

Management of Common Bile Duct Stones in Cirrhotic Patients with Coagulopathy: A Comparison of Supra-Papillary Puncture and Standard Cannulation Technique

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Abstract

Background and Study Aims Bleeding is not uncommon following endoscopic sphincterotomy. Supra-papillary puncture (SPP) might be safer than standard cannulation (SC) techniques in patients with coagulopathy. The aim of the study was to compare the safety and effectiveness of SPP and SC.

Patient and Methods This was a prospective case control intervention study. Decompensated cirrhotic patients with coagulopathy and choledocolithiasis underwent SC and SPP methods for biliary access.

Results One hundred five patients (56 [53.3%] men, mean [SD] age 56 [15.8]) underwent ERCP. SC and SPP were performed in 63 and 42 patients, respectively. Biliary access was achieved in 56/63 (89%) and 40/42 (95%) of patients undergoing SC and SPP, respectively ($P = 0.13$; 95% CI [-0.16; 0.03]). Complications occurred in 10/63 (15.8%) patients undergoing SC and 5/42 (11.9%) SPP ($P = 0.28$; 95% CI [-0.17, 0.16]). Five (7.9%) and two

(3.2%) episodes of post-sphincterotomy bleeding was seen in the SC and SPP groups, respectively ($P = 0.36$; 95% CI [-0.16, 0.05]). In contrast, three (4.8%) episodes of pancreatitis were seen in the SC and none in the SPP group ($P = 0.05$; 95% CI [0.001; 0.004]). A cost-effectiveness analysis demonstrated that SPP is an acceptable alternative at an ICER of US\$ 5,974.92 per additional successful procedure.

Conclusion SPP is a safe and effective technique for the management of common bile duct stones in decompensated cirrhotic patients. Conditional to the willingness-to-pay and to the local ERCP-related costs, SPP is also a cost-effective alternative to the SC methods. SPP is associated with a lower rate of complications but larger studies to validate these findings are necessary.

Keywords ERCP (Endoscopic retrograde cholangiopancreatography) · CBD (Common bile duct) · Endoscopy · Portal hypertension

Abbreviations

ERCP	Endoscopic retrograde cholangiopancreatography
SC	Standard cannulation
SPP	Supra-papillary puncture
NKS	Needle knife sphincterotomy
PT-INR	Prothrombin time-international normalized ratio
CBD	Common bile duct
BS	Biliary sphincterotomy
CI	Confidence interval
SD	Standard deviation
CT	Computer tomography
ACER	Average cost-effectiveness ratio
ICER	Incremental cost-effectiveness ratio
WTP	Willingness to pay

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Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is a common gastrointestinal procedure and is the method of choice for treatment of pancreatic and biliary disorders. Despite its relative safety, the risk of complications is not trivial [1–5]. While the development of post-ERCP pancreatitis is attributed to unintentional effects on the pancreatic duct (i.e. forceful contrast injection, mechanical and thermal damage, elevated intraductal pressure), bleeding and perforation often result from cautery used during sphincterotomy. Alternative techniques which aim to improve the rate of bile duct access and also decrease the risks of ERCP complications have been published in small case series. Methods such as EUS-guided formation of fistulous tracts between the biliary tree and the gastrointestinal lumen (i.e. stomach and duodenum), with subsequent placement of either an endoprosthesis or progression of a guidewire in a rendezvous fashion, have been proposed [6–10]. EUS can also assist in the cannulation of the bile duct [11], but the safety, effectiveness and robustness of these methods for both benign and malignant conditions remain to be assessed in large prospective trials.

We have previously described an alternative approach to access and treat a variety of conditions of the biliary tree [12–14]. The supra-papillary puncture (SPP) technique consists of a transmural puncture of the distal common bile duct through the roof of the major ampulla using a modified needle-catheter (Artifon catheter[®], Scitech-Goiânia, Brazil). Because this approach avoids the orifice of the pancreatic duct and does not require the use of cautery, the average incidence of complications such as post-ERCP pancreatitis and bleeding using this technique was lower than the reported rates following conventional cannulation techniques [12–14]. In the current study, we aimed to evaluate the procedural outcomes of standard cannulation (SC) and SPP in decompensated Child B and C cirrhotic patients with coagulopathy who underwent ERCP for choledocolithiasis.

Patient and Methods

Study Population

Patients with suspected choledocolithiasis referred for ERCP at the Gastrointestinal Unit of two tertiary care hospitals (Hospital Ana Costa, Hospital Estadual de Sapopemba) in São Paulo were enrolled in this study. The underlying population from which the study participants were selected is a racially and ethnically diverse metropolitan city, ranked as the sixth largest city in the world (over 20 million in population). The experimental

population consisted of patients with high probability for CBD stones and an established diagnosis of cirrhosis. Study participants (age 19–87) had clinical, laboratory, radiological and/or endosonographic evaluation suggestive of biliary obstruction due to choledocolithiasis. The parameters used to risk stratify patients for common bile duct stones prior to ERCP have been validated by Barkun et al. [15]. The diagnostic criteria of cirrhosis of the liver used in this study have been validated as well [16, 17]. This includes a nodular macroscopic appearance of the liver (i.e. in patients with history of cholecystectomy), a previous liver biopsy interpretation, a radiological exam revealing a liver with irregular contour or clinical findings characteristic of decompensated liver disease in a patient with risk factors for cirrhosis.

After initial evaluation by the primary provider, patients were referred to the pancreato-biliary team, offered to participate in the study and enrolled if all inclusion and exclusion criteria were met. An MRCP was performed in all patients and only those with findings suspicious for choledocolithiasis underwent ERCP. Patients who agreed to undergo SPP were considered the intervention group and patients who preferred to undergo the ERCP under the conventional cannulation techniques were considered the unexposed group. This study was not randomized and there was no allocation concealment. Cases were the individuals in both groups who developed the outcome of interest (i.e. complications), and controls were those who had an uneventful procedure. Patients who underwent SPP were considered the intervention group and those undergoing ERCP using conventional cannulation techniques were considered the control group. The inclusion criteria were the following: (1) decompensated liver disease (Child-Pugh Score B or C); (2) elevated prothrombin time (PT–INR) which failed to correct with administration of 10 mg IV vitamin K and/or two units of fresh frozen plasma; (3) high probability for common bile duct stone. Exclusion criteria were the following: (1) previous endoscopic (i.e. ERCP) or surgical treatment for pancreatic or biliary disease; (2) previous surgery of the upper gastrointestinal tract (i.e. Billroth, Roux-en-Y anastomosis); (3) American Society of Anesthesiologist (ASA) criteria IV or V; (4) endoscopic or radiographic evidence of ampullary malignancy.

Endoscopic Intervention

All ERCP procedures were performed by two biliary endoscopists who were randomly allocated for both SC and SPP interventions. Cannulation was defined as insertion of a catheter (i.e. sphincterotome, cannula, Artifon catheter) into the distal CBD which allowed opacification of the biliary tree with contrast, passage of a guidewire and performance of therapeutic maneuvers. Unsuccessful ERCP

was considered when cannulation of the CBD could not be achieved either with SC or SPP.

SC consisted of attempts to cannulate the CBD with conventional instruments (i.e. sphincterotomes). The use of guidewires, cannulas and sphincterotomes was at the discretion of the responsible endoscopist and were considered as standard cannulation techniques. Following cannulation, the papillary orifice was opened using a standard biliary sphincterotome and blended electrocautery while using a ValleyLab generator. However, pre-cut biliary sphincterotomy was not considered as standard cannulation and the utilization of this technique to gain access to the CBD was considered, for the purpose of the study, as an unsuccessful ERCP. Prophylactic pancreatic duct stent placement and biliary sphincteroplasty were not performed in any patient in the SC group. SPP of the bile duct was performed using the Artifon catheter in the direction of the CBD at a point corresponding to the proximal third of the line between the transversal fold and the papillary ostium (see video demonstration). After needle puncture of the bile duct, the position of the catheter was confirmed by careful insertion and progression of a 0.025/0.0018-inch diameter guidewire followed by slow injection of contrast. If guidewire insertion into the bile duct did not occur, gentle lateral movements were carried out, with simultaneous attempts to pass the guidewire into the bile duct. According to the diameter of the bile duct and the anticipated type of intervention and instrument required (i.e. balloon, basket, lithotripter), the supra-papillary puncture site was dilated with either an 8-mm or a 10-mm balloon dilation catheter. The instruments used for therapeutic interventions were introduced through the SPP site and the procedure was completed.

Study Outcome

We hypothesized that, in patients with cirrhosis and high probability for common bile duct stones, SPP was associated with fewer complications than SC followed by biliary sphincterotomy (BS). The null hypothesis that no difference existed between these two strategies was then tested against an alternative hypothesis that a difference in complications and efficacy existed. In order to compare patients treated with SC to SPP (intervention group), the outcome of consecutive cirrhotic patients referred for ERCP for management of CBD stones was analyzed.

The primary outcome of our study was rate of complications (bleeding, perforation, pancreatitis). The secondary outcomes were the procedural success rate, time to cannulation measured in minutes and number of attempts made to access the biliary tree. Procedure success was defined separately for each intervention. In patients undergoing SC techniques, it was defined as introduction of a catheter into the major ampullary orifice, successful

access of the bile duct, followed by injection of contrast (cholangiogram) and therapeutic interventions (i.e. biliary sphincterotomy, stone extraction, stent placement). A successful SPP procedure was considered when a “puncture” with the Artifon catheter resulted in progression of the wire into the proximal common bile duct, followed by a cholangiogram and the respective therapeutic interventions (i.e. dilation of the tract, stent placement, stone extraction). The primary outcome measure of this study (complication) is a dichotomous variable and was expressed as a proportion. Standard criteria for bleeding, perforation and post-ERCP pancreatitis were used [18–20]. Presence of pancreatitis following ERCP was defined as follows: (1) New or worse typical pain (epigastric radiating to the back) associated with tenderness to palpation; (2) Elevation of serum amylase or lipase >3 times the upper limit of normal; (3) Both (1) and (2) persist for 24 h after the ERCP. Severity of pancreatitis was defined as follows: Mild (hospitalization required for 2–3 nights), moderate (hospitalization required for 4–10 nights) and severe (hospitalization required for more than 10 nights, or developed one of the following complications: death, pancreatic necrosis, pseudocyst formation, required surgical or nonsurgical drainage or debridement). Complication-related length of stay, additional procedures or investigations within 30 days were recorded. Cardiac and respiratory complications were recorded. Lastly, mortality and direct costs were also assessed. Patients were followed for 30 days to ensure capture of all clinically relevant events. Variables evaluated in relation to the observed complications included demographic (age, gender, race), clinical (Child-Pugh score, platelet count and PT-INR prior to the intervention) and procedural (diameter of the CBD, number of stones, appearance of the major ampulla, number of attempts to cannulate, procedure success).

Statistical Analysis

Descriptive analysis was conducted by comparing means, proportions and confidence intervals (CI) from baseline values. A normal approximation for a binominal distribution was used to test the difference in complication rate between the interventions under evaluation, SC and SPP. If the difference in incidence rate of complications between SC and SPP ranged from –2 to 2%, it was considered to be clinically equivalent. Ninety-five percent confidence interval for the ratio difference was calculated and placed in context with the authors’ area of clinical equivalence [21]. Regression analysis was carried out to identify independent variables which would be associated with the development of complications (dependent variable). Once significant variables were identified by univariate analysis, clinically significant variables were considered in the

creation of predictive models. Selection of independent variables for the multivariate analysis was then performed using Bayesian methodology with Bayesian Information Criterion (BIC) to identify models predicting development of complications. For all hypothesis testing, the null hypothesis was rejected and the alternative hypothesis accepted, when the probability (P) of an alpha-error was equal or less than 5%.

Cost-Effectiveness Analysis

Accurate costs for ERCP do not exist. Calculation was captured from a third party payer perspective and based on equipment, hospital stay, need for additional investigations, and complication-related hospital stay. Applying average direct cost estimates for therapeutic ERCP, the accessories used (i.e. cannulatome, sphincterotome, Artifon catheter, wire, balloon, basket, stent) and the complication-related length of stay, the total amount of monetary resources spent in the SC and SPP was calculated. The rates were converted from Brazilian Real (R\$) to US dollars (US\$) to allow generalizability of results. We attached these costs to the respective intervention and calculated the cost-effectiveness of each strategy according to a decision-based rule [22]. The study was approved by the Hospitals Ethics Committee and conducted according to the text of the Declaration of Helsinki (1964).

Results

Baseline Measurements

One-hundred thirty-two patients were evaluated and 105 patients with documented choledocolithiasis were enrolled in the study. Sixty-three patients were assigned to the SC (non-intervention group) and 42 to SPP (intervention group). In the SC and SPP groups, 33 (52%) and 23 (54%)

patients were male, respectively. The mean age was 56.2 years (SD 17.5 years) in the SC and 55.7 years (SD 13.5 years) in the SPP groups. Table 1 summarizes the baseline characteristics of both groups.

Endoscopic Intervention

The median number of CBD stones was similar in both groups (median = 2.0), but the mean was greater among patients undergoing SPP. The SC group had on average 2.1 stones (SD 1.2) while patients undergoing SPP had 2.76 (SD 1.8) ($P = 0.04$ [0.01, 1.18]). The size of the largest stone was also slightly larger in the SPP group. The mean size of stones was 5.9 mm (SD 1.4) and 6.9 mm (SD 1.9) in the SC and SPP groups respectively, $P = 0.04$ [0.01, 1.18]. The mean diameter of the CBD was higher among patients undergoing SPP. On average, the CBD diameter in the SPP group was 7.9 mm (SD 2.0) compared to 9.2 mm (SD 1.8) in the SC group ($P < 0.001$ [0.52, 2.07]). Table 1 shows the ERCP findings for both SPP and SC groups.

ERCP was successful in 91.4% (96/105) of patients, 88.8% (56/63) in the SC and 95% (40/42) in the SPP ($P = 0.23$; 95% CI [-0.03; 0.17]). The failures in both groups were managed either with repeat procedure or with pre-cut sphincterotomy. The time interval from positioning of the duodenoscope in the descending duodenum and successful access of the CBD was not different between the intervention and the non-intervention groups ($P = 0.87$; 95% CI [-1.26, 1.08]). However, the number of attempts to access the CBD was significantly lower in the SPP group ($P < 0.001$; 95% CI [-2.80, -0.89]). Access to the CBD was achieved after a mean of 3.87 attempts in patients undergoing SC versus 2.02 attempts in the SPP group.

Patients undergoing ERCP with SC techniques had a higher rate of complications than those treated with SPP. However, the difference in complication rate did not achieve a statistical significance. Table 2 shows the incidence of complications in both groups. A total of 10/63

Table 1 Demographic characteristics and ERCP findings of patients in SPP and SC groups

Characteristics	Supra-papillary puncture ($n = 42$)	Standard cannulation ($n = 63$)
Age (mean [SD], years)	55.7 (13.5)	56.2 (17.5)
Male gender (n , %)	23 (54%)	33 (52%)
Child-Pugh classification (B [n ,%]; C [n ,%])	18 (42.8%); 24 (57.2%)	22 (34.9%); 41 (65.1%)
Prothrombin time-INR (mean [SD])	2.14 (0.50)	2.74 (0.95)
Platelet count/ml (SD)	37,809 (7,606)	32,587 (10,225)
Number of CBD stones (mean, SD)	2.7 (1.8)	2.1 (1.2)
Stone diameter (mean [SD], mm)	6.9 (1.9)	5.9 (1.4)
Diameter of CBD (mean [SD], mm)	9.2 (1.8)	7.9 (2.0)
Time until access of CBD (mean [SD], min)	4.2 (3.3)	4.3 (2.6)
Number of attempts (mean [SD])	2.0 (1.3)	3.8 (2.9)

Table 2 Complications observed in patients undergoing bile duct access with supra-papillary puncture (SPP) and standard cannulation (SC)

Success rates and complications	Supra-papillary puncture (<i>n</i> = 42)	Standard cannulation (<i>n</i> = 63)	Hypothesis testing (<i>P</i> value, 95% CI)
Success rate (<i>n</i> , %)	40 (95%)	56 (88.8%)	<i>P</i> = 0.86 (−0.04, 0.16)
Overall complication rate (<i>n</i> , %)	5 (11.9%)	10 (15.8%)	<i>P</i> = 0.28 (−0.17, 0.09)
Bleeding (<i>n</i> , %)	2 (3.2%)	5 (7.9%)	<i>P</i> = 0.16 (−0.13, 0.03)
Pancreatitis (<i>n</i> , %)	0	3 (4.8%)	<i>P</i> = 0.05 (0.01, 0.004)
Perforation (<i>n</i> , %)	3 (7.1%)	2 (3.2%)	<i>P</i> = 0.82 (−0.05, 0.12)

(15.8%) complications occurred in patients having SC and 5/42 (11.9%) undergoing SPP (*P* = 0.28; 95% CI [−0.17, 0.09]). Five (7.9%) and two (3.2%) episodes of post-sphincterotomy/puncture bleeding were seen in the SC and SPP groups, respectively (*P* = 0.16, 95% CI [−0.13, 0.03]). The episodes of bleeding were treated with immediate transfusion of platelets and fresh frozen plasma. In contrast to bleeding-related complications, three (4.8%) episodes of pancreatitis were seen in the SC group while patients in the SPP did not experience this complication (*P* = 0.05; 95% CI [0.01; 0.04]). A total of two episodes of perforation were observed in the SC (3.2%) and three (7.1%) in the SPP (*P* = 0.82; 95% CI [−0.05, 0.12]). These complications were diagnosed by CT scan and managed conservatively. There were no deaths in both SPP and SC groups. Table 2 shows the complications observed in the SC and SPP groups.

A multivariate logistic regression analysis was carried out to identify clinically relevant variables associated with the development of complications. After adjustment for other independent variables, a longer interval time to cannulation (OR 1.17; 95% CI [1.0; 1.37]) and a larger size of CBD stone (OR 1.62, 95% CI [1.0; 2.66]), but not the method of cannulation (OR 0.57; 95% CI [0.16; 2.02]) were identified as predictors of complications.

Cost-Effectiveness Analysis

The individual costs for each procedure and the total costs for patients allocated to SC and SPP according to the Associação Médica Brasileira (AMB) are demonstrated in Table 3. The absolute monetary values observed in the SC and the SPP group were different because of the higher number of patients allocated to SC. Moreover, a difference in accessories utilization existed in between groups since the Artifon catheter and balloon dilators were only used in the SPP group, while sphincterotomes were solely utilized in the patients treated with SC. In the intention-to-treat analysis, the SC group was less costly (mean US\$ 5,619.91 per case) but also less effective than SPP group. The SPP was more expensive and more effective than SC at an ICER of US\$ 5,974.92 per each additional successful

ERCP case. An intention-to-treat threshold analysis revealed that SPP costs would need to be reduced by approximately US\$ 201.00 in order to make it dominant over SC. In this scenario, SPP would become less expensive and more effective than SC in the management of choledocolithiasis of patients with coagulopathy.

Discussion

Over the past 25 years, ERCP with biliary sphincterotomy has become the standard treatment for patients at intermediate and high-risk probability for choledocolithiasis owing to its lower risks of complications and death [23]. The incidence and severity of complications such as pancreatitis seem to be decreasing with the widespread use of wire-guided cannulation and better patient selection as well as the use of pancreatic duct stent placement in high-risk patients [24, 25]. However, successful cannulation rates have become relatively unchanged and cannulation of the CBD is the limiting step to procedural success. When conventional methods of biliary cannulation do not succeed, alternative approaches to obtain biliary access are often utilized [26, 27]. The strategy most commonly used is precut sphincterotomy using a needle-knife (NKS) [28, 29]. Although, the overall incidence of complications following NKS in tertiary care centers has been reported to be similar to conventional sphincterotomy in otherwise healthy patients [30], its use in the community setting is less common owing to the risk of adverse events and potential legal consequences [31]. Moreover, a number of variations of precut sphincterotomy exist, which decreases the external validity of the data using this technique. Placement of prophylactic pancreatic stents, involvement of the ampullary orifice (or not) and the type of current are some of the modifications which can affect the outcome and limit the inference on NKS effectiveness and adverse effect profile [32]. While the sparing of the ampullary orifice and use of pancreatic stents are associated with lower rates of pancreatitis, the use of cutting current has been shown to increase the chance of bleeding. Except for case reports,

Table 3 Individual, total and difference in direct medical costs in the supra-papillary puncture (SPP) and standard cannulation (SC) groups

Health care intervention	Cost per unit (US\$)	SPP (<i>n</i> = 42)	SC (<i>n</i> = 63)	Difference of the means (SPP–SC)
ERCP ^a	825.00	36,300.00	57,750.00	–52.38
Sphincterotome	346.50	N/A	21,829.50	–346.50
Artifon catheter	320.00	13,440.00	N/A	320.00
Needle knife	600.00	1,200.00	4,200.00	–38.09
Wire	250.00	10,500.00	15,750.00	0
Basket	696.50	29,253.00	43,879.50	0
Balloon dilator	300.00	12,600.00	N/A	300.00
Miscellaneous ^b	N/A	53,845.00	71,698.50	–17,583.00
Mean (\$/patient)	N/A	2,877.09	2,497.73	–379.35
Total	N/A	120,838	157,357.50	
Effectiveness	N/A	95.2%	88.8%	6.34%
ACER	N/A	3,020.95	2,809.95	N/A
ICER	5,974.92	N/A	N/A	N/A

ACER average cost-effectiveness ratio, ICER incremental cost-effectiveness ratio

^a Includes hospital and physician fees

^b Endoclip, plastic stent, injection needle, in-hospital care (ICU and regular floor, transfusions, medications)

there are no prior studies addressing the safety and effectiveness of NKS in patients with underlying coagulopathy.

Patients with chronic liver disease have a higher prevalence of gallbladder stones than otherwise healthy individuals and not uncommonly require cholecystectomy and biliary manipulation for treatment of gallbladder stone diseases [33, 34]. Endoscopic management of choledocholithiasis in this population is more difficult because of underlying coagulopathy and increased risk of post-sphincterotomy bleeding. Balloon dilation of the biliary sphincter has been proposed as an alternative to sphincterotomy in patients with uncorrectable coagulopathy but with an increased risk of post-ERCP pancreatitis [35]. We have previously described the supra-papillary puncture (SPP) technique of biliary cannulation and have demonstrated its safety and effectiveness after initial failures using SC techniques [12]. In our experience, SPP is successful in 90% of cases in which conventional cannulation techniques failed. The complication rate in these series was approximately 17% but a cause-effect relationship could not be evaluated because of the study design. The high rate of complications was confounded by the sequential format of the study since the major ampulla had been previously manipulated and cannulation attempted by conventional techniques. The present study was the first to directly compare SPP to SC. A direct comparison between the standard of practice to a new method could only be performed under a unique clinical scenario where the risks of the conventional methods were significantly increased. The mandatory clinical equipoise for the investigation was governed by the presumptive safety benefits of the SPP

technique in this high-risk subset of patients, since SPP does not involve cautery and the expected high rates of bleeding seen with the use of tissue desiccation in coagulopathic patients does not exist. While a head-to-head comparison between SPP and SC as a primary method of biliary access in healthy individuals is unlikely to be clinically relevant, the results of this investigation provide substantial background for future studies comparing NKS and SPP in non-coagulopathic patients in whom biliary cannulation failed using standard cannulation techniques.

In the present study, we compared SC technique to SPP in patients with cirrhosis, low platelet count, prolonged PT-INR and therefore at high risk for bleeding. Our results showed that the absolute number of complications in the SPP was lower than in the SC group, although the difference did not achieve a statistical significance. However, a subgroup analysis demonstrated that patients undergoing SPP were less likely to develop pancreatitis than those treated with SC techniques. We believe the reason for this finding is two-fold. First, the SPP technique avoids manipulation of the common channel. The access to the bile duct is obtained through a single puncture cephalad to the ostium of the major ampulla. Once the wire is advanced into the proximal CBD and a cholangiogram is obtained, balloon dilation of the SPP tract is performed. SPP also minimizes the undesired injection of contrast and progression of wires into the pancreatic duct when the main objective of the study is the biliary system. Second, SPP does not use cautery. The likelihood of either thermal injury to the pancreatic parenchyma or edema of the ampulla is consequently lower than SC. In contrast to the

conventional balloon dilation of the biliary sphincter, dilation of the SPP tract is performed away from the ampullary orifice, which minimizes the likelihood of a temporary mechanical obstruction of the pancreatic duct. After dilation of the SPP tract, extraction of the stones with either balloon or basket could be successfully carried out in all patients. In contrast to NKS, SPP does not entail the use of cautery. All perforations resulted from the needle puncture itself and/or due to fistulotomy (SC group); consequently these cases were sealed, uncomplicated and treated conservatively. The episodes of perforation observed in the SPP group occurred during the initial punctures, while trying to gain CBD access. Similarly, bleeding episodes were mild to moderate episodes and required only endoscopic therapy and transfusion but no additional interventions or surgery. There were no fatal complications.

The economic evaluation comparing the two interventions showed that SPP was more costly but associated with a higher amount of net health benefits (higher cannulation rate and less complication) than SC. The lower number of complications in the SPP arm contributed to decrease costs, but did not offset the higher intrinsic costs of the SPP procedure itself. In addition to the Artifon catheter, the supra-papillary puncture technique required dilation of the fistulous tract, a step usually not required during standard stone extraction using sphincterotomes. The necessity to use a biliary balloon for accomplishment of a SPP-guided stone extraction resulted in an increment of US\$ 300.00 per procedure, which had significant influence in the cost-effectiveness results.

SPP is a new method to access the biliary tree and few endoscopists have been exposed to it. Although within the scope of therapeutic biliary endoscopy, success rate in SPP may be lower for newcomers due to existence of a learning curve intrinsic to all endoscopic interventions. Endoscopic research has an inherent risk of observation bias due to the lack of blinding of the endoscopists who are interested in part of the study and want to demonstrate significant results. The non-sequential design of our investigation was a major strength because it permitted the formation of two independent groups. Enrolment into SPP was not conditional to a SC failure, a subjective decision of the endoscopist, who is unblinded and ultimately susceptible to bias. However, the lack of randomization increased the chance of forming groups unbalanced for both known and unknown confounders. Indeed, patients in the SPP group were more likely to have a higher number and larger CBD stones than SC patients. In contrast, patients allocated to the SC group had a longer PT (INR). An *ad hoc* multivariate regression analysis was carried out to adjust for possible confounding issues. Independent variables associated with the development of complications were identified, but it did not include either SPP or SC. Considering the difficulty to identify and recruit decompensated

cirrhotic patients for this type of study, the number of patients was relatively large and provided important information. Nonetheless, the study was probably underpowered for a number of hypothesis testing analyses.

In summary, we demonstrated that, in patients with coagulopathy due to cirrhosis and no previous attempts of CBD cannulation, SPP was a safe and effective method to access the biliary system and remove common bile duct stones. When compared to SC, SPP was associated with a low rate of overall adverse events and reduced the risk of post-ERCP pancreatitis. SPP is slightly more expensive than SC, although savings in procedure-related complications might offset this difference depending on local costs. Further studies comparing SPP to NKS for cases of unsuccessful cannulation are needed before routine use in unselected patients can be recommended.

Conflict of interest Everson Artifon holds a patent for the Artifon Catheter (Scitech, Goiânia, Brasil). Drs Dayse Aparicio, Renato Baracat, Christiano M. Sakai, Ruel T. Garcia, Decio S Couto, Todd H Baron and Ms Vanessa Teich have no conflict of interest or financial ties to disclose. Dr Eduardo B. da Silveira is on the speakers' bureau for Genentech, Inc. The conduct of this investigation and the preparation of the manuscript were not supported by any private or public grant. Dr Everson Artifon holds a patent for the Artifon Catheter (Scitech, Goiânia, Brasil) and Dr Eduardo da Silveira is on the speaker's bureau for Genentech, Inc..

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