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LIVER FAILURE/CIRRHOSIS/PORTAL HYPERTENSION

Esophageal Balloon Tamponade Versus Esophageal Stent in Controlling Acute Refractory Variceal Bleeding: A Multicenter Randomized, Controlled Trial

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Balloon tamponade is recommended only as a "bridge" to definitive therapy in patients with cirrhosis and massive or refractory esophageal variceal bleeding (EVB), but is frequently associated with rebleeding and severe complications. Preliminary, noncontrolled data suggest that a self-expandable, esophageal covered metal stent (SX-ELLA Danis; Ella-CS, Hradec Kralove, Czech Republic) may be an effective and safer alternative to balloon tamponade. We conducted a randomized, controlled trial aimed at comparing esophageal stent versus balloon tamponade in patients with cirrhosis and EVB refractory to medical and endoscopic treatment. Primary endpoint was success of therapy, defined as survival at day 15 with control of bleeding and without serious adverse events (SAEs). Twenty-eight patients were randomized to Sengstaken-Blakemore tube (n = 15) or SX-ELLA Danis stent (n = 13). Patients were comparable in severity of liver failure, active bleeding at endoscopy, and initial therapy. Success of therapy was more frequent in the esophageal stent than in balloon tamponade group (66% vs. 20%; *P* = 0.025). Moreover, control of bleeding was higher (85% vs. 47%; *P* = 0.037) and transfusional requirements (2 vs 6 PRBC; *P* = 0.08) and SAEs lower (15% vs. 47%; *P* = 0.077) in the esophageal stent group. TIPS was used more frequently in the tamponade group (4 vs. 10; *P* = 0.12). There were no significant differences in 6-week survival (54% vs. 40%; *P* = 0.46). *Conclusion:* Esophageal stents have greater efficacy with less SAEs than balloon tamponade in the control of EVB in treatment failures. Our findings favor the use of esophageal stents in patients with EVB uncontrolled with medical and endoscopic treatment. (Hepatology 2016;63:1957-1967)

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Acute bleeding from esophageal varices (AVB) carries a death rate ranging from 12% to 20% during the acute episode, which, by consensus, is defined as the first 5 days after the patient reaches the hospital.[1-3] Failure to control bleeding or early rebleeding leads to a very high mortality, ranging from 30% to 50%, suggesting that failure of initial treatment should be considered a strong predictor of mortality in patients with AVB.[2-5]

Treatment for AVB according to current guidelines is based on early and cautious blood volume resuscitation, early administration of IV vasoactive drugs (terlipressin, somatostatin, or analogs) and of prophylactic

Abbreviations: AE, adverse event; AVB, acute variceal bleeding; EVB, esophageal variceal bleeding; HCC, hepatocellular carcinoma; ITT, intent-to-treat; IV, intravenous; MOF, multiorgan failure; PO, per os, oral administration; PRBC, packed red blood cell; RCT, randomized, controlled trial; SAEs, serious adverse events; SC, subcutaneous; TIPS, transjugular intrahepatic portosystemic shunt; UGI, upper gastrointestinal.

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antibiotics, and, within the first 6-12 hours of admission, once hemodynamic stabilization is achieved, upper gastrointestinal (UGI) endoscopy to confirm the source of bleeding and provide endoscopic therapy, preferably variceal banding ligation(2,6). Control of AVB is achieved with this approach in approximately 80% of cases.(7) However, there are still 20% of patients with so-called refractory AVB requiring rescue therapy with transjugular intrahepatic portosystemic shunt (TIPS) or surgery to control the acute bleeding episode, frequently preceded by balloon tamponade as a bridge.(7)

The Sengstaken-Blakemore tube is the most widely used for balloon tamponade providing bleeding control rates of up to 90%.(8-23) However, it should only be used under intensive care facilities by skilled staff, because severe, life-threatening complications arise in 20%-60% of the cases.(6-23) The main complications are aspiration pneumonia, esophageal rupture, asphyxia resulting from balloon migration, esophageal ulcers, tongue, nose or lips necrosis, arrhythmia, and chest pain. These complications increase with prolonged use; therefore, esophageal balloon tamponade should not be maintained for over 24 hours.(2,3,6) Moreover, bleeding restarts upon balloon deflation in up to 50% of cases.(8-23)

Recently, a dedicated self-expandable, covered esophageal metal stent has been introduced as an alternative to esophageal balloon tamponade in AVB. Hubmann et al. reported the results of the esophageal stent in a retrospective series published in two consecutive articles including 39 patients with uncontrolled AVB.(24,25) Patients received a self-expandable, covered esophageal metal stent (SX-ELLA Danis; ELLA-CS, Hradec Kralove, Czech Republic). The esophageal stent was deployed without major complications, achieving control of AVB in all but 1 case. Two to fourteen days after, esophageal stents were withdrawn. There was 100% applicability of further therapy (endoscopic, radiological, or surgical). The only reported adverse event (AE) was not serious and consisted in stent migration in 7 cases. Thirty-day survival was 74%.(25) More recently, UK investigators reported their experience in an uncontrolled series of 10 patients with refractory AVB treated with the SX-ELLA Danis stent that was successfully placed in 9 patients, achieving control of bleeding in 7 of 10 and allowing bridging the patients to definitive therapy. The procedure was safe, with no procedure-related serious adverse events (SAEs).(26)

According to these data, we hypothesized that the use of self-expandable esophageal stents could provide a better balance of benefits and harms than balloon tamponade in treatment of patients with acute bleeding from esophageal varices refractory to medical and endoscopic therapy.

Materials and Methods

STUDY DESIGN

The present prospective, randomized, controlled, parallel-group trial was conducted in nine teaching hospitals in Spain: Hospital Clínic, Barcelona (Coordinating Center); Hospital de la Santa Creu i Sant Pau, Barcelona; Hospital Germans Trias i Pujol, Badalona; Hospital Ramón y Cajal, Madrid; Hospital Puerta de Hierro, Madrid; Hospital Marqués de Valdecilla, Santander; Hospital Gregorio Marañón, Madrid; Hospital Central de Asturias, Oviedo; and Hospital de la Vall d'Hebrón, Barcelona.

The study was conducted in accord with the Declaration of Helsinki and was approved by the ethical committee of the nine participating hospitals and by the Ministry of Health and fulfilled the guidelines of Good Clinical Practice in clinical trials. The study was registered in an independent clinical trial database (www.clinicaltrials.gov; identifier: NCT01242280). Written informed consent was obtained from each

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participant or legal representative or next of kin depending on the clinical condition of the patient.

All data were recorded on regularly monitorized case report forms that were entered into a database by the same investigator (A.E.). All authors had access to the study data and had reviewed and approved the final manuscript.

PARTICIPANTS

All patients admitted between March 2009 and January 2013 with the diagnosis of cirrhosis and suspected AVB were screened for participation in the study. Patients were considered eligible for inclusion if they met the Baveno II criteria[27] for acute esophageal variceal bleeding (EVB) and fulfilled one of the following criteria:

- Refractory AVB: Failure to control bleeding despite pharmacological and endoscopic therapy. Failure to control bleeding was defined, according to Baveno IV criteria,[28] as evidence of continuous digestive bleeding and either hematemesis (or nasogastric aspirate >100 mL of fresh blood) 2 hours after the start of combined pharmacological and endoscopic therapy or decrease in hemoglobin values >3 g versus previous values (without blood transfusion).
- Massive variceal bleeding. Defined as an upper digestive bleeding in which no hemodynamic stability (systolic arterial pressure >70 mm Hg and heart rate <100 beats per minute) could be achieved despite rapid infusion of volume expanders and/or blood transfusion.[28]

Exclusion criteria were: (1) failure to fulfill entry criteria; (2) age <18 years; (3) esophageal rupture; (4) esophageal, gastric, or upper respiratory tract tumor; (5) esophageal stenosis; (6) recent esophageal surgery; (7) previous esophageal balloon tamponade to treat the index bleed; (8) large hiatal hernia precluding the correct placement of the esophageal devices; (9) known hepatocellular carcinoma (HCC) beyond the Milan criteria; (10) terminal disease; and (11) failure to provide written consent to participate in the study.

INTERVENTIONS

All patients with cirrhosis admitted because of UGI bleeding received vasoactive therapy with somatostatin (250-500 μg/h, intravenous [IV] infusion) or terlipressin (2 mg/4 hours, IV) as well as prophylactic antibiotics (norfloxacin 400 mg/day per os, oral administration [PO] or ceftriaxone 1 g/day IV in high-risk patients) according to the center policy. Written consent was obtained from the legal representative or next of kin in encephalopatic patients. Such patients were also prophylactically intubated before endoscopy. Then, upper endoscopy was done to diagnose the source of bleeding and performing band ligation if EVB was confirmed. Vasoactive therapy was scheduled for 2-5 days.

In three of the participating hospitals (Hospital Clínic, Hospital de la Santa Creu i Sant Pau, Barcelona; Hospital Puerta de Hierro, Madrid), patients that were Child-Pugh class C (<14 points) or B but that had active bleeding at initial endoscopy despite being on IV vasoactive drugs, were considered for early pre-emptive TIPS.[29] All other decisions for TIPS were as rescue therapy after declaring treatment failure (see below).

Patients fulfilling inclusion criteria with no exclusion criteria were randomized to the esophageal stent or the balloon tamponade group. Analgesia with paracetamol (1 g/8 hours, IV) or methadone (5 mg/8 hours, subcutaneous [SC]) was provided for esophageal stenting and balloon tamponade. In addition, conscious sedation with IV propofol (20-30 mg) was given as needed.

BALLOON TAMPONADE

We used four lumen Sengstaken-Blakemore (Minnesota) tubes without radiological guidance, as previously described,[8-23] under intensive care facilities (Fig. 1A). The gastric balloon (lumen 1) was inflated with 150-200 mL of air and then pulled on the gastroesophageal junction and secured under slight traction. The esophageal balloon (lumen 2) was inflated with air to a pressure of 40-50 mm Hg. The pressure of the balloon was checked every 2 hours. Supraglottic secretions were continuously aspirated (lumen 3) to avoid or reduce the risk of bronchoaspiration. Gastric content (lumen 4) was examined hourly to check for the presence of blood in the gastric content. A chest X-ray was performed within 12 hours to assess the correct placement of the Sengstaken-Blakemore tube. The esophageal balloon was deflated after 24 hour of inflation.

ESOPHAGEAL STENT

We used the SX-ELLA Danis stent (ELLA-CS), a dedicated, removable, covered, and self-expanding esophageal metal stent that was deployed in the lower esophagus without radiological or endoscopic assistance (Fig. 1B). The esophageal stent had radio-opaque markers at both ends and at midpoints that were used to assess both its position and expansion by a plain chest

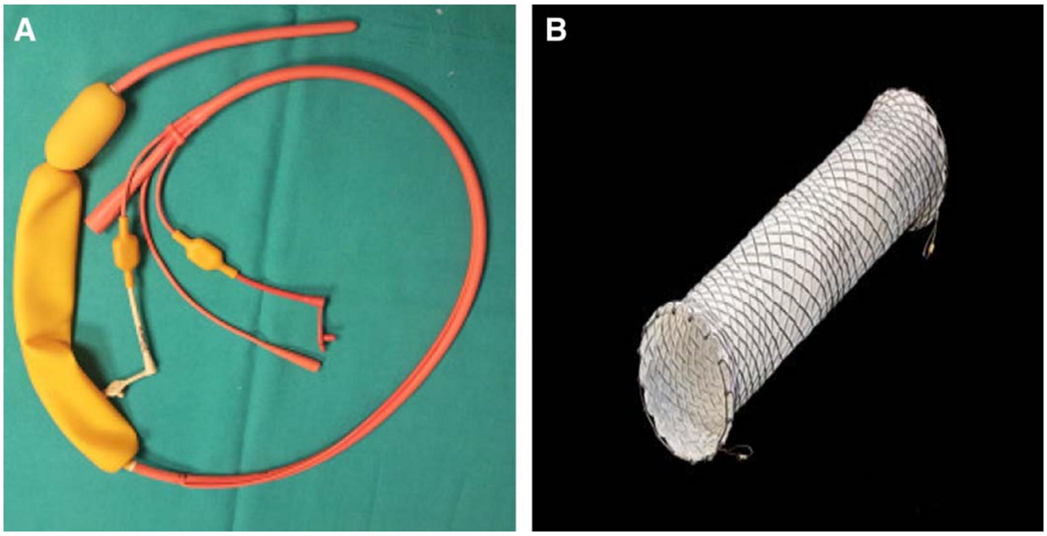

FIG. 1. Devices used in the study. (A) Four-lumen Sengstaken-Blakemore tube. The lumens correspond to gastric balloon, esophageal balloon, gastric aspiration, and supraglottic aspiration. (B) SX-ELLA Danis stent (ELLA-CS, Hradec Kralove, Czech Republic) completely expanded (25 mm of diameter). There were two retrieval loops at both stent ends.

X-ray performed immediately and at 12 hours after its placement. Retrieval of the esophageal stent was scheduled at 7 days using a specifically designed system (PEX-ELLA or extractor for SX-ELLA stent Danis). The use of a second esophageal stent was allowed in case of incorrect position of the initial one detected during the first 24 hours after its placement.

All attending physicians participating in the study were trained in positioning both the esophageal stent and the balloon tamponade by performing at least 20 or as much as required procedures, respectively, in a phantom system provided by the manufacturer.

Failure of the therapies under study was defined as the development of any of the following criteria: (1) death; (2) continuous bleeding as shown by hematemesis (or >100 mL of fresh blood by nasogastric tube) 2 hours after the placement of the assigned device or decrease in hemoglobin >3 g versus previous values (without blood transfusion); or (3) SAE.

Before declaring failure, we assessed both the adequate position and functioning of the devices. In case of a malpositioned device, the problem was corrected. TIPS was considered the rescue therapy of choice.

RANDOMIZATION

The randomization sequence was generated by computer in a 1:1 ratio, stratified for the degree of liver failure (Child-Pugh class A or B/C). Patients were allocated to esophageal stent or balloon tamponade by contacting by fax the coordinating center on a 24/7/365 basis. The treatment code was kept at the coordinating center in sealed, consecutively numbered, opaque envelopes prepared by an administrative assistant not participating in the study.

All patients were followed for a period of 6 months or death.

ENDPOINTS

The primary endpoint was a combination of absence of digestive bleeding + absence of SAEs + survival during the first 15 days after inclusion. This composite endpoint is based on a modified Baveno III definition of treatment failure (which considers success of therapy being alive without bleeding at day 5 plus absence of SAEs).[30] We expanded the period for considering failure to 15 days because the esophageal stent can be deployed for 1 week and to allow time to recognize SAEs that may have developed while in place.

All SAEs were included regardless of their possible/probable relationship with the procedures under study.

Secondary endpoints were as follows:

- Absence of bleeding at day 15 and at 6 weeks from inclusion
- Survival at day 15 and at 6 weeks from inclusion

- Overall transfusional requirements (units of packed red blood cells [PBRCs])
- Device-related AEs
- Length of hospital stay
- Applicability of definitive hemostatic therapy
- Use of additional therapeutic resources (TIPS, derivative surgery or additional endoscopic therapy).

SAMPLE SIZE

Reported efficacy, AEs, and mortality in patients with cirrhosis and refractory variceal bleeding treated with balloon tamponade range from 42% to 86%, 5% to 85%, and 8% to 42%, respectively.[8-23] To increase the incidence of the primary endpoint by 35% with the use of the esophageal stent, with alpha 0.05 and beta 0.20, the study should include 46 patients (23 per arm).

Because of the lack of recent and adequate data to calculate the sample size, we planned an interim analysis after the inclusion of 60% of the initial sample size (28 patients). The study would be terminated if the interim analysis showed significant statistical differences in the primary endpoint ($P < 0.02$) or futility (lack of differences) or at 3 years (end of the grants funding the study).

STATISTICAL ANALYSIS

Statistical analysis was performed following an intention-to-treat (ITT) strategy. A clean file was constructed by using the SPSS statistical package (SPSS, Inc., Chicago, IL) after entering all the case report forms. The SPSS statistical package was used to analyze the results. Data are reported as means with standard deviations or median (ranges). Categorical variables were compared using the Fisher's exact test, and continuous variables were compared with the unpaired Student *t* test (or the nonparametric Mann-Whitney's rank-sum test, when required). The actuarial probability curves of survival were constructed by using Kaplan-Meier's method and compared with the log-rank test. Data were censored at the time of endpoint achievement or at the end of follow-up. Statistical significance was established at a P value <0.05.

MANUSCRIPT

All the coauthors had access to the study data and had reviewed and approved the final manuscript.

Results

From March 2009 to January 2013, 58 patients eligible for the study (liver cirrhosis and AVB refractory to pharmacological and endoscopic therapy) were admitted in the four participating hospitals that included patients into the study (Fig. 2). The remaining five hospitals did not include patients because of problems in logistic and training support. Thirty of the

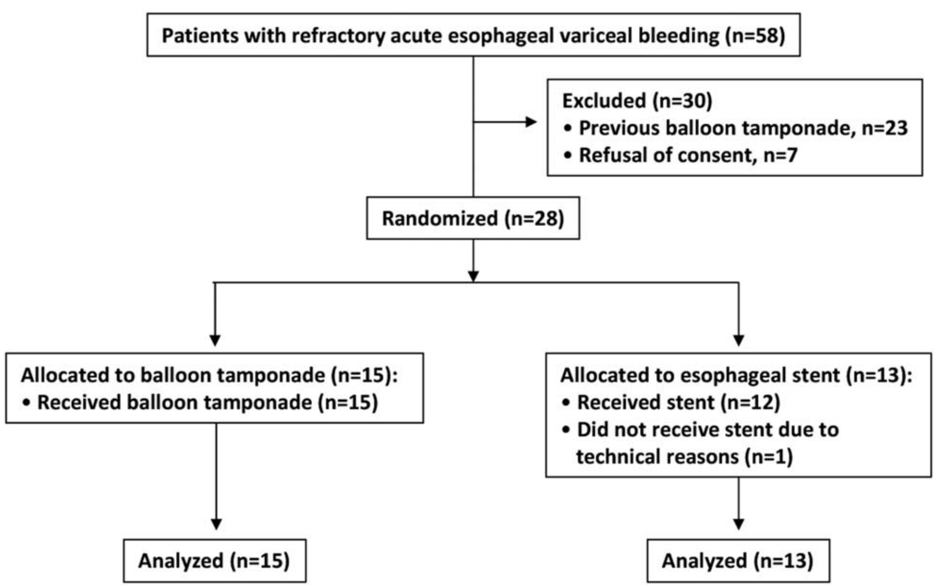

FIG. 2. Flow chart of the study.

TABLE 1. Clinical and Demographic Characteristics of the Patients

Variable	Esophageal Stent (n = 13)	Balloon Tamponade (n = 15)	*P* Value
Age, years*	69 (40-81)	54 (35-79)	0.04
Sex, male/female (n)	13/0	12/3	0.09
Etiology of cirrhosis, alcohol/HCV/others (n)	8/3/2	7/4/4	0.84
Child-Pugh class A/BC (n)	3/10	2/13	0.50
Child-Pugh score at admission*	9.5 (7-11)	10 (6-14)	0.57
MELD score at admission*	16.5 (9-32)	17 (11-25)	0.82
Active alcoholism, yes/no (n)	4/9	7/8	0.39
Previous variceal bleeding, yes/no (n)	6/7	9/6	0.46
On prophylaxis from bleeding, yes/no (n)	6/7	10/5	0.27
Shock at index bleed, yes/no (n)	5/8	10/5	0.14
Hematocrit at admission (%)*	24 (15-44)	23.5 (11-40)	0.51
Active bleeding at initial endoscopy, yes/no (n)	4/9	7/8	0.39
Criteria for early-TIPS† after first bleeding, yes/no (n)	6/5	10/5	0.53
Orotracheal intubation before initial endoscopy, yes/no (n)	5/8	4/11	0.41
Size of esophageal varices, small/large (n)	3/10	1/14	0.12
Endoscopic therapy, yes/no (n)	11/2	12/3	0.42
Banding ligation	8	9	
Sclerotherapy	3	3	
PRBC before inclusion (UU)*	4 (0-19)	3 (0-20)	0.93
Prophylactic antibiotics, yes/no (n)	12/1	15/0	0.26
Portal vein thrombosis, yes/no (n)	1/12	2/13	0.74
HCC (within Milan criteria), yes/no (n)	2/11	2/13	0.73

*Median (ranges).
†In the 26 patients included in the three participating hospitals using early-TIPS. Criteria for early TIPS were as follows: Child-Pugh C (<14 points) or Child-Pugh B + active bleeding at initial endoscopy.
Abbreviations: HCV, hepatitis C virus; MELD, Model for End-Stage Liver Disease.

fifty-eight eligible patients were not included because of previous treatment with balloon tamponade during the index bleed (n = 23) or refusal of consent (n = 7). Therefore, 28 patients were finally included (11 at the Hospital Clínic, Barcelona; 13 at the Hospital de la Santa Creu i Sant Pau, Barcelona; 2 at the Hospital Germans Trias i Pujol, Badalona; and 2 at the Hospital Puerta de Hierro, Madrid). Fifteen were randomized to balloon tamponade and 13 to esophageal stent. Of the 26 patients included at the three hospitals performing early-TIPS, 16 were eligible for an early preemptive TIPS before entering the study (because of the characteristics of the initial bleeding; Table 1). As shown in Table 1, patients randomized to balloon tamponade or esophageal stent were similar except for a lower age in the balloon tamponade group.

The assigned therapy was applied in all patients in the balloon tamponade group and in 12 of 13 in the esophageal stent group (92%). One patient in the esophageal stent group received balloon tamponade because of a defect in the stent delivery system; however, following an ITT strategy, the outcome of this patient was counted within the esophageal stent group. All patients had a complete 6-week follow-up, but 2 of them were lost afterward.

Most patients had advanced liver failure: 23 (82%) belonged to Child-Pugh class B or C. Because of the small sample size, no exploratory subgroup analysis was performed. Thirty-nine percent of the patients were included because of massive bleeding.

All except 1 case underwent initial endoscopy showing esophageal varices as the source of bleeding. In the remaining patient, endoscopy confirming AVB was delayed after initial therapy.

PRIMARY ENDPOINT

Table 2 summarizes the main results of the study. As shown, success of therapy, defined by the primary composite endpoint (absence of digestive bleeding + absence of SAEs [regardless of their relationship with the devices under study] and survival at 15 days), was more frequently observed in the esophageal stent than in the balloon tamponade group (66% vs. 20%; $P = 0.025$). Figure 3A shows the actuarial probability of being free of treatment failure in esophageal stent and balloon tamponade-treated patients (61.5% vs. 20% during the first 15 days after randomization, respectively; $P = 0.056$).

TABLE 2. Main Results of the Study (ITT Analysis)

Variable	Esophageal Stent (n = 13)	Balloon Tamponade (n = 15)	*P* Value
Inclusion criteria, n (%)			0.93
Failure of combined therapy	8 (62)	9 (60)	
Massive bleeding	5 (38)	6 (40)	
Interval admission-inclusion, days*	1.5 (0-7)	1 (0-25)	0.60
Success of therapy, n (%)	8 (66)	3 (20)	0.025
Absence of bleeding, 15 days, n (%)	11 (85)	7 (47)	0.037
Absence of SAEs, n (%)	11 (84)	8 (53)	0.077
Survival at 15 days, n (%)	9 (69)	8 (47)	0.39
Absence of bleeding, 6 weeks, n (%)	7 (54)	7 (47)	0.25
Absence of device-related SAE, n (%)	12 (92)	9 (60)	0.049
Causes of death (15 days; n)			0.044
Hypovolemic shock	1	6†	
MOF after sepsis	3	1	
Survival at 6 weeks, n (%)	7 (54)	6 (40)	0.46
Use of additional resources (during the hospital stay), n (%)	4 (31)	11 (73)	0.059

*Median (ranges).
†One of these patients exsanguinated after esophageal rupture.

ABSENCE OF CONTINUED OR FURTHER BLEEDING

Absence of continued or further bleeding at 15 days was higher in the esophageal stent group than in the balloon tamponade group (85% vs. 47%; *P* = 0.037; Table 2). There were no significant differences between the two groups in absence of bleeding at 6 weeks (54% vs 47%; *P* = 0.25; Table 2). The lack of differences between groups at 6 weeks is likely to have been influenced by the more frequent use of TIPS as a rescue therapy in the tamponade group (see below).

SURVIVAL

There were no significant differences in 15-day (69% vs. 47%) and 6-week (54% vs. 40%) survival between the esophageal stent and the balloon tamponade groups (odds ratio: 2.5; 95% confidence interval: 0.9-7.0; Table 2; Fig. 3B).

At day 15, there were 11 deaths, including 1 death directly related to the devices under study (a case of esophageal rupture after balloon tamponade). Overall, 7 deaths were the result of hypovolemic shock and 4 to multiorgan failure (MOF) after sepsis (Table 2). Deaths resulting from hypovolemic shock were more frequent in the balloon tamponade group (6 vs. 1; *P* = 0.044).

AEs

Table 3 shows in detail the AEs observed during the whole study. There were 20 AEs observed in 15 patients: 4 (31%) randomized to esophageal stent and 11 (73%) to balloon tamponade (*P* = 0.024). The incidence of SAEs between the two groups approached, but did not reach, statistical significance (15% vs. 47%; *P* = 0.077). The number of patients showing SAEs probably related to the devices under study was significantly higher in the balloon tamponade-treated patients than in the esophageal stent group (6 vs. 1; *P* = 0.049; Table 3). The most frequently observed AE was bronchoaspiration and aspiration pneumonia. Five patients treated by balloon tamponade developed aspiration pneumonia (requiring mechanical ventilation in all of them), whereas this complication was not observed in any of the patients receiving esophageal stent (Table 3).

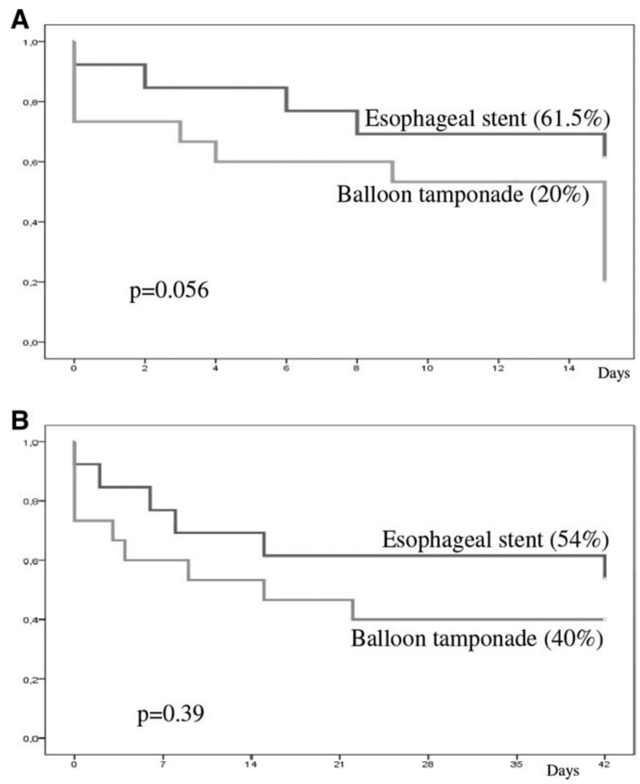

FIG. 3. Actuarial probability of: (A) being free of treatment failure (combination of absence of digestive bleeding + absence of SAEs + survival, during the first 15 days after inclusion in the study); (B) 6-week survival.

TABLE 3. AEs

Variable	Esophageal Stent (n = 13)	Balloon Tamponade (n = 15)	*P* Value
Total number of AEs, n	6	14	
SAEs, n			
Cardiorespiratory arrest	1	1	
Aspiration pneumonia	0	5	
Esophageal rupture	0	1	
SBP and hepatorenal syndrome	1	0	
Mild AEs, n			
Infections	2	1	
Esophageal ulcer (not bleeding)	1	1	
Bronchoaspiration not causing pneumonia	1	3	
Seizures	0	1	
Transitory acute stroke	0	1	
Patients with at least one AE, n (%)	4 (31)	11 (73)	0.024
Patients with at least one SAE, n (%)	2 (15)	7 (47)	0.077
Patients with at least one device-related SAE, n (%)	1 (8)	6 (40)	0.049

Abbreviation, SBP, spontaneous bacterial peritonitis.

OTHER OUTCOMES

Table 4 shows additional results of the study. As shown, TIPS was used in 14 patients, 10 in the balloon tamponade group versus 4 in the esophageal stent group ($P = 0.12$). Of these, 13 were done in the initial 2 days of admission, including 6 performed as emergency rescue TIPS (4 in the balloon tamponade group and 2 in the esophageal stent group; not significant). The last TIPS was placed as elective therapy in a patient from the esophageal stent group 10 days after admission.

All patients, except the 9 dying early, were started on definitive treatment to prevent rebleeding. Apart from the 14 receiving TIPS, 5 were treated with combined endoscopic band ligation plus nonselective beta-blockers (all in the esophageal stent group; Table 4). Two of these five patients were considered for early TIPS at admission, but managed medically after their condition improved under esophageal stent treatment.

Patients in the esophageal stent group received less PRBC transfusion than those in the balloon tamponade group (3 ± 3.3 vs. 6 ± 4.8; $P = 0.08$; Table 4). Patients included in the latter group were fewer days on vasoactive drugs than those randomized to esophageal stent ($P = 0.002$). This was because of the earlier use of TIPS as a definitive therapy in the balloon tamponade patients (which led to withdrawing vasoactive drugs).

Most patients required orotracheal intubation to preserve airway because of either the intensity of variceal bleeding, the need to repeat upper endoscopy, or the use of sedation for the placement of the assigned device. After the procedure, patients randomized to balloon tamponade were more prone to need opiates for pain controlling than those randomized to esophageal stent (93% vs. 62%; $P = 0.091$).

Discussion

Treatment of AVB is now highly standardized in both the supportive and the hemostatic approach resulting in high bleeding-control rate and low bleeding-related mortality, which has markedly decreased over the past recent years.[1,6,7] Moreover, we are now able not only to identify patients at high risk of treatment failure, but also to prevent failures by using more aggressive therapies.[29,31] However, despite the strict application of the currently recommended gold-standard therapy—combined pharmacological and endoscopic therapy and prophylactic antibiotics—as well as providing early pre-emptive TIPS in high-risk cases, some patients with advanced cirrhosis will still experience refractory variceal bleeding, with failure of therapy or massive bleeding with not even time to perform a pre-emptive TIPS. On the other hand, in some cases, TIPS may be contraindicated by the presence of portal vein thrombosis or concomitant diseases (i.e., active sepsis, advanced liver

TABLE 4. Other Outcomes

Variable	Esophageal Stent (n = 13)	Balloon Tamponade (n = 15)	*P* Value
Secondary prophylaxis after inclusion, n (%)	9 (69)	10 (67)	0.89
Definitive treatment, n (%)			0.015
EBL + nonselective beta-blockers	5 (39)	0	
TIPS	4 (31)	10 (67)	
Interval inclusion-TIPS (in patients receiving it)*	2 (1-10)	1 (0-2)	0.065
Days on vasoactive drugs*	6 (3-8)	3 (1-7)	0.002
Severe hepatic encephalopathy after inclusion, n (%)	5 (39)	11 (73)	0.063
PRBC after inclusion*	2 (0-12)	6 (0-15)	0.08
Orotracheal intubation after inclusion, n (%)	8 (67)	13 (87)	0.21
Days on orotracheal intubation*	2 (0-15)	4 (0-15)	0.38
Requirement of opiates as analgesia, n (%)	8 (62)	13 (93)	0.091
Days with the device in place*	5 (0-12)	1 (0-2)	0.003
Days in ICU (index bleed)*	8 (2-16)	8 (1-28)	0.93
Days in hospital (index bleed)*	14 (0-24)	14 (0-41)	0.55

*Median (ranges).
Abbreviations: EBL, esophageal banding ligation; ICU, intensive care unit.

failure with a Child-Pugh score $\geq$14, and so on),[7] and as for today, many centers cannot offer early, preemptive TIPS.

Treatment of the cases with refractory AVB is a challenge. Balloon tamponade as a bridge to rescue TIPS is the only accepted therapy for this indication.[2,3,6] However, although balloon tamponade is highly effective in the temporary control of bleeding, it can give rise to major AEs, can only be maintained for 24 hours, and results in a high rate of recurrent bleeding upon balloon deflation.[7-23] Recently, pilot uncontrolled studies suggested that self-expandable, covered esophageal metal stents may represent a new alternative that may allow achieving a high rate of control of bleeding with a low incidence of severe complications in patients with refractory AVB.[24-26,32] However, the series published so far are mostly retrospective reports of single-center experience; include patients treated by a variety of indications; definitions and treatment not always followed the recommended guidelines; and all lack appropriate controls, so the true value of esophageal stents in the treatment of refractory variceal bleeding remains conjectural.[32]

Our study is the first RCT comparing balloon tamponade (Sengstaken-Blakemore tube) versus self-expandable, esophageal metal stents (SX-ELLA Danis stent) in refractory esophageal AVB, defined as acute bleeding from esophageal varices that could not be controlled despite the application of standard-of-care medical therapy according to the Baveno V-VI recommendations.[2,3,6] Thus, we restricted the treatment scenario to the worse accepted situation for the use of balloon tamponade, which explains the low number of patients included.

The results of our multicenter randomized, controlled trial (RCT) show that the use of self-expandable esophageal stents provides a better balance of benefits and harms than balloon tamponade, and represents a safe and effective option to control the bleeding in patients with AVB refractory to medical and endoscopic therapy. Indeed, the primary composite endpoint of absence of digestive bleeding with absence of SAEs and survival at day 15 after inclusion was achieved in 66% of the cases in the esophageal stent group, but only in 20% in the balloon tamponade group ($P < 0.025$). The advantage of esophageal stents over balloon tamponade was further evidenced by analyzing separately the components of the composite endpoint (Table 2) and very specially those of control of bleeding and development of SAEs. The higher efficacy of esophageal stents in controlling refractory AVB was reinforced by a lower need for PRBC transfusion and less frequent use of additional resources, including significantly lower use of TIPS, as compared with patients allocated to balloon tamponade. Owing mostly to the low numbers, some of these differences were only of borderline significance or failed to reach full statistical significance (Table 4).

The incidence of AEs was also significantly lower in patients randomized to esophageal stent than in those allocated to receive balloon tamponade. In our opinion, the most important difference in this group of patients with advanced liver failure lies in the high incidence of device-related SAEs observed in the balloon tamponade group as compared to the esophageal stent group, mainly considering that the development of these extremely serious complications in such patients often resulted in use of additional resources and, occasionally, death. Despite differences in control of bleeding and in the incidence of SAEs, no significant differences in survival were observed. This might be owing, at least in part, to the extensive use of TIPS, which was performed to prevent recurrent bleeding upon balloon deflation or as early rescue therapy in two thirds of the patients in the balloon tamponade group.

Another important issue is that the temporal effectiveness of the two devices clearly differed. Whereas balloon tamponade could only be maintained with the esophageal balloon inflated for a maximum of 24 hours, esophageal stents remained in place for a median of 5 days (range, 0-12). This fact influenced the subsequent treatment offered to patients to prevent rebleeding. Indeed, as already mentioned, most patients on balloon tamponade received a TIPS. Patients of the esophageal stent group having the "temporary" hemostatic method in place for a median of 5 days were effectively "bridged" to elective therapy, resulting in a decreased requirement of TIPS (4 cases vs. 10 in the balloon tamponade group; $P = 0.12$).

This study has limitations that should be considered. First, this study was conducted only in high-risk patients (those with massive bleeding or failure of initial gold-standard therapy), so we do not know if the use of esophageal stents may achieve better results when used in patients with high-risk AVB, but before developing failure of therapy. However, we deliberately chose this population because it represents the only one where the use of balloon tamponade is indicated as per consent guidelines.[2,3,27,28] Also, it was felt unethical to use these therapies in an "expanded" indication because of the high index of severe complications known to be associated with balloon tamponade.[8-23]

Second, the series includes a relatively low number of patients. However, the characteristics of the study population that asks for immediate randomization and emergency application of balloon tamponade or of a new treatment device (the esophageal stent, which most centers are not familiar with) make it very difficult to conduct such a study and to recruit a larger number of patients. Therefore, the possibility that another RCT with a larger sample size is eventually performed is very low. Third, the initially planned sample size matched the final recruitment. In the 3-year trial period, we were able to include the number of patients requested to perform the predesigned interim analysis, and this showed significant differences in several endpoints, including the major trial endpoint. Finally, it is worth noting that the main cause for excluding potential candidates was the previous use of emergency balloon tamponade before admission to the participating hospitals, some patients already presenting with serious complications related to balloon tamponade (including esophageal tears); out of a controlled trial, this complication may actually benefit from treatment with esophageal stents.[32]

In summary, even in the context of the short number of patients included, this RCT shows that self-expandable, covered, esophageal metal stents are more effective than balloon tamponade for the temporary control of massive or refractory esophageal AVB in patients with cirrhosis of the liver. These better results are owing to both a greater hemostatic effect and a lower rate of SAE, especially of aspiration pneumonia, with the use of esophageal stents. Because esophageal stents can be left safely in place for over 5 days, this procedure would be specially valuable for centers without facilities for early TIPS. Thus, our findings favor a greater use of esophageal stents in patients with esophageal AVB uncontrolled with medical and endoscopic treatment. Whether esophageal stents may also be used in other circumstances, as in "difficult patients" before declaring failure of combined endoscopic and pharmacological treatment, should be specifically investigated in future studies.

Appendix

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