST

There are few differences between general endoscopic treatments for non-variceal gastrointestinal bleeding and endoscopic treatments for delayed hemorrhage after EST. They are including Hemostyptic sprays, Thermocoagulation [8, 9], hemoclip [10], injection treat-

ment [11], and so on. But, for hemoclip, it's more difficult to operate under duodenal endoscopy than euthyscope because of narrow operation space.

Hemostyptic spray aims at cleaning the operating field for the coming operation. The hemostatic effect of hemostyptic spray is temporary and uncertain because the solution just constricts blood vessel and doesn't seal blood vessels. So hemostyptic spray is a good auxiliary operation not the primary and unique choice. In this study, all case accepted spray treatment and got the clear view for the next operation. Clear view is very important. Every operation without clear view is dangerous, it maybe lead to more serious bleeding, perforation and so on.

Thermo-coagulation is an effective and convenient for small venous bleeding and errhysis. It can seal blood vessels and get permanent hemostasis. But for the thermotherapy with contact method, re-bleeding even more serious will be happened when the separation between probe and tissue. So the advantage of no-touch APC was highlighted, there are few cases with re-bleeding after APC therapy, because the probe do not touch the tissue. At the same time, for APC therapy, distance, direction and power should be taken into consideration. In this study, 10 patients accepted common thermo-coagulation therapy with needle knife and no case happen re-bleeding. Do not directly return the needle knife is very important, because this motion will avulse the tissue after electric coagulation and lead to more larger bleeding surface. So, we keep the outer sleeve fixed, and take the needle core back outer tube, then leave the wound. The APC therapy can avoid this problem because the probe doesn't touch the tissues. There are 3 cases accepted APC and got hemostasis. From this study we can conclude that coagulation therapy is simple and effective.

Injection therapy is a common and simple way to hemostasis. It stops bleeding by hydrostatic tamponading pressure, vasoconstriction and possibly a secondary inflammatory reaction. As hemostyptic spray, the effect of this treatment is also temporary as the injected fluid dissipates. Because coagulation is simple and easy to get, so, in this study, this therapy was not taken to stop bleeding after EST.

There are the others endoscopic treatments for delayed hemorrhage after EST. Local injection is one of useful treatments for delayed bleeding after EST. There are two reasons. First, local injection improves the tissue stress and oppresses the breaking vessel. Second, inject such as hypertonic saline-epinephrine, epinephrine, vasoconstrictive agent will greatly reduce bleeding [12]. For the arterial bleeding, endoscopic hemoclip is a good choice, especially for a protruding vessel. But, it's quite difficult to release the clip in a narrow space through duodenoscope [13]. For diffuse bleeding from a vague vessel, clip is not a suitable choice compare with coagulation. Temporary placement of fully covered stent seems to be an effective treatment for delayed hemorrhage after EST. It was evidenced that all achieved hemostasis in 8 participants [13].

All patients who suffer from delayed hemorrhage and accept endoscopic therapy should accept ERCP and clean the bile duct. Because blood clot could obstruct the bile duct and induce infection.

The difference between medicine and combined treatment for the delayed hemorrhage

For the patients with delayed hemorrhage after endoscopic sphincterotomy, in addition to supplement the blood volume and the daily need liquid, hemostatic drugs and proton pump inhibitors are necessarily. The purpose of those drugs is to promote the formation of thrombus to stop bleeding. Hemocoagulase can promote the platelet aggregation, release a series of blood coagulation factors, and promote thrombosis and hemostasis in the bleeding site. Esomeprazole can effectively avoid the disintegration of blood clots. So, medicine treatment for delayed hemorrhage because of small vessel damage is effective, but for hemorrhage of the larger blood vessels damage, especially arterial hemorrhage is uselessly. The purpose of medicine treatment combined with endoscopic treatment not only to promote the formation of thrombus, but also to seal the damaged vessel and reach the purpose of hemostasis. So, combined therapy is more effective for homeostasis compared with single drug therapy. This study also proved this point, for the mild bleeding, single drug therapy is effective, but for mild serious bleeding, the combined therapy is more effective than single medicine treatment.

Interventional operation for delayed hemorrhage

For the patients with continuous and serious bleeding, it is very difficult to get the clean field through endoscopy. Thus, endoscopic treatment is not suitable for those patients and interventional endovascular therapy should be considered. Interventional endovascular therapy is the primary choice for the patients with serious hemorrhage in the emergency therapy [14, 15]. There are two aims in this operation, first, medical gelatin sponge maybe block up the bleeding vessels; second, it also confirms the bleeding location, especially for the patients who need traditional surgery, interventional endovascular therapy avoids the other reasons, such as gastric cardia tear. The disadvantage of this treatment is also obvious, the effect of medical gelatin sponge is short, for some patients, re-bleeding will be happened after about a week. In this study, 3 patients with serious delayed hemorrhage accepted interventional operation and 2 cases stopped bleeding, but, active bleeding didn't had be found by angiography in the other case. This patient was again active bleeding after back to the ward. In this study, another disadvantage was found. Interventional therapy is useful in continued bleeding. But for the intermittent bleeding, it's useless in the period of bleeding stops, because the bleeding vessel wasn't found.

Traditional surgery for delayed hemorrhage

The advantages of traditional surgery is effective [16]. On the other hand, it also causes huge damage to the patients.

Conclusion

Large EST has more risks than small EST concerning delayed hemorrhage. Delayed bleeding after EST should be treated by different levels. Adapted therapy adopted for different levels bleeding is very important for the patients.

Disclosure of conflict of interest

None.

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