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1 Comparison of trans-gastric *vs* trans-enteric (trans-duodenal or trans-jejunal) endoscopic ultrasound guided gallbladder drainage using lumen apposing metal stents

Grover *et al.* TD, TG, cautery, EUS-GBD, and LAMS

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7 Abstract

BACKGROUND

Endoscopic ultrasound guided gallbladder drainage (EUS-GBD) is being increasingly used in practice (either as a bridge to cholecystectomy in high-risk patients or as destination therapy in non-surgical patients). Stents are used to create a conduit between the lumen of the gallbladder (GB) and the intestinal lumen through the gastric or enteric routes. Among the various types of stents used, cautery-enhanced lumen apposing metallic stents (LAMS) may be associated with fewer adverse events (AEs).

AIM

To compare the clinical success, technical success, and rate of AEs between transgastric (TG) and trans-enteric [transduodenal (TD)/transjejunal (TJ)] approach to GB drainage. Further, we analyzed whether using cautery enhanced stents during EUS-GBD impacts the above parameters.

1 METHODS

Study was registered in PROSPERO (CRD42022319019) and comprehensive literature review was conducted. Manuscripts were reviewed for the data collection: Rate of AEs, clinical success, and technical success. Random effects model was utilized for the analysis.

RESULTS

No statistically significant difference in clinical and technical success between the TD/TJ and TG approaches ($P > 0.05$) were noted. There was no statistically significant difference in the rate of AEs when comparing two-arm studies only. However, when all studies were included in the analysis difference was almost significant favoring the TD/TJ approach. When comparing cautery-enhanced LAMS with non-cautery enhanced LAMS, a statistically significant difference in the rate of AEs was observed when all the studies were included, with the rate being higher in non-cautery enhanced stents (14.0% vs 37.8%; $P < 0.01$).

CONCLUSION

As per our study results, TD/TJ approach appears to be associated with lower rate of adverse events and comparable efficacy when compared to the TG approach for the EUS-GBD. Additionally, use of cautery-enhanced LAMS for EUS-GBD is associated with a more favorable adverse event profile compared to cold LAMS. Though the approach chosen depends on several patient and physician factors, the above findings could help in deciding the ideal drainage route when both TG and TD/TJ approaches are feasible.

Key Words: Transduodenal; Transgastric; Cautery; Endoscopic ultrasound guided gallbladder drainage; AXIOS

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Core Tip: Endoscopic ultrasound guided gallbladder drainage (EUS-GBD) is increasingly used in management of gallbladder disease. EUS-GBD can be achieved using trans-gastric or trans-enteric (trans-duodenal or trans-jejunal) approach There are currently no randomized controlled trials comparing these two approaches. We

performed a meta-analysis of the existing literature on EUS guided gallbladder drainage. Trans-enteric approach was observed to have a more favorable safety profile compared to trans-gastric approach. Further use of cautery enhanced lumen apposing metallic stents (LAMS) to achieve EUS-guided GBD was associated with lesser adverse effects when compared to use of non-cautery enhanced (cold) LAMS.

INTRODUCTION

Acute cholecystitis is an acute inflammation of the gall bladder (GB) characterized by the clinical syndrome of right upper quadrant pain, fever, and leukocytosis. The primary underlying etiology is gallstones, but 5%-10% of cases may be due to acalculous cholecystitis^[1]. Open or laparoscopic cholecystectomy is the definitive treatment; however, many patients with acute cholecystitis are not good surgical candidates due to comorbidities. Percutaneous gallbladder drainage (PT-GBD) has emerged as an alternative but is limited by complications such as recurrent cholecystitis, bile peritonitis, puncture-induced hemorrhage, drain site pain, and infection^[2]. PT-GBD is a temporizing treatment modality that can be a bridge to surgery until patient's clinical status improves. Often patients are unable to undergo surgery and are left with a permanent percutaneous drain^[3,4].

Endoscopic ultrasound guided gallbladder drainage (EUS-GBD) is a minimally invasive alternative to PT-GBD. It is preferred due to its comparable clinical and technical success and minimal adverse events (AEs)^[5]. Even though EUS-GBD initially was an alternative to surgery, the current indications have expanded to include: Destination therapy in poor surgical candidates, bridging to cholecystectomy, conversion of PT-GBD to EUS-GBD, alternative to failed PT-GBD or failed ET-GBD (endoscopic trans-papillary GBD) or alternative to failed EUS-guided biliary drainage (EUS-BD)^[3]. Drainage of the GB is done by either transduodenal (TD)/transjugal (TJ) or transgastric (TG) approach. This allows for decompression of the GB by bypassing the obstruction. The best transluminal access to achieve gallbladder drainage has not been well established. In addition, there is limited literature comparing trans-gastric

and trans-enteric (TD/TJ) approaches for EUS-GBD^[6,7,18]. With the increasing use of EUS-GBD, it becomes important to ascertain the best trans-luminal approach to gallbladder drainage. Hence, we undertook a study to analyze the available evidence on this topic.

EUS-GBD can be achieved using plastic stents, self-expandable metal stents (SEMS) and lumen apposing metallic stents (LAMS). LAMS maintains a strong seal, reducing the risk of bile leakage and stent migration. Hence, LAMS is ideal for EUS-GBD^[8,19,20]. The novel cautery-enhanced LAMS (hot) is being increasingly used and has the advantage of completing the procedure in one step without additional exchanges and reducing the need for fluoroscopic assistance compared to non-cautery enhanced (cold) LAMS^[9,10]. The design of the stent with flares at both ends may mitigate risk of stent migration^[21]. Our study aimed to compare the clinical success, technical success, and rate of AEs between the approaches used for the site of puncture and the type of LAMS used for EUS-GBD.

MATERIALS AND METHODS

The study was registered in The International Prospective Register of Systematic Reviews (PROSPERO), and a comprehensive literature search was done on PubMed, Embase, Scopus, CENTRAL, CINAHL, and Web of Science. The literature search was done using words: “Ultrasonography”, “Endosonography”, “Endosonograph”, “Endoscopic ultrasound”, “lumen apposing metal stent”, “LAMS”, “transgastric”, “transduodenal”, hot” or “cold” AND “Gallbladder diseases”, Gallbladder”, “biliary”, “cholecyst”, AND “drainage”, “drain”. The references of the included studies were thoroughly reviewed. In total, 3707 studies were screened. For the comparison of TG and TD/TJ approach, twenty-four met the inclusion criteria (Figure 1). The inclusion criteria included randomized or nonrandomized controlled clinical trials and prospective and retrospective studies. Due to a lack of data, abstracts presented at conferences and case series (with four or more patients) were also included in the study. Reviews, meta-analyses, animal studies, letters from the editor, case reports, opinion

articles, and editorials were not included. The other exclusion criteria included animal studies and studies in languages other than English. No age and gender restrictions were applied. A post-hoc analysis was done to compare the cautery-enhanced (hot) *vs* non-cautery enhanced approach and only twelve studies met the above-mentioned inclusion criteria (Figure 2). Manuscripts were reviewed for the data collection: rate of AEs, clinical success, and technical success. The search was conducted again couple of days prior to the submission of this manuscript for the emerging data. Random effects models were estimated using Comprehensive Meta-Analysis (Biostat Inc.) software. A *P* value of less than 0.05 was considered significant.

RESULTS

The analysis was done using two methods. Method 1 included analysis of studies with patients in both arms only and method 2 included analysis of the studies. Due to limited data, we could not analyze the baseline characteristics and specific AEs. In the majority of the studies, technical success was defined as adequate access and drainage of the GB with the placement of the LAMS stent. Clinical success was described as a decline in serum bilirubin levels in patients with obstructive jaundice to 10% of the initial levels and improvement of cholestatic parameters in those without jaundice.

TG vs TD/TJ

Analyses were done by two methods. Pooled odds ratios for AE, clinical success and technical success were calculated (Table 1).

Method 1: Analysis of studies with patients in both arms only. *TG vs TD/TJ*: Pooled odds ratio (95% confidence interval), *P* value: AEs (6 studies): 1.58 (0.46-5.45), *P* = 0.47; clinical success (3 studies): 0.30 (0.06-1.48), *P* = 0.14; and technical success (3 studies): 0.30 (0.05-1.89), *P* = 0.20.

Method 2: Analysis of all studies (in total 15 using TD/TJ approach and 9 using TG approach). ¹ TG vs TD/TJ: AEs (Studies: 9 vs 15): 27.5% (17.1%-41.1%) vs 15.2% (9.5%-23.6%), $P = 0.07$; clinical success (Studies: 6 vs 13): 83.3% (71.0%-91.0%) vs 91.7% (82.4%-96.3%), $P = 0.16$; and technical success (Studies: 9 vs 15): 91.3% (83.6%-95.6%) vs 95.3% (90.7%-97.7%), $P = 0.22$.

Cautery enhanced vs non-cautery enhanced LAMS

Analyses were done by two methods. Pooled odds ratios for AE, clinical success and technical success were calculated (Table 2).

Method 1: Analysis of studies with patients in both arms only. Cautery-enhanced vs non-cautery enhanced-pooled odds ratio (95% confidence interval); P value: AEs (2 studies): 0.55 (0.19-1.64), $P = 0.28$; clinical success (2 studies): 1.81 (0.50 to 6.61; $P = 0.37$). There was only one study that compared the technical success of both the arms.

Method 2: Including all the studies (in total 9 using cautery-enhanced LAMS and 3 using non-cautery enhanced LAMS). Cautery-enhanced vs non-cautery-enhanced-pooled percentage (IQR), P value: AEs (Studies: 9 vs 3): 14% (9.1%-21.0%) vs 37.8% (26.5%-50.6%), $P \leq 0.001$; Clinical success (Studies: 11 vs 3): 89.9% (86.1%-92.7%) vs 93.4% (72.8%-90.3%), $P = 0.12$, and technical success (Studies: 11 vs 3): 94.4% (91.3%-96.4%) vs 93.8% (86.3% vs 97.3%), $P = 0.82$.

DISCUSSION

⁹ Traditionally, early laparoscopic cholecystectomy is the gold standard treatment for cholecystitis^[1,10]. In patients who are poor surgical candidates due to comorbidities, conservative management or percutaneous drainage of the GB is recommended. In the CHOCOLATE trial, for patients with a high APACHE II score, urgent laparoscopic cholecystectomy was associated with a reduced hospital length of stay, complications, and reinterventions compared to percutaneous drainage^[11]. Hence, patients with

cholecystitis should undergo cholecystectomy even in emergent conditions if well tolerated. Cholecystectomy has the additional advantage of obviating the future risk of recurrent cholecystitis.

Recent studies have reported EUS-GBD as a minimally invasive alternative to percutaneous drainage for cholecystitis in patients who are poor surgical candidates^[12]. EUS-GBD has been studied for technical success, clinical success, and rate of AEs comparable to standard percutaneous techniques with decreased tube-related complications, including tube dislodgement, migration, obstruction and peri-tubal leakage^[2,12,13]. In a meta-analysis by Luk *et al*^[13], EUS-GBD was reported to have comparable technical and clinical success; however, EUS-GBD was associated with lower post-procedure adverse events, shorter hospital stays, and fewer reinterventions and readmissions compared to PT-GBD.

The efficacy and feasibility of EUS-GBD using different stents, including plastic stents, SEMS, and LAMS has been well documented^[14-17]. Stent placement can result in complications such as stent migration, occlusion, bleeding, bile leak and pneumoperitoneum and associated morbidity. Plastic double pigtail stents are commonly associated with bile leaks, bile peritonitis and stent migration. SEMS provides the advantage of longer stent patency and prevents bile leakage but risk of stent migration remains. Both plastic stents and SEMS do not maintain apposition to seal the gap and reliably form a fistula. LAMS is considered an ideal stent due to its ability to make a firm seal with decreased complications^[7,8,21].

The drainage of the GB is done by creating a cholecysto-enteric communication, via either TD/TJ or TG approach under the endoscopic/endosonographic guidance. In the TD approach, the retro-peritoneal duodenum is relatively immobile and thus provides a stable access site to the neck of GB which is the puncture site in this approach^[6]. In addition, the inflamed GB wall may become adherent to the wall of the duodenum/jejunum lending further stability during the access. Compared to stomach, the wall of duodenum/jejunum has less peristaltic activity which may the risk of stent migration and stent occlusion due to tissue overgrowth^[6,15]. Potential for reflux of food

contest into the gallbladder may be lesser with TD approach resulting in reduced risk of stent occlusion or infection related to reflux^[6,7]. The flow of food into the biliary system during EUS-GBD can lead to cholangitis or obstructive jaundice by occluding the stent. Due to the above reasons, TD/TJ is thought to be a safer option, but it has several limitations^[6,7]. One of the limitations is the technical difficulty in accessing the neck of the GB, the puncture site in the TD/TJ approach. With TG approach the access point is usually the gallbladder body which provides a larger landing zone for deployment of the inner flange of the lumen apposing metal stent^[6].

The thicker wall of the stomach may have larger perforating blood vessels (as compared to the duodenum) which can increase the risk of bleeding during transluminal access of the gallbladder. Management of delayed AEs may be easier with TG approach as the stomach is more accessible at laparoscopy compared to the duodenal bulb and thicker gastric wall permits more reliable wound closure^[6]. Our study aimed to compare the clinical success, technical success, and rate of AEs between the approaches used for the site of puncture, *i.e.*, TD/TJ *vs* TG.

Our meta-analysis showed no statistically significant difference in the clinical and technical success between the TD/TJ and TG approaches. In addition, we did not observe any statistically significant difference in the rate of AEs when comparing the two-arm studies only; however, the difference was almost significant (TG *vs* TD/TJ: 27.5% *vs* 15.2%, $P = 0.07$) when all the studies were analyzed with higher rates of AE noted with the TG approach. The commonly noted AEs with EUS-GBD include stent migration, stent occlusion, biliary peritonitis, pneumoperitoneum and recurrence of cholecystitis due to food impaction^[14].

We also analyzed the above outcomes when deploying the cautery-enhanced (hot) *vs* non-cautery enhanced (cold) LAMS for EUS-GBD. The cautery-enhanced LAMS is a novel, fully covered, self-expanding stent with an electrocautery-enhanced delivery system ideal for EUS-GBD. Due to its “all-in-one” nature, the direct introduction of the device into the GB without prior placement of a guidewire eliminates the need for multiple steps and accessory exchanges^[8]. The one step procedure with cautery-

enhanced (hot) LAMS decreases the procedure time and the need for fluoroscopic assistance. The complications are further decreased by the hemostatic effect of cautery and absence of need for tract dilation likely reduces risk of bleeding and bile leak^[9,10]. Deployment of non-cautery enhanced (cold) LAMS is wire guided and carries the risk of loss of wire access and attendant problems which do not apply to cautery enhanced LAMS. Hence, the cautery-enhanced LAMS is expected to have lesser rate of AEs as compared to non-cautery enhanced.

In our study, we did not observe any significant difference in the technical and clinical success between the cautery enhanced and non-cautery enhanced LAMS in EUS-GBD. No significant difference was observed in the rate of AEs between the two approaches when studies with both arms only were analyzed; however, a significant difference ($P < 0.01$) was noted in the rate of AEs when all the studies were included in the analysis, with the AEs being higher in non-cautery enhanced compared to cautery-enhanced LAMS.

There are several limitations to our study. The number of included studies was small due to data sparsity; thus, the results of this study might be underpowered. Additionally, the studies were done at several different centers, and the heterogeneity amongst various centers weakens the reliability of the results. Furthermore, since the number of studies was less than 10, publication bias is difficult to address. In addition to publication bias, selection bias, lead-time bias, and confounding factors cannot be excluded. Several studies reported their experience with EUS-GBD but did not aim to compare TD/TV *vs* TG approaches. With first method of analyzing studies with both arms, we were able to compare TD/TJ approach *vs* TG approach by the same operator. This helped reduce performance bias and data heterogeneity. However, these studies were not conducted with the primary aim of comparing both approaches. Some of the findings from our analysis did not reach statistical significance due to data sparsity. When we used the second method and included all studies in our analysis, due to the increase in available data, some findings were statistically significant. However (as some case series reported one approach only and pooled data included multiple

operators) the analyzed data was quite heterogeneous. Given the sparse data and heterogeneity of the data we are unable to perform GRADE analysis and make recommendations based on GRADE methodology. Sufficiently powered randomized control trial should be done to compare the clinical outcomes of TD/TJ *vs* TG approach. Given the significantly reduced procedure time and ease of deployment of cautery enhanced LAMS for EUS-GBD, it is unlikely that a randomized controlled trial will be conducted to compare cautery enhanced *vs* and non-cautery enhanced LAMS to validate our findings.

CONCLUSION

Based on our study findings, cautery-enhanced LAMS deployment appears safer than non-cautery enhanced stent deployment for EUS-GBD. The TD/TJ approach may be associated with a more favorable AE profile with equal efficacy when compared to TG approach for EUS-GBD. While decision regarding approach to trans-luminal GB drainage depends on endoscopist preference and patient-specific anatomic considerations such as proximity of GB to the gastrointestinal tract lumen, it would be helpful to know which approach (trans-gastric *vs* trans-duodenal) has a favorable AEs profile especially when both approaches are feasible in a given patient. If EUS-GBD is a bridge to cholecystectomy, surgery appears feasible with both TG and TD/TJ approaches^[22,23] but data regarding preferred approach is lacking^[6].

ARTICLE HIGHLIGHTS

Research background

Adequately powered RCTS are need to confirm the findings in our retrospective study.

Research motivation

Transduodenal endoscopic ultrasound guided gallbladder drainage (EUS-GBD) appeared to be safer than transgastric drainage. Hot lumen apposing metallic stents (LAMS) is better than cold LAMS.

Research objectives

As per our study transduodenal approach appeared to have a more favorable adverse event (AE) profile with comparable technical and clinical success when compared to transgastric approach. Cautery enhanced LAMS has a more favorable AE and shorter procedure time than cold LAMS.

Research methods

¹ Literature search was done using PubMed, Embase, Scopus, CENTRAL, CINAHL, and Web of Science database. The inclusion criteria included randomized or nonrandomized controlled clinical trials and prospective and retrospective studies. Due to a lack of data, abstracts presented at conferences and case series (with four or more patients) were also included in the study. Reviews, meta-analyses, animal studies, letters from the editor, case reports, opinion articles, and editorials were not included. ³ The other exclusion criteria included animal studies and studies in languages other than English. No age and gender restrictions were applied. A post-hoc analysis was done to compare the cautery-enhanced (hot) *vs* non-cautery enhanced approach and only twelve studies met the above-mentioned inclusion criteria. Manuscripts were reviewed for the data collection: Rate of AEs, clinical success, and technical success. The search was conducted again couple of days prior to the submission of this manuscript for the emerging data. Random effects models were estimated using Comprehensive Meta-Analysis (Biostat Inc.) software. ⁵ A *P* value of less than 0.05 was considered significant.

Research results

Compare trans-gastric *vs* trans-enteric EUS-GBD based on available literature. Compare AE profile, technical success and clinical success of both approaches. As a secondary outcome compare cautery enhanced LAMS use *vs* non-cautery enhanced (cold) LAMS.

Research conclusions

Identify if any transgastric or transenteric EUS-GBD is better based on existing literature.

Research perspectives

EUS-GB being increasingly used either as bridge to cholecystectomy or as destination therapy. GB can be accessed by transgastric or transenteric route. However, it is unclear if one approach is better than the other.

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Figure Legends

Figure 1 PRISMA flow diagram. PRISMA flow diagram elucidating screening and selection studies for comparison of transduodenal/transjejunal *vs* transgastric approaches.

Figure 2 PRISMA flow diagram elucidating the screening and selection of studies for comparison of cautery-enhanced *vs* non-cautery enhanced approaches.

Figure 3 Forrest plot. Forrest plot illustrating the comparison of rate of AEs (A), clinical success (B), and technical success (C) between transduodenal/transjejunal *vs* transgastric approaches including studies with patients in both arms only (method 1).

Figure 4 Forrest plot. Forrest plot illustrating the comparison of parameters between cautery enhanced (hot) *vs* non-cautery enhanced (cold) approaches including with studies with patients in both arms only (method 1).

Table 1 Comparison of rate of adverse events, clinical success and technical success between the approaches according to puncture site (transduodenal/transjejunal *vs* transgastric)

	¹ <i>n</i> of studies	Pooled odds ratio (TG <i>vs</i> TD/TJ) or AE (%)	95%CI	<i>P</i> value
Method 1: Including studies with patients in both arms only				
Adverse events	6	1.58	0.46-5.45	0.47
Clinical success	3	0.30	0.06-1.48	0.14
Technical success	3	0.30	0.05-1.89	0.20
Method 2: Including all studies				
Adverse events	¹ 9 <i>vs</i> 15	27.5% <i>vs</i> 15.2%	(17.1%-41.1%) (9.5%-23.6%)	<i>vs</i> 0.07
Clinical success	¹ 6 <i>vs</i> 13	83.3% <i>vs</i> 91.7%	(71.0%-91.0%) (82.4%-96.3%)	<i>vs</i> 0.16
Technical success	¹ 9 <i>vs</i> 15	91.3% <i>vs</i> 95.6%	(83.6%-95.6%) 90.7%-97.7%)	<i>vs</i> 0.22

TG *vs* TD/TJ: Transduodenal/transjejunal *vs* transgastric; AE: Adverse event; 95%CI: 95% confidence interval.

Table 2 Comparison of the parameters between cautery-enhanced and non-cautery enhanced approaches for endoscopic ultrasound guided gallbladder drainage

	<i>n</i> of studies	Pooled odds ratio (cautery-enhanced <i>vs</i> non-cautery enhanced) or AEs (%)	95%CI	<i>P</i> value
Method 1: Including studies with patients in both arms only				
Adverse events	2	0.55	0.19-1.64	0.28
Clinical success	2	1.81	0.50-6.61	0.37
Method 2: Including all studies				
Adverse events	9 <i>vs</i> 3	14.0% <i>vs</i> 37.8%	(9.1%-21.0%) <i>vs</i> (26.5%-50.6%)	0
Clinical success	11 <i>vs</i> 3	89.9% <i>vs</i> 93.4%	(86.1%-92.7%) <i>vs</i> (72.8%-90.3%)	0.12
Technical success	11 <i>vs</i> 3	94.4% <i>vs</i> 93.8%	26.5%-50.6%	0.82

AE: Adverse event; 95% CI: 95% confidence interval.

13%

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