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EXHIBIT 47

Methods: Data of patients diagnosed as Hemosuccus Pancreaticus between March 2005 and March 2014 was retrospectively reviewed from a prospectively maintained database.

Results: Twenty patients were diagnosed as Hemosuccus Pancreaticus. Seventeen patients were males and three were females (17 : 3). The presentation was with overt GI bleed in 17 patients (85%), anemia in two (10%) and epigastric pain in one patient (5%). Twelve, six and two patients had associated chronic pancreatitis, tropical pancreatitis and acute pancreatitis respectively. Bleeding through the ampulla could be identified at UGI scopy in nine patients (45%). CT Angiography was performed in 11 patients (55%).The arterial feeder was splenic artery in 10(50%),GDA in 8(40%) and pancreatico-duodenal vessels in 1(5%),hepatic artery in one (5%). Coil embolisation of feeding vessels was attempted in eleven (55%) and was succesfull in 11 (77.8%). 9 (45%) required surgery. The rebleeding rate was 18% following embolisation which was treated by re-embolisation in one and surgery in one. The mortality was 10%.

Conclusion: In a hemodynamically stable patient Angio-embolisation offers better immediate control of bleeding and is the preferred and safe initial treatment. Surgical intervention is indicated in a patient with hemorrhagic shock, impending rupture failed embolisation or if there is associated conditions which warrant definitive surgery.

Malignant HPB Diseases

APHPB-0441

SHORT-TERM OUTCOME OF LAPAROSCOPIC RADIOFREQUENCY ABLATION FOR HEPATOCELLUAR CARCINOMA IN LIVER CIRRHOSIS: THE SAFETY AND EFFICACY

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Objectives: Radiofrequency ablation (RFA) has been a legitimate treatment for primary and metastatic hepatocellular carcinoma (HCC) with liver cirrhosis. The laparoscopic RFA has replaced percutaneous RFA in HCCs that were considered to be infeasible because of poor sonic window, adjacent organ and major vessels. The aims of this study is to assess the clinical data and short-term outcome to evaluate efficacy and safety of laparoscopic RFA for HCCs with cirrhosis.

Methods: Between September 2009 to August 2014, 45 consecutive HCC patients with cirrhosis were treated by laparoscopic RFA. Most patients had hepatitis B (60%) and Child-Pugh class B status (90%). Median age was 60 years (range, 49–84). The short-term outcome was evaluated by radiologic images in 3-, 6-, and 9 months.

Results: Laparoscopic RFA was done in all patients and 49 HCC nodules was completely ablated. There was no procedure related morbidity and mortality. The HCC nodules consisted of primary (n = 22), recurred (n = 19) and metastatic lesions (n = 8). Median nodule diameter was 17 mm (range, 8–40). The 19 (45%) nodules were located in segment 8. Median time of RFA was 14 min (range, 7–28), while total operative time was 130 min (range, 63–303). The combined procedure were adhesiolysis (n = 17), cholecystectomy (n = 2), colorectal surgery (n = 1). The hospital stay was 5 days (range, 3–22). The 3-, 6-, and 9-months disease-free survival rate was 97.2%, 83.2%, and 78.6% respectively.

Conclusion: Laparoscopic RFA is a safe and effective therapeutic option for HCCs infeasible to percutaneous RFA in patients with cirrhosis. The laparoscopic RFA combines the advantage of clinical outcomes comparable to those percutaneous RFA.

APHPB-0442

CURRENT STATUS OF LAPAROSCOPIC HEPATECTOMY, AND OUR TECHNIQUE FOR SAFETY OPERATION

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Objectives: In about 10 years laparoscopic hepatectomy is spreading in our country. Only partial resection and lateral segmentectomy has been applied to national insurance. But currently, many reports of laparoscopic anatomical resection is increasing, because technical improvement of laparoscopic hepatectomy has been achieved via the development of surgical devices. We also experienced cases of anatomical resection in recent years. So now, we report our situation of laparoscopic hepatectomy, and our technique for safety operation.

Methods: Laparoscopic hepatectomy was introduced in our department from 2010. Initially, we used hybrid approach at mobilization for right or left lobe. From 2012, pure laparoscopic approach has become possible in all caeses with technical improvement. From 2013, we introduced pre-coagulation technique by the monopolar forceps using soft-coagulation with saline dripping for all parenchymal dissection line.

Results: 47 patients who have performed laparoscopic hepatectomy were identified between 2010 and 2014. The mean age was 65.9 years (range 29–87), 33 were men. There are 32 cases of HCC, nine cases of liver metastasis, two cases of cholangiocellular carcinoma, and four of the benign tumors. It was applicable for partial resection in 37, subsegmentectomy in 3, segmentectomy in 4, and lobectomy in 3. Tumor localization, S1/S2/S3/S4/S5/S6/S7/S8: 2/6/6/10/5/9/6/7. The mean tumor size was 2.4 cm diameter (range 1–4.6). The mean operation time was 267.9 min. There was no severe complication. After introduction of pre-coagulation by soft-coagulation, intraoperative blood loss significantly decreased (p = 0.0465).

Conclusion: Laparoscopic hepatectomy with pre-coagulation by soft-coagulation is safe and useful.

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EXHIBIT 48

	Classification	Therapy	Bleeding cause	Comment
UGIB	b	Hemospray	- Gastric carcinoma	
			Duodenal ulcer	4 days ago therapy with clips
		Clip, Hemospray	- EMR duodenal adenoma	
			Peptic ulcer	
		Clip, Injection, Hemospray	- Peptic ulcer	
	Ib	Hemospray	- Gastric carcinoma	
			- Duodenal ulcer ESD/EMR stomach	- Monotherapie Hemospray
	II (Bleeding prophylaxis)	Hemospray	- EMR duodenal adenoma (2x)	- Bleeding prophylaxis
LGIB	active bleeding	Hemospray	Tumor infiltration rectum	- Recurrent bleeding after 11 days: Clip and Hemospray
			Tumor infiltration colon	Recurrent bleeding after 8 days: APC
		Clip and Hemospray	- EMR cecum	- In the course bleeding prophylaxis
			Peptic ulcer	
	Bleeding prophylaxis	Hemospray	Tumor infiltration rectum Tumor infiltration colon	- Bleeding prophylaxis after initial therapy

Sa1610

Efficacy of Hemostasis by Soft Coagulation Using Endoscopic Hemostatic Forceps in Comparison With Argon Plasma Coagulation for Acute Peptic Ulcer Bleeding: Preliminary Results of a Prospective Randomized Trial

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Background/Aims: Endoscopic high-frequency soft coagulation is available for the management of bleeding or nonbleeding visible vessels during endoscopic submucosal dissection. However, its efficacy on peptic ulcer bleeding has not been elucidated so far. The aim of this study was to evaluate the efficacy of hemostasis with soft coagulation using hemostatic forceps by comparing it with argon plasma coagulation (APC) in a prospective, randomized trial. Methods: During the period of January 2012 to December 2013, 97 patients with peptic ulcer bleeding were enrolled in this study. All of these patients were randomly assigned into two groups: epinephrine injection plus argon plasma coagulation (APC group) or epinephrine injection plus soft coagulation using hemostatic forceps (Forceps group). The primary outcome measure was recurrence of bleeding within 7 days and 30 days after initial hemostasis. Secondary outcomes measures were initial hemostasis rate, duration from initial hemostasis to the recurrence of bleeding, complication rate, and hospital mortality. Results: Patient demographics and ulcer characteristics including lesion size and Forrest classification were comparable between the groups. A total of the 45 (93.8%) of 48 patients in APC group and 46 (93.9%) of 49 patients in Forceps group were successfully treated with APC or soft coagulation alone, respectively. Initial endoscopic hemostasis with single or combined modality was achieved in all patients. Four patients (8.3%) in APC group and six patients (12.2%) in Forceps group experienced recurrent bleeding within 30 days (p = 0.740). Rebleeding rates within 7 days were 4.2% (2/48) and 10.2% (5/49) in the APC and Forceps groups, respectively (p = 0.436). Mean duration from initial hemostasis to the recurrence was similar (4.7 5.8 vs. 4.7 4.0; p = 0.986). There was no significant difference in terms of the volume of the epinephrine solution injection (6.6 vs. 5.9 mL), mean number of units of blood transfusion (3.3 vs. 3.6 units), complication rate (0% vs. 4.1%), mean hospital stay (8.9 vs. 7.9 days), and hospital mortality (4.2% vs. 4.1%). Conclusions: This study showed that soft coagulation using endoscopic hemostatic forceps is as effective and safe as argon plasma coagulation in the treatment of patients with acute peptic ulcer bleeding.

Treatment results of enrolled patients

	APC (n = 48)	Forceps (n = 49)	P-value
Initial hemostasis with single modality	45 (93.8%)	46 (93.9%)	1.000
Initial hemostasis combined with other endoscopic modality	3 (6.2%)	3 (6.1%)	1.000
Epinephrine (ml)	6.6 3.7	5.9 3.2	0.317
Emergency surgery	0	0	
Angiographic embolization	0	0	
Total complication	0 (0%)	2 (4.1%)	0.495
- Perforation	0	0	
- Aspiration pneumonia	0	2	
Total procedure time (minute)	20.2 11.2	18.1 7.9	0.286
Coagulation time (minute)	3.7 2.0	3.8 1.7	0.816
Blood transfusion (unit)	3.3 2.8	3.6 2.3	0.458
- Before endoscopy	1.2 1.5	2.5 1.8	0.990
- After endoscopy	2.1 2.2	2.5 1.8	0.343
Recurrent bleeding within 7 days	2 (4.2%)	5 (10.2%)	0.436
Recurrent bleeding within 30 days	4 (8.3%)	6 (12.2%)	0.740
- Duration from initial hemostasis (day)	4.7 5.8	4.7 4.0	0.986
- Endoscopic hemostasis	4	5	
- Angiographic embolization	0	1	
Overall mortality	2 (4.2%)	2 (4.1%)	1.000
- Bleeding related	1	0	
- Non-bleeding related	1	2	
Hospital stay (day)	8.9 9.7	7.9 3.9	0.481

Values are mean SD

Sa1611

Treatment of Chronic Radiation Proctopathy With Radiofrequency Ablation

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Background: Chronic radiation proctopathy (CRP) is a common problem in patients receiving pelvic radiation. Current ablative therapies have the potential for deep tissue injury leading to ulcerations, perforation, and fistulas. Radiofrequency ablation (RFA) therapy avoids deep tissue injury and is a promising treatment for CRP. The aim of this study is to assess the long-term safety and efficacy of RFA for the treatment of CRP. Methods: This is a multicenter, retrospective analysis of a prospectively collected database of all CRP patients treated with RFA at VA Boston Healthcare System in Massachusetts, and Sarasota Memorial Hospital and Suncoast Endoscopy of Sarasota in Florida. RFA treatment was performed using HALO90TM or HAL-O60TM device (Covidien) at energy setting of 12J/cm^2. The primary endpoint of the study was complete resolution of the rectal bleeding. Secondary endpoints included visually scored improvement of CRP on endoscopic follow-up, improvement in hemoglobin, and adverse events related to the procedure. Endoscopic severity of CRP was scored using an accepted rectal telangiectasia density (RTD) grading scale. Descriptive analysis was done using mean, standard deviation, median, range as applicable. Pre-treatment and post-treatment RTD scores and hemoglobin levels were compared using Wilcoxon signed-rank test. Results: 39 consecutive male patients (mean age 72.9 6.6 years) were included in the study. 59% had prior medical therapy and 36% had failed prior endoscopic therapy (mostly argon plasma coagulation). Mean number of RFA session was 1.49 (median 1, range 1-4) with mean interval of 18 weeks between sessions. On average patients received 13 6.5 applications of RFA per session. Rectal bleeding stopped completely in all patients during the mean follow-up of 28 months (range 7-53). There was a significant improvement in mean hemoglobin level from 11.8 2 to 13.5 1.6 gm% (p<0.0001) with an absolute mean increase of 1.7gm% (95% CI: 1.2-2.2) after treatment (Figure 1A). Endoscopic severity also improved significantly with an improvement in mean RTD score from 2.68 0.48 to 0.68 0.98 (p<0.0001) with an absolute mean decrease of 2 (95% CI: 1.64-2.36) (Figure 1B). Treatment with RFA led to discontinuation of blood transfusion and iron therapy in 92% and 82% patients, respectively. Mild, transient anorectal pain was reported after 12% treatment sessions. Rectal ulcers, fistula, or stricture formation was not seen in any patient. Conclusions: RFA therapy led to complete resolution of rectal bleeding in all treated CRP patients, with improvement in clinical and endoscopic indices without any major complications. This is the first study to report the long-term efficacy and safety of RFA for the treatment of CRP. Further controlled studies are needed to establish RFA as the endoscopic therapy of choice for treatment of CRP.

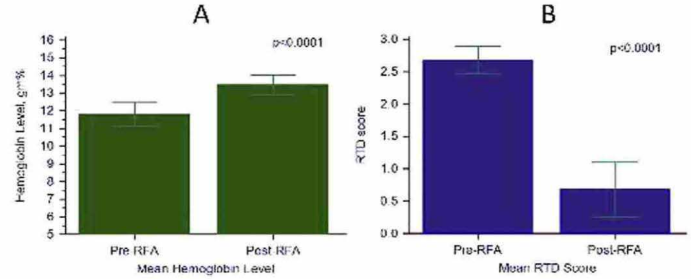

Figure 1. Changes in hemoglobin level (A) and endoscopic score (B) after RFA.

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EXHIBIT 49

Surg Endosc
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VIDEO

Laparoscopic liver resection using a monopolar soft-coagulation device to provide maximum intraoperative bleeding control for the treatment of hepatocellular carcinoma

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Abstract

Background The popularity of laparoscopic liver resection (LLR) is spreading, worldwide, because the intraoperative blood loss is less than for open hepatectomy and it is associated with a shorter hospitalization period [1–6]. During LLR, intraoperative hemostasis is difficult to achieve, unlike during laparotomy where bleeding can be stopped instantly [7–10]. Our LLR method for the treatment of hepatocellular carcinoma (HCC) includes maximal control of intraoperative bleeding using a monopolar soft-coagulation device. Although we use a monopolar soft-coagulation device to control bleeding during LLR, while coagulating the thin blood vessels, we also developed a maneuver (the hepatocyte crush method: HeCM) to allow liver transection to progress while liver parenchymal cells are being crushed.

Method Between January 2008 and March 2016, we performed total LLR on 150 hepatocellular carcinoma patients (144 partial liver resections and six left lateral sectionectomies) using the maneuver shown in the video.

Results The patients had Child–Pugh Scores of grade A ($n = 100$), B (42), or C ($n = 8$) and the localizations of tumor were segment (S) 1($n = 7$), S2 (19), S3 (23), S4 (28), S5 (17), S6 (26), S8 (17), and S8 (29). The median blood loss was 30 (range 0–490) g during a median surgical time of 207 (range 127–468) min. One patient required conversion to a laparotomy due to the presence of severe adhesions; none of the patients required conversion due to intraoperative hemorrhage. The peak aspartate aminotransferase (AST) level was 320 (range 57–1964) IU/L. Although some patients showed high AST levels, none showed signs of hepatic failure. The median postoperative hospital stay duration was 6 (range 3–21) days. Postoperative complications occurred in seven cases (4.7%), including intraabdominal abscesses ($n = 2$), wound infections (2), intraabdominal hemorrhage (1), bile duct stricture (1), and umbilical hernia (1). The mortality was zero.

Conclusion HeCM, combined with the use of a monopolar soft-coagulation device, is a good technique for reducing bleeding during liver resection in patients with HCC.

Keywords Laparoscopic liver resection · Liver transection method · Intraoperative bleeding · Monopolar soft-coagulation device

Compliance with ethical standards

Disclosures Drs. Mitsuo Miyazawa, Masayasu Aikawa, Katsuya Okada, Yukihiro Watanabe, Kojun Okamoto and Isamu Koyama have no conflicts of interest or financial ties to disclose.

Electronic supplementary material The online version of this article (doi:10.1007/s00464-017-5829-x) contains supplementary material, which is available to authorized users.

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EXHIBIT 50

Conclusions: Obesity appears to represent an adverse prognosticator with respect to operative blood loss. However, it does not appear to predict disease specific outcomes or intra-operative outcomes.

UP-01.206

Prognosis and Characteristics of Renal Cell Carcinoma in Hemodyalisis Patients: Comparison Between Unilateral and Bilateral Occurrence

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Introduction and Objective: Patients with end-stage renal disease (ESRD) requiring hemodyalisis (HD) have a higher incidence of renal cell carcinoma (RCC) compared to the general population. Patients with bilateral sporadic RCC have a poor prognosis compared to those with unilateral RCC. Moreover, bilateral metachronous occurrence of sporadic RCC was associated with an unfavorable prognosis compared with bilateral synchronous occurrence. In the previous report, cancer specific prognostic factors for HD patients with RCC have not been discussed. In the present study, we analyzed the prognosis and characteristics of RCC in HD patients after radical nephrectomy and compared those with unilateral and bilateral occurrence.
Materials and Methods: Two-hundred and forty six HD patients who underwent radical nephrectomy for RCC were the subjects of the present study. Of these, unilateral RCC occurred in 201 patients, bilateral synchronous in 15 and bilateral metachronous in 30. Cancer specific survival was accessed by Kaplan-Meier method.
Results: Cancer specific survival was not significantly different between two groups. (5-year: unilateral, 90%; bilateral, 90%; P 0.9509). Seventeen patients of 201 (8.5%) with unilateral occurrence and 4 patients of 45 (8.9%) with bilateral occurrence died from kidney cancer in the follow up periods. The presence of ACDK (unilateral, 73%; bilateral 91%; P 0.00319) and mean duration of hemodialysis before surgery (unilateral: 157 91months, bilateral: 189 83.5, P 0.0319) are significantly different between the two groups. Bilateral occurrence had more multifocal tumors than with unilateral occurrence (bilateral: 74%, unilateral: 30%, P 0.0001). Pathological findings (unilateral: clear cell 84%, papillary cell 14%, bilateral: clear cell 76%, papillary 22%), tumor grade, tumor size and pathological stage were not significantly different between the two groups. Longer duration of HD before surgery (P 0.0091), tumor size (P 0.0112) and tumor grade (P 0.0062) were unfavorable prognostic factors for death from RCC as shown by multivariate analysis.
Conclusion: The type of occurrence of RCC, unilateral or bilateral, in HD patients did not appear to have influenced the cancer specific survival. Patients with long duration of HD have to be followed strictly, because they tend to have bilateral kidney cancer and poor cancer prognosis.

UP-01.207

Thermal Damage of the Soft Coagulation in Pig's Kidney

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Introduction and Objective: A suture of the kidney after a tumor resection in partial nephrectomy sometimes induces bleeding by the surgical needle, and an injury of the arcuate or interlobbar artery causes of pseudo-aneurism or arterio-venous fistura. Furthermore, the ligation of normal kidney tissues makes ischemic damage. It is well-known the soft coagulation is useful and safety for stopping of hemorrhage and leakage in lung, liver and pancreas surgery. Major complications of partial nephrectomy are also hemorrhage and leakage of urine. Then, we applied the soft coagulation on partial nephrectomy to avoid sutures, and reported this novel method was safety and useful. On the other hand a high temperature by an electrosurgical knife may damage normal kidney tissues. Here, we investigated the thermal effect of the soft coagulation using a pig's kidney.
Material and Methods: Using a pig's kidney, the maximum temperature of surface and section were measured by a thermography on condition of the soft coagulation effect 7 (SC7), effect 3 (SC3), forced coagulation (FC) and spray coagulation (Sp). The maximum temperature at 5mm and 7mm deep were measured by a thermometer on condition of SC7 and SC3.
Results: The maximum surface temperature on SC7, SC3, FC and Sp were 88.3°, 99.2°, 176.1° and over 250°, respectively. The maximum section temperature on SC7, SC3, FC and Sp were 110.6°, 144.1°, 158.6° and over 250°, respectively. The maximum temperature at 5mm and 7mm deep were 58°, 31.5° on SC7 and 85°, 62° on SC3, respectively.
Conclusions: The maximum temperature on SC7 or SC3 is lower than on FC or Sp. The thermal damage of kidney tissues is within 5mm or less on SC7. The thermal damage of normal kidney tissues using the soft coagulation is limited, and this has possibility to protect the residual renal function.

UP-01.208

Survival Following Nephrectomy for Advanced Renal Cell Tumors With Renal Vein Involvement

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Introduction and Objective: Advanced renal cell cancer (RCC) with renal vein involvement is associated with a poor prognosis.However, a multimodal approach consisting of cytoreductive nephrectomy, systemic therapy and metastasectomy have been useful in prolonging the overall and progression free survival. The objective is to determine the oncological outcome in our case series of patients who underwent radical nephrectomy for stage T3 and T4 renal carcinoma.
Materials and Methods: Twenty-four consecutive patients underwent radical nephrectomy (n 18) or cytoreductive nephrectomy (n 6), with or without systemic therapy.
Results: Mean age of the cohort was 65 10yrs (M:F 5:1). Seventeen and 6 patients underwent open and laparoscopic nephrectomy, respectively.Mean follow-up time was 27 22months. The tumor was inoperable in one patient.The proportion of disease stages were: T3a (46%), T3b (46%), T3c and T4 (8%).In 6 patients, the disease was already metastatic.Five patients received adjuvant systemic therapy (sunitinib or interferon) at 59 21days following surgery.Second line (n 4), third line (n 2), and fourth line (n 1) systemic therapy was administered in some patients.Four patients have died from disease progression.Kaplan-Meier analysis revealed overall survival to be 86% at 24 months.
Conclusions: A multimodal approach consisting of radical surgery and systemic

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EXHIBIT 51

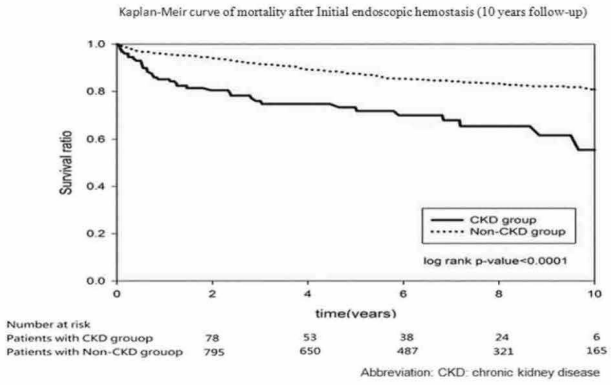

Figure 2. Kaplan-Meir curve of mortality after initial endoscopic hemostasis (10 years follow-up)

Mo1372

Investigation of Overt Upper Gastrointestinal Hemorrhage in Patients Administered DAPT and NOAC

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Background: In association with the increase in prevalence of heart disease, the numbers of patients administered dual anti-platelet therapy (DAPT), and novel oral anticoagulants (NOACs) have increased. However, the risks of overt upper gastrointestinal hemorrhage associated with DAPT and NOAC have not been sufficiently elucidated. Objectives: To elucidate the rates and risk factors of overt upper gastrointestinal hemorrhage in patients administered DAPT and NOAC. Subjects and Methods: The subjects of this study were patients who were administered DAPT or NOAC for an extended period at our hospital during the 5-year period, and with whom esophagogastroduodenoscopy (EGD) was carried out because of some sort of gastrointestinal symptoms. Upper gastrointestinal hemorrhage was classed as overt, and endoscopic hemostasis was carried out.

The following investigations were carried out:

1. The rates of upper gastrointestinal tract hemorrhage with DAPT and NOAC administration were determined.
2. The risks of upper gastrointestinal tract hemorrhage with DAPT and NOAC administration were investigated with different background factors [*H. pylori* infection, concomitant NSAID administration, and concomitant proton-pump-inhibitor (PPI) administration, etc.]. Results: The numbers of patients in the DAPT and NOAC groups were 191 and 58, respectively.

1. The number of hemorrhagic patients in the DAPT group was 25 (13%), and the number in the NOAC group was 5 (8.6%). There was no significant difference between these groups ($p = 0.49$).
2. In the DAPT group, no significant differences in the background factors were found between the hemorrhagic and non-hemorrhagic groups. Among patients concomitantly administered PPIs, 14 of 128 (10.1%) were hemorrhagic, whereas among those not administered PPIs 11 of 63 (17.1%) were hemorrhagic, and there was again no significant difference between these groups ($p = 0.21$), but the odds ratio was 0.61.

In the NOAC group, no significant differences in any background factors were found between the hemorrhagic and non-hemorrhagic groups. Among patients concomitantly administered PPIs, 1 of 26 (3.8%) were hemorrhagic, whereas among those not administered PPIs 4 of 32 (12.5%) were hemorrhagic, and there was again no significant difference between these groups ($p = 0.27$), but the odds ratio was 0.28. Conclusions: No significant difference in hemorrhage rates was found between the DAPT and NOAC groups, the rate of overt upper gastrointestinal hemorrhage being approximately 10% in both groups. In both the DAPT and NOAC groups, a tendency toward inhibition of overt upper gastrointestinal hemorrhage was found with concomitant PPI administration, and prophylactic PPI administration is therefore considered to be important.

Mo1373

Soft Coagulation With Hemostatic Forceps Was Useful for Endoscopic Hemostasis in Upper Gastrointestinal Bleeding in Japan

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Background: Upper gastrointestinal bleeding (UGIB) is the most common gastroenterological emergency with considerable morbidity and mortality. Endoscopic high-frequency soft coagulation with hemostatic forceps has been used for hemostasis during endoscopic submucosal dissection of gastric tumors in Japan, and this procedure has been applied for hemostasis in patients with nonvariceal UGIB. Our previous prospective randomized study demonstrated that soft coagulation was equivalent to hemoclips for hemostasis of UGIB (Arima S, et al. J Gastroenterol 45: 501-5, 2010). The aim of the present study was to examine clinical outcome of nonvariceal UGIB between two periods during the last 12 years for evaluation of availability and effectiveness of soft coagulation. Methods: The medical records of 568 patients who underwent emergency endoscopy for nonvariceal UGIB from September 2002 to August 2014 were evaluated retrospectively. The patients were divided into two periods: the first period was from September 2002 to August 2008 and the second period was from September 2008 to September 2014. Characteristics of these patients were analyzed for comparison of availability and efficacy in endoscopic hemostasis between two different procedures, soft coagulation using hemostatic forceps and hemoclips. Results: Among the 568 patients with UGIB, 230 were in the first period and 338 patients were in the second period. *Helicobacter pylori* infection ratio was significantly lower in the second period compared to the first period (62.8% vs. 77.4%, $p<0.001$). The proportion of patients taking antithrombotics was not different between the two periods. While peptic ulcer lesions were the main cause of bleeding (85.2%) during the both study periods, bleeding caused by other lesions, such as esophagitis, increased in the second period ($p<0.001$). Primary endoscopic hemostasis was successfully achieved in 220 out of 230 (95.6%) patients in the first period and in 321 out of 338 (95.0%) patients in the second period, with no significant difference between the two periods. Re-bleeding ratio (13.0% vs. 9.1%) and mortality within one month (0.9% vs. 2.7%) was not different between the two periods. Majority of applied modality for endoscopic hemostasis was hemoclips in the first period, and soft coagulation was mainly applied for hemostasis in the second period. Soft coagulation with hemostatic forceps was applied more often for hemostasis significantly in the second period compared to the first period (77.9% vs. 10.6%, $p<0.001$). Conclusions: The present retrospective analysis indicates that endoscopic hemostasis by soft coagulation using hemostatic forceps has been widely applied for hemostasis in UGIB with validity and safety in Japan.

Mo1374

Gastrostomy Timing and its Influence on ICU and Hospital Length of Stay

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Introduction: Patients undergoing tracheostomy (TR) after prolonged mechanical ventilation typically experience temporary dysphagia with increased risk of aspiration. While early nutritional support in critically ill patients is associated with positive outcomes, temporary feeding methods are associated with significant complications. Gastrostomy placement (PEG) is a minimally invasive method of nutritional support with low morbidity and mortality. Bedside PEG performed simultaneously with TR may decrease anesthesia exposure, procedural times, duration of ventilation, and ICU length of stay (LOS). There are currently no guidelines for the ideal timing of PEG placement as it relates to TR in the critically ill, ventilator-dependent population. Aim: To assess the impact of PEG and TR timing on ICU and hospital LOS. Methods: This is an IRB-approved retrospective investigation of prospectively collected data that includes all 404 patients admitted to our 16 bed ICU who received TR between 10/1/05 and 08/30/15. 262 of these underwent PEG; 143 did not. We abstracted demographics, functional status, severity of illness scores, and clinical outcomes, including hospital mortality and discharge status of survivors, from the ICU's database. Observed:expected mortality ratios were calculated using APACHE IV methodology. We compared clinical outcomes of those who did and did not receive PEG, and further stratified outcomes of patients with PEG by timing in relation to TR: 111 within 48 hours of TR and 120 > 48 hours after TR. An additional 30 had PEG > 48 hours before TR. Results: Patients who received PEG compared to those that did not, had similar age, admitting service, and severity of illness (Table 1). Those with no PEG had higher functional status and were more likely to be discharged to home, but also had higher mortality and higher observed:expected mortality ratios, reflecting differing preferences regarding intensity of therapy, including resuscitation status, between the 2 groups. All patients who received PEG had similar age, severity of illness, and ICU LOS. Patients who received PEG within 48 hours of TR were more likely to be admitted with a surgical diagnosis and had a higher functional status than did patients who received PEG > 48 hours after TR (Table 2). Though ICU LOS was similar between the 2 groups, hospital LOS was significantly shorter for patients receiving PEG within 48 hours of TR than for PEG placed > 48 hours after TR. Conclusion: Early PEG placement, within 48 hours of tracheostomy, was associated with shorter hospital LOS in this heterogeneous cohort of critically ill patients, compared to delayed PEG placement. These findings have significant implications for hospital resource utilization. These data must be considered hypothesis generating and suggest the need for further study including a randomized trial of PEG timing.

BUKRINSKY
EXHIBIT 52

Determination of optimal monopolar coagulation settings for upper GI bleeding in a pig model

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Background: Monopolar electrocautery has had a limited role in the endoscopic therapy of nonvariceal upper GI bleeding because of the lack of speci" cally designed endoscopic instruments and limited data on how to use this technology for endoscopic applications.

Objective: To determine the optimal power settings and durations of endoscopic monopolar electrocautery for nonvariceal gastric bleeding.

Design: Twelve pigs underwent creation of cautery lesions by using a novel monopolar electrocautery device designed for endoscopic hemostasis control. The ef" cacy as measured by the depth of cautery and safety of monopolar electrocoagulation were evaluated in acute and survival phases.

Interventions: Monopolar electrocautery was applied to the stomach with power settings of 25, 50, and 75 W for durations of 2 to 5 seconds.

Main Outcome Measurement: The extent of cautery injury was assessed histologically by a blinded pathologist.

Results: An optimal cautery effect was achieved with 50 W of power and durations of cautery of 2 and 3 seconds. For 25 W, durations of cautery of 4 and 5 seconds resulted in good but often super" cial cautery effect. For 75 W, durations of cautery of 2 and 3 seconds resulted in good cautery effect, but with marginal safety. The visual diameter of monopolar cautery lesions correlated with the histological depth of the cautery lesions. No adverse effects were observed.

Limitations: Study conducted in a nonbleeding pig stomach model; thus, results may not apply to control of GI bleeding in patients.

Conclusions: Based on a nonbleeding pig model, we suggest that the initial settings for monopolar soft coagulation in clinical use should be 50 W for 2 to 3 seconds. (Gastrointest Endosc 2010;72:796-801.)

Nonvariceal upper GI bleeding is a common clinical condition responsible for more than 400,000 hospitalizations per year in the United States.[1,2] Despite many advances in medical and endoscopic therapies, the mortality rate for nonvariceal upper GI bleeding remains high at 5% to 14%.[3,4] A major determinant of mortality is rebleeding, which occurs in as many as 20% of patients who receive endoscopic therapy. The options for endoscopic therapy of nonvariceal upper GI bleeding include injection cautery and mechanical modalities. A common current practice is to use combination therapy that includes submucosal injection of dilute epinephrine along with a thermocoagulation modality (commonly multipolar electrocoagulation such as bicap) or mechanical compression with

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the use of endoscopic clips. Despite the ef" cacy of the currently available modalities to treat nonvariceal upper GI bleeding, there is a clear need for additional techniques that may be more effective or can complement existing endoscopic treatment modalities to avoid rebleeding.

Monopolar electrocautery is an established and effective hemostasis technology that is widely used in the operating room. The published experience using the endoscopic application of monopolar electrocautery for the control of nonvariceal upper GI bleeding is limited. There was one randomized, controlled trial comparing monopolar electrocautery with combination therapy (epinephrine injection and heater probe) in the management of patients with upper nonvariceal GI bleeding.[5] This study showed that monopolar electrocautery resulted in improved primary hemostasis and less rebleeding compared with combination therapy. In addition, monopolar electrocautery has been used in patients undergoing endoscopic mucosal dissection for the removal of super" cial gastric cancers. In this technique, bleeding induced by mucosal dissection is immediately controlled by the grasping of the bleeding site and the application of monopolar electrocautery.[6]

There has been a lack of speci" cally designed instruments for monopolar endoscopic hemostasis control; until recently, only hot biopsy forceps designed for removal of polyps have been available.[7,8] A new endoscopic cautery device has become available that combines a grasping forceps with rotational ability (Coagrasper; Olympus Medical Systems, Center Valley, Pa). This device has several designed changes compared with standard hot biopsy forceps that make it more favorable for the treatment of GI bleeding. Instead of a cup con" guration with a cutting edge designed for tissue removal as in hot biopsy forceps, this device has a " at, noncutting surface with a beveled edge. Furthermore, there is 360-degree rotational ability to facilitate orientation to optimally engage tissue. Thus far, there are very limited data on how to use endoscopic monopolar technology for endoscopic hemostasis applications, particularly, the exact power settings and durations of therapy for optimal clinical ef" cacy and safety.[9-11] In this study, we evaluated a range of power settings and durations of endoscopic monopolar electrocautery device to determine the optimal power settings and duration for control of nonvariceal upper gastric bleeding in a porcine model.

METHODS

Adult female domestic pigs were used for these studies. All endoscopic treatments and follow-up examinations were performed by one endoscopist (J.J.L.) for consistency of technique during the procedure. A monopolar coagulation probe (Coagrasper; Olympus Medical Systems) (Fig. 1) was used for all treatments. The electrosurgical generator used was the Olympus ESG 100 (Olympus Medical Systems); all lesions were created by using the soft coagulation setting. Soft coagulation is the purest form of coagulation in that there is no spark generated to initiate a cut. Compared with forced coagulation (which combines coagulation with some cutting), soft coagulation has a deeper coagulation and hemostasis effect. The power settings tested were 25, 50, and 75 W in combination with the soft coagulation waveform. The durations of monopolar soft coagulation application evaluated were 2, 3, 4, and 5 seconds. The study protocol was reviewed and approved by the Animal Care and Use Committee for Health Sciences at the University of Alberta.

After induction of anesthesia, the pigs were intubated and anesthesia maintained with iso" urane for all endoscopic procedures. After the animal was anesthetized, a standard upper endoscope was passed through the esophagus into the stomach for a detailed inspection. This was followed by lavage and clearing of any remaining gastric contents. The monopolar coagulation device was then passed through the accessory channel of the endoscope, and a uniform and consistent pulling force was applied to grasp the gastric mucosa in the body of the stomach for the creation of electrocautery lesions. Because the angle of the grasping and the pressure applied to tent the tissue will directly affect the depth of injury, each cautery lesion was created by 1 endoscopist by using grasp-and-tent technique. The monopolar cautery device was used to grasp the tissue perpendicular to the mucosal tissue plane for each lesion, and consistent pressure was applied to pull the tissue and produce tenting during the cautery period. An endoscopic clip was placed to mark the location of the " rst cautery lesion (25 W for 2 seconds) before the creation of the additional electrocautery lesions. Three rows (each power setting) of 4 electrocautery lesions (varying durations of durations) were produced (Fig. 2). The duration of the electrocautery application was standardized with a timer. The rows of lesions indicated the wattage applied, with the " rst row being 25 W, the second row 50 W, and the third row 75 W. Within each row were the 4 variable durations of the electrocautery application. The " rst was 2 seconds of cautery application, the second was 3 seconds, the third was 4 seconds, and the fourth was 5 seconds.

There were 2 phases in this study: an acute phase to evaluate the extent of injury and a survival phase to evaluate the safety and long-term effects. In the acute phase, electrocautery lesions were created followed by immedi-

Figure 1. The monopolar hemostatic forceps, with specially designed jaws to grasp tissue and rotational ability.

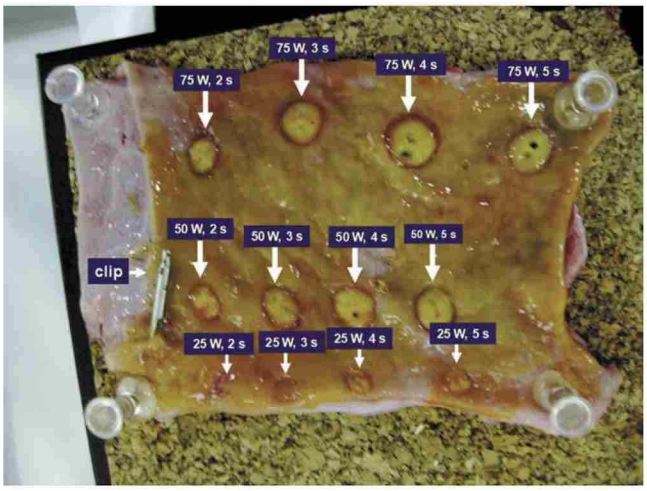

Figure 2. Porcine stomach ex vivo after systematic application of monopolar electrocautery. Each row of 4 cautery lesions corresponds to a power level with varying durations of therapy. An endoscopic hemoclip was placed to facilitate accurate orientation of specimen.

ate killing of the animals. The survival phase of the study involved creating electrocautery lesions followed by a 1-week survival before killing the animals. For the survival phase of the study, pigs underwent creation of the endoscopic electrocautery lesions in a similar fashion as in the acute phase of the study. However, the setting of 75 W at 5 seconds was omitted because of concerns by the animal care and use committee. After the endoscopic procedure, the animals recovered from the anesthesia and were given free access to solid food, " uids, and a marshmallow containing ranitidine 150 mg twice daily. The animals were then returned to normal activity and observed twice daily by a trained animal technician for evidence of GI hemorrhage, vomiting, and change in oral intake or activity patterns. After 1-week survival, the animals underwent a repeat endoscopy before being killed.

Histology specimens from all animals were " xed in formalin and sectioned and stained with hematoxylin and eosin. The depth of injury was scored according to the following system: mucosa (1), muscularis mucosa (2), submucosa (3), muscularis propria (4), and serosa (5). All specimens were reviewed by an independent pathologist blinded to the treatment status of the animal. We de" ned optimal endoscopic cautery as showing effect within the submucosa but not involving the muscularis propria. Avoiding cautery of the muscularis propria should minimize the possibility of a transmural burn and perforation or motility complications from monopolar soft coagulation.

Statistical analysis

The means of the depth and diameter of the electrocautery lesions created were compared by using the Wilcoxon rank-sum test. The differences were judged to be statistically signi" cant when the P value was .05.

RESULTS

Twelve adult female domestic pigs (mean weight, 52 kg) were used for these studies; 8 pigs were allocated to the acute phase of the study and 4 pigs to the survival phase to investigate the ef" cacy, safety, and long-term effects of monopolar electrocautery.

Acute phase

The maximal histological depth of the monopolar cautery effect depending on power setting and duration of cautery with soft coagulation is shown in Table 1. For the 25-W power setting, durations of cautery of 2 and 3 seconds resulted predominantly in super" cial effects. However, when the duration was increased to 4 and 5 seconds, the cautery extended at least into the submucosa in 50% of animals, although otherwise the effects were predominantly super" cial. For the 50-W setting, durations of cautery of 2 and 3 seconds consistently resulted in cautery effect in the submucosa. However, when durations of cautery were extended to 4 and 5 seconds, at least 50% of animals showed deep cautery effect in the muscularis propria. For the 75-W setting, durations of cautery of 2 and 3 seconds predominantly resulted in cautery effect extending into the submucosa. However, there was some cautery effect of the muscularis propria at these settings (25% for 75 W at 3 seconds). Durations of cautery of 4 and 5 seconds consistently showed deep cautery effects in the muscularis propria.

The mean diameters of monopolar cautery lesions for each power setting and duration are shown in Figure 3. The mean diameter of the cautery lesions was signi" cantly larger for higher wattages for a given duration of therapy. In addition, with each power setting, longer durations of monopolar cautery tended to result in larger-diameter lesions.

Table 1. Histological level of gastric injury in 8 nonsurvival pigs after monopolar coagulation

Power setting (W)	Duration (s)	Maximal cautery depth
	3	1, 1, 1, 1, 2, 2, 3, 3
	5	1, 2, 2, 2, 3, 3, 3, 3
	3	3, 3, 3, 3, 3, 3, 3, 4
	5	3, 3, 3, 3, 4, 4, 4, 4
	3	3, 3, 3, 3, 3, 3, 4, 4
	5	3, 3, 4, 4, 4, 4, 4, 4

Numbers relate to histological level of injury (see text).

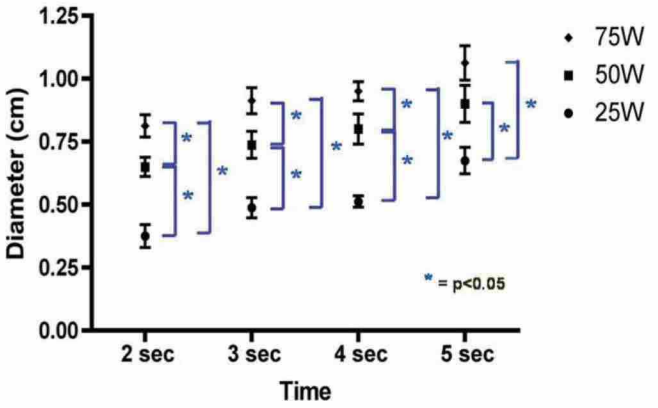

Figure 3. The diameter of electrocautery lesions with varying durations of monopolar cautery for each power setting.

The diameter of monopolar cautery lesions was correlated with the histological depth of the cautery lesions and is shown in Figure 4. With increasing diameter of the monopolar cautery lesion, there was an association with increasing depth of cautery effect with an R^2 0.3974. Overall cautery diameters of 4 to 8 mm corresponded best to a depth of cautery effect into the submucosa.

Survival phase

No adverse clinical effects were observed in the 4 survival animals during the 7 days of observation after application of monopolar electrocautery. There were no animals with fevers, altered behavioral patterns, GI bleeding, or signs of perforation. Necropsy of all animals revealed no sign of peritonitis or visible gastric serosal injury. Histological analysis of the stomachs showed signs of healing and overall a pattern of cautery effect depths similar to that of the acute-phase animals. There were no survival phase animals with deep cautery effects involving the serosa.

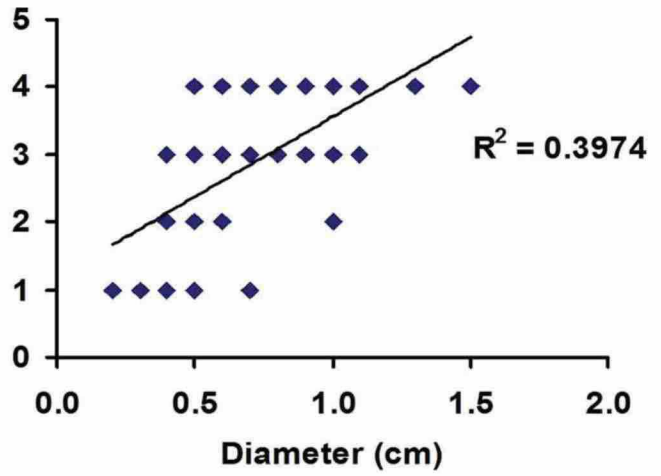

Figure 4. Correlation of the histological depth of monopolar electrocautery (1 mucosa, 2 muscularis mucosa, 3 submucosa, 4 muscularis propria, and 5 serosa) with the diameter of cautery lesions.

DISCUSSION

In this study, we varied power settings and durations of therapy for monopolar electrocautery for nonvariceal upper GI endoscopic hemostasis to determine optimal cautery parameters. In a porcine gastric model, we showed that the optimal monopolar electrocautery lesions depend on both the power settings and durations of therapy; for a power setting of 25 W, a good duration of therapy is 4 and 5 seconds, although there is still a signi" cant super" cial-only cautery effect. However, for a power setting of 50 W, the most favorable duration of cautery is 2 or 3 seconds. This optimal combination resulted in the cautery lesion that consistently extended into the submucosa with rare effect on the muscularis propria. Although a power setting of 75 W with durations of therapy of 2 and 3 seconds also resulted in an adequate submucosal cautery, there was inconsistent depth of cautery involving the muscularis propria. The diameter of the cautery lesion of 4 to 8 mm corresponded to the optimal depth of cautery of the submucosa. The " ndings of our study are speci" c to the application of electrocautery lesions in the gastric wall. The thickness of the gastric wall varies from 3 to 6 mm, depending on the exact location and amount of distention of the stomach. In the duodenum and colon, the intestinal wall is much thinner, usually about 3 mm in thickness. Thus, the application of the monopolar coagulation including power settings and durations of therapy will need to be adjusted when applied to other locations.

Although multiple modalities for endoscopic control of nonvariceal bleeding are currently available, rebleeding remains a signi" cant problem and is responsible for much of the morbidity and mortality associated with this condition. There is still a need for more effective endoscopic cautery methods with either improvements in existing hemostatic modalities or the development of new therapeutic modalities. Monopolar electrocautery is an established method of hemostasis widely used in surgery but not typically used for endoscopic control of nonvariceal upper GI bleeding. Monopolar cautery requires the placement of a grounding pad and thus has the potential to cause a greater depth of penetration of the cautery lesion compared with the commonly used endoscopic methods of hemostasis of multipolar or bipolar electrocautery. Until recently, endoscopic monopolar cautery was applied by using a hot biopsy forceps, which has a cupped cutting surface that is not ideal for hemostasis. The recent availability of a speci" cally designed endoscopic forceps with a " at contact surface and rotational ability allows further exploration of this treatment modality for endoscopic control of upper nonvariceal GI bleeding.

Monopolar endoscopic electrocautery is often used for hemostasis control during endoscopic submucosal dissection. In this technique, arterial bleeding is frequent ly induced during the dissection and needs to be quickly controlled. The grasping of the bleeding lesion by a monopolar forceps and direct cautery of the lesion is a rapid and convenient method to control the hemorrhage. It should be noted that the technique of using monopolar endoscopic hemostasis is different from that of multipolar devices that use mild to moderate pressure applied by the probe on the lesion to cause coaptive coagulation. In monopolar electrocautery, the lesion or vessel is grasped and pulled gently toward the endoscope, resulting a slight tenting of the mucosa before the application of monopolar electrocautery. Control of bleeding by monopolar cautery allows the dissection to resume without interference with the visualization of the operating " eld, as can occur by the application of hemoclips. In addition, the grasp-and-tent technique used in this study may not be feasible for some of the lesions seen in clinical settings of GI bleeding, such as a visible vessel in a " brotic peptic ulcer or postpolypectomy ulcer.

There are studies that suggest that the use of monopolar electrocautery to control bleeding in patients with nonvariceal upper GI bleeding may be a very effective treatment modality. In the randomized study by Soon et al,[5] the monopolar technique used was a hot biopsy forceps with "light pressure applied to the target." There also may be some special applications that are more responsive to the use of monopolar electrocautery compared with other currently available hemostasis methods. For instance, bleeding from submucosal tumors of the GI tract such as a GI stromal tumor can be particularly dif" cult to control with current treatment modalities. Monopolar cautery may offer a technique that results in deeper cautery and has the potential to treat this type of lesion more effectively. We have anecdotal experience of achieving endoscopic control of bleeding by using monopolar cautery in submucosal lesions that have not previously responded to other treatment modalities. Other possible therapeutic applications of monopolar coagulation include polypectomy bleeding, Dieulafoy's lesion, and management of a Mallory-Weiss tear.

There are several potential limitations to our study. This study was done in a porcine model with applications of monopolar electrocautery only to the gastric mucosa. Although our results are likely applicable to the human stomach, we did not test monopolar electrocautery of the esophagus, small bowel, or colon, and thus our results should not be extrapolated to treatment of bleeding in those areas. Furthermore, we did not test an actively bleeding animal model; rather, we performed this study in a nonbleeding model with histological depth of cautery injury used to indicate cautery success and safety. This assumes that the optimal depth of cautery needs to involve the submucosa but should not extend into and through the muscularis propria layer for safety reasons. It is possible that more or less cautery may be needed depending on the site and type of GI bleeding. We did not test the effect of repeated applications of monopolar electrocautery, which are typically needed to adequately treat patients with multipolar electrocautery methods. Although we found a correlation of the diameter of cautery injury and the depth of cautery, this should only be used as a rough measure of cautery effect and likely should only be applied to humans as a safety measure, not to exceed the indicated cautery diameters. Finally, another factor to consider is that most of the patients requiring bleeding control have preexisting conditions that may in" uence cautery injury not re" ected in this animal model.

In conclusion, monopolar electrocautery is an endoscopic therapeutic modality that can be used to control nonvariceal upper GI bleeding. Control of bleeding induced during endoscopic submucosal dissection is commonly currently performed with monopolar electrocautery. The recent availability of an endoscopic device designed speci" cally for the control of GI bleeding facilitates the application of this technology. We determined optimal power settings and durations of therapy in a pig model for producing electrocautery that consistently involves the submucosa but not the muscularis propria. Based on this nonbleeding study in pigs, we suggest that the initial settings for monopolar soft coagulation in clinical use should be 50 W for 2 to 3 seconds. We do not believe that the optimal settings for hemostasis of ulcer bleeding for patients have been de" ned in this animal model. Future clinical studies are needed to verify our " ndings for hemostasis control of bleeding ulcer and other lesions.

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BUKRINSKY
EXHIBIT 53

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HOW-I-DO-IT ARTICLE

Closure method for thick pancreas stump after distal pancreatectomy: soft coagulation and polyglycolic acid felt with fibrin glue

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Abstract
Purpose Pancreatic fistula (PF) remains an obstacle to safe distal pancreatectomy (DP). A thick pancreatic parenchyma is a major risk factor for PF. In this paper, we elucidate the feasibility of the new closure method using soft coagulation and polyglycolic acid felt with fibrin glue.
Methods In 2009–2013, 96 patients underwent DP with a novel closure method for pancreatic stump that utilized soft coagulation and polyglycolic acid felt with fibrin glue. We evaluated amylase levels in drainage fluid on postoperative days (POD) 1 and 3 and the incidence of postoperative PF according to International Study Group of Pancreatic Fistula (ISGPF) definitions.
Results Drain amylase levels on POD1 and POD3 were 275 and 241 U/L, respectively, and ISGPF-defined Grade B/C PF rates were 16.7 %. No clinical factors were significantly associated with PF. Average pancreatic parenchymal thicknesses were similar in PF-positive and PF-negative patients (10.4± 2.6 mm vs. 10.1±2.2 mm, P=0.639). There was no significant difference in the postoperative PF rate between patients with thick (≥12 mm) and thin (<12 mm) pancreas (11.1 vs. 18.8 %, P=0.544).
Conclusion Our novel pancreatic stump closure method appears to be simple and effective, particularly in patients with thick pancreas.

Keywords Distal pancreatectomy · Pancreatic fistula · Soft coagulation · PGA felt · Fibrin glue

Introduction

Distal pancreatectomy (DP) is a standard procedure in the treatment of benign or malignant lesions in the body or tail of the pancreas [1]. Despite recent advances in surgical techniques and postoperative management, the incidence of pancreatic fistula (PF) after DP remains high, ranging from 12 % to 34 % [2–5]. A PF can trigger severe postoperative complications, such as intra-abdominal hemorrhage, intra-abdominal abscess, and ileus, which can result in long hospital stays and higher medical fees. Preventing PF is crucial for the safety of DP. Although several techniques have been advocated to close the stump of the remnant pancreas, such as hand-sewn closure, stapler closure, ultrasonic dissection, seromuscular patches, and pancreaticoenteric anastomosis, it remains unclear which of these techniques is optimal [6–10]. Currently, stapler and hand-sewn closures are widely performed as standard techniques [11, 12]. Although several studies have reported that stapler closure contributes to a reduction in PF after DP [13–16], a randomized clinical trial to test the efficacy of stapler closure in DP in comparison with hand-sewn closure (DISPACT trial) revealed that stapler closure did not significantly reduce the incidence of PF [17].

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Previous reports have assumed that the development of PF after DP is caused by leakage of pancreatic fluid from both the main and peripheral pancreatic ducts on the cut plane of the remnant pancreas [18–21]. Secure closure of both of the main and peripheral pancreatic ducts on the pancreatic stump is important to reduce the incidence of postoperative PF (POPF) after DP. The stapler technique can close both the main and peripheral pancreatic ducts at one time by compressing the stump, whereas the typical hand-sewn technique can close the peripheral pancreatic duct by fish-mouth closure after ligation of the main pancreatic duct (MPD). However, compressing the pancreas itself could cause injury to the pancreatic parenchyma during both techniques, potentially leading to clinically relevant PF, especially in cases with a thick pancreatic parenchyma. Indeed, a thick pancreatic parenchyma is reported to be a risk factor for increased incidence of POPF [11, 22–24]. In this context, closure of the pancreatic stump, with minimization of injury to the pancreatic parenchyma, is critical to decreasing the risk of PF after DP.

We have developed a novel closure method that utilizes soft coagulation combined with reinforcement with polyglycolic acid (PGA) felt and fibrin glue. The advantage of this method is that the pancreatic parenchyma is not compressed, but only sealed upon closing of the pancreatic stump after DP, which minimizes damage to the pancreatic parenchyma. As a result, this method is potentially useful, especially in cases with a thick pancreatic parenchyma. In this study, we investigated the feasibility of this new method for management of the pancreatic stump; we focused in particular on how the thickness of the pancreatic parenchyma influences the risk of PF development.

Patients and methods

Patients

A total of 96 patients who underwent distal pancreatectomy (DP) at our hospital from 2009 to 2013 were enrolled in this study. All patients underwent the new closure method, which utilized soft coagulation combined with reinforcement with PGA felt and fibrin glue. Table 1 lists the clinical characteristics of the enrolled patients. There were 73 patients with pancreatic cancer (PC) and 11 with intraductal papillary mucinous neoplasm (IPMN). The remaining 12 patients had other diseases, such as mucinous cyst neoplasm (MCN) and pancreatic neuroendocrine tumors (PNET). The average thickness of the pancreas was 10.4±2.6 mm. Sixty-seven patients received preoperative chemoradiotherapy, which was associated with a decreased rate of postoperative pancreatic fistula (POPF) in our previous report [25].

Table 1 Characteristics of the patients

Characteristics	n=96
Age (years)	64.1±10.4
Sex (male/female)	61/35
BMI	22.6±3.0
PC/IPMN/other disease	73/11/12
Diabetes (−/+)	62/34
Operating time (min)	326.1±102.0
Blood loss (mL)	997.5±575.6
Diameter of MPD (mm)	2.68±1.45
Thickness of pancreas (mm)	10.4±2.6

BMI body mass index, *IPMN* intraductal papillary mucinous neoplasm, *MPD* main pancreatic duct, *PC* pancreatic cancer

Surgical procedure

All pancreatic resections were performed by the same surgical team in accordance with a standardized procedure used at our hospital. The cut line of the pancreas was almost directly above the portal vein in most patients regardless of disease, although in some of the patients with PC, the cut line was more proximal to the pancreas because of the location of the cancer. In all patients, the pancreas was cut with a scalpel followed by ligation of the main pancreatic duct (MPD). The MPD was ligated by U stitches made with a nonabsorbable suture (5-0 Ti-Cron®; Coviden Japan, Tokyo, Japan). Next, the cut surface was soft coagulated using the VIO soft coagulation system (VIO300D; ERBE, Marietta, GA, USA). VIO was set to soft coagulation mode with an effect level of 6, and the surface was coagulated by rubbing the electrode back and forth until the surface turned white in color. Soft coagulation was performed carefully so as not to damage the MPD with the U-stitch sutures. After coagulation, PGA felt (Neoveil® 50×50 mm; Gunze Co., Kyoto, Japan) was applied to the coagulated surface with fibrin glue (Beriplast P Combi-Set; CSL Behring, Tokyo, Japan). First, the PGA felt was soaked in a thrombin solution (liquid A) in a petri dish. Next, the liquid A–soaked PGA felt was applied to the coagulated surface and wrapped around the surface after spraying fibrinogen liquid (liquid B) on the surface. After wrapping the PGA felt on the surface of the pancreatic stump, it was rubbed tight against the cut plane by the surgeon's fingers (Fig. 1). In all patients, two closed suction drains were placed on the pancreas stump and in the left subphrenic space. We usually measured the concentration of amylase in the pancreas stump drainage fluid on postoperative days (POD) 1 and 3 after DP as an indicator of PF. PF was assessed according to the International Study Group of Pancreatic Fistula (ISGPF) definition [26]. The drainage tube was usually removed about 7 days postoperatively in cases with no abdominal complications.

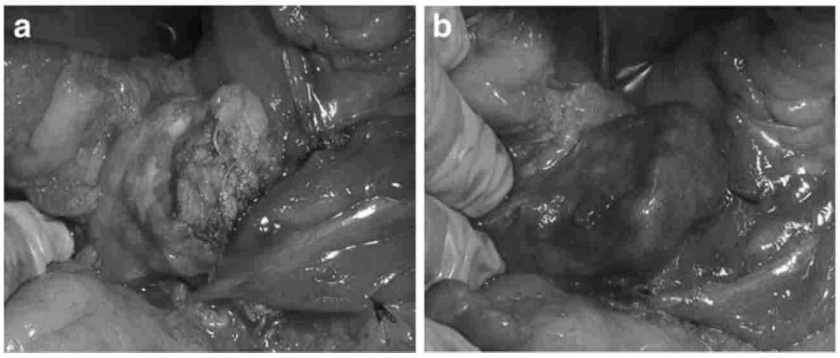

Fig. 1 The pancreatic stump was closed by wrapping the PGA felt with fibrin glue on the surface. The surface of pancreatic stump was coagulated using the VIO soft coagulation system before wrapping. **a** Before wrapping. **b** After wrapping

Measurement of thickness of the pancreas

We measured the thickness of the pancreas from the computed tomography (CT) images collected most recently prior to surgery. The thickness of the pancreas was measured at the expected cut line of the pancreas, which is usually just above the portal vein in our institute, although the cut line was shifted to the head or tail of the pancreas in some cases due to the location of tumors. A previous report indicated that a thick pancreatic parenchyma (cut-off values of <12 or ≥12 mm were used) was an independent risk factor for PF [11]. In this study, we also employed a cut-off value of ≥12 mm to classify the pancreatic parenchyma as thick and <12 mm to classify it as thin.

Statistical analysis

All data are reported as mean±standard deviation (SD) and/or as median. Fisher's exact test for categorical data and Student's *t* test or Mann–Whitney *U* test for continuous data were performed as appropriate. Comparisons of continuous variables were performed using *t* tests (i.e., age, BMI, operation time, blood loss, diameter of MPD, and thickness of pancreatic parenchyma) and Mann–Whitney *U* test (i.e., amylase activity in drainage fluid on POD 1 and POD 3). Previously reported factors associated with an increased risk of PF, such as patient age, obesity, malignancy, longer operating time, and thickness of the pancreatic parenchyma [3, 4, 21, 27, 28], were assessed to determine the clinical impact of these factors on POPF. Data analyses were performed with IBM SPSS statistics version 21.0 (IBM Japan Business Logistics, Tokyo, Japan), and a *P* value of <0.05 was considered to be statistically significant.

Table 2 Amylase levels in drainage fluid and incidence of postoperative pancreatic fistula defined by the ISGPF

Measurements	*n*=96
POD 1 drain amylase, U/L; median (range)	275 (36–13,801)
POD 3 drain amylase, U/L; median (range)	241 (18–32,185)
ISGPF grade A/B/C, *n* (percentage)	17 (17.7)/15 (15.6)/1 (1.0)

ISGPF International Study Group of Pancreatic Fistula, *POD* postoperative day

Results

Drain amylase levels on POD 1 and 3 were 275 and 241 U/L, respectively, and ISGPF grade A/B/C PF was observed in 17 patients (17.7 %), 15 patients (15.6 %), and 1 patient (1.0 %) (Table 2). Table 3 shows the impact on POPF of the clinical factors that we tested; no factor was significantly associated with the occurrence of POPF. In previous reports, thick pancreatic parenchyma was significantly associated with an increased incidence of POPF [11, 22–24]; however, in our study, the average thickness of the pancreatic parenchyma in PF-negative patients was 10.4±2.6 mm, which was not significantly different from that of the PF-positive patients (10.1±2.2 mm) (*P*=0.639).

Next, we assessed the impact of thickness of the pancreatic parenchyma on the incidence of PF and drain amylase levels. As shown in Table 4, there was no difference in postoperative drain amylase levels between patients with thin and thick

Table 3 Impact on postoperative pancreatic fistula of clinical factors measured in the study

Clinical factors	No PF (*n*=80)	PF (*n*=16)	*P* value
Age (years)	63.8±10.8	65.6±7.8	0.44
Sex (male/female)	51:29	10:6	0.924
BMI	22.6±3.0	22.8±2.9	0.745
Diabetes (−/+)	52/28	10/6	0.849
Disease (PC/not PC)	61/19	12/4	0.915
Operating time (min)	325.2±106.2	330.5±20.6	0.829
Blood loss (mL)	987.6±584.7	1046.7±544.3	0.709
Diameter of MPD (mm)	2.73±1.54	2.44±0.90	0.32
Extended resection (−/+)	20/60	4/12	0.999
Thickness of pancreas (mm)	10.4±2.6	10.1±2.2	0.639

BMI body mass index, *PC* pancreatic cancer, *PF* pancreatic fistula, *MPD* main pancreatic duct

Table 4 Postoperative drain amylase levels and ISGPF-defined fistulas in patients with thin and thick pancreatic parenchyma

Measurements	Thin (n=69)	Thick (n=27)	P value
POD 1 drain amylase, U/L; median (range)	243 (36–13,801)	535 (59–5875)	0.893
POD 3 drain amylase, U/L; median (range)	183 (18–6687)	449 (47–32,185)	0.325
ISGPF grade B/C, n (percentage)	13 (18.8 %)	3 (11.1 %)	0.544

ISGPF International Study Group of Pancreatic Fistula, *POD* postoperative day

pancreatic parenchyma. Moreover, the incidence of PF in patients with thin and thick pancreatic parenchyma was not significantly different (18.8 vs. 11.1 %, P=0.544).

Postoperative complications other than POPF was observed in 12 patients (12.5 %); wound infections in three patients, postoperative bleeding in two patients, delayed gastric emptying (DGE) in two patients, abdominal abscess which was not related to POPF in one patient, and other complications such as infectious enteritis in four patients.

Discussion

The novel method that we describe in this report comprises several components in an effort to decrease the risk of POPF. First, the MPD was ligated to prevent the major cause of PF. Next, pancreatic leakage from the peripheral pancreatic duct was decreased by using a soft-coagulation system. The use of a soft-coagulation system for pancreatic resection was first reported by Nagakawa et al. in 2008 [19]. The authors reported that the soft-coagulation system effectively sealed the small pancreatic ducts in burst pressure tests in dogs after distal pancreatectomy. In their report, both ligation of the MPD and sealing of the peripheral pancreatic duct with a soft-coagulation system effectively eliminated the causes of PF. All of these procedures can be performed without compressing or shearing the pancreatic parenchyma, and minimization of the damage to the remnant pancreas contributed to the comparable outcomes with respect to POPF in the thin and thick pancreas groups. The thickness of the pancreatic parenchyma is a significant risk factor when conventional methods are used, as stated in previous reports (Table 5). Kawai et al. reported that the incidence of PF in patients with thick pancreatic parenchyma (≥12 mm) was 72 %, which was significantly higher than that in patients with thin pancreatic parenchyma (<12 mm, 11 %) (P<0.001) [11]. Furthermore, Eguchi et al. showed that the thickness of the pancreatic parenchyma in the remnant was an independent risk factor for PF when using conventional closure methods [23]. By contrast, our results suggest that the PGA method is useful regardless of the thickness of the pancreatic parenchyma.

We used fibrin glue together with PGA felt to seal the pancreatic stump. The efficacy of PGA felt and fibrin glue for tissue sealing has been widely reported in the lung, liver, and pancreas [29–31]. The Beriplast P® Combi-Set consists of two separate vials that contain individual reagents (fibrinogen solution and thrombin solution), which form a fibrin clot upon being combined. Itano et al. examined five different combination procedures with PGA felt and fibrin sealant to cover pleural defects in lungs from swine and reported that a specific method in which PGA felt was soaked in thrombin solution and applied to the coagulated surface after spraying fibrinogen

Table 5 Thickness of pancreatic parenchyma as a risk factor for pancreatic fistula after conventional closure methods

Authors	Closure method	Number of patients		ISGPF grade B/C
Eguchi et al. (2012) [23]	Hand-sewn/stapler	Total	48	12 (25.0 %)
		Thin (<13 mm)	26	2 (7.7 %)
		Thick (≥13 mm)	22	10 (45.5 %)
Kawai et al. (2013) [11]	Stapler	Total	45	16 (35.5 %)[a]
		Thin (<12 mm)	27	3 (11.1 %)[a]
		Thick (≥12 mm)	18	13 (72.2 %)[a]
Okano et al. (2013) [24]	Stapler	Total	31	7 (22.6 %)
		Thin (<16 mm)	21	1 (4.7 %)
		Thick (≥16 mm)	10	6 (60.0 %)
Present study	PGA felt	Total	96	16 (16.7 %)
		Thin (<12 mm)	69	13 (18.8 %)
		Thick (≥12 mm)	27	3 (11.1 %)

ISGPF International Study Group of Pancreatic Fistula

[a] ISGPF grade A were also included

liquid on the surface was the most effective method for sealing pleural defects [32]. In our current series, we employed this method for pancreatic remnant closure.

In our institute, pancreatic cancer patients with T3 or T4 of Japanese Pancreatic Society (JPS) criteria underwent neoadjuvant chemoradiation therapy (NACRT) and we have reported the good prognosis of patients with NACRT. We previously reported that NACRT not only decreased pancreatic exocrine activity at the resection plane but also resulted in atrophic and fibrotic tissue in the pancreatic parenchyma [25], which resulted in a lower incidence of PF after DP using the hand-sewn method for stump closure. By contrast, in our current series, there was no difference in the PF rate between patients with and without NACRT (16.4 vs. 17.2 %, P= 0.99) (Supplementary Table 1). This result indicates that our new closure method does not increase the incidence of POPF, even in patients with soft pancreatic parenchyma, and we can state that this method is also useful regardless of the pancreatic elasticity as well as the thickness of pancreas.

There are many reports on stump closure methods after DP, and each method has both advantages and disadvantages. Therefore, it is important to choose the appropriate closure method on a case-by-case basis to prevent POPF. In our opinion, our new method, which uses a soft-coagulation system and PGA felt with fibrin glue, shows promise as a closure method for patients with a soft or thick pancreas.

Conclusion

Our novel pancreatic stump closure method using soft coagulation and polyglycolic acid felt with fibrin glue can close the pancreatic stump without compressing the pancreatic parenchyma, so it appears to be simple and effective, especially in cases with a thick pancreatic parenchyma.

Conflicts of interest None.

Author contribution Akita H: study conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript

Takahashi H, Sakon M, and Ishikawa O: critical revision of manuscript

Gotoh K, Kobayashi S, and Yano M: acquisition of data

Sugimura K, Miyoshi N, Noura S, and Oue M: acquisition of data, analysis and interpretation of data

Fujiwara Y and Motoori M: analysis and interpretation of data

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EXHIBIT 54

49 NO. 6 American Journal of Clinical Gastroenterology 472-476 O1-7

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ALIMENTARY TRACT: Original Articles
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A Randomized Trial of Monopolar Soft-mode Coagulation Versus Heater Probe Thermocoagulation for Peptic Ulcer Bleeding suppl 1

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Abstract

Background and Aim: Endoscopic therapy has been demonstrated to be effective in achieving hemostasis for bleeding peptic ulcers. Thermal coagulation is one of the most commonly used methods, with a high success rate. Recently, endoscopic submucosal dissection for early gastric carcinoma was developed and hemostasis with soft coagulation using hemostatic forceps was introduced. The aim of this study was to compare the hemostatic efficacy of soft coagulation with heater probe thermocoagulation for peptic ulcer bleeding.

Methods: Patients who visited our hospital with hematemesis or melena underwent emergency endoscopy. Inclusion criteria were presentation with an actively bleeding ulcer, a nonbleeding visible vessel, or an adherent clot. Patients were excluded if they were unwilling to give written informed consent or had a bleeding gastric malignancy. Patients

were randomized to receive endoscopic hemostasis with soft coagulation (Group S) or heater probe thermocoagulation (Group H). The primary endpoint was the primary hemostasis rate and secondary endpoints were rebleeding rate, complications, and the procedure time.

Results: Between May 2010 and February 2012, a total of 111 patients (89 gastric ulcers and 22 duodenal ulcers) were enrolled. Primary hemostasis was achieved in 54 patients (96%) in Group S and 37 (67%) in Group H (P<0.0001). Rebleeding occurred in 7 patients in Group H and none in Group S. Of these 7 patients, urgent surgery was performed in 1. Perforation occurred in 2 patients in Group H, which was managed conservatively.

Conclusions: For patients with gastroduodenal ulcer bleeding, soft coagulation using monopolar hemostatic forceps is more effective than heater probe thermocoagulation for achieving hemostasis.

Key Words: duodenal ulcer bleeding, gastric ulcer bleeding, heater probe thermocoagulation, peptic ulcer bleeding, soft coagulation.

Peptic ulcer bleeding remains the most common cause of hospitalization for acute nonvariceal gastrointestinal bleeding. [1] Although endoscopic therapy is clearly effective in achieving hemostasis for bleeding peptic ulcers, mortality caused by such ulcers still amounts to 10%. [1–5] Over the last 3 decades, endoscopic methods for achieving hemostasis rank as a major advance in the management of bleeding peptic ulcer, providing significantly better outcomes compared with either medical or surgical therapy. [6–9]

Recently, monopolar electrocoagulation using a soft-coagulation system and hemostatic forceps has been used to manage bleeding during endoscopic submucosal dissection. [10] This system regulates temperature rises up to just below boiling point, high enough to denature protein, without generating sparks. Therefore, the tissue shrinks with dehydration and degeneration, which effectively seals the vessel lumen to achieve hemostasis. The efficacy and safety of soft coagulation for the treatment of bleeding peptic ulcers has been reported by several investigators. [11–13] However, no randomized controlled prospective study has compared soft coagulation with the thermal method of endoscopic hemostasis.

The aim of this study was therefore to compare the efficacy of monopolar electrocoagulation using a soft-coagulation system with a well-established thermal method of endoscopic hemostasis (heater probe) in patients with actively bleeding or high-risk peptic ulcers.

METHODS

Patients admitted with hematemesis or melena were considered for the study. Inclusion criteria were that they presented with an actively bleeding ulcer (spurting or oozing), a nonbleeding visible vessel, or an adherent clot. Patients were excluded if they or their relatives were unwilling to give written informed consent or had a bleeding gastric malignancy.

Randomization of eligible patients was carried out at the time of endoscopy by an individual uninvolved with the procedure who opened sealed envelopes containing treatment assignments. Patients were randomized to receive endoscopic hemostasis with soft coagulation (soft-coagulation group) or heater probe thermocoagulation (heater probe group). The protocol was approved by the local Ethics Committee of our hospital.

Upper gastrointestinal endoscopy was performed within 24 hours of clinical onset. Endoscopy was carried out with a water-jet videoendoscope (GIF Q260J; Olympus Co. Tokyo, Japan). Endotherapy was performed by the endoscopists, each with at least 2 years' experience of upper gastrointestinal endoscopy.

In the soft-coagulation group, endoscopic hemostasis with soft coagulation was performed using monopolar, rotatable hemostatic forceps (FD-410LR; Olympus Co.) and an electrosurgical unit (ICC-200; ERBE, Tübingen, Germany) at soft-mode coagulation with a 70 W current. The hemostatic forceps were applied directly over the bleeding vessels or visible vessels. If there was an adherent clot on the ulcer bed, coagulation was performed after the removal of the clot using the forceps or a 3-pronged device. In the heater probe group, a heater probe unit (HPU-20; Olympus) was used and pulses of 20 to 30 J were given. During therapy, the distal tip of the heater probe was applied directly to the bleeding site. If bleeding occurred after the probe was withdrawn, the procedure was repeated until the bleeding stopped. When it was difficult to maintain a good view because of blood spurting or oozing during the procedure, hypertonic saline-epinephrine (HSE) was injected into the ulcer bed or around the ulcer.

When the allocated treatment failed to achieve hemostasis, the other method was applied at least 5 minutes after the allocated treatment was started (supplementary treatment). When bleeding decreased, the allocated treatment was continued for >5 minutes. If hemostasis was not achieved using these methods, a hemoclip or argon plasma coagulation was applied. If the endoscopic treatment was still unable to stop the bleeding, intervention radiology or surgical treatment was used.

Patients' vital signs were monitored until they became stable. Blood transfusions were given to maintain the Hb concentration at around 8 to 9 g/dL. The Rockall score was estimated as reported previously.[14] A positive history of nonsteroidal anti-inflammatory drugs or antithrombolytic agents was defined as >1 nonsteroidal anti-inflammatory drug or antithrombolytic agent daily within 7 days of admission. The presence of *Helicobacter pylori* was determined by a rapid urease test or the presence of serum IgG antibody to *H. pylori*.

Initial hemostasis was considered to have been achieved when accomplished by the single allocated method. A second-look endoscopy was routinely performed to confirm hemostasis within 24 hours of treatment. When the second-look endoscopy revealed hemostasis, primary hemostasis was considered to have been achieved. After second-look endoscopy, patients were permitted to eat. Lansoprazole 30 mg was given intravenously every 12 hours for 2 days, then orally at 30 mg/d for 2 months.

Rebleeding was suspected when the patient presented with either tarry stools or hematemesis within 14 days after initial hemostasis and was confirmed when emergency endoscopy revealed active bleeding from the ulcers. When the patient complained of abdominal pain after treatment, abdominal x rays were taken or computed tomography was performed to confirm the perforation.

The primary endpoint was the primary hemostasis rate and secondary endpoints were rebleeding rate, adverse events, and the procedure time.

Sample size was calculated according to our previous experience with monopolar electrocoagulation using a soft-coagulation system and thermal coagulation using a heater probe. The primary hemostasis rates of soft coagulation

versus heater probe were 95% and 75%, respectively. A sample size of 52 was required for each group to have a power of 80% by the Fisher exact test to detect a difference at an #=0.05 level of significance.

The significance of differences between groups was determined by $\#^2$ testing or the Fisher exact test for discontinuous variables and the Mann-Whitney *U* test for continuous variables. *P* values <0.05 were considered to be statistically significant.

RESULTS

Between May 2010 and February 2012, a total of 224 patients whose main symptoms were hematemesis or tarry stool received emergency endoscopy and 123 patients were found to have actively bleeding or high-risk ulcerative lesions. Of these, 12 patients were excluded because of gastric malignancy. Thus, 111 patients (89 gastric ulcers and 22 duodenal ulcers) were enrolled in the study, of whom 56 were assigned to the soft-coagulation group and 55 to the heater probe group (Fig. 1). There were no significant differences between the 2 groups in the background characteristics affecting the outcomes (Table 1).

FIGURE 1. Overall schema of patient enrollment and randomization.

TABLE 1. Patients' Clinical Characteristics

Table 2 shows clinical outcomes. The frequency of HSE usage was lower in the soft-coagulation group than in the heater probe group, but this difference was not significant (*P*=0.070). Primary hemostasis was achieved in 54 patients (96%) in the soft-coagulation group but only in 37 patients (67%) in the heater probe group (*P*<0.001). Sixteen patients in the latter received additional hemostasis with soft coagulation because the allocated treatment failed to achieve hemostasis within 5 minutes and it failed to decrease the bleeding. Ultimately, they achieved hemostasis. In contrast, only 2 patients in the soft-coagulation group received heater probe treatment to achieve hemostasis. The duration of endoscopic therapy was shorter in the soft-coagulation group than in the heater probe group, but this was also not statistically significant (*P*=0.10).

TABLE 2. Results for Patients Receiving Endoscopic Therapy

Rebleeding occurred in 7 patients (13%) in the heater probe group in contrast to none in the soft-coagulation group (*P*<0.01). Of these 7 patients, 5 received only the allocated treatment and 2 received heater probe thermocoagulation, followed by soft coagulation. Rebleeding occurred in 2 patients before the second-look endoscopy and in 5 patients after the second-look endoscopy. One patient with a duodenal ulcer in the heater probe group had tarry stool and presented with shock 19 hours after the treatment. Emergency endoscopy was performed, but the patient needed urgent surgery and then died of uremia about 2 months after the treatment.

Perforation occurred in 2 patients in the heater probe group. Both had actively bleeding gastric ulcers, and received heater probe thermocoagulation together with HSE injection and soft-coagulation therapy. Because perforation was minor and peritoneal signs were localized, they were managed conservatively.

DISCUSSION

Endoscopic treatment has been demonstrated to be effective in achieving hemostasis for bleeding peptic ulcers. Several hemostasis methods, such as thermal coagulation, mechanical clipping, and injection therapy are available, and can be selected for treatment. [15–21] In the present paper, we introduced a novel method of thermal coagulation with soft-mode for peptic ulcer bleeding and demonstrated prospectively that it proved more efficient for achieving hemostasis than heater probe thermocoagulation with regard to primary hemostasis and rebleeding.

Heater probe coagulation is popular in the United States because of its relatively low cost, portability, easy maintenance, high efficacy, and safety. Thermal coagulation monotherapy achieved initial hemostasis in 95% of patients, with rebleeding occurring in 14% to 16%. For thermal coagulation combined with injection therapy, rebleeding still occurred in 12% to 15%. [17,22,23] Several studies have demonstrated the efficacy of combination therapy (injection therapy followed by heater probe coagulation) for the control of bleeding from peptic ulcer and reduction in rebleeding. [24] Dual therapy with epinephrine has been used to improve visualization because epinephrine injection may reduce or stop bleeding. [19] However, the use of epinephrine plus thermal coagulation resulted in a significantly higher perforation rate compared with thermal coagulation monotherapy. [22]

Monopolar electrocoagulation using a soft-coagulation system is a unique coagulation mode that automatically regulates output voltage <200 V, causing the generation of Joule heat alone. [25] The heat induces denaturation of proteins, but without tissue carbonization. This method is based on the fact that the protein within the target tissue is effectively coagulated at a temperature between 70 and 80°C due to the Joule heat generated in the tissue. [26] In contrast, conventional monopolar electrosurgical units involve both Joule heating generated by the passing of electrical current through the electrical resistance of human tissue, which results in tissue temperatures well above the boiling point, and intensive heat generated by high voltage components, which forms carbonized eschar. In cases with excessive use of electrical current, the area affected by coagulation can extend into deep tissue and the risk of perforation becomes high. Thus, in soft coagulation, intensive heat coagulation leading to perforation can be avoided because a more accurate estimate of when to turn off the electricity by checking vapor efflux is possible. In fact, in the present study, minor perforation occurred in 2 patients in the heater probe group but none in the soft-coagulation group.

The efficacy of soft coagulation for actively bleeding peptic ulcer was first reported as a "4+1" contact method. [27] This approach coagulated 4 sites around the blood vessel first, and then the blood vessel itself using hot biopsy forceps. The rate of initial hemostasis was 100% with no case of recurrent bleeding. A multicenter pilot study in Japan reported favorable results in that tentative hemostasis for peptic ulcer using hemostatic forceps was achieved in 98.4% and rebleeding occurred in only 11.5%. [12] In a randomized trial to compare the effectiveness of soft coagulation with metallic hemoclips for bleeding gastric ulcers, 85% of enrolled patients were successfully treated with soft coagulation and 2% experienced recurrent bleeding. [11] In the present prospective study, the primary hemostasis rate was 96% and the rebleeding rate was zero. These results convinced us that soft coagulation could become a promising hemostatic method for nonvariceal gastroduodenal bleeding.

In our study, soft coagulation proved more efficient for achieving hemostasis than heater probe thermocoagulation with regard to primary hemostasis. The following reasons for this could be considered. First, it is difficult to set a heater probe precisely on the bleeding point in an emergency situation. Even when probe placement is accurate, respiratory motion or collected blood lakes commonly prevent continuous contact. In soft coagulation, the first step for hemostasis

is to grasp the bleeding point by forceps, already resulting in transient hemostasis. Grasping is a simple basic technique for endoscopists, used for taking biopsies, so all are practiced in this. Second, in soft coagulation, it is easy to judge the timing of when the thermal coagulation should be terminated. Hemostasis can be achieved when the vapor efflux is observed after soft coagulation for about 1 to 2 seconds. However, bleeding often recurs after removing the probe in heater probe thermal coagulation. It is difficult to master judging for how long to electrify to achieve hemostasis without risking perforation. Therefore, in our cases, the frequency of requiring supplementary treatment was increased in the heater probe group relative to soft coagulation because the latter provided reliable hemostasis.

There are some limitations to our study. (1) It was carried out at a single center in Japan. The different experience of monopolar soft-mode coagulation and heater probe thermocoagulation might have some influence on our results. (2) Supplementary treatment for treatment failure was more frequently required in the heater probe group. There might have been an inevitable selection bias in judging when to stop the allocated treatment. To minimize this selection bias, allocated treatment was performed for at least 5 minutes before changing. However, if the allocated treatment had been continued until hemostasis was achieved, the success rate in the heater probe group might have been higher. However, this would have required a longer procedure time resulting in severe adverse events such as pneumonia. (3) Finally, the efficacy of other monopolar hemostatic forceps or bipolar hemostatic forceps for this approach needs to be verified.

In conclusion, monopolar soft-mode coagulation with hemostatic forceps yielded a higher hemostasis success rate, lower rebleeding rate, and lower supplementary treatment rate compared with conventional thermal coagulation. Furthermore, the duration of the procedure and occurrence of adverse events were similar in both groups. These results indicate that soft coagulation is feasible and safe in clinical practice.

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EXHIBIT 55

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ORIGINAL ARTICLE—ALIMENTARY TRACT

Evaluation of hemostasis with soft coagulation using endoscopic hemostatic forceps in comparison with metallic hemoclips for bleeding gastric ulcers: a prospective, randomized trial

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Abstract
Background Endoscopic high-frequency soft coagulation, recently developed in Japan, is available for the management of gastric bleeding in cases of bleeding gastric ulcers and bleeding during endoscopic submucosal dissection. The aim of this study was to evaluate the efficacy of hemostasis with soft coagulation for bleeding gastric ulcers by comparing it with hemoclips in a prospective, randomized trial.
Methods During the period of April 2006 to March 2008, 96 patients that had gastric ulcers with bleeding or nonbleeding visible vessels were enrolled in this study. All of the 96 patients were randomly divided into two groups: endoscopic hemostasis with soft coagulation (Group I) or endoscopic hemoclipping (Group II).
Results A total of 41 (85%) out of 48 patients in Group I and 38 (79%) out of 48 patients in Group II were successfully treated with soft coagulation or clipping alone, respectively. The endoscopic hemostasis rate for the initial modality in combination with another endoscopic procedure performed after the initial method was 98% in both groups. One patient in Group I (2%) and five patients in Group II (10%) experienced recurrent bleeding. The time required to achieve hemostasis was shorter in Group I compared with Group II (9.2 ± 11.1 vs. 13.6 ± 9.4 min; $P < 0.05$).
Conclusions This study revealed that soft coagulation is as effective as hemoclipping for treating bleeding gastric ulcers. The time required to achieve hemostasis was shorter with the soft coagulation procedure.

Keywords Recurrent bleeding · Clip · Proton pump inhibitor · Visible vessels

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Introduction

Since 1983, when Marshall and Warren [1] succeeded in isolating *Helicobacter pylori* (*H. pylori*) for the first time, the subsequent rapid accumulation of basic and clinical research has resulted in a marked change in the concept and treatment of upper gastrointestinal diseases. There is a close relationship between *H. pylori* infection and peptic ulcers [2], and much progress has been made in approaches to eradicate *H. pylori* in order to treat and/or prevent gastric and duodenal ulcers [3]. The eradication of *H. pylori* is known to reduce the recurrence of peptic ulcers [4, 5] and rehemorrhage [6]. However, upper gastrointestinal bleeding is still one of the most common and serious clinical complications of peptic ulcers [7–13]. In the past 25 years, various endoscopic hemostatic methods for bleeding ulcers have been developed, and endoscopic hemostasis is the first-choice treatment for upper gastrointestinal bleeding. These methods may be classified into three categories: thermal or electrical coagulation methods (e.g., heater probe, laser, electrocoagulation, and argon plasma coagulator), mechanical hemostatic methods (e.g., hemoclipping and banding), and local injection methods (e.g., pure ethanol, epinephrine, ethanolamine oleate, histoacryl, polidocanol).

Soft coagulation with an electrosurgical unit using endoscopic hemostatic forceps, a type of high-frequency coagulation, is available for the management of gastric bleeding during endoscopic submucosal dissection [14]. This method might be applicable for the hemostasis of a bleeding gastric ulcer. To our knowledge, no prospective studies have evaluated its effects on bleeding ulcers. Therefore, the aim of this study was to evaluate the efficacy of soft coagulation for treating bleeding gastric ulcers by comparing it with hemoclips, which are commonly used for the hemostasis of bleeding gastric ulcers.

Materials and methods

Patients

Between April 2006 and March 2008, 96 patients with gastric ulcers with bleeding or non-bleeding visible vessels were enrolled in this study. A visible vessel was defined as a raised red or black spot that was resistant to gentle washing of the ulcer base [15, 16]. Before endoscopic examination, informed consent was obtained all patients who received emergency endoscopy because of suspected gastro-intestinal bleeding. All of the consecutive 96 patients were randomized into one of two groups according to a table of random permutations, and the applied hemostasis method was determined before endoscopic examination. Group I was initially treated with soft coagulation. Group II was initially treated with clipping. When the endoscopist judged that the initial hemostasis was not completely obtained by the allocated method, any additional hemostatic method was performed. We compared the two groups in terms of initial hemostasis success with the allocated single method as well as treatment time required to achieve hemostasis (from the start of the application of clipping or soft coagulation to the attainment of initial hemostasis). Additionally, recurrent bleeding was evaluated. This study was performed according to the guidelines of the committee on clinical practice of Saga Medical School Hospital, and was approved by the institutional review boards.

Methods

Emergency endoscopy was performed as soon as possible, and within 3 h after visiting our hospital, by endoscopists with over 6 years of experience. No other medication, except lidocaine pharyngeal spray, was used for premedication. A forward-viewing endoscope (Q240, Q260, H260 or Q260J, Olympus, Tokyo, Japan) was used to examine the patients.

For the subjects in Group I, soft coagulation was performed using an electrosurgical unit (ICC200, ERBE Elektronedizin, Tübingen, Germany) and monopolar hemostatic forceps (Radial Jaw™ 3 Hot Biopsy Forceps, Boston Scientific Co, Boston, MA, USA) inserted through the biopsy channel of the endoscope. When the covering clot adhered to the ulcer base, the endoscopist removed the clot using an irrigation system or the hemostatic forceps to detect the vessel. The closed forceps were gently pressed to the target and the endoscopist applied an electric current for 1–2 s. The output of the equipment was set from 50 to 80 W, and the endoscopist coagulated four sites surrounding the blood vessel initially and coagulated the blood vessel itself [17]. This soft coagulation process was repeated until hemostasis was confirmed.

For patients in Group II, hemoclips (HX-610-135, HX-610-135S, hemoclip, Olympus Optical, Tokyo, Japan) were placed on the ulcer base to bind the visible bleeding or nonbleeding vessels. When a vessel could not be visualized because of a massive clot covering the ulcer base, the clot was removed with an irrigation system. Hemoclipping was performed continuously until hemostasis was confirmed.

After the initial endoscopic hemostasis, all of the patients were given an intravenous H2-receptor antagonist for 1–2 days during fasting. After confirming hemostasis by follow-up endoscopy, the patients were re-fed and given an oral proton pump inhibitor. In patients with unstable vital signs or continued tarry or bloody stools during the hospital stay, emergency endoscopy was performed to determine whether any additional treatment was needed. Rebleeding was defined as follows: (1) blood in the stomach 24 h after the initial treatment, or stigmata of a recent hemorrhage at the ulcer base, or (2) fresh hematemesis and/or melena accompanied by either shock or a fall in hemoglobin level of greater than 2.0 g/dl within a 24-h period. Patients who experienced rebleeding were treated with an endoscopic hemostatic treatment selected by the endoscopist, and which was deemed to be most appropriate for the individual patient. Transcatheter arterial embolization or emergency surgery was performed in the event of: (1) rebleeding that could not be treated with endoscopic therapy; (2) recurrent bleeding after the third endoscopic treatment, or; (3) the total amount of blood transfused being more than 2000 ml.

Evaluation of data

Initial hemostasis with the allocated method, recurrent bleeding, time to achieve hemostasis with the allocated method, and 30-day mortality (from the time of initial hemostasis) were evaluated and compared between the two groups. Recurrent bleeding was defined as rebleeding within 7 days after the initial hemostasis. Statistical analyses were carried out using χ^2 tests and Mann–Whitney's U test, as appropriate. Differences were considered significant if the probability of the difference occurring by chance was

less than 5 in 100 ($P < 0.05$). All results are expressed as mean ± standard deviation (SD), unless otherwise stated.

Results

Table 1 shows the background characteristics of the patients in both groups. There were no significant differences between the two groups regarding age, sex ratio, ulcer history, hemoglobin level at emergency endoscopy, co-morbidities, anticoagulants and/or anti-platelet drug use, nonsteroidal anti-inflammatory drug use, and *H. pylori* infection. As shown in Table 2, the location of the gastric ulcer was not statistically different between the two groups. The bleeding state, as indicated by Forrest classification, and the sizes of the gastric ulcer and the visible vessel did not differ between the two groups. The years of experience of the endoscopists who performed the emergency endoscopy were not different in the two tested groups.

Table 3 shows the results of endoscopic hemostasis in both groups. Initial hemostasis with soft coagulation alone was successful in 41 (85%) out of the 48 patients in Group I. Initial hemostasis with clipping alone was successful in 38 (79%) out of 48 patients in Group II. The initial hemostasis rate with a single modality was not different between the two groups. The endoscopic hemostasis rate for the initial modality in combination with another endoscopic procedure performed after the initial method was 98% in both groups. Two patients (one patient in each group) were treated by transcatheter arterial embolization, and no patient required a surgical operation. One patient in Group I (2%) and five patients in Group II (10%) experienced recurrent bleeding within 7 days. The rebleeding rate tended to be higher in Group II, but the difference was not statistically significant. All of the patients with rebleeding were successfully treated by the endoscopic hemostasis method selected by the endoscopist. The time required to achieve hemostasis was significantly shorter in Group I compared with Group II (9.2 ± 11.1 vs. 13.6 ± 9.4 min; $P < 0.05$). One patient in Group I died within 1 month after the initial hemostasis because of lung cancer.

Table 1 Patient characteristics in the two tested groups

	Group I ($n = 48$)	Group II ($n = 48$)
Age	69.1 ± 10.9	68.4 ± 10.7
Sex ratio (males:females)	31:17	31:17
Ulcer history (+:−)	36:12	36:12
Hb (mg/dl)	8.8 ± 2.6	8.3 ± 2.8
Co-morbidities		
Hypertension	24	17
Diabetes mellitus	12	4
Anticoagulants and/or anti-platelet drug use	18	11
NSAID use	18	18
H. pylori infection	32	41

Values are mean ± SD

Group I, patients treated with soft coagulation; Group II, patients treated with hemoclips; NSAIDs, nonsteroidal anti-inflammatory drugs

Table 2 Characteristics of the bleeding gastric ulcers

	Group I ($n = 48$)	Group II ($n = 48$)
Main location		
Upper part of the stomach	8	13
Middle part of the stomach	33	32
Lower part of the stomach	7	3
Forrest classification		
Ia	8	6
Ib	7	6
IIa	33	36
Size		
Ulcer size (mm)	17	22
Visible vessel size (mm)	1.4	1.5

Values are mean ± SD

Group I, patients treated with soft coagulation; Group II, patients treated with hemoclips

Table 3 Hemostasis ratio, recurrent bleeding within 7 days, and time required to achieve hemostasis

	Group I ($n = 48$)	Group II ($n = 48$)
Initial hemostasis with single modality	41/48 (85%)	38/48 (79%)
Initial hemostasis combined with other endoscopic methods	47/48 (98%)	47/48 (98%)
Recurrent bleeding	1/48 (2%)	5/48 (10%)
Emergency surgery	0/48 (0%)	0/48 (0%)
Mortality within 1 month	1/48 (2%)	0/48 (0%)
Perforation	0/48 (0%)	0/48 (0%)
Required time for hemostasis (min)	9.2 ± 11.1*	13.6 ± 9.4

Values are mean ± SD

Group I, patients treated with soft coagulation; Group II, patients treated with hemoclips

* $P < 0.05$ compared with Group II

Discussion

Over the past 25 years, improvements in endoscopic hemostatic methods have provided safe and effective hemostasis. Several prospective controlled studies and

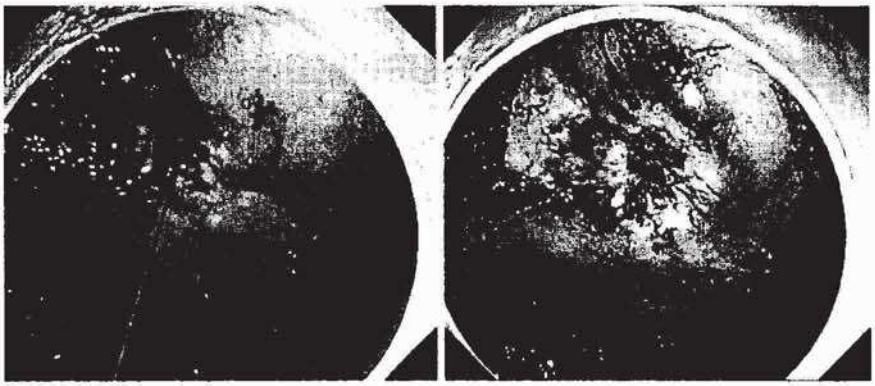

Fig. 1 Hemostasis of the bleeding gastric ulcer with soft coagulation

meta-analyses have demonstrated the efficacy of endoscopic hemostasis [18–32]. In these studies, endoscopic hemostasis was performed with local injection therapy, thermal coagulation therapy or mechanical hemostatic methods such as clipping, and there were few statistical differences between these procedures with regard to the hemostatic rate (ranging from 70.0 to 98.5%). Nevertheless, each procedure has advantages and drawbacks associated with the difficulty of the procedure, extent of tissue injury, and frequency of complications. The hemoclipping method for hemostasis was reported for endoscopic hemostasis, and several prospective randomized studies and a meta-analysis have demonstrated the efficacy of this method. In most of these studies, the permanent haemostatic rate with hemoclipping ranged from 89.0 to 98.5% [18–20, 31–34].

Hemostasis with soft coagulation performed using endoscopic hemostatic forceps was mainly introduced to manage bleeding during endoscopic submucosal dissection [14]. This coagulation method has now been widely utilized to manage cases of bleeding gastric ulcers in Japan. However, no prospective and/or randomized studies have evaluated the efficacy of soft coagulation for bleeding gastric ulcers. The present prospective randomized study evaluated whether the soft coagulation method was as effective as endoscopic hemoclipping for treating bleeding gastric ulcers. The results of this study indicate that the hemostasis rate with soft coagulation is equivalent to that with hemoclipping. Furthermore, the rate of rebleeding within 7 days tended to be lower with soft coagulation than with hemoclipping, and the time required to achieve hemostasis was shorter with soft coagulation than with hemoclipping. These findings can be considered advantages of the endoscopic soft coagulation method for treating bleeding gastric ulcers.

The soft coagulation method has some merits compared with the conventional thermal coagulation therapy. During soft coagulation, the tissue is coagulated without any carbonization or spark because the voltage is controlled below 200 V. The coagulated tissue is not peeled during coagulation, unlike in the conventional coagulation method, which might explain the low rate of recurrent bleeding in this study. In fact, as shown in Fig. 1, the coagulated tissue with high electrical resistance was not burned more than necessary. Another advantage of soft coagulation is the shallow depth of the coagulation tissue, which might prevent perforation after the therapeutic procedure. In fact, we did not experience any complications involving perforation in this study in either group.

There are several limitations associated with endoscopic soft coagulation. When the gastric ulcer is submerged in water and/or has a high volume of tissue, coagulation of the vessel may be difficult because of leaking electricity. Furthermore, devices for soft coagulation, including disposable hemostatic forceps, are relatively expensive compared with other hemostasis methods for treating bleeding gastric ulcers.

In conclusion, this study demonstrated that the novel endoscopic hemostatic method of soft coagulation was as effective as hemoclipping for treating bleeding gastric ulcers. In addition, the time required to achieve hemostasis with soft coagulation was shorter than that needed when using hemoclipping. Our findings suggest that soft coagulation should be considered for the hemostasis of bleeding gastric ulcers.

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EXHIBIT 56

27 NO. 9 ECRI Health Devices Journal 365

ECRI Health Devices Journal
September 01, 1998

ECRI Problem Reporting System

Hazard Report

Hewlett-Packard Viridia Telemetry System Can Disable Viridia Information Center Central Station

Problem

Two member hospitals have reported instances of operational difficulties involving the Hewlett-Packard (HP) Viridia Information Center, or VIC (Model M3150A), which is the central station for the Viridia Patient Care System. Specifically, the VIC became sluggish (cursor movement and response to mouse clicks were slow), then either automatically shut down and restarted itself or became disabled. These incidents occurred while the VIC was being used with the optional Viridia Telemetry System (Model M2600A).

No injuries or adverse effects have been reported. However, all patient monitoring is lost while the VIC is disabled and during the three- to five-minute shutdown-and-restart process. If a patient being monitored by a VIC that is disabled or is undergoing shutdown and restart should experience a problem, no alarms will sound to notify clinicians that the patient is in distress.

The frequency of the problem's occurrence varies with the use pattern at each reporting hospital. The hospitals experienced frequencies ranging from weekly to once every two to three weeks.

Discussion

The reported problem results when the following common sequence of events occurs: (1) A telemetry patient's leads are removed or become disconnected. (2) The removal or disconnection activates the Lead Fallback mode (a mode that automatically switches the displayed ECG waveform to a different lead during a disconnection to allow monitoring to continue). (3) The patient's monitoring is placed in the Standby mode by the user at the VIC. The Lead Fallback mode uses space in virtual memory and ordinarily releases that memory once normal monitoring resumes. However, if monitoring is placed in the Standby mode while in the Lead Fallback mode, the system will not release virtual memory, even when normal monitoring begins again. Repeated instances of this sequence use up more and more virtual memory, until there is not enough remaining for the system to function properly. After a time, central station operation becomes sluggish or nonreactive. (The user may see a box warning of low virtual memory.) The system will eventually either shut down and restart automatically, leaving patients unmonitored for three to five minutes, or become disabled, requiring that it be shut down and restarted manually, which could take far longer.

The problem causes all telemetry monitoring and alarms to be lost at the VIC. It also prevents the VIC from receiving information from any bedside monitors networked to it. The bedside monitors themselves will still function correctly, but if their alarms have been disabled or have had their volume turned down — as is often done with bedside monitors networked to a central station — no alarms will sound for a patient in distress. Therefore, alarms from such monitors may be missed while the VIC is disabled.

A system that becomes disabled can go unnoticed for some time. In addition, systems that need to be shut down and restarted manually will require either a service password or access to the central station computer, which may necessitate calling a technician. These delays can further increase the period during which patients are not monitored to 10 to 30 minutes or more.

Supplier's Action

HP issued Service Notes (M3150A-038, dated June 26, 1998, updated by M3150A-042, dated August 3, 1998) describing this failure mode. HP subsequently released a software upgrade, version A.02.17, on August 24, 1998 (described in Service Note M3150A-043). This upgrade is available at no charge through the HP field service organization, but it will not be automatically installed in all systems (in other words, HP is not treating this as a recall or mandatory update). The Service Notes describe the failure as affecting all software releases (including the latest production version, A.02.15).

Service Note M3150A-038 recommends the following "workarounds" — that is, possible ways to allow the Viridia system to function while waiting for the software upgrade:

- Before putting a patient's monitoring into the Standby mode, make sure it is not in the Lead Fallback mode. To do this, check that all leads are properly attached to the patient, and check the central station monitor to be sure there are no "Leads Off" alarms.

- At scheduled intervals, implement the Normal Shutdown function. The schedule for this step will depend on the system-use profile and will have to be determined for each site.

Service Note M3150A-042 recommends the following workarounds:

- Before removing the leads from the patient, either disconnect the lead set from the telemetry transmitter or remove the battery.

- Every other day, take the system out of monitoring mode (for example, by implementing the Date and Time Setup function), which will free up the virtual memory. This takes two to three minutes, compared with three to five minutes for a scheduled shutdown and restart.

HP field service representatives have also suggested that hospitals turn the Lead Fallback feature off.

When the reporting hospitals attempted to implement these workarounds, the problem decreased in frequency but was not eliminated. At HP's suggestion, one of the hospitals changed from using five leads and two waveforms to using three leads and one waveform. This was intended to prevent the Lead Fallback mode from activating, theoretically eliminating the problem. However, the problem continued to occur.

Conclusions

This problem will cause telemetry monitoring to be lost; it can also cause the loss of central station monitoring of patients on bedside monitors. The duration of monitoring loss can vary from two minutes for a scheduled memory-restoration procedure (such as Date and Time Setup) to 30 minutes or more if a technician needs to be called to restart the system manually.

The workarounds provided by HP are not acceptable. They require specific processes that are burdensome for nursing personnel; moreover, they do not ensure that the problem will be avoided. The hospitals that reported this problem to ECRI were not willing to shut down and restart the system periodically because of the loss of patient monitoring this entailed. They also did not want to turn off the Lead Fallback feature because it would increase the burden on nursing staff by requiring immediate action every time a lead came off a patient.

Recommendations

1 If you are using the VIC, contact your HP field service representative to receive the upgraded software, version A.02.17 (or later, if available). This is recommended even for hospitals not currently experiencing a problem, since a simple change in the procedure for removing a patient from telemetry could trigger the problem.

2 Until the upgrade is installed, alert staff to this problem, report any problems with the VIC to your HP field service representative, and implement the HP workarounds most acceptable to your facility.

Supplier Information:

Hewlett-Packard Co., Medical Products Group [101883], 3000 Minuteman Road, Andover MA 01810-1099, USA; Phone: (800) 934-7372, (978) 687-1501; Fax: (978) 686-7262; Web site: http://www.hp.com/go/medical.

These products are marketed worldwide, except for the Middle East.

Reporting Policies

We encourage our members, healthcare providers, patients, and manufacturers to report all medical device related incidents and deficiencies to us so that we can determine whether a report reflects a random failure or one that is likely to recur and cause harm. These reports can be generic or model specific. Although many of these reports do not result in a Hazard Bulletin ("pink sheet"), Hazard Report, or User Experience Network™ (UEN™) article, we inform the reporting party of our database search findings, as well as of our findings and opinions when appropriate. As soon as we become aware of device hazards and problems, we inform the manufacturers and invite them to respond constructively. We add all reports, including those that are not published, to our internal confidential databases to track trends of device failure or lot-specific defects.

A **Hazard Report** describes a possible source of peril, danger, or difficulty. We publish reports about those units in which we have identified a fault or design feature that *might*, under certain circumstances, place patients or users at risk, providing recommendations on how to correct or avoid the problem. Publication of a Hazard Report on a specific brand name and model of device in no way implies that competitive devices lack hazardous characteristics.

When deciding whether to discontinue using a device that ECRI believes poses a risk, hospital staff should balance the needs of individual patients, the clinical priorities, and the availability of safer or superior products against the information we provide in a Hazard Report. Clinical judgment is more significant than an administrative, engineering, or liability decision. Users often can take precautions to reduce the possibility of injury while waiting for medical equipment to be modified or replaced.

UEN articles describe problems that we believe are unlikely to pose a significant risk of harm. Typically, they include the hospital's report and ECRI's comment; when appropriate, we also include the manufacturer's response and recommendations for corrective action. Most of these reports describe common or nuisance problems that can be corrected with an available modification or revised operating or maintenance procedures.

Please send problem reports to us in a letter or by using one of the problem reporting forms in your black *Health Devices* binder behind the yellow tab. The binder front matter describes the three forms — ECRI's yellow Problem Reporting Form and FDA's MedWatch forms (yellow, voluntary; white, mandatory), which we can forward to FDA for you through our Computerized Problem Reporting System (CPRS). You can also send reports to ECRI by fax; our fax number is (610) 834-1275. Or you can telephone your report directly by calling (610) 825-6000, Monday through Friday, 9:00 AM to 5:00 PM, eastern time. The identity of the reporting individual or institution is never revealed without permission.

Ignition of Debris on Active Electrosurgical Electrodes

Problem

A member hospital reports that flames briefly flashed from the tip of an active electrosurgical electrode during a tonsillectomy. The patient was not harmed and no surrounding materials caught fire, but the risk that the fire could have spread or caused significant injury certainly existed. After the flash, staff noted that the shaft insulation near the tip of the electrode was badly melted and therefore suspected that a defect in the electrode might have initiated the fire.

While the reported problem occurred with an electrode extension blade, ECRI has investigated similar cases in which other types of active electrodes, such as suction/coagulator probes, were being used.

Discussion

Identifying the Cause

Based on ECRI's experience with electrosurgery and in investigating surgical fires, we concluded that it was unlikely that any defect in the electrode itself would have started the fire. We have investigated numerous incidents, many of them involving severe patient injuries, in which sponges or tracheal tubes in the patient's mouth, nose, or throat were ignited under circumstances similar to those described in this report. In several of these cases, defective active electrodes were suspected as the ignition source, but our investigations revealed that these fires were actually started by ignition of tissue debris or other flammable material on the electrode tip. In each case, ignition was possible, in part, because of locally elevated oxygen concentrations. We concluded that the brief burst of flames in the reported incident was caused by similar circumstances — namely, the ignition of tissue debris on the electrode tip while the tip was in an area with an elevated oxygen concentration.

Contrary to many reports of surgical fires, the active electrode itself is unlikely to burn. This is due to its metal and plastic construction. While some plastics will burn, most of the plastics used in the manufacture of active electrodes and tracheal tubes have such high ignition temperatures that they will not burn in surgical circumstances — except in the presence of another fire or, perhaps, laser energy. The damage to the active electrode insulation reported in this incident was likely caused by the heat of the flame or by excessive resistive heating of the metal electrode tip resulting from a buildup of charred tissue debris, or eschar, on the tip.

Avoiding Similar Occurrences

Strategies for avoiding and extinguishing fires typically focus on controlling or eliminating one or more of the three factors required for combustion: an ignition source, a fuel source, and an oxygen source. Complicating matters during monopolar electrosurgery is the fact that one of the combustion factors, an ignition source, will always be present.

The cutting and arcing coagulation techniques used during monopolar electrosurgery require that electrical sparks be produced at the active electrode to achieve the desired tissue effect. Under certain circumstances (e.g., in an oxygen-enriched atmosphere), these sparks could ignite nearby fuels such as sponges, tracheal tubes, or drapes. Most surgeons are well aware of this possibility and know they can reduce the risk of combustion by keeping the electrode tip away from ignitable fuels. Less well known, however, is the fact that tissue adhering to the electrode can itself become an ignitable fuel.

The transformation of tissue into a fuel occurs when excessive heating of the electrode tip causes sizable pieces of tissue to stick to the electrode surface. Sticking is most likely to occur when contact with tissue is made during use of an arcing technique, such as "spray" coagulation, because of the tremendous heat generated at the tip during such activations. (Sticking can occur even several seconds after electrosurgical unit [ESU] activation because the heat in the electrode tip does not dissipate immediately.) With additional use, the electrode tip remains hot, transforming the tissue debris on its surface into a charred material called eschar. With sufficient heating, eschar can become a glowing ember and pose a fire hazard both as an ignition source and as a fuel. Exacerbating this situation is the fact that the eschar coating will impede electrosurgical current across the electrode tip, which in turn will increase the resistive heating of the tip.

Surgeons can minimize the likelihood of excessive heating of the electrode tip and of eschar buildup on the tip by selecting ESU modes prudently and by cleaning the tip when needed. We discuss these strategies in detail in Recommendation 2, below.

While surgical staff cannot completely remove the risks presented by the electrode as an ignition source, they can usually control the availability of fuel and oxygen at the surgical site. In addition to eschar, other fuel sources that have contributed to fires we investigated — but that could have been eliminated from the procedure — include dry cotton sponges and segments of latex rubber catheters (which users slipped over the active electrode to extend the insulation). In the first example, wetting and wringing out the cotton sponges before using them would have dramatically reduced their flammability without significantly reducing blood absorption. In the second example, the electrode simply should not have been modified, especially with a material such as latex rubber, which — although it may have seemed like an appropriate insulating material — is actually highly flammable. (Note that modifying electrodes may increase the healthcare provider's liability should a fire or other accident occur.)

With respect to oxygen sources, most ESU activations do not occur in the immediate vicinity of an elevated oxygen concentration. However, some procedures will require that electrosurgery be applied in places where an elevated oxygen concentration is likely to be present (e.g., in the throat). In these cases, certain precautions can be taken to reduce the risk of fire. For example, during surgery in the throat or mouth, the surgeon will typically use a tracheal tube with a balloon-like cuff that is inflated to occlude the airway surrounding the tube; this cuff prevents oxygen from leaking from the airway into the throat and mouth. But in some procedures (e.g., on pediatric patients), cuffed tracheal tubes cannot be used because of anatomical limitations. When cuffless tracheal tubes must be used, clinicians will typically pack the airway surrounding the tracheal tube with gauze or sponges to minimize oxygen leakage. However, this technique is not always effective in preventing oxygen from leaking into the throat and mouth. To reduce the risk of fire in such situations, we advise that the surgical staff take steps such as those described in Recommendation 5, below.

Recommendations

1 Alert operating room personnel that tissue buildup on the tip of active electrosurgical electrodes poses a fire hazard and that the risk of fire is significantly greater in locations where an elevated oxygen concentration is likely to be present, such as in the throat and mouth.

2 Take the following steps to avoid eschar buildup on the tips of active electrodes (such as suction/coagulators):

A Use tip-cleaning aids to clean electrode tips as needed. Abrasive pads are available for cleaning standard electrodes. For cleaning "nonstick" electrodes, we recommend using a damp sponge instead (abrasive pads will erode Teflon and silicone nonstick electrode coatings).

B Minimize heating of the active electrode tip by using short ESU activations at the minimum power setting necessary to produce the desired effect.

C Allow sufficient time for heat in the active electrode tip to dissipate (1) between activations and (2) before touching it to tissue after the electrode has been activated using an arcing technique.

D Avoid using ESU modes intended for arcing coagulation (e.g., Coag, Spray, Fulgurate) during cutting and contact coagulation techniques. If used for these techniques, arcing coagulation modes will produce spattering of debris and cause tissue to stick to the electrode tip. Modes appropriate for cutting are typically labeled Pure Cut or Blend. Modes intended for contact coagulation are typically labeled Desiccate or Soft Coag, but cutting modes are also appropriate for this application. *

3 Do not modify or add to the insulation of active electrodes. Contact your supplier or ECRI if you need help obtaining an electrode tip design that is not currently available to you.

4 Minimize the flammability of materials that need to be present where electrosurgery is to be applied. Sponges and gauze packing should be wetted and wrung out before use.

5 Ensure that oxygen concentration is not elevated in any area where electrosurgery will be applied. One method for minimizing oxygen levels is to ventilate the patient with air or a low oxygen concentration, instead of a high concentration, for at least one minute before ESU activation. During surgery in the oropharyngeal cavity, another method is to use suction to scavenge residual oxygen from the mouth.

ECRI encourages hospitals to make this Hazard Report and other instructional material on electrosurgery available to surgeons and OR nurses. We also stress the importance of providing periodic instruction on the rudiments of electrosurgery, as required by Section 7-6.5 of the National Fire Protection Association's *Standard for Health Care Facilities.* * Furthermore, ECRI advocates advanced training for clinicians in techniques that optimize the safety and effectiveness of electrosurgery. For additional information and recommendations on the topics covered in this article, refer to our earlier Hazard Report, "Fires from Oxygen Use during Head and Neck Surgery," in *Health Devices* 24(4), April 1995.

Reversal of Access Port Gaskets on Hill-Rom Air-Shields Isolette Infant Incubators

Problem

A member hospital reports that a 1.45 kg (3.2 lb) newborn pushed open the door covering an access port on a Hill-Rom Air-Shields Isolette infant incubator and fell out of the port to the floor. (No serious injuries were reported, but the potential for great harm certainly existed.) The clinical engineering department found that the door had not latched securely because the gasket around the port had been installed backwards following disassembly for routine cleaning.

Discussion

The hood of the Isolette incubator has two ports; users insert their arms through cuffs attached to the port to access the infant. When not in use, each port is covered by a door that is held closed with a latch. A flexible gasket fits around the perimeter of each port to seal the door and provide a place to attach the cuffs.

The gaskets must be removed for cleaning once a week. However, they are not marked to indicate which side should be placed inside the hood during reinstallation. The gasket must be positioned with its curved larger lip on the inside of the incubator (see figure). If the gasket is installed with the curved lip on the outside, the lip may prevent the door from seating completely, and the latch may not fully engage. If this occurs, the door may be held closed and appear to be latched, but will be able to be opened by applying only a small force. (However, if enough force is applied to close the door, the latch will completely engage, even though the gasket has not been installed properly. This could fool users into thinking that the gasket installation is correct.)

Isolette Models C100QT, C200QT, C400QT, C450QT, C500QT, C550QT, and TI500 have this gasket design. The operator's manual includes a cross-sectional diagram that indicates proper orientation of the gasket. However, ECRI believes the manual is unlikely to be read by the staff responsible for removing, cleaning, and reinstalling the gaskets.

Supplier's Corrective Action

The supplier has redesigned the gasket. The new design (Hill-Rom Air-Shields Part No. 6812003) is reversible. Misinstalling the new gasket is less likely because misinstallation would conspicuously interfere with proper closing of the door — by either preventing the door from closing or preventing it from sealing with the gasket. Units produced since January 1997 incorporate the redesigned gasket.

Recommendations

1 Determine whether your facility has Isolette incubator Models C100QT, C200QT, C400QT, C450QT, C500QT, C550QT, or TI500.

2 Contact the supplier's customer service department at (800) 523-5756 or (215) 675-5200 to obtain the redesigned gaskets.

3 Until the new gaskets are installed, instruct staff that the gasket must be installed so that the curved lip is on the inside of the incubator. Hang a copy of the gasket installation diagram (included in the operator's manual) in the area where the incubators are cleaned.

4 Inform the nursery and the pediatric intensive care unit about the hazard. Instruct staff to inspect the doors for proper latching before each use of the incubator.

Cross-section of the access port gasket (old design) correctly installed. The curved larger lip of the gasket is positioned inside the incubator. The supplier has made a new gasket design available that should minimize the likelihood of misinstallation.

Supplier Information:

Hill-Rom Air-Shields, A Hillenbrand Co. [339679], 330 Jacksonville Road, Hatboro PA 19040-2211, USA; Phone: (800) 523-5756, (215) 675-5200; Fax: (215) 675-1859.

The Hill-Rom Air-Shields Isolette is marketed worldwide.

Footnotes

Physiologic Monitoring Systems [12-636]
Physiologic Monitoring Systems, Acute Care [12-647]
Physiologic Monitoring Systems, Telemetric [13-987]
ECG Monitors, Telemetric [13-988]

Electrodes, Electrosurgical, Active [16-860]
Electrosurgical Units [11-490]

* For more information on the appropriate selection and use of ESU modes, refer to the Technology Overview and the Technology Management Guide in our November 1997 Evaluation of electrosurgical units (*Health Devices* 26[11]).

* National Fire Protection Association (NFPA). *Standard for health care facilities*. Quincy (MA): NFPA; 1996. NFPA 99-1996.

Incubators, Infant, Mobile [17-432]
Incubators, Infant, Transport [12-114]

End of Document

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EXHIBIT 57

coag abbreviation

Medical Definition of *coag*

coagulate; coagulation

Learn More about *coag*

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Resources for *coag*

CITE

Dictionary Entries near *coag*

coactivator
coadapted
coadministration
coag

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EXHIBIT 58