EUS-guided biliary drainage or enteroscopy-assisted ERCP in patients with surgical anatomy and biliary obstruction: an international comparative study

Introduction

Endoscopic ultrasound-guided biliary drainage (EUS-BD) is now an established technique mainly in patients who fail ERCP for various reasons, including gastric outlet obstruction, presence of duodenal stents, and surgically-altered upper gastrointestinal (gastrointestinal) anatomy [1–4]. Although multiple studies have shown excellent efficacy and good safety outcomes with EUS-BD when performed by experts, its use specifically in patients with surgically-altered upper gastrointestinal anatomy has not been well studied. Enteroscopy-assisted ERCP (e-ERCP) is most commonly used for biliary access in patients with surgically-altered upper gastrointestinal anatomy with reported suboptimal clinical success rates between 48% and 70% [5]. In addition, e-ERCP is technically challenging, time consuming, and requires specialized equipment (e.g., balloon enteroscopy, accessories of appropriate length) [6]. Alternative methods of biliary access in these patients include laparoscopy-assisted ERCP and percutaneous biliary access [7]. Laparoscopy-assisted ERCP is only feasible in patients with Roux-en-Y gastric bypass anatomy, is relatively invasive, and requires coordination with a surgeon. Percutaneous biliary accesses is associated with non-trivial morbidity, is relatively invasive, requires repeated interventions and can negatively impact quality of life [1].

EUS-BD using transgastric access to the left liver lobe has been widely reported [8–10]. This is particularly useful in patients with surgically-altered upper gastrointestinal anatomy as it avoids the need for enteroscopy. It is currently unknown how e-ERCP and EUS-BD compare in such patients. The primary aim of this study was to compare the clinical efficacy of both techniques in patients with surgically-altered upper gastrointestinal anatomy. Secondary goals were to compare both groups in terms of technical success, proce-

Background and study aims: How enteroscopy-assisted ERCP (e-ERCP) and endoscopic ultrasound-guided biliary drainage (EUS-BD) compare in patients with surgically altered upper gastrointestinal anatomy is currently unknown. The aims of this study were to compare efficacy and safety of both techniques and study predictors of these outcomes.

Patients and methods: This was an international, multicenter comparative cohort study at 10 tertiary centers. Outcomes data included technical success (biliary access with cholangiography and stent placement [when indicated]), clinical success (resolution of biliary obstruction) and adverse events (AEs) (graded according to the ASGE lexicon).

Results: A total of 98 patients underwent EUS-BD (n = 49) or e-ERCP (n = 49). Technical success was achieved in 48 (98%) patients in the EUS-BD group as compared to 32 (65.3%) patients in the e-ERCP group (OR 12.48, P < 0.001). Clinical success was attained in 88% of patients in EUS-BD group as compared to 59.1% in the e-ERCP group (OR 2.83, P < 0.03). Procedural time was significantly shorter in the EUS-BD group (55 min vs 95 min, P < 0.0001). AEs occurred more commonly in the EUS-BD group (20% vs. 4%, P < 0.01). However, the majority (90%) of AEs were mild/moderate. Length of stay was significantly longer in the EUS-BD group (6.6d vs. 2.4d, P < 0.0001).

Conclusions: EUS-BD can be performed with a higher degree of clinical efficacy and shorter procedure time than e-ERCP in patients with surgically-altered upper gastrointestinal anatomy. Whether or not this approach should be first-line therapy in this patient population is highly dependent on the indication for the procedure, the patient’s anatomy, and local practice and expertise.
dural time, and rate and severity of adverse events (AEs). In addition, we studied predictors of clinical success and occurrence of AEs.

Patients and methods

This was an international, multicenter, retrospective comparative cohort study at 10 tertiary centers (3 United States, 3 European, 3 Asian and 1 South American). e-ERCP patients were recruited from 2 centers with published expertise on e-ERCP and EUS-BD patients from 8 centers with published expertise on EUS-BD. All procedures were performed between January 2008 and December 2014. All patients with surgically altered upper gastrointestinal anatomy who presented with benign or malignant biliary obstruction and subsequently underwent e-ERCP (2 centers) or EUS-BD (8 remaining centers) were included. Type of stent chosen was at the discretion of the treating endoscopist and was according to preference, expertise, cost, anatomy and availability. Relevant variables included demographics, type of surgical anatomy, enteroscopy technique, EUS-BD technique, and etiology of biliary obstruction. This retrospective study was approved by the Institutional Review Boards for Human Research and complied with Health Insurance Portability and Accountability Act (HIPAA) regulations at each participating institution.

Definitions

Technical success was defined as successful biliary access with cholangiography, stent placement in the desired location as determined endoscopically and/or radiographically, and/or stone removal, whenever indicated. Clinical success was defined as resolution of biliary drainage and reduction in serum total bilirubin by 50% at 1 week or less than 3 mg/dL at 2 weeks after the procedure in jaundiced patients. Procedure-related AEs were recorded and included: peritonitis, bile leak, cholangitis, bleeding, pancreatitis, intraperitoneal stent migration, subcapsular liver hematoma, pneumoperitoneum, perforation, retained sheared wire, and procedure-related death. All hospitalizations, procedures, and/or surgeries needed to treat procedure-related complications were tracked and recorded. Adverse events were graded according to the ASGE lexicon’s severity grading system [11].

Procedural techniques

EUS-guided biliary drainage

Procedures were performed by interventional endoscopists with expertise in EUS, ERCP and interventional EUS. Procedures were performed as previously described [3]. The major anatomical modification in patients with surgical upper gastrointestinal anatomy was typically the absence of duodenal access. The majority of cases were typically performed using transgastric or transjejunal (in patients with total gastrectomy) access with hepatogastrostomy or hepatojunostomy, respectively.

Rendezvous (RV) technique. A linear echoendoscope was used to achieve initial biliary access within a segment of dilated bile duct proximal to the site of obstruction. The tip of the echoendoscope was positioned in the gastric fundus. A 19-gauge or 22-gauge fine needle aspiration (FNA) needle (Echotip, Cook Medical, Winston-Salem, NC; or Expect 19 Flex, Boston Scientific, Natick, MA) was used to puncture a biliary segment with access confirmed by aspiration of bile and cholangiogram. Depending on the needle chosen either a 0.035-inch, 0.025-inch, or 0.018-inch guidewire was then advanced into the bile duct. The smaller 0.018-inch wires were exchanged for larger wires before stent placement. The echoendoscope and needle were angled to facilitate antegrade guidewire passage through the site of obstruction and across the papilla/anastomosis with coiling of the wire in the small bowel. The echoendoscope was then withdrawn leaving the guidewire in place. An endoscope was passed to the papilla/anastomosis and a snare or biopsy forceps was used to grasp the guidewire and withdraw it through the endoscope with subsequent stent placement as per standard e-ERCP techniques.

Direct transluminal (TL) technique [hepatogastrostomy (HGS), hepatoduodenostomy (HDS), or hepatojunostomy (HJS)]. In TL cases, the entire procedure was performed using the echoendoscope. After a biliary segment was accessed as described above, the biliary-enteric fistula was dilated with a catheter (e.g. 6 Fr cystostome; Cysto-Gastro set, Endo-flex, Voerde, Düsseldorf, Germany) or balloon, and a variety of devices were used to facilitate stent placement. These devices were selected based on the patient’s anatomy and features of the obstructing stricture. Stent insertion was then performed leaving at least 3 cm of stent with the gastrointestinal lumen to avoid intraperitoneal stent migration.

Antegrade stenting (AGS). The dilated biliary ductal segment was punctured with an FNA needle and contrast was then injected through the needle to provide a cholangiogram. A hydrophilic guidewire was advanced through the needle and manipulated across the ampulla/anastomosis. The FNA needle was then removed, and the tract was created using a 6 Fr cystostome (Cysto-Gastro set, Endo-flex, Voerde, Düsseldorf, Germany) or dilated as described above. To facilitate antegrade stent placement, structures, when present, were dilated before advancing the stent through the therapeutic channel of the echoendoscope over the guide wire. The stent was then deployed either across the stricture transpapillary or trans-anastomotic in patients with biliary-enteric anastomoses.

Enteroscopy-assisted ERCP

Procedures were performed using single-balloon enteroscope (SBE, Olympus Optical, Tokyo, Japan), double balloon-enteroscope (DBE, Fujifilm Medical, Tokyo, Japan) or pediatric colonoscope (Olympus). e-ERCP using SBE and DBE were performed as described before. Advancement through the small bowel was achieved with a series of cycles using a push-and-pull technique. A pediatric colonoscope was occasionally used at the discretion of the endoscopist. A transparent cap was attached to the tip of the endoscope according to the preference of the operator. Accessories compatible with enteroscopes were used during ERCP.

Statistical analysis

Results are reported as mean ± standard deviation (SD) or median (range) for quantitative variables and percentages for categorical variables. Outcomes between EUS-BD and e-ERCP groups were compared using the Student’s t test (or the Wilcoxon rank-sum test if required) for continuous variables and the chi-square test (or Fisher’s exact test if required) for categorical variables. Univariable analysis was performed by using logistic regression to assess factors (RY anatomy native papilla, age, gender, baseline bilirubin, and technique, EUSBD vs e-ERCP) associated with clinical success and AEs. Multivariable regression analysis was performed taking into account the variables, native papilla, RY anat-
A total of 98 patients (mean age 58 yr, female 67%) underwent endoscopic biliary drainage or enteroscopysisted ERCP in 2. There was a higher frequency of malignant obstruction in the EUS-BD group as compared to the e-ERCP group ($P<0.0001$), but higher frequency of RA anatomy ($P<0.0001$) and native ampulla ($P=0.0001$) in the e-ERCP group ($P=0.0001$). Technical success was achieved in 48 (98%) patients in the EUS-BD group as compared to 32 (65.3%) patients in the e-ERCP group (OR 12.48, 95% CI 2.69 - 57.78, $P=0.001$). Among the 17 technical failures in the e-ERCP group, 11 resulted from failure to reach the ampulla or enteric-biliary anastomosis and 6 were due to failed cannulation. Clinical success was attained in 88% of patients in EUS-BD group as compared to 59.1% in the e-ERCP group (OR 2.83, 95% CI 1.10 - 7.31, $P=0.03$). Procedural time was significantly shorter in the EUS-BD group as compared to the e-ERCP group ($P<0.0001$).

### Table 1: Baseline patient and procedural characteristics of 98 patients.

| Variable                           | Total (n=98) | EUS-BD (n=49) | e-ERCP (n=49) | $P$ value |
|------------------------------------|--------------|---------------|---------------|------------|
| Age (yrs), mean ± SD               | 58 ± 13.9    | 62.48 ± 14.9  | 53.6 ± 11.46  | $P<0.001$  |
| Female, n (%)                      | 66 (67.3)    | 22 (44.8)     | 44 (89.7)     | $P<0.001$  |
| Malignant indication, n (%)        | 35 (35.7)    | 33 (67.4)     | 2 (4)         | $P<0.001$  |
| RY anatomy, n (%)                  | 69 (70)      | 24 (49)       | 45 (92)       | $P<0.001$  |
| Native papilla, n (%)              | 66 (67)      | 24 (49)       | 42 (85.7)     | $P<0.001$  |
| Baseline bilirubin, mean ± SD      | 5.1 ± 6.2    | 8.8 ± 6.6     | 1.4 ± 2.5     | $P<0.001$  |
| Stent material, n (%)              |              |               |               | NA         |
| Metal                              | 40 (40.8)    | 24 (49)       | 42 (85.7)     | $P<0.001$  |
| Plastic                            | 18 (16.4)    | 3 (6.1)       | 32 (65.3)     | $P<0.001$  |
| No stent                           | 40 (40.8)    | 42 (85.7)     | 29 (59.1)     | $P=0.03$   |
| Procedure duration (min), mean ± SD| 77 ± 41      | 55 ± 36       | 95.7 ± 38.5   | $P<0.001$  |
| Length of hospital stay (day), median (range) | 3 (0 – 30) | 1 (0 – 15) | 32 (65.3) | $P<0.001$  |
| Technical success, n (%)           | 80 (81.6)    | 48 (98)       | 32 (65.3)     | $P=0.001$  |
| Clinical success, n (%)            | 72 (73.4)    | 43 (88)       | 29 (59.1)     | $P=0.03$   |
| Adverse events, n (%)              | 12 (12.2)    | 10 (20.4)     | 2 (4.1)       | $P=0.03$   |
| All                                | 11 (11)      | 3 (6.1)       | 1 (2)         | $P=0.61$   |
| Mild                               | 4 (4)        | 2 (4)         | 1 (2)         | $P=0.06$   |
| Moderate                           | 7 (7.1)      | 6 (12.2)      | 1 (2)         | $P=0.06$   |
| Severe                             | 1 (1)        | 1 (2)         | 0 (0)         | $P=0.5$    |
| Death                              | 0 (0)        | 11 (22)       | 0 (0)         | NA         |
Table 3  Univariate analysis of factors associated with clinical success and AEs.

| Clinical success | OR     | 95% CI  | P value |
|------------------|--------|---------|---------|
| EUS-BD vs ERCP   | 2.83   | 1.10 – 7.31 | 0.03    |
| RY anatomy       | 0.829  | 0.30 – 2.28  | 0.72    |
| Native papilla   | 1.035  | 0.40 – 2.70  | 0.94    |
| Age              | 1.02   | 0.99 – 1.06  | 0.13    |
| Female           | 4.5    | 1.2 – 16.7  | 0.02    |
| Baseline bilirubin | 1.0   | 0.95 – 1.1  | 0.47    |

Adverse events

| EUS-BD vs ERCP | OR     | 95% CI  | P value |
|----------------|--------|---------|---------|
| RY anatomy     | 0.51   | 0.15 – 1.77 | 0.29    |
| Native papilla | 1.69   | 0.43 – 6.71  | 0.45    |
| Age            | 1.0    | 0.96 – 1.06  | 0.54    |
| Female         | 2.4    | 0.64 – 9.42  | 0.18    |
| Baseline bilirubin | 1.0   | 0.94 – 1.13  | 0.48    |

EUS-BD = endoscopic ultrasound-guided biliary drainage; ERCP = endoscopic retrograde cholangiopancreatography

Discussion

Enteroscopy-assisted ERCP has been utilized extensively for biliary access and interventions in patients with surgically altered upper gastrointestinal anatomy, but with suboptimal results [5, 12]. EUS is an ideal modality for visualization and access of the biliary tree in such patients as the left lobe of the liver is readily seen transgastrically. The current study is the first to compare e-ERCP and EUS-BD in such patients who present with biliary obstruction. A total of 98 patients underwent either EUS-BD (n=49) or e-ERCP (n=49). Rates of technical success (98% vs 65%) and clinical success (88% vs 60%) were both significantly higher in patients who underwent EUS-BD, although anatomy and procedural indications were significantly different between groups. EUS-BD procedures were significantly less time consuming with an average of 40 minutes saved per procedure. The rate of AEs was significantly higher in the EUS-BD group, although the vast majority were not severe. The length of stay was significantly longer in the EUS-BD group, but that could be due to underlying pathology (predominantly malignant) rather than the procedure technique itself.

A number of studies have described the use of e-ERCP in patients with surgically-altered upper gastrointestinal anatomy. Shah and colleagues presented a multicenter US experience with e-ERCP in patients with surgically altered pancreatochiliary anatomy [12]. A total of 129 patients had 180 e-ERCP with RYGB (n=63) and RY hepaticojejunostomy (n=45) as the most commonly encountered surgical anatomy. Successful ERCP was achieved in 63% of patients and was similar between RYGB and other long-limb surgical bypass patients. AEs occurred in 12% of patients. Skinner and colleagues performed a systematic review of e-ERCP performed in patients with surgical upper gastrointestinal anatomy [5]. A total of 945 procedures in 679 patients who had a variety of post-surgical upper gastrointestinal anatomical configurations were included. Overall ERCP success was 74%. Among patients with RYGB anatomy, ERCP success was achieved in 70% of cases. In patients who had undergone a RY with either a pancreato-duodenectomy or hepaticojejunostomy, ERCP success was 76%. In patients with Billroth II anatomy, the rate of success with ERCP was 90%. The overall rate of AEs was 3.4%. Outcomes of e-ERCP in the current study are in line with these published results, which illustrate moderate success and excellent safety of e-ERCP in such patients.

Dedicated studies on EUS-BD in patients with altered anatomy are scarce. Siripun et al. reported a systematic review of all reported EUS-BD in such patients [13]. Seventy four cases were included for analysis. The pooled technical success, clinical success, and AE rates were 89%, 91%, and 17.5%, respectively. Reported

Table 4  Univariate and multivariable analysis of factors associated with clinical success.

|                  | Unadjusted | Adjusted |
|------------------|------------|----------|
|                  | OR         | 95% CI   | P value | OR         | 95% CI   | P value |
| EUS-BD vs ERCP   | 2.83       | 1.10 – 7.31 | 0.03    | 4.31       | 1.28 – 14.54 | 0.02    |
| RY anatomy       | 0.829      | 0.30 – 2.28 | 0.72    | 1.48       | 0.41 – 5.35  | 0.54    |
| Native papilla   | 1.035      | 0.4 – 2.70   | 0.94    | 1.75       | 0.54 – 5.61  | 0.34    |

EUS-BD = endoscopic ultrasound-guided biliary drainage; ERCP = endoscopic retrograde cholangiopancreatography
complications included pancreatitis, abdominal pain, hematomata, cholangitis, minor bleeding, and peritoneal stent migration, with no mortalities. Itoi et al. reported on EUS- transhepatic antegrade stone removal in patients with surgically altered anatomy with excellent outcomes [14]. These results are similar to the reported outcomes of >EUS-BD in general [15]. In addition, these outcomes are in agreement with results from the current study.

e-ERCP offers some advantages over EUS-BD. It is an established procedure that is widely available and practiced. Dedicated ERCP devices compatible for use through enteroscopes are available from multiple manufacturers. Furthermore, the procedure is very safe with rare severe AEs and is associated with moderate clinical success rate. Management of choledocholithiasis using e-ERCP remains the main technique of choice as the EUS-guided approach remains challenging. On the other hand, EUS-BD also has multiple benefits over e-ERCP. The biliary system is readily accessible transgastrically, which avoids the need for the time consuming navigation deep into the small bowel. EUS-BD is therefore a more efficient procedure as was shown in the current study. Success of EUS-BD is not affected by long surgical limbs and angulations (e.g. at the jejunojunostomy). This is reflected by a higher clinical success of EUS-BD as was also shown in the current study. Lastly, EUS-BD allows placement of the larger self-expandable metallic stents when needed, which is associated with improved drainage and longer patency rates as compared to plastic stents.

It is important to highlight other established endoscopic methods that can also be employed in patients with surgically-altered upper gastrointestinal anatomy, including ERCP through a gastroscope tract and laparoscopy-assisted ERCP in patients with RYGB anatomy. A study comparing outcomes of ERCP via gastroscopy and eERCP for patients with previous RYGB found that ERCP via gastrosopy was successful in 95% of cases, whereas e-ERCP was successful in 63% of cases. However, the rate of AEs was higher with ERCP via gastrosopy (14.5%) compared with e-ERCP (14.5% vs 3.1%, P=0.02). The authors concluded that ERCP via gastrosopy has a higher success rate than e-ERCP but is hindered by the gastrosopy maturation delay and a higher morbidity [16]. Another study comparing laparoscopy-assisted ERCP (n=24) with eERCP (n=32) in patients with RYGB showed 100% ERCP success rate in the laparoscopy-assisted ERCP group and 59% in the e-ERCP group [7]. In patients with a Roux limb plus ligament of Treitz to jejunoojunostomy anastomosis limb length of more than 150cm, successful e-ERCP was only achieved in 25% of patients. Complications were minor and infrequent in both groups. A cost analysis showed that patients with a Roux limb plus ligament of Treitz to jejunoojunostomy anastomosis limb length of less than 150cm should be offered e-ERCP first, and those with longer limbs should proceed directly to laparoscopy-assisted ERCP [7].

There are significant limitations to the current study. First, all procedures were performed by experts in pancreaticobiliary endoscopy, therefore, results may not be generalizable. It is a retrospective study with inherent limitations due to the study design. Patients from each group were selected from different centers according to expertise and center-effect was not accounted for. Finally, the baseline characteristics of patients were not similar between the two groups. The majority of patients undergoing e-ERCP had benign disease and RYGB anatomy as opposed to the EUS-BD group where the majority of patients had malignant indications for biliary drainage and non-RYGB surgically altered upper gastrointestinal anatomy. As such, the outcome of any direct comparison between the 2 techniques is subject to significant selection bias. Randomized studies are need for optimal comparison but will be extremely difficult to perform as stratification for long limbs, dilated biliary system and other variables will be necessary.

These data suggest that EUS-BD can be performed with a high degree of clinical efficacy and moderate safety in patients with surgically-altered upper gastrointestinal anatomy. Whether this approach should be first-line therapy in this patient population is highly dependent on the indication for the procedure, the patient’s anatomy and finally, local practice bias and expertise in either e-ERCP or EUS-BD. We believe that EUS-BD is still best offered to patients after a failed initial e-ERCP; however, in patients with malignant biliary obstruction and expected long surgical limbs, the rate of technical failure of e-ERCP is high and EUS-BD can be offered as a first-line modality if appropriate expertise is available.

**Competing interests:** Dr. Khashab is a consultant for Boston Scientific and Xlumena. Manuel Perez-Miranda is a consultant for Boston Scientific. Dr. Kunda is a consultant for Boston Scientific, Olympus and Xlumena.
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