

MANAGEMENT OF BLEEDING AFTER ENDOSCOPIC BILIARY SPHINCTEROTOMY IN PATIENTS WITH OR WITHOUT COAGULOPATHY DEFECTS

By

**Hamdy El-Badry Seddik, Mohamed Mohamed Al-Kurdi and Sameh
Gabr Attia**

Department of General Surgery, Faculty of Medicine Al-Azhar University, Cairo, Egypt

Corresponding author: Hamdy Elbadry Seddik

Mobile: 01004440236, **E-mail:** hamdyelbadry1985@gmail.com

ABSTRACT

Background: Post Endoscopic sphincterotomy (ES) bleeding is a common complication, and it can be challenging to manage post ES bleeding through a side-viewing endoscope.

Objective: To establish a well-accepted clinical strategy for management of bleeding after endoscopic biliary sphincterotomy in patients with or without coagulopathy defects.

Patients and Methods: This prospective interventional selective study was carried out on 100 consecutive patients with jaundice at General Surgery Department, Al- Azhar University Hospitals (Cairo) Egypt. All patients underwent ERCP during the period between January 2016 and August 2019. Patients were divided into 2 equal groups according to presence or absence of coagulopathy: Group A without coagulopathy defect, and group B with coagulopathy defect.

Results: Among 100 patients with endoscopic retrograde cholangiopancreatography (ERCP), post ES bleeding was recorded in 33 patients. Only 1 of 33 was among group A which represented 3% of bleeding cases, and 1% of the total. The cause was vigorous sphincterotomy. Of 33 patients, 32 were among group B, and represented 97% of bleeding cases, and 32% of total cases in our study. The arrangement of the use of different hemostatic measures in our study was based on accessibility of the facilities and also severity of bleeding. In mild cases, bleeding stopped simply with balloon tamponade. If not, adrenaline spray was used. Endoclip was used for difficult and recurrent cases. Delayed bleeding occurred (1 ± 7 days -mean, 2.5 days) following the procedures. Among the 9 patients with delayed bleeding, 7 patients were managed by endoscopic intervention. The other 2 patients managed conservatively by drugs and intravenous fluids with. No patient required angiography or surgery for delayed bleeding.

Conclusion: Patients must be carefully assessed and prepared pre procedure. Centers must be equipped with all hemostatic measures and facilities. Endoscopists must be well trained and qualified. Bleeding was controlled in all patients easily without mortality.

Key words: Sphincterotomy, Coagulopathy, Bleeding, ERCP.

INTRODUCTION

Since the first bile duct cannulation in 1968, the technical approach and practice of ERCP have rapidly flourished alongside technological advancements

(*Rustagi and Jamidar, 2015*). The development of non-invasive investigations such as magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS) has meant

that ERCP has evolved from a diagnostic tool to a primary therapy in the management of pancreaticobiliary disorders (*Chahal and Baron, 2013*).

As our techniques and technology improved, the complexity of the cases and subsequently adverse events decreased. The most common events are post-ERCP pancreatitis, hemorrhage, perforation, and cholangitis (*Chandrasekhara, 2017*).

Endoscopic sphincterotomy (ES) is the most frequent therapeutic maneuver during ERCP. Post-ES bleeding is a common complication of ES which has been reported in as few as 0.1 but up to 2% of cases (*Hammerle et al., 2012*). The true incidence is unknown, and variable rates are described due to retrospective study design, lack of standardized definitions, and insufficient data on relevant patients and physician factors (*Chandrasekhara, 2017*).

Post-ES bleeding most often resolves spontaneously. Thus, endoscopic therapy was suggested to be undertaken for the treatment of endoscopically significant immediate bleeding or clinically significant delayed bleeding. Endoscopic therapy such as injection, balloon tamponade, thermal, and mechanical methods as haemoclip or self-expandable stent alone or in combination. If refractory bleeding occurs, repeated endoscopic hemostatic therapy, angiographic embolization, or surgery is required (*Kwon et al., 2013*).

A number of risk factors for post sphincterotomy bleeding have been suggested by retrospective and prospective studies, which include coagulopathy before the procedure, anticoagulation within three days after

procedure (*Hori et al., 2014*), child class C cirrhosis, renal failure, cholangitis before the procedure (*Boustière et al., 2011*), peripapillary diverticulum, Billroth II gastrectomy, stenosis of the orifice of the papilla of Vater, stone impaction (*Korkmaz and Temel 2013*), ampullary tumor, extension of prior sphincterotomy, and length of incision and low mean case volume of the endoscopist (*Hammerle et al., 2012*).

The present work aimed to establish a well-accepted clinical strategy for management of bleeding after endoscopic biliary sphincterotomy in patients with or without coagulopathy defects.

PATIENTS AND METHODS

This prospective interventional selective study was carried out on 100 consecutive patients with jaundice at General Surgery Department, Al-Azhar University Hospitals, Cairo. All patients underwent ERCP during the period between January 2016 and August 2019. Patients were divided into two equal groups:

Group A without coagulopathy defect, and **Group B** with coagulopathy defect. Informed consents and explanation of the procedure to all patients were documented.

All patients were subjected to:

I. Clinical evaluation including:

Full history taking and clinical examination including general and local abdominal examination.

II. Laboratory investigations

including: Complete blood count, prothrombin time, activity, INR, serum alanine transaminase level, serum

aspartate transaminase level, serum bilirubin, alkaline phosphatase, gamma glut amyl transferees, hepatitis markers, serum albumin level, fasting and two hours' postprandial blood glucose level, renal functional tests and serum electrolytes.

III. Imaging include: Pelvi-abdominal ultrasonography and magnetic resonance cholangio-pancreatography for all patients. Computerized tomography if indicated and chest x-ray for malignant patients with pulmonary metastasis.

IV. Cardiac assessment and Pulmonary function tests for malignant patients with lung metastasis.

ERCP was done under general anesthesia except if there was a contraindication as cardiac patients or patients with impaired pulmonary function.

Inclusion criteria: Patients with bleeding during or after ERCP procedure (up to 15 days afterward), patients with risk of bleeding and coagulopathy defect classified as group B if platelets count less than 50,000/uL, INR greater than 1.5, initiation of anticoagulant therapy within 3 days of procedure, use of NSAIDs or Clopidogrel before procedure, liver cirrhosis and renal impairment. Patients were carefully assessed and prepared pre procedure to a platelet counts greater than 50,000 IU/L, and an INR less than 1.5 which were considered adequate to perform ES.

Severity of bleeding was classified as mild (endoscopic evidence of bleeding, with a hemoglobin decrease <3 g/dL, without blood transfusion), moderate (requires blood transfusion of 4 units or

less, without angiographic or surgical intervention), or severe (requires >4 units of blood transfusion or intervention).

The arrangement of the use of different hemostatic measures in our study was based on accessibility of the facilities and also severity of bleeding. Balloon tamponade was performed with a dilating catheter (10 mm \times 4 cm), and ballooning time was 3 -5 minutes and can be repeated. Epinephrine was either injected (1:10,000 dilutions; 3 ± 20 mL) or irrigated (1:50,000 dilutions; 30 ± 50 mL). Thermotherapy was attempted with the sphincterotome wire or heater probe, and the power setting was on forced coagulation mode of 30 W. Hemostasis can be achieved by placement of one or more hemoclips at the bleeding site. Endoscopic treatment was considered successful if there was no further bleeding or if recurrence was controlled endoscopically. Once initial hemostasis was achieved, patients were admitted and vital signs were observed. NSAIDs, antiplatelet agents, and coumadin were stopped for 3 days after ERCP procedure. Fresh frozen plasma infusions were given for patients with prolonged INR to maintain INR below 1.5. Platelets were transfused to patients with platelets count less than 50,000/ml.

Statistical Analysis:

Data were collected, tabulated and statistically analyzed. Qualitative data were expressed as number and percentage. Mean (\bar{x}), standard deviation (SD), percentage (%), median and range. Chi-square test (X^2 - test) was used to compare between qualitative data and Mann-Whitney test (U) was used to compare between two quantitative variables if they

were not normally distributed. Statistically significant data was considered when $P \leq 0.05$.

RESULTS

The age of patients ranged between 32 to 57 years old with mean age 44.5 ± 12.5 . Fifty-five were female and 45 were males (**Fig.1**).

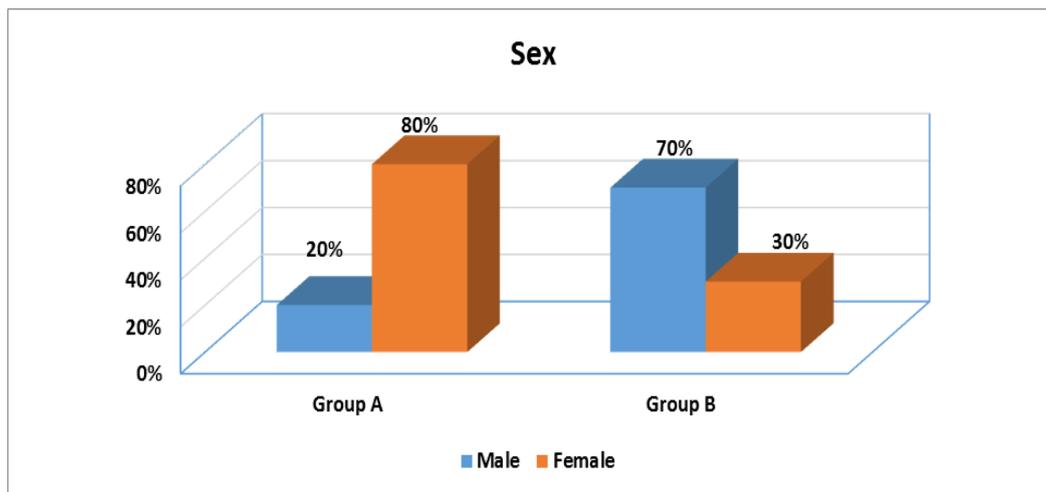


Figure (1): Sex distribution of patients in both groups

All patients were presented with obstructive jaundice. According to clinical, laboratory and radiological data, the cause of jaundice and consequently the indications of ERCP were mainly stone and malignant obstruction (**Fig.2**).

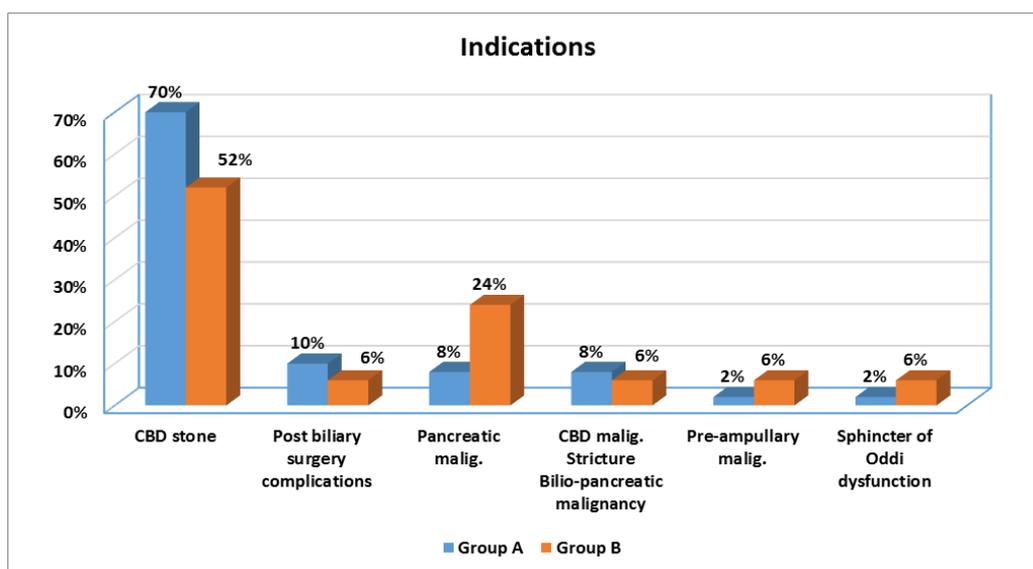


Figure (2): Distribution of Indications of ERCP in patients of both groups

Post ES bleeding was recorded in 33 patients. Only one patient was among group A which represented 3% of bleeding cases and 1% of the total, and the cause was vigorous sphincterotomy. Thirty-two patients were among group B

and represented 97% of bleeding cases and 32% of total cases in our study. Delayed bleeding occurred at arrange of (1±7 days) with 2.5 as a mean ± SD) following the procedures. Seven patients were managed endoscopically. The other

2 patients were managed conservatively by drugs and intravenous fluids with no failure to achieve hemostasis. No patient required angiography or surgery for delayed bleeding (Fig.3).

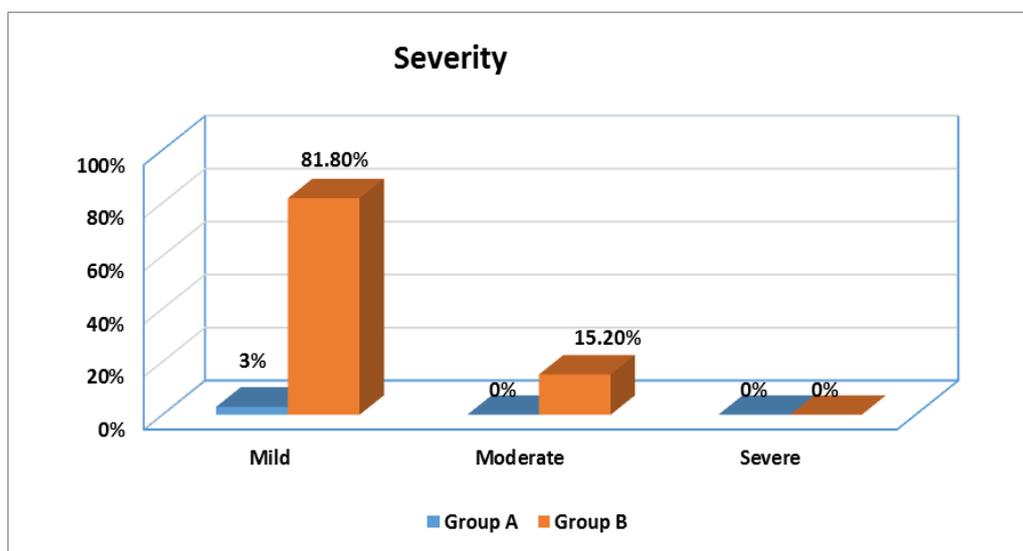


Figure (3): Distribution of severity of bleeding in both groups

All patients underwent pelvi-abdominal ultrasound and MRCP. In cases of malignant jaundice, MRCP showed

96% sensitivity due to its failure in cases of peri-ampullary carcinoma which were diagnosed by CT (Table 1).

Table (1): Comparison between MRCP and U/S sensitivity

Variants	Sensitivity	
	MRCP sensitivity	U/S sensitivity
Calcular jaundice	100%	60%
Malignant jaundice	96%	20%

Bilirubin level was elevated in patients of both groups but showed more elevation in group B patients. Thrombocytopenia and INR elevation were presented in group B patients.

Alkaline Phosphatase and Gamma GT were elevated in patients of both groups but showed more elevation in group B patients (Table 2).

Table (2): Laboratory parameters

Parameters \ Groups	Group A (N=50)	Group B (N= 50)	Mann-Whitney U test	P.value
Total bilirubin (mg/dL) (mean±SD) Median Range	0.77±4.23 0.75 0.5-0.82	5.86±7.28 5.05 3-6.7	5.87 U	0.001 HS
INR (mean±SD) Median Range	1.08±0.10 0.89 0.4-1.4	1.10±0.25 0.9 0.4-1.4	5.63 U	0.403 NS
Creatinine (mg/dL) (mean±SD) Median Range	1.02±0.76 0.89 0.4-1.4	1.40±1.72 1 0.9-1.3	5.53 U	0.001 HS
Alk. phosphatase (IU/L) (mean±SD) Median Range	140±20 0.135 122-148	220±50 210 200-230	4.89 U	0.001 HS
Gamma GT (U/L) (mean±SD) Median Range	48±10 44.5 32-60	60±40 55 42-70	5.46 U	0.001 HS

ERCP succeeded in 100% of cases. Failed cannulation was in 2 cases at the first session, but succeeded at the second one. The arrangement of the use of different hemostatic measures in our study was based on accessibility of facilities and severity of bleeding. In mild cases, bleeding stopped simply with balloon tamponade. If not, adrenaline spray was

used. Endoclip was used for difficult and recurrent cases. In group A bleeding occurred in one patient and controlled by adrenaline spray. In group B, delayed bleeding occurred in 9 patients. Two patients were managed conservatively and 7 patients submitted for second session ERCP (Table 3).

Table (3): Success rate of different endoscopic hemostatic therapies in immediate and delayed bleeding

score Method	Success	%	Failure	%	X ²	p.value
Immediate bleeding						
Ballon tamponade	5/33	15%	28	85	26.8	0.001
Adrenaline injection	14/28	50%	14	50%		
Thermotherapy	6/14	43%	8	57%		
Endoclip	8/8	100%	0	0%		
Delayed bleeding						
Adrenaline injection	1/7	14.3%	6	85.7%	24.5	0.001
Thermotherapy	1/6	16.7%	5	83.3%		
Endoclip	5/5	100%	0	0%		

Epinephrine spray was associated with higher rates of cholangitis, whereas

thermotherapy was associated with higher rates of pancreatitis (**Table 4**).

Table (4): Comparison of complication rate of different hemostatic measures

Measures	Characteristics		Cholangitis	
	Pancreatitis			
Epinephrine spray	2	28.6%	5	50%
Thermo-therapy	4	57.1%	2	20%
Endo-clip	0	0%	0	0%
Balloon Tamponade	1	14.3%	3	30%

DISCUSSION

Our study revealed that coagulopathy is the most important factor determining persistence and recurrence of bleeding after ES. Prolonged INR was the most significant risk factor that can be controlled pre-procedure by good hydration and vitamin K injection and this decrease risk of bleeding significantly. Other risk factors include liver cirrhosis, platelet count < 50,000/uL, renal impairment, use anticoagulant drugs and NSAIDs within 3 days of the procedure.

The European consensus recommended the discontinuation of clopidogrel 5 days before the procedure and continuation of aspirin use for high-risk endoscopic procedures such as ES (*Wei-Chen et al., 2017*). However, an Asian study revealed an increased risk of post-ES bleeding even when aspirin was withheld for 1 week (10% vs. 4%). There was an approximately two-fold increased risk of bleeding with aspirin usage in a systemic study that support our study to include aspirin use as a risk factor for bleeding (*Kwon et al., 2013*). Risk factors include presence of coagulopathy, thrombocytopenia, initiation of anticoagulants within 3 days after ES, liver cirrhosis, hemodialysis, periampullary diverticulum, and relatively

low case volume on the part of the endoscopist (*Keswani et al, 2017*).

In our study, most cases of immediate minor bleeding stopped by balloon compression because of its availability during the procedure. Other studies revealed that injection with epinephrine is the most widely described endoscopic method involves (*Chahal and Baron, 2013*).

Our results highlighted the importance of coagulopathy in the development of persistent and recurrent bleeding. From 50 patient without coagulopathy in group A, only one patient developed bleeding (2%). while 50 patients with coagulopathy in group B, 32 of them developed bleeding (64%). Generally, the incidence of bleeding varies from 1% to 48% depending on what definition is applied. It varies between self-limiting and life-threatening and is associated with a considerable mortality rate of 0.3% (*Neuhaus, 2019*).

In a retrospective study, post-ES bleeding occurred in 12.6% patients. The risk factors associated with post-ES bleeding were liver cirrhosis, end-stage renal disease and previous antiplatelet drug use. Delayed bleeding occurred within 1 to 7 days, and 60% of the patients received endoscopic evaluation. In the

delayed bleeding group, the successful hemostasis rate was 71.4% and 65% of the patients had ceased bleeding without endoscopic hemostasis therapy (*Lin et al., 2017*).

In our study, among 100 patients with ERCP, post ES-bleeding was recorded in 33% of patients (immediate and delayed bleeding were noted in 72.7 % and 27.3 % of patients, respectively). Of them 97% were among group B and 3% were among group A which was higher than those seen in previous studies. The difference may be due to that we divided patients into two equal groups. All patients in group B were at high risk of bleeding and the applied definition of bleeding included any degree of bleeding. In other studies, the timing of post-ES bleeding may be immediate or up to 10 days following ES. Minimal bleeding is common and most often resolves spontaneously. Thus, endoscopic therapy was suggested to be undertaken for endoscopically significant immediate bleeding or clinically significant delayed bleeding (*Balmadrid and Kozarek, 2013*).

In our study, Epinephrine was either injected (1:10,000 dilutions; 3±20 mL) or irrigated (1:50,000 dilutions; 30±50 mL). Some endoscopists injected about 0.3 mL of 1:10,000 diluted epinephrine around the post-ES bleeding point using a sclerosing injection needle (*Chung et al., 2011*).

In our study, the initial success rate of our patients treated with epinephrine injection was 45.45% with recurrence of bleeding in 3.03%. Thermotherapy was found to be effective in 18.18% with recurrence of bleeding in 3.03%. No refractory cases, and no angiographic embolization or surgery was required.

In our study, self-expandable biliary stent was not used because of success of other measures and higher cost effect limits its use to refractory cases, while Balloon tamponade succeeded to achieve hemostasis in 15% of cases. In a retrospective analysis, hemostasis was achieved in all patients using SEMS after failure of other measures (*Abdel Samiea and Theilmann, 2012*).

In our study, endoclip was an effective treatment in 24.24% of cases with no recurrence after initial control of bleeding. The use of epinephrine was associated with cholangitis in 50%, and 28.6% developed pancreatitis. Thermocoagulation was associated with pancreatitis in 57.1%, and 20% developed cholangitis. The outcome of the endoclippping was not statistically different. Balloon tamponade was associated with pancreatitis in 14% and cholangitis in 30% of patients. A previous study revealed that the risk of cholangitis was higher with the use of epinephrine spray. Post-ES bleeding was associated with higher rate of pancreatitis (8%). The risk was higher with electrocoagulation which may due to inaccurate target and thus papillary trauma occurred later (*Wei-Chen et al., 2017*).

Complications associated with endoscopic hemostasis may occur, but it may be difficult to distinguish which of these were related to the ERCP itself and which were related to the treatment of bleeding (*ASGE. 2017*).

CONCLUSION

Endoscopic interventional therapy for immediate post-ES bleeding may lead to better localization of bleeding point and prevention of delayed bleeding. Realizing

the effectiveness of each therapeutic modality and appropriate management of various degrees of bleeding are important so we should assess benefit risk ratio.

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مناجزة النزيف بعد قطع عضلة الصمام المرارى أثناء المنظار في المرضى الذين يعانون والذين لا يعانون من خلل في التجلط

حمدي البدرى حمدي صديق، محمد محمد الكردي، سامح جبر عطية

قسم الجراحة العامة بكلية الطب، جامعة الأزهر

خلفية البحث: يعتبر النزيف بعد قطع عضلة الصمام المرارى أثناء المنظار من المضاعفات الشائعة والتحكم فيه عن طريق المنظار أحد أهم التحديات.

الهدف من البحث: إنشاء إستراتيجية ملائمة لإدارة النزيف بعد قطع عضلة الصمام المرارى أثناء المنظار في المرضى الذين يعانون والذين لا يعانون من خلل في تجلط الدم.

المرضى وطرق البحث: أجريت هذه الدراسة الانتقائية التداخلية المستقبالية في الفترة بين يناير ٢٠١٦ وأغسطس ٢٠١٩ بقسم الجراحة العامة بمستشفيات جامعة الأزهر بالقاهرة على مائة مريض يعانون من ارتفاع نسبة الصفراء بالدم.

وقد خضع جميع المرضى لعمل منظار قنوات مرارية بعد تقسيمهم بالتساوى الى مجموعتين:

المجموعة (أ): لا يعانون من خلل في تجلط الدم.

المجموعة (ب): يعانون من خلل في تجلط الدم.

نتائج البحث: من بين ١٠٠ مريض خضعوا لعمل منظار قنوات مرارية، تم تسجيل نزيف في ٣٣ مريضاً فقط، ١ من ٣٣ كان ضمن المجموعة أ والتي تمثل ٣٪ (من حالات النزيف) ١٪ من المجموع (وكان السبب هو قطع العضلة العاصرة القوية. ٣٢ من ٣٣ من بين المجموعة ب وتمثل ٩٧٪ من حالات النزيف (٣٢٪ من إجمالي الحالات) في دراستنا. إعتد ترتيب إستخدام الوسائل المختلفة لإيقاف النزيف في دراستنا على إمكانية توافرها والوصول إليها وكذلك شدة النزيف، وفي الحالات الخفيفة، توقف النزيف ببساطة باستخدام البالونة، وإذا لم يكن الأمر كذلك، يتم إستخدام رذاذ الأدرينالين. وقد تم استخدام الدباسات في الحالات الصعبة والمتكررة، وحدث نزيف متأخر (١ ± ٧ أيام بمتوسط ٢,٥ يوم)

بعد الإجراءات بين ٩ مرضى، وقد تم إيقاف النزيف في ٧ مرضى بالتدخل بالمنظار. أما المريضان الآخران فقد تم علاجهما تحفظياً بواسطة الأدوية والسوائل ولم يحتاج أى مريض اثناء الدراسة لتدخل جراحى.

الاستنتاج: قد يكون نزيف ما بعد قطع عضلة الصمام المرارى من المضاعفات الخطيرة في بعض الحالات خاصة في المرضى الذين يعانون من خلل في التجلط. لذلك، يجب تقييم المرضى بعناية والتحضير الجيد لاجراء منظار القنوات المرارية جيداً بحيث يتم التحكم في النزيف بسهولة وبدون مضاعفات.