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Treating delayed endoscopic sphincterotomy-induced bleeding: Epinephrine injection with or without thermotherapy

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Abstract

AIM: To compare the hemostatic efficacy between epinephrine injection alone and epinephrine injection combined with thermotherapy for delayed post-endoscopic sphincterotomy (ES) bleeding.

METHODS: Cases with delayed post-ES bleeding undergoing epinephrine injection alone (epinephrine injection group, n = 26) or epinephrine combined with thermotherapy (combination therapy group, n = 33) in our institution between 1999 and 2007 were retrospectively investigated. The main outcome measurements were: initial endoscopic hemostasis, re-bleeding, complications, requirement of angiographic embolization or surgery, requirement for blood transfusion, and mortality.

RESULTS: The initial hemostatic efficacy was 96.2% for epinephrine injection alone and 100% for combination therapy (P = 0.44). There were four patients with re-bleeding in each group (16.0% *vs* 12.1%, P = 0.72). There was only one complication of pancreatitis from the combination therapy group. Three patients (11.5%) in the epinephrine injection group and one patient (3%) in the combination therapy group required angiographic embolization or surgery (P = 0.31). The total number of blood transfusions was not significantly different between the two groups (3.5 ± 4.6 U *vs* 3.5 ± 4.5 U, P = 0.94). There was no bleeding-related death in either group.

CONCLUSION: Epinephrine injection alone is as effective as epinephrine injection combined with thermotherapy for the management of delayed post-ES bleeding.

Key words: Bleeding; Endoscopic retrograde cholangiopancreatography; Endoscopic sphincterotomy; Epinephrine; Thermotherapy

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INTRODUCTION

Endoscopic sphincterotomy (ES) is the cornerstone of therapeutic endoscopic retrograde cholangiopancreatography (ERCP). The incidence of post-ES bleeding varies from 0.76%-2% to 10%-48%, depending on the definition applied[1-6]. Post-ES bleeding is classified as immediate or delayed according to the timing of presentation[7]. Although endoscopically observed bleeding at the time of ES occurs in approximately 10%-30% of cases, the majority of immediate post-ES bleeding episodes are self-limiting and can usually be managed conservatively[5,8-10]. In contrast, delayed post-ES bleeding is often of clinical significance and requires more invasive intervention[10-13].

The methods of endoscopic hemostasis for post-ES bleeding mirror those for peptic ulcer bleeding. For a bleeding peptic ulcer, epinephrine injection therapy is effective to stop bleeding and additional endoscopic treatment such as thermocoagulation after epinephrine injection can reduce the re-bleeding rate, need for surgery, and mortality[14]. However, the bleeding mechanism for post-ES bleeding is different from that of peptic ulcer bleeding[15]. It is unclear whether the hemostatic effect for post-ES bleeding would be similar to that of peptic ulcer bleeding if the same endoscopic methods are applied. There are a few series that specifically describe endoscopic hemostasis of post-ES bleeding, but none of them have a comparative study design[4,5,9,13,15-17]. Therefore, this retrospective study was conducted to compare the hemostatic efficacy between epinephrine injection alone and epinephrine injection combined with thermotherapy in patients with delayed post-ES bleeding.

MATERIALS AND METHODS

Ethics

The study protocol was approved by the ethical committee at Change Gung Memorial Hospital (IRB No.: 98-0734B).

Definitions in this study

Immediate post-ES bleeding: Any hemorrhage induced by ES and warranting endoscopic hemostasis within the procedure of ERCP.

Delayed post-ES bleeding: Any hemorrhage after completion of ERCP and manifested by melena, hematemesis or hematochezia associated with a decreased hemoglobin level from baseline.

Re-bleeding: Patients had clinical evidence of recurrent bleeding after initial successful endoscopic hemostasis, and underwent another endoscopy or procedure for the treatment of bleeding.

Coagulopathy: Patients with thrombocytopenia (defined as platelet count < 80 000/μL), coagulopathy (defined as prolonged prothrombin time > 3 s of the control value) and renal failure requiring hemodialysis were considered for statistical analysis as a combined "coagulopathy" group[18].

Patients

Between 1999 and 2007, 3542 patients underwent 3654 biliary ES procedures at Chang-Gung Memorial Hospital, Linkou Medical Center. ES was performed with a standard pull-type sphincterotome (KD-6G10Q-1; Olympus Co., Tokyo, Japan, or Ultratome and Tapertome; Boston Scientific Co., Spencer, IN, USA). A feedback-controlled generator was used (Erbe, ICC350; Erbe, Tubingen, Germany) and set for Endocut mode (output limit 120 W). In difficult cases (279 cases; 7.64%) for deep cannulation, precut sphincterotomy was carried out using a needle-knife papillotome (267 cases, Huibregtse single lumen needle knife; Cook Medical Inc., Winston-Salem, NC, USA) or a standard pull-type sphincterotome (12 cases). Sixty-six patients (1.86% of patients or 1.81% of procedures) met the criteria of delayed post-ES bleeding during the study period. Seven of the 66 patients were excluded because they underwent thermal therapy alone (five cases), epinephrine injection plus hemoclipping (one case), or epinephrine injection combined with thermocoagulation and hemoclipping (one case). The remaining 59 patients were enrolled in the study. Of these 59 patients, 26 patients who underwent epinephrine injection therapy alone were classified as the "epinephrine injection group" and 33 patients who underwent epinephrine injection combined with thermotherapy were classified as the "combination therapy group".

This study retrospectively analyzed the hemostatic efficacy for control of delayed post-ES bleeding between epinephrine injection therapy alone and epinephrine injection combined with thermotherapy. The outcome assessments compared between the groups were; initial endoscopic hemostasis, re-bleeding, complications, requirement of angiographic embolization or surgery, requirement for blood transfusion, and mortality.

Endoscopic therapy

Dilute epinephrine (1:10 000) was injected in 0.5-2 mL aliquots into and around the bleeder at the sphincterotomy site until the bleeding was controlled. The group undergoing dual treatments received additional thermotherapy, including heat probe coagulation (18 cases), bipolar coagulation (gold probe, three cases), monopolar coagulation (hot biopsy forceps, 11 cases), and argon plasma coagulation (APC, one case). The heat probe device was not available in our institution after September 2007, and the gold probe was used as the substitute instrument. The settings and application were similar to those used for peptic ulcer bleeding[19,20]. Endoscopic therapies were carried out within 24 h after initial symptoms of bleeding for inpatients (50 cases), or after arrival in the emergency room for outpatients (nine cases). Epinephrine monotherapy or dual therapy was carried out according to the endoscopist's preference. There was a trend towards performing combination therapy after 2004 (only five patients underwent combination therapy before 2004).

Statistical analysis

Data in the text and tables are expressed as mean ± SD. The difference was compared using the two-sample *t*-test for continuous variables and the χ^2-test or Fisher's exact test for categorical variables. The analyses were performed with statistical software of SPSS 15.0 version for Windows. A P value of < 0.05 was considered statistically significant.

Table 1 Clinical characteristics of patients in the two groups (mean ± SD)

	Epinephrine injection group (*n* = 26)	Combination therapy group (*n* = 33)	*P* value
Age (yr)	60.6 ± 18.1	56.1 ± 14.2	0.30
Gender (Male/Female)	14/12	20/13	0.60
Indications			0.48
Choledocholithiasis	22	24	
Malignant obstruction	2	3	
Others	2	6	
Possible bleeding risk factors			
Coagulopathy[1]	6	7	0.86
Bile duct stones	22	24	0.27
Precut sphincterotomy	1	6	0.12
Periampullary diverticulum	4	4	0.72
Bleeding during ES[2]	11	15	0.81
Cholangitis before procedure	11	16	0.64

[1]Coagulopathy including: prolonged prothrombin time > 3 s of the control value; Platelet count < 80000/μL; end-stage renal disease requiring hemodialysis; [2]All post-ES bleeding occurred during ERCP and required endoscopic hemostasis. ES: Endoscopic sphincterotomy.

Table 2 Bleeding severity, and bleeding stigmata at initial endoscopy

	Epinephrine injection group (*n* = 26)	Combination therapy group (*n* = 33)	*P* value
Bleeding severity			0.61
Mild	9	9	
Moderate	10	17	
Severe	7	7	
Bleeding stigmata			0.70
Active oozing	12	12	
Oozing under an adherent clot	6	7	
Non-bleeding visible vessel	0	1	
Non-bleeding clot	4	9	
Non-bleeding red spots	4	4	

Table 3 Clinical outcomes according to endoscopic therapy (mean ± SD) *n* (%)

	Epinephrine injection group (*n* = 26)	Combination therapy group (*n* = 33)	*P* value
Initial hemostasis	25 (96.2)	33 (100)	0.44
Re-bleeding[1]	4 (16.0)	4 (12.1)	0.72
Embolization or surgery	3 (11.5)	1 (3.0)	0.31
Bleeding-related death	0	0	1
Transfusion requirement (U)	3.5 ± 4.6	3.5 ± 4.5	0.94

[1]Re-bleeding after initial successful therapeutic endoscopy.

RESULTS

During ERCP, 854 (24.11%) patients experienced immediate post-ES bleeding. All patients underwent epinephrine injection, and 32 had additional endoscopic therapy. By definition, delayed bleeding occurred in 26 (3.04%) of the 854 patients. The time to onset of delayed bleeding was not significantly different between patients with and without immediate post-ES bleeding (2.8 ± 2.7 d *vs* 3.3 ± 2.7 d, $P = 0.5$).

Clinical characteristics of the 59 patients with delayed post-ES bleeding are outlined in Table 1. There were no significant differences in the mean age, sex distribution, and indications for ERCP between the two groups. None of the participants used anticoagulants from 3 d before or till 3 d after ERCP, and all the ES procedures were performed by experienced endoscopists. Thus, the established risk factors of post-ES bleeding included coagulopathy, bile duct stones, precut sphincterotomy, periampullary diverticulum, immediate post-ES bleeding, and cholangitis before ERCP[9,21]. There was no statistical difference between the two groups with regard to these parameters. The drop in hemoglobin from baseline was 31 ± 22 g/L in the epinephrine injection group and 37 ± 22 g/L in the combination therapy group ($P = 0.26$). The time period between ES and hemorrhage ranged from 9 h to 16 d, and was not statistically different between the two groups (3.5 ± 3.6 d *vs* 2.8 ± 1.6 d, $P = 0.32$).

Data regarding bleeding severity and bleeding stigmata at initial endoscopy are listed in Table 2. Bleeding severity was classified according to the established criteria[10]. There were 9, 10 and 7 cases of mild, moderate, and severe bleeding, respectively, in the epinephrine injection group, and 9, 17 and 7 cases, respectively, in the combination therapy group ($P = 0.6$). At initial endoscopy for delayed post-ES bleeding, the bleeding stigmata were classified as active oozing, oozing under an adherent clot, non-bleeding visible vessel, non-bleeding adherent clot, and non-bleeding red spots. There was no statistically significant difference between the two groups when the bleeding stigmata were compared with respect to these parameters ($P = 0.70$).

Clinical outcome data are summarized in Table 3. The total injected volume of dilute epinephrine was 7.8 ± 5.8 mL (range: 3-30 mL) in the epinephrine injection group and 9.1 ± 6.2 mL (range: 3-30 mL) in the combination therapy group ($P = 0.48$). Initial hemostasis was successfully attained in 25 patients from the epinephrine injection group and 33 patients from the combination therapy group (96.2% *vs* 100%, $P = 0.44$). Initial hemostasis was not achieved in 1 patient treated with epinephrine injection alone and the patient went directly to surgery.

The re-bleeding rate was 16% (4 of 25) for the epinephrine injection group and 12.1% (4 of 33) for the combination therapy group. The difference, however, was not significant ($P = 0.72$). The treatment for the four patients with re-bleeding from the epinephrine injection group was as follows: 2 underwent 1 session of endoscopic treatment and the bleeding stopped; 1 went directly to angiographic embolization at re-bleeding; and 1 underwent 1 session of endoscopic treatment for the first re-bleeding - surgery rather than endoscopic treatment was performed to control bleeding at the second re-bleeding. The treatment for the four patients from the combination therapy group was as follows: 1 underwent 1 session of endoscopic treatment and the bleeding stopped; 2 underwent 3 sessions of endoscopic

treatment due to repeated re-bleeding and the bleeding was finally controlled, and 1 underwent 2 sessions of endoscopic combination therapy and surgery was required to finally control bleeding.

None of the patients from the epinephrine injection group experienced any complications of endoscopic hemostasis. One of the patients from the combination therapy group experienced mild pancreatitis after initial endoscopic hemostasis (epinephrine injection plus APC). Another patient from the combination therapy group developed mild pancreatitis after endoscopic treatment (epinephrine injection + heat probe + APC + hemoclipping) for the third episode of re-bleeding. The total number of patients requiring angiographic embolization or surgery to control bleeding was 3 in the epinephrine injection group and 1 in the combination therapy group (11.5% *vs* 3.0%, $P = 0.31$). The total number of blood transfusions was not significantly different between the two groups (3.5 ± 4.6 U *vs* 3.5 ± 4.5 U, $P = 0.94$). There was no bleeding-related death in either group.

DISCUSSION

Although the endoscopic approach for post-ES bleeding is similar to that for peptic ulcer bleeding, there is no consensus with regard to the optimal endoscopic hemostasis for treating post-ES bleeding[7]. For peptic ulcer bleeding, epinephrine injection is the most commonly used, and highly effective, method for control of bleeding; its hemostatic efficacy is comparable to that of epinephrine in combination with additional thermotherapy[14,19]. From the literature review, it appears that epinephrine injection is the most widely used method for hemostasis of post-ES bleeding. Its success rate in the cases reported in two large series was 97.5% and 100%[5,9]. The present study shows that epinephrine monotherapy is also highly effective for controlling delayed post-ES bleeding. In addition, the results demonstrate that epinephrine monotherapy is as effective as epinephrine injection combined with thermotherapy, similar to that for peptic ulcer bleeding.

Data regarding bleeding peptic ulcer management suggest that epinephrine injection alone does not achieve permanent hemostasis, and an additional endoscopic treatment such as thermotherapy can reduce the re-bleeding rate[14]. There are only a few studies that discuss re-bleeding after endoscopic treatment for post-ES bleeding. Ferreira *et al*[13] reported a re-bleeding rate of 28.4% for 74 patients undergoing various endoscopic treatments for delayed post-ES bleeding. The present study found that the re-bleeding rate between epinephrine monotherapy and combination therapy is not significantly different (16% *vs* 12.1%, $P = 0.72$), implying that additional thermotherapy does not seem to reduce the risk of re-bleeding. Interestingly, the additional thermotherapy used by the endoscopists in this study was most likely performed with the intention of reducing the re-bleeding risk rather than primary hemostasis, since epinephrine injection alone was highly effective for initial hemostasis. This practice was probably due to the experience of the endoscopists; they applied lessons learned in treating bleeding peptic ulcers.

Thermotherapy alone using multipolar electrocoagulation or a heat probe device has been reported to be effective for controlling post-ES bleeding[16,17]. Contact thermal therapy, however, has an accurate placement problem, as has been described in bleeding peptic ulcers[19,22]. In our experience, using a duodenal scope to perform contact thermal therapy is technically difficult when massive bleeding obscures the visual field. In contrast, epinephrine injection does not require accurate targeting. Injection close to the bleeding point will suffice to control bleeding, resulting in a better endoscopic view for more accurate targeting of the additional contact thermal therapy. Under such circumstances, combination therapy is a reasonable alternative.

In this study, none of the patients developed any clinically significant complications after endoscopic epinephrine injection therapy alone. This result confirms those reported in the literature that epinephrine monotherapy is very safe for hemostasis of post-ES bleeding[5,9,13]. Pancreatitis was the most common complication of endoscopic combination therapy for delayed post-ES bleeding[13]. In the present study, the only two patients who experienced pancreatitis after endoscopic hemostasis also underwent combination therapy. It is reasonable to consider that an additional thermal procedure would increase risk of complication(s), as has been described in the management of bleeding peptic ulcers[14,22].

Any bleeding that occurs during ES increases the risk for occurrence of delayed bleeding, and it is suggested that treating "endoscopically significant" immediate bleeding may reduce the risk of delayed bleeding[1,5,9]. However, the results of the present study do not support this idea: 24.11% of the patients had undergone endoscopic hemostasis for immediate post-ES bleeding, but the rate of clinically significant delayed bleeding was still high (1.81%). The discrepancy between this result and others is possibly because there is no consensus on what is endoscopically significant bleeding and who should receive endoscopic treatment. Furthermore, endoscopically significant bleeding may not become clinically significant[9,23].

There were more patients requiring angiographic embolization or surgery in the epinephrine injection group (3/26 *vs* 1/33). This result should be interpreted with caution. At re-bleeding, endoscopic treatment was not offered to two of the three patients from the epinephrine injection group: one patient went directly to angiographic embolization at re-bleeding and the other one patient received surgery at the second re-bleeding. In contrast, two patients from the combination therapy group underwent three sessions of endoscopic treatment rather than surgery at their repeated re-bleeding, and the bleeding episodes were finally controlled. Surgery was once the only treatment choice for post-ES bleeding

in early ES, but its usage has fallen from 3% to less than 0.1% because of the improvements in endoscopic techniques and equipment[1,10,24]. Therefore, endoscopic treatment may be offered to patients with re-bleeding prior to more invasive therapy.

The current study has several limitations. Firstly, it is not a prospective, randomized study. We do not know if there were any of the patients undergoing dual therapy because of epinephrine monotherapy failure. However, as discussed above, an additional thermotherapy was performed possibly to reduce re-bleeding risk rather than epinephrine monotherapy failure. Secondly, four different thermal methods resulted in the heterogeneity of the combination therapy group. It is not known whether different thermal methods would have had similar hemostatic efficacy, although there are no published data indicating that one method is superior to the others.

In summary, the present results show that epinephrine injection is as effective as epinephrine in combination with thermotherapy for treating delayed post-ES bleeding. Considering that epinephrine injection is safe and easy to perform, and that an additional thermotherapy may increase the risk of complications, we would suggest epinephrine injection alone as the first-line therapy for patients with delayed post-ES bleeding.

COMMENTS

Background

With the improvements of endoscopic techniques and equipment, the management of post-endoscopic sphincterotomy (ES) bleeding has shifted from surgery to endoscopic therapy. Delayed post-ES bleeding is less prevalent than immediate post-ES bleeding but it is often of clinical significance and requires more invasive intervention. The endoscopic treatments for delayed post-ES bleeding mirror those for peptic ulcer bleeding. However, the optimal method for treating this type of bleeding has not been determined.

Research frontiers

This is the first study to compare the hemostatic efficacy between epinephrine injection alone and epinephrine injection combined with thermotherapy for delayed post-ES bleeding.

Innovations and breakthroughs

From the literature review, epinephrine injection is the most commonly used and highly effective method to control post-ES bleeding. The study results further demonstrate that epinephrine monotherapy is as effective as epinephrine injection combined with thermotherapy for controlling delayed post-ES bleeding. In addition, an additional thermotherapy does not seem to reduce the risk of re-bleeding.

Applications

The results of this study suggest that epinephrine injection alone can be the first-line therapy for patients with delayed post-ES bleeding.

Terminology

Immediate post-ES bleeding: Any hemorrhage induced by ES and warranting endoscopic hemostasis within the procedure of endoscopic retrograde cholangiopancreatography (ERCP). Delayed post-ES bleeding: Any hemorrhage occurring after completion of ERCP and manifested by melena, hematemesis or hematochezia associated with a decreased hemoglobin level from baseline.

Peer review

Title reflects the major topic and contents of the study. Abstract gives a clear description of the materials and methods, results and conclusions. Significant points have been convincing. Detailed description of methods is provided and statistical methods used are appropriate. Results provide sufficient data to draw firm conclusions. In discussion valuable conclusions are provided. References are appropriate, relevant, and updated. Tables are appropriately presented.

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