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WJGE mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal endoscopy and covering a wide range of topics including capsule endoscopy, colonoscopy, double-balloon enteroscopy, duodenoscopy, endoscopic retrograde cholangiopancreatography, endosonography, esophagoscopy, gastrointestinal endoscopy, gastroscopy, laparoscopy, natural orifice endoscopic surgery, proctoscopy, and sigmoidoscopy.

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Retrospective Cohort Study

Improved diagnostic yield of endoscopic ultrasound-fine needle biopsy with histology specimen processing

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Abstract

BACKGROUND

Endoscopic ultrasound-guided fine needle biopsy (EUS-FNB) has emerged as a safe, efficacious alternative to fine needle aspiration (FNA) for tissue acquisition. EUS-FNB is reported to have higher diagnostic yield while preserving specimen tissue architecture. However, data on the optimal method of EUS-FNB specimen processing is limited.

AIM

To evaluate EUS-FNB with specimen processing as histology *vs* EUS-FNA cytology with regards to diagnostic yield and specimen adequacy.

METHODS

All EUS-FNA and EUS-FNB performed at our institution from July 1, 2016, to January 31, 2018, were retrospectively analyzed. We collected data on demographics, EUS findings, pathology, clinical outcomes, and procedural complications in two periods, July 2016 through March 2017, and April 2017 through January 2018, with predominant use of FNB in the second data collection time period. FNA specimens were processed as cytology with cell block technique and reviewed by a cytopathologist; FNB specimens were fixed in formalin, processed for histopathologic analysis and immunohistochemical staining, and reviewed by an anatomic pathologist. Final diagnosis was based on surgical pathology when available, repeat biopsy or imaging, and length of clinical follow up.

RESULTS

One hundred six EUS-FNA and EUS-FNB procedures were performed. FNA alone was performed in 17 patients; in 56 patients, FNB alone was done; and in 33 patients, both FNA and FNB were performed. For all indications, diagnostic yield

Sofiya Reicher is a consultant for Boston Scientific; all other authors have no conflicts of interest.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at sreicher@dhs.lacounty.gov. Consent was not obtained, but the presented data are anonymized and risk of identification is low.

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was 47.1% (8/17) in FNA alone cases, 85.7% (48/56) in FNB alone cases, and 84.8% (28/33) in cases where both FNA and FNB were performed ($P = 0.0039$). Specimens were adequate for pathologic evaluation in 52.9% (9/17) of FNA alone cases, in 89.3% (50/56) of FNB alone cases, and 84.8% (28/33) in cases where FNA with FNB were performed ($P = 0.0049$). Tissue could not be aspirated for cytology in 10.0% (5/50) of cases where FNA was done, while in 3.4% (3/89) of FNB cases, tissue could not be obtained for histology. In patients who underwent FNA with FNB, there was a statistically significant difference in both specimen adequacy ($P = 0.0455$) and diagnostic yield ($P = 0.0455$) between the FNA and FNB specimens (processed correspondingly as cytology or histology).

CONCLUSION

EUS-FNB has a higher diagnostic yield and specimen adequacy than EUS-FNA. In our experience, specimen processing as histology may have contributed to the overall increased diagnostic yield of EUS-FNB.

Key words: Fine needle biopsy; Endoscopic ultrasound; Fine needle aspiration; Pancreatic cancer; Histology; Cytopathology

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Core tip: Endoscopic ultrasound-guided fine needle biopsy (EUS-FNB) is rapidly gaining in popularity. However, the optimal method for EUS-FNB specimen processing is not well defined, with recent studies on fine needle biopsy (FNB) varying widely in the use of histology vs cytology for FNB sample evaluation. Our data suggest that processing FNB specimens in formalin for histology, followed by evaluation by an anatomic pathologist, could contribute to overall improved diagnostic yield of EUS-FNB. An additional benefit is the decreased need for on-site cytopathology.

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INTRODUCTION

Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is a well-established modality for tissue acquisition of a variety of lesions in the gastrointestinal tract and surrounding structures. It has low complication rates and high diagnostic yield^[1,2].

However, several factors can limit the sensitivity of EUS-FNA. EUS-FNA samples are typically processed as cytology, which does not allow for preservation of tissue architecture necessary for diagnosis of diseases such as gastrointestinal stromal tumor (GIST)^[3], lymphoma^[4], autoimmune pancreatitis^[5], and pancreatic lesions with non-hypovascular contrast-enhancement pattern on EUS^[6]. The diagnostic yield of EUS-FNA may be further compromised by the limited availability of on-site cytopathologists^[7-11].

EUS-guided fine needle biopsy (EUS-FNB) has emerged as an alternative to EUS-FNA for tissue acquisition, with a reported similar rate of complications^[12,13]. Initial studies have demonstrated its non-inferiority and possible superiority, depending on the indication^[14-19]. FNB needle tip design enables the procurement of an intact core tissue, and the preserved architecture allows for histological and immunohistochemical evaluation. Studies differ in their approach to FNB sample processing as histology vs cytology. There is limited data on which approach is preferable.

We evaluate the performance of EUS-FNB with specimen processing as histology vs EUS-FNA cytology with regards to diagnostic yield and specimen adequacy.

MATERIALS AND METHODS

Data was retrospectively collected on all patients who underwent EUS-FNA or EUS-FNB from July 1, 2016, to January 31, 2018, at our institution, a large tertiary safety-net hospital. Data was collected in two periods: July 2016 through March 2017, and April 2017 through January 2018.

Procedures were performed by three experienced endosonographers who each have performed over 1000 EUS procedures. FNA specimens were collected for cytology in Plasma-Lyte A injection solution pH 7.4 (Baxter Healthcare Corporation, Deerfield, IL, United States), processed as a cell block with the Collodion bag technique^[20,21], and subsequently evaluated by a cytopathologist. FNB specimens were collected, immediately fixed in formalin, and sent to pathology, where they were processed for histopathologic analysis and immunohistochemical staining in accordance with a previously reported standardized protocol^[22], and subsequently evaluated by an anatomic pathologist. Rapid on-site evaluation is not available at our institution.

Echoendoscopes used were GF-UE160-AL5, GF-UC140-AL5, GF-UC140P-AL5, and GF-UCT180 (Olympus America, Center Valley, PA, United States). EUS-FNA and FNB needles were from a variety of manufacturers: Expect FNA and Acquire FNB needles (Boston Scientific, Marlborough, MA, United States), SharkCore FNB needles (Medtronic, Sunnyvale, CA, United States), and EchoTip ProCore FNB needles (Cook Medical, Bloomington, IN, United States).

Data collected from hospital Electronic Health Records and EUS databases included patient demographics, clinical outcomes, and pathology. Procedure-related data included indications, technical aspects, and complications.

Standardized definitions of specimen adequacy and diagnostic yield were used^[23]. Specimen adequacy was defined as the percentage of lesions sampled in which the specimens were from the intended site and sufficient for diagnosis by a pathologist. Acellular or hypocellular samples were considered inadequate. Diagnostic yield was defined as the percentage of lesions sampled in which a tissue diagnosis was obtained. Final diagnosis was based on surgical pathology when available, repeat biopsy or imaging, and length of clinical follow up.

The study was approved by the Institutional Review Board (#31297-01).

Statistical analysis

Statistical analysis was performed using Fisher's exact test, Kruskal-Wallis test, and McNemar's test, with *P* value < 0.05 as statistically significant. The Bonferroni correction was applied to all sub-group analyses. All analyses were performed with R, version 3.6.0 (R Core Team, Vienna, Austria), and reviewed by a biostatistician, Youngju Pak, Ph.D., from the UCLA Clinical and Translational Science Institute at Harbor-UCLA Medical Center.

RESULTS

Demographics

From July 2016 through January 2018, EUS-FNA or EUS-FNB was performed in 106 procedures in 97 patients. The mean patient age was 55.5 years (23-84), and 41.5% were males (Table 1).

The most common indications were pancreatic mass 31.1% (33/106), gastric mass 17.9% (19/106), liver biopsy 14.2% (15/106), and pancreatic cyst 13.2% (14/106). Other conditions evaluated included lymph nodes, biliary abnormalities, extraluminal lesions, pancreatitis, rectal masses, small bowel lesions, mediastinal lesions, and esophageal lesions (Table 2).

FNA alone was performed in 17 cases (16.0%); in 56 cases (52.8%), FNB alone was done; and in 33 cases (31.2%), FNA with FNB was performed. There was an overall mean of 3.3 (1-8) passes per needle; the mean was 3.4 (1-5) passes per needle in FNA alone cases, 3.4 (1-8) in FNB alone cases, and 2.8 (1-8) in cases where both FNA and FNB were performed (Table 1). The most commonly used needle size was 22-Gauge; a 22-Gauge FNA needle was used in 60.0% (30/50) of FNA needle cases, and a 22-Gauge FNB needle was used in 82.0% (73/89) of FNB cases.

Diagnostic yield

For all indications, diagnostic yield was 47.1% (8/17) in FNA alone cases, and 85.7% (48/56) in FNB alone cases (Table 3).

Table 1 Baseline patient and procedural characteristics

	FNA alone (<i>n</i> = 17)	FNB alone (<i>n</i> = 56)	FNA with FNB (<i>n</i> = 33)	<i>P</i> value
Age, mean (range)	55.2 (30-75)	55.0 (23-84)	56.6 (37-76)	0.7502
Male, <i>n</i> (%)	5 (29.4)	24 (42.9)	15 (25.5)	0.5533
Needle type				
FNA needle (Expect)	16	0	31	-
Franseen needle (Acquire)	0	50	32	-
Fork-tip needle (SharkCore)	0	3	0	-
Reverse bevel needle (ProCore)	0	1	1	-
Other ¹	0	1	3	-
Not documented	1	3	2	-
Needle passes, mean (range)	3.4 (1-5)	3.4 (1-8)	2.8 (1-8)	-

Multiple needle types were used in the same procedure.

¹Other needles include EZ shot FNA needle (Olympus) and Moray Micro Forceps (US endoscopy) through a 19-Gauge FNA needle. EUS: Endoscopic ultrasound; FNA: Fine needle aspiration; FNB: Fine needle biopsy.

Table 2 Indications for endoscopic ultrasound-guided fine needle aspiration and endoscopic ultrasound-guided fine needle biopsy

Indication (<i>n</i> = 106)	<i>n</i> (%)
Pancreatic mass	33 (31.1)
Gastric mass	19 (17.9)
Liver biopsy	15 (14.2)
Pancreatic cyst	14 (13.2)
Lymph node	6 (5.7)
Biliary	5 (4.7)
Extraluminal	4 (3.8)
Pancreatitis	4 (3.8)
Rectal	2 (1.9)
Small bowel	2 (1.9)
Mediastinal	1 (0.9)
Esophageal	1 (0.9)

Table 3 Diagnostic yield and specimen adequacy, *n* (%)

	Diagnostic yield	Specimen adequacy
FNA alone (<i>n</i> = 17)	8 (47.1)	9 (52.9)
FNB alone (<i>n</i> = 56)	48 (85.7)	50 (89.3)
FNA with FNB (<i>n</i> = 33)	28 (84.8)	28 (84.8)

FNA: Fine needle aspiration; FNB: Fine needle biopsy.

There was a significant difference in diagnostic yield between the three groups (Fisher's exact test, $P = 0.0039$). In sub-group analysis, there was a significant difference between the FNA alone and FNB alone groups, (Fisher's exact test, Bonferroni adjusted, $P = 0.0067$) and between the FNA alone and FNA with FNB groups (Fisher's exact test, Bonferroni adjusted, $P = 0.0238$), but not between the FNB alone and FNA with FNB groups (Fisher's exact test, Bonferroni adjusted, $P = 1$).

In cases where both FNA and FNB were performed in the same procedure, the overall diagnostic yield was 84.8% (28/33); 60.6% (20/33) in samples from FNA needles and 81.8% (27/33) in samples from FNB needles. There was a statistically significant difference in diagnostic yield (McNemar's test, $P = 0.0455$) between the FNA and FNB specimen subgroups.

Specimen adequacy

Specimens were adequate in 52.9% (9/17) of FNA alone cases and adequate in 89.3% (50/56) of FNB alone cases (Table 3).

There was a significant difference in sample adequacy between the three groups (Fisher's exact test, $P = 0.0049$). In sub-group analysis, there was a significant difference between the FNA alone and FNB alone groups, (Fisher's exact test, Bonferroni adjusted, $P = 0.0072$), but not between the FNA alone and FNA with FNB groups (Fisher's exact test, Bonferroni adjusted, $P = 0.063$), or between the FNB alone and FNA with FNB groups (Fisher's exact test, Bonferroni adjusted, $P = 1$).

In cases where both FNA and FNB were performed, overall specimen adequacy was 84.8% (28/33); samples from FNA needles were adequate in 60.6% (20/33), while samples from FNB needles were adequate in 81.8% (27/33). There was a statistically significant difference in specimen adequacy (McNemar's test, $P = 0.0455$) between the FNA and FNB specimen subgroups.

In 10.0% (5/50) of FNA cases, tissue could not be aspirated for cytology, while in 3.4% (3/89) of FNB cases, core tissue could not be obtained for histology. In 2 cases of pancreatic cystic lesions, when samples from FNB needles were grossly inadequate for histology, material was sent for cytology instead.

EUS-FNA/FNB of pancreatic masses

EUS-FNA or EUS-FNB performed for pancreatic masses produced adequate samples for pathologic analysis in 30/33 (90.9%). There was a trend towards improved sample adequacy from the first to second data collection time period with the predominant use of FNB (Fisher's exact test, $P = 0.0524$). 26 patients had pancreatic malignancy on final diagnosis. Sensitivity for pancreatic malignancy was 96.2% (25/26); one case of benign EUS-FNB was confirmed malignant operatively. There were no cases of false positive EUS-FNA or EUS-FNB. Yield for malignancy for all pancreatic masses sampled via FNA or FNB was 75.8% (25/33). Importantly, there was a significant increase in the diagnostic yield from 46.2% (6/13) in the first collection period to 95.0% (19/20) in the second data collection time period (Fisher's exact test, $P = 0.0026$). Mean follow up was 29.1 months (21.7-32.4).

Complications

Two patients (1.9%) had minor post-procedural bleeding after EUS-FNB; one was self-limiting, and one required the use of a hemoclip. There were no infectious complications due to FNA or FNB in our cohort; all patients (14/14) undergoing EUS-FNA of cystic lesions received prophylactic antibiotics.

DISCUSSION

The preferred approach to specimen preparation and processing of EUS-FNB samples is not well defined. In a recent trial evaluating the clinical performance of a fork-tip FNB needle (SharkCore, Medtronic, Sunnyvale, CA, United States), all FNB specimens were processed for histology^[12]. However, in a trial examining the clinical performance of a Franseen needle (Acquire, Boston Scientific, Marlborough, MA, United States), 42.5% of FNB specimens were only sent for cytology, even though 90.3% of specimens had an adequate tissue core^[13]. Diagnostic concordance in cytology specimen analysis varies significantly^[24,25]. Inter-study heterogeneity has prevented identification of independent factors that contribute to the higher diagnostic yield of EUS-FNB noted in many studies. Recent studies have suggested alternate methods to increase diagnostic yield. In particular, contrast-enhanced EUS could be of significant benefit in characterizing pancreatic lesions^[6], and touch-imprint cytology allows for processing of a single specimen for both cytology and histology^[26].

Our institution has transitioned from the predominate use of EUS-FNA to EUS-FNB, and thus, to processing tissue core for histology rather than cytology. In our experience, utilization of EUS-FNB led to significant improvements in both diagnostic yield and specimen adequacy, as suggested by statistically significant differences in both parameters between FNA and FNB subgroups in patients who underwent FNA

and FNB for the same lesion. Our results are comparable to recently published studies demonstrating specimen adequacies of 90.3% for a Franseen needle, 67% to 84.6% for a fork-tip needle, and 92.6% for a reverse bevel FNB needle (ProCore, Cook Medical, Bloomington, IN, United States)^[12,13,27,28].

Limitations of our study include its retrospective nature, being a single-center experience, the use of multiple FNB needle types, and the heterogeneity of lesion types sampled.

In conclusion, EUS-FNB with subsequent processing of tissue core for histology improves diagnostic yield and specimen adequacy compared to EUS-FNA cytology. Specimen processing as histology may have contributed to the overall increased diagnostic yield of EUS-FNB.

ARTICLE HIGHLIGHTS

Research background

Endoscopic ultrasound-guided fine needle biopsy (EUS-FNB) has emerged as a safe, efficacious alternative to EUS-guided fine needle aspiration (EUS-FNA) for tissue acquisition. EUS-FNB is reported to have higher diagnostic yield while preserving specimen tissue architecture.

Research motivation

Data on the optimal method of EUS-FNB specimen processing is limited.

Research objectives

We evaluate EUS-FNB with specimen processing as histology *vs* EUS-FNA cytology with regards to diagnostic yield and specimen adequacy.

Research methods

A retrospective observational study of all EUS-FNA and EUS-FNB procedures performed at our institution from July 1, 2016, to January 31, 2018, was performed. The primary outcomes were diagnostic yield and specimen adequacy.

Research results

106 EUS-FNA and EUS-FNB procedures were analyzed. For all indications, diagnostic yield was 47.1% (8/17) in FNA alone cases, 85.7% (48/56) in FNB alone cases, and 84.8% (28/33) in cases where both FNA and FNB were performed ($P = 0.0039$). Specimens were adequate for pathologic evaluation in 52.9% (9/17) of FNA alone cases, in 89.3% (50/56) of FNB alone cases, and 84.8% (28/33) in cases where FNA with FNB were performed ($P = 0.0049$). In patients who underwent FNA with FNB, there was a statistically significant difference in both specimen adequacy ($P = 0.0455$) and diagnostic yield ($P = 0.0455$) between the FNA and FNB specimens.

Research conclusions

The study suggests that EUS-FNB with processing of tissue core for histology improves diagnostic yield and specimen adequacy compared to EUS-FNA cytology. Specimen processing as histology may have contributed to the overall increased diagnostic yield of EUS-FNB.

Research perspectives

Prospective research is needed to clarify optimal specimen processing of EUS-FNB in clinical settings with varied resources.

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Retrospective Study

Which scope is appropriate for endoscopic retrograde cholangiopancreatography after Billroth II reconstruction: An esophagogastroduodenoscope or a colonoscope?

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Institutional review board

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Abstract

BACKGROUND

Recently, with the advent of more advanced devices and endoscopic techniques, endoscopic retrograde cholangiopancreatography (ERCP) in Billroth II (B-II) patients has been increasingly performed. However, the procedures are difficult, and the techniques and strategies have not been defined.

AIM

To reveal the appropriate scope for ERCP in B-II patients.

METHODS

Sixty ERCP procedures were performed on B-II patients between June 2005 and May 2018 at Fukushima Medical University Hospital, and in 44 cases, this was the first ERCP procedure performed by esophagogastroduodenoscopy (EGDS) or colonoscopy (CS) after B-II gastrectomy. These cases were divided into two groups: 17 cases of ERCP performed by EGDS (EGDS group) and 27 cases of ERCP performed by CS (CS group). The patient characteristics and ERCP procedures were compared between the EGDS and CS groups.

RESULTS

The procedural time was significantly shorter in the EGDS group than in the CS

Ethics Committee of Fukushima Medical University.

Informed consent statement:

Patients were not required to provide informed consent for the study because the analysis used anonymous clinical data obtained after each patient agreed to treatment by written consent. For full disclosure, see the details of the study published on the home page of Fukushima Medical University.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: No additional data are available.

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group [median (range): 60 (20-100) *vs* 90 (40-128) min, *P* value < 0.01]. CS was an independent factor of a longer ERCP procedural time according to the univariate and multivariate analyses (odds ratio: 3.97, 95%CI: 1.05-15.0, *P* value = 0.04).

CONCLUSION

Compared to CS, EGDS shortened the procedural time of ERCP in B-II patients.

Key words: Endoscopic retrograde cholangiopancreatography; Billroth II reconstruction; Esophagogastroduodenoscopy; Colonoscopy

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Core tip: This study aimed to reveal the appropriate scope for endoscopic retrograde cholangiopancreatography (ERCP) in Billroth II (B-II) patients. Sixty ERCP procedures were performed in B-II patients, and in 44 cases, this was the first ERCP procedure performed by esophagogastroduodenoscopy (EGDS) or colonoscopy (CS) after B-II gastrectomy. The procedural time was significantly shorter in the EGDS group than in the CS group. CS was an independent factor of a longer ERCP procedural time according to the univariate and multivariate analyses. Compared to CS, EGDS shortened the procedural time of ERCP in B-II patients.

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INTRODUCTION

In the past, percutaneous cholangiography or biliary drainage was mainly performed in patients who underwent gastrectomy or intestinal reconstructive surgery^[1]. Recently, with the advent of more advanced devices and endoscopic techniques, endoscopic cholangiography and biliary drainage have been increasingly performed in these patients. Although endoscopic retrograde cholangiopancreatography (ERCP) in Billroth II (B-II) patients has been previously reported^[2-19], the procedures are difficult, and the techniques and strategies have not been defined.

Initially, ERCP was performed in B-II patients using a side-viewing endoscope^[2,3]. However, it is difficult to insert the side-viewing endoscope into the afferent loop, and the risk of bowel perforation was reported to be greater for ERCP in B-II patients when a side-viewing endoscope was used than when a forward-viewing endoscope was used^[20]. Therefore, a forward-viewing endoscope has recently been used for this procedure and has been shown to be as effective as a side-viewing endoscope for ERCP in B-II patients^[20-22].

Among the reports describing the use of a forward-viewing endoscope, some have described the use of esophagogastroduodenoscopy (EGDS)^[9,12,15,17,19], and others have described the use of long endoscopes (e.g., a colonoscopy, single-balloon endoscope, or double-balloon endoscope)^[7,8,16,19]. Therefore, this study aimed to reveal which scope (an esophagogastroduodenoscopy or a colonoscopy) is appropriate for ERCP in B-II patients.

MATERIALS AND METHODS

Study design and ethics

This study was a retrospective study to investigate the appropriate scope for ERCP in B-II patients. This study was approved by the Institutional Review Board of Fukushima Medical University.

Patients

Sixty ERCP procedures were performed in B-II patients between June 2005 and May 2018 at Fukushima Medical University Hospital (Figure 1). Among these cases, 44 involved ERCP by EGDS or colonoscopy (CS) after B-II gastrectomy. Sixteen cases were excluded from this study because in these cases, this was not the first ERCP performed by EGDS or CS. Five cases involved ERCP by both EGDS and CS. The 44 patients were divided into two groups: 17 cases of ERCP by EGDS (EGDS group) and 27 cases of ERCP by CS (CS group). Patients were not required to provide informed consent for this study because this investigation used anonymous clinical data obtained after each patient had agreed to examination or treatment by written consent. For full disclosure, see the details of this study published on the home page of Fukushima Medical University.

Endoscopic retrograde cholangiopancreatography procedure

Before ERCP was started, patients were intravenously administered 300 mg of gabexate mesylate. After the patients were sedated with midazolam under blood pressure and oxygen saturation monitoring, an endoscope with a cap attached to the tip was inserted. The endoscope used was randomly chosen by each endoscopist. After the entrance of both the afferent loop and the efferent loop was observed, the endoscope was advanced to the afferent loop, reaching the papilla of Vater. Insertion into the afferent loop was performed with confirmation of the running direction by X-ray images. In the EGDS group, cannulation was initiated after the papilla was turned to the 9 to 11 o'clock position (Figure 2A). In the CS group, cannulation was initiated after the papilla was turned to the 6 o'clock position (Figure 3A and B). In patients with biliary or pancreatic ductal strictures, a biliary stent was inserted after endoscopic sphincterotomy (EST).

In patients with biliary ductal stones, EST and endoscopic papillary balloon dilation (EPBD) or endoscopic papillary large balloon dilation (EPLBD) were performed, as appropriate (Figures 2 and 3). EPBD was performed if the transverse diameter of the largest stone was > 8 mm and bile duct stones were difficult to remove by EST alone or if a peripapillary diverticulum was present. EPLBD was performed if the transverse diameter of the largest stone was > 12 mm, if many bile duct stones were difficult to remove by EST alone or if sufficient EST was difficult because of a peripapillary diverticulum. Stones that were too large to be ejected after EPBD or EPLBD were destroyed by catheter fragmentation. If complete stone clearance was difficult, then a biliary stent was inserted.

A GIF-Q240X, GIF-Q260, or GIF-Q260J (Olympus, Tokyo, Japan) scope was used in the EGDS group. A PCF-Q260AI, PCF-Q260AL, PCF-PQ260L, or SIF-Q260 (Olympus) scope was used in the CS group. PCF-PQ260L and SIF-Q260 scopes were used in one patient each. A D-201-11304 (Olympus) was used as the cap attached to the tip of the GIF-Q240 scope. A D-201-10704 (Olympus) was used as the cap attached to the tip of the GIF-Q260 scope. A D-201-12704 (Olympus) was used as the cap attached to the tip of the PCF-Q260AI and PCF-Q260AL scopes. A D-201-10704 (Olympus) was used as the cap attached to the tip of the PCF-PQ260L and SIF-Q260 scopes. A Tandem XL (Boston Scientific Japan, Tokyo, Japan), MTW ERCP tapered catheter (MTW Endoskopie, Wesel, Germany) or a Swing Tip PR-233Q (Olympus) was used as the ERCP catheter. EST was performed using an RX needle knife XL (Boston Scientific) or Billroth II sphincterotome (Cook Japan, Tokyo, Japan). A Hurricane RX biliary balloon dilatation catheter (Boston Scientific) was used for EPBD. A CRE biliary balloon dilatation catheter (Boston Scientific) or a Giga or Giga II balloon (Century Medical, Tokyo, Japan) was used for EPLBD. A Trapezoid RX basket catheter (Boston Scientific) or an FG-V425PR basket catheter (Olympus) was used to crush and remove stones. A Flexima biliary stent (Boston Scientific) or a Zimmon biliary stent (Cook Japan, Tokyo, Japan) was used as the biliary stent. All of these devices can be used with both the GIF-Q260J and PCF-Q260AI colonoscopes. The Swing Tip PR-233Q, Hurricane RX biliary balloon dilatation catheter, Giga balloon, Trapezoid RX basket catheter, and Flexima biliary stent cannot be used with both the GIF-Q240X and the GIF-Q260 scopes. The Swing Tip PR-233Q, Hurricane RX biliary balloon dilatation catheter, and Trapezoid RX basket catheter cannot be used with the PCF-Q260AL scope. In the two patients in whom the PCF-PQ260AL or SIF-Q260 scope was used, the papilla of Vater could not be observed, and ERCP devices were not used with the scope.

Examination items

The characteristics of the patients (age, sex, period after B-II reconstruction, diseases treated with B-II reconstruction, untreated papilla of Vater, antithrombotic drug use,

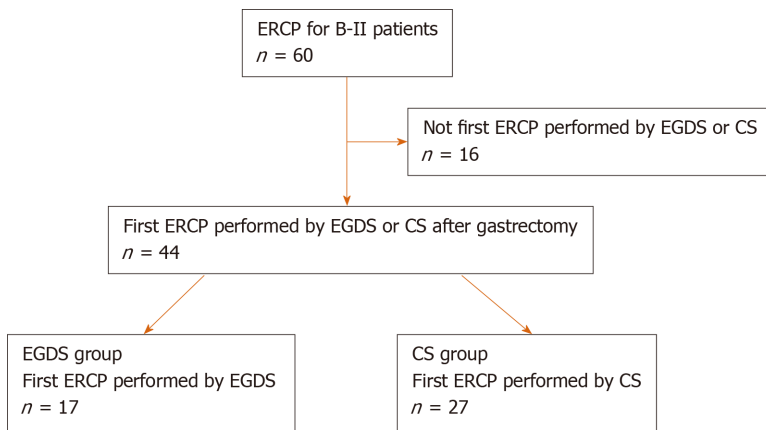


Figure 1 Target of this study. In all, 60 cases of endoscopic retrograde cholangiopancreatography (ERCP) after Billroth II were performed. Among them, 44 cases were first procedures performed by esophagogastroduodenoscopy (EGDS) or colonoscopy (CS) after gastrectomy. Seventeen patients who underwent the first ERCP procedure by EGDS were included in the EGDS group. Twenty-seven patients who underwent the first ERCP procedure by CS were included in the CS group. ERCP: Endoscopic retrograde cholangiopancreatography; EGDS: Esophagogastroduodenoscopy; CS: Colonoscopy; B II: Billroth II.

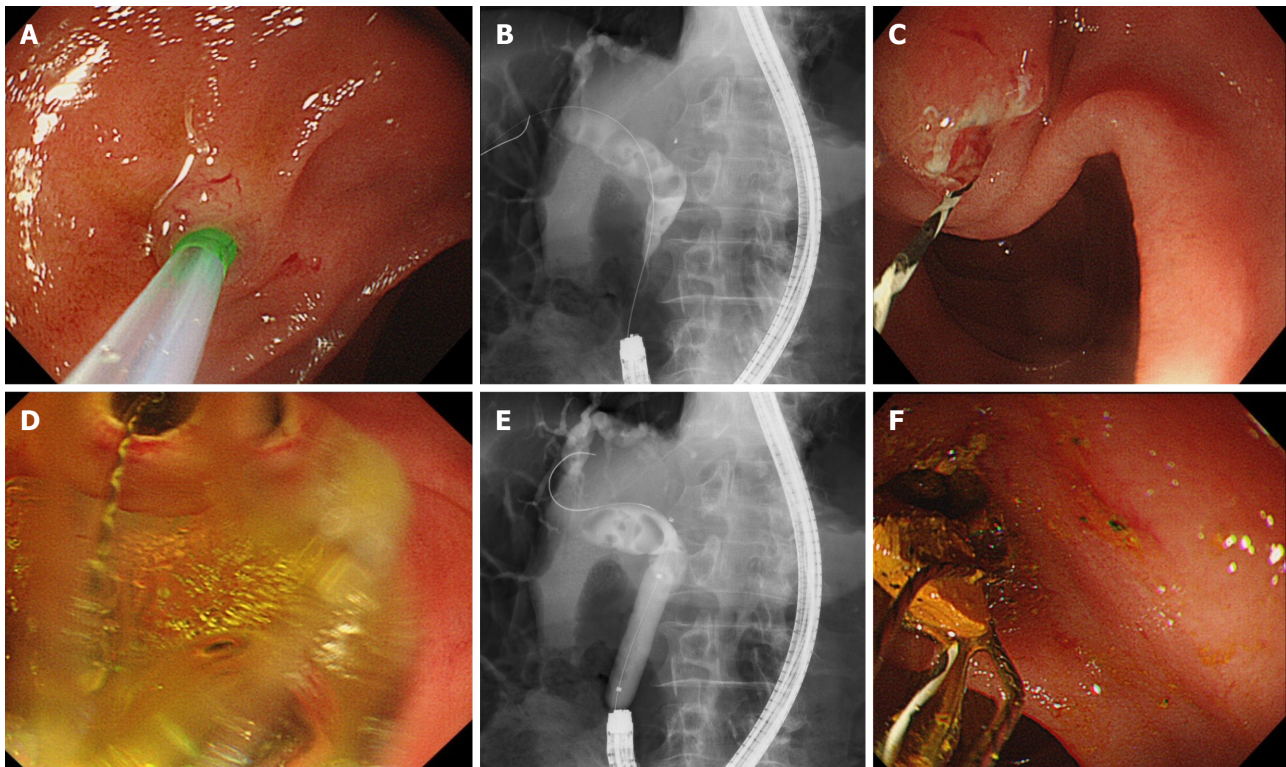


Figure 2 A case from the esophagogastroduodenoscopy group. A: After the papilla was positioned at 11 o'clock, biliary cannulation was performed; B: Common bile duct stones were confirmed by cholangiography; C, D and E: Endoscopic sphincterotomy and endoscopic papillary large balloon dilation were performed; F: Common bile duct stones were removed.

periampullary diverticulum, diseases, transverse diameter of the largest stone, and number of stones) and ERCP procedure details [EST, EPBD or EPLBD, procedural time, papilla of Vater access, stone clearance, stone destruction, procedural success, and post-ERCP pancreatitis (PEP)] were compared between the EGDS and CS groups. Additionally, the relationship between the duodenal and catheter directions (cross or parallel) and the observation of papilla of Vater in the front were compared as factors of scope usability between the EGDS and CS groups (Figure 4). The duodenal and catheter directions were determined from the X-ray images of the biliary cannulation. An untreated papilla of Vater was defined as one that had not undergone incision or dilation. If all biliary stones were removed, the intended procedures (for example, biliary duct or pancreatic duct investigation or stenting) were performed using the first endoscope, and this was defined as stone clearance or procedural success. The

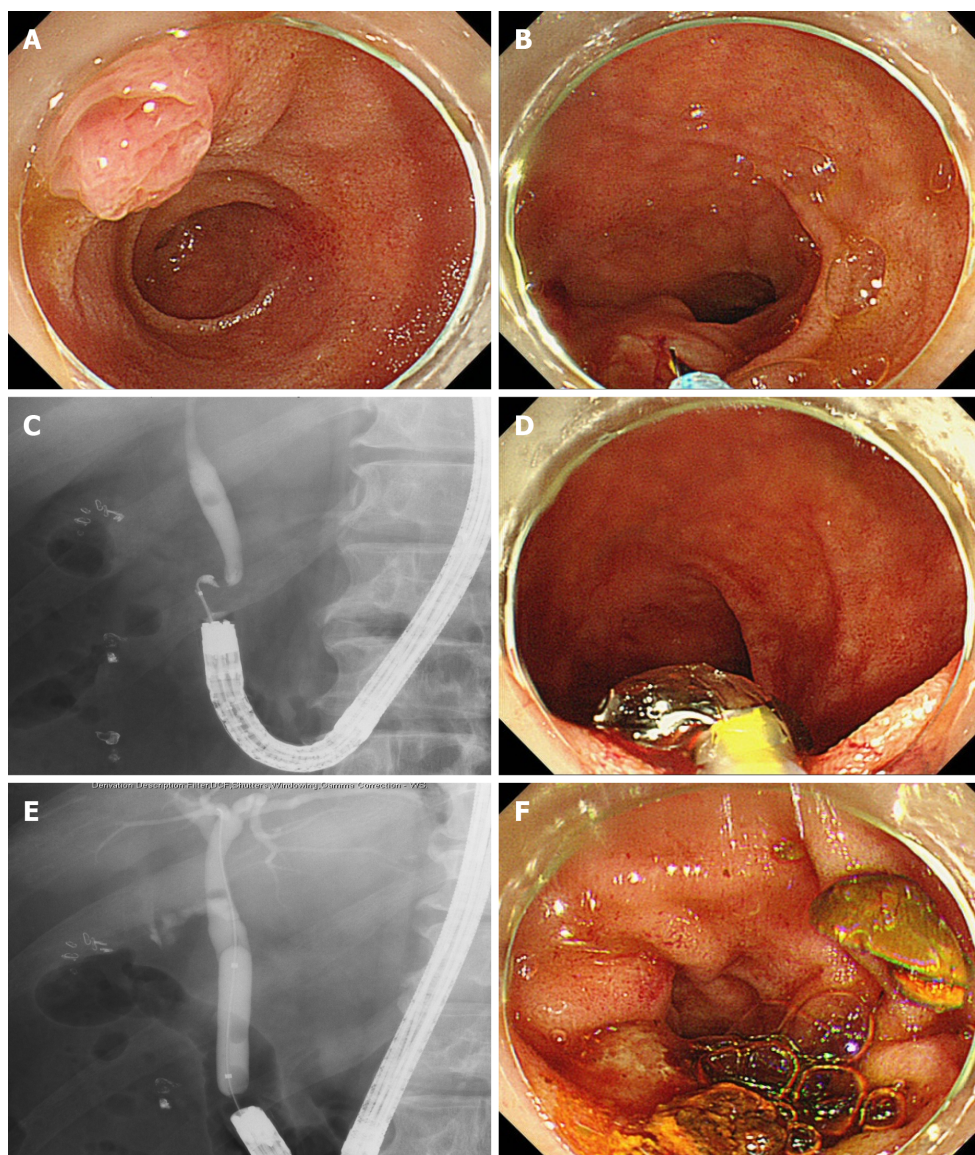


Figure 3 A case from the colonoscopy group. A: The papilla of Vater was difficult to observe in the front; B: The papilla was positioned at 6 o'clock; C: A common bile duct stone was confirmed by cholangiography; D and E: Endoscopic papillary large balloon dilation was performed after endoscopic sphincterotomy; and F: Common bile duct stones were removed.

diagnosis of PEP was performed according to Cotton's criteria^[23]. If patients were observed to have an elevated serum amylase level more than three times the normal upper limit with abdominal pain at more than 24 h after ERCP, they were diagnosed with PEP. Furthermore, peripancreatic inflammation was confirmed in all PEP cases by contrast-enhanced CT.

Statistical analysis

Age, period after B-II reconstruction, and transverse diameter of the largest stone were compared by Student's *t* test. The procedural time and number of stones were compared using the Mann-Whitney *U* test. Nominal variables were compared by Fisher's exact test. Factors influencing the ERCP procedural time were investigated by logistic regression analysis. A *P* value < 0.05 was defined as statistically significant. All statistical analyses were performed using the EZR platform (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). EZR is a modified version of the R commander, which was designed to perform functions that are frequently used in biostatistics^[24].

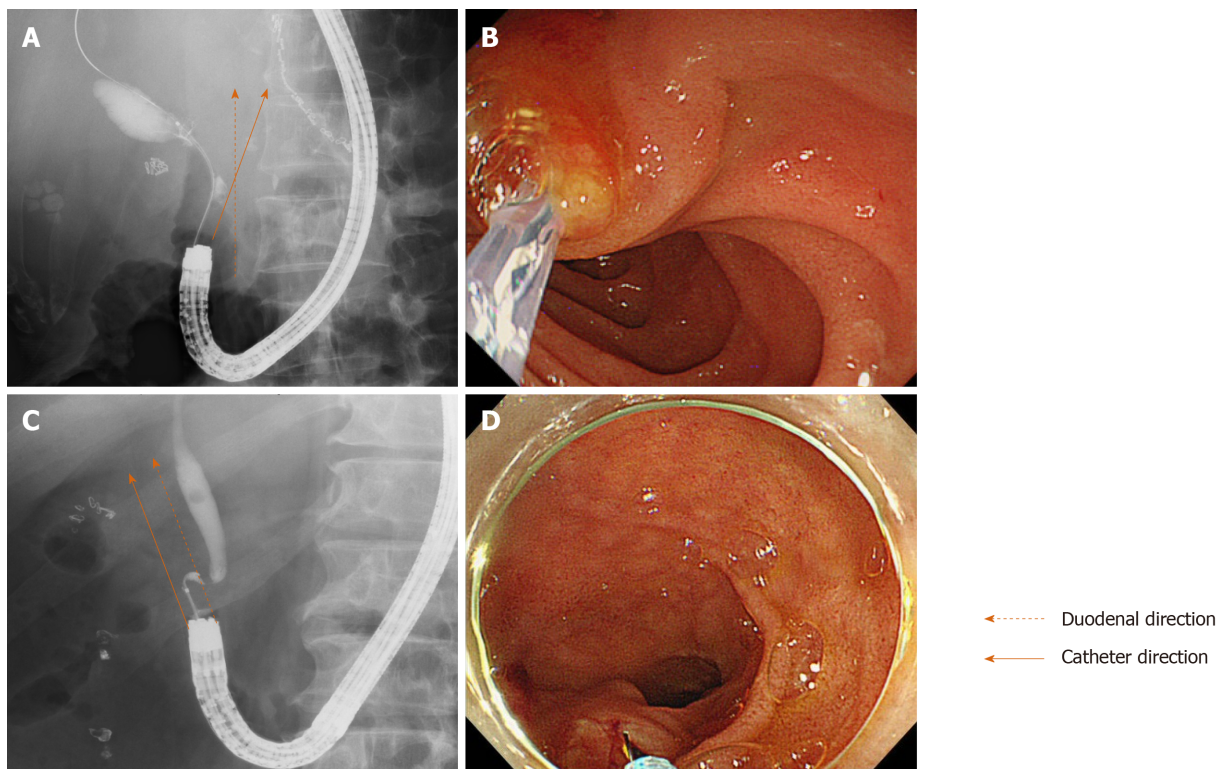


Figure 4 The duodenal and catheter directions in esophagogastroduodenoscopy and colonoscopy groups. A and B: The duodenal direction and catheter direction crossed when endoscopic retrograde cholangiopancreatography was performed by esophagogastroduodenoscopy; C and D: The duodenal direction and catheter direction ran parallel in endoscopic retrograde cholangiopancreatography when colonoscopy was performed.

RESULTS

The patient characteristics were not significantly different between the two groups (Table 1). The ERCP procedural time was significantly shorter in the EGDS group than in the CS group [median (range): 60 (20-100) *vs* 90 (40-128) min, *P* value < 0.01] (Table 2).

The procedural success rate was not significantly different between the EGDS group and the CS group (82.4% *vs* 63.0%, *P* value = 0.20). Procedural success was difficult to achieve in three patients in the EGDS group. Among them, one patient underwent surgery; in another patient, procedural success by ERCP was not achieved using an SIF-H290-S (Olympus) single-balloon scope, and the patient finally underwent conservative treatment; in the last patient, procedural success was not achieved by ERCP using an SIF-H290-S scope but was finally achieved by ERCP using a PCF-Q260AL scope. Procedural success was not achieved in ten patients in the CS group. Among them, procedural success was achieved in four patients by ERCP using a Q260J scope and in one patient by a second ERCP procedure using a PCF-Q260AI scope. Percutaneous transhepatic biliary drainage was performed in four patients (procedural success was achieved in two patients by ERCP with the rendezvous technique). One patient subsequently underwent conservative treatment.

CS was an independent factor of a longer ERCP procedural time, as determined by univariate and multivariate analyses (Table 3).

Regarding the factors influencing scope usability, crossing of the duodenal and catheter directions was observed more often in the EGDS group than in the CS group (cross/parallel: 11/3 *vs* 8/15, *P* value = 0.02) (Table 4). Observation of the papilla of Vater in the front was achieved more often in the EGDS group than in the CS group.

DISCUSSION

In this study, EGDS was compared with CS for performing ERCP in B-II patients. The results showed that compared to CS, EGDS shortened the ERCP procedural time.

An increasing number of ERCP procedures after gastrectomy have been performed in patients who have undergone B-II reconstruction, and several scopes have been

Table 1 Comparison of patient characteristics between the esophagogastroduodenoscopy and colonoscopy groups

	EGDS group (n = 17)	CS group (n = 27)	P value
Age (yr, mean \pm SD)	75.2 \pm 13.0	75.7 \pm 13.0	0.88
Sex, male/female	15/2	22/5	0.69
Period after B-II reconstruction (yr, mean \pm SD)	36.8 \pm 13.8	36.8 \pm 13.8	1.0
Diseases treated with B-II reconstruction			
Gastric ulcer, n	10	11	
Duodenal ulcer, n	3	9	
Gastric cancer, n	2	4	
Pyloric stenosis, n	1	1	
Gastric ptosis, n	1	1	
Unknown, n		1	
Untreated papilla of Vater, n (%)	15 (88.2)	27 (100)	0.14
Antithrombotic drugs, n (%)	2 (11.8)	5 (18.5)	0.69
Periampullary diverticulum, n (%)	1 (5.9)	3 (11.1)	1.0
Disease, n			
Bile duct stone	11	20	0.52
Others	6	7	
Biliary ductal cancer	3	2	
Pancreatic cancer	1	3	
Chronic pancreatitis	1	1	
Benign biliary stricture	1	1	
Transverse diameter of the largest stone (mm, mean \pm SD)	10.2 \pm 4.8	12.2 \pm 3.8	0.24
Number of stones [n, median (range)]	4 (1 - 30)	2 (1 - 6)	0.18

EGDS: Esophagogastroduodenoscopy; CS: Colonoscopy; B-II: Billroth II.

used. As mentioned in the introduction, the side-viewing endoscope was initially used for ERCP in B-II patients^[2,3]. However, recently, forward-viewing endoscopes have been used. Byun *et al*^[9], Park *et al*^[12], Ki *et al*^[17], and Jang *et al*^[15] used an esophagogastroduodenoscope. However, Abdelhafez *et al*^[19] used a colonoscope, and Itoi *et al*^[7] and Kawamura *et al*^[16] used a single-balloon enteroscope. Lin *et al*^[8] used a double-balloon endoscope. Although it is unknown which scope is most efficient, the esophagogastroduodenoscope was reported to shorten the procedural time. In most reports, the procedural time was not described. However, a study reported that the average EGDS procedural time was 36.3 min^[15], which is a short time. EGDS was superior to procedures with a longer scope because the papilla of Vater can be observed in the front (Figures 2A, 3A, 3B, 4A, 4B, 4E, 5A, and 5B) because the esophagogastroduodenoscope can be curved up to 210 degrees, while a colonoscope can be curved up to 180 degrees. The duodenal direction and the catheter direction could easily be crossed in ERCP using EGDS (Figure 4 and Table 4). However, these two directions tended to run parallel in ERCP using CS. In fact, in three cases, it was difficult to cannulate the bile duct by CS, whereas bile duct cannulation was successful by EGDS (Figure 5).

Interestingly, although the procedural success rate was not significantly different between the two groups, the procedural time was shorter in the EGDS group. For patients who have undergone B-II reconstruction, the radiation exposure dose is decreased with EGDS. The exposure dose is also lower for the medical staff, who can thus perform more ERCP procedures. As such, EGDS is the first choice for ERCP in patients who have undergone B-II reconstruction.

There are several limitations to this study. First, this study was a retrospective and small study, and it was performed at a single institute. In the future, prospective and

Table 2 Comparison of endoscopic retrograde cholangiopancreatography procedural characteristics between the esophagogastroduodenoscopy and colonoscopy groups

	EGDS group (<i>n</i> = 17)	CS group (<i>n</i> = 27)	<i>P</i> value
EST, <i>n</i> (%)	7 (41.2)	19 (70.4)	0.07
EPBD or EPLBD, <i>n</i> (%)	6 (35.3)	13 (48.1)	0.54
Procedural time [min, median (range)]	60 (20-100)	90 (40-128)	< 0.01
Papilla of Vater access, <i>n</i> (%)	14 (82.4)	25 (92.6)	0.36
Stone clearance, <i>n</i> (%)	6/11 (54.5)	8/19 (42.1)	1.0
Stone destruction, <i>n</i> (%)	3/11 (27.3)	6/19 (31.6)	1.0
Procedural success, <i>n</i> (%)	14 (82.4)	17 (63.0)	0.20
Adverse events, <i>n</i> (%)	0 (0)	0 (0)	
PEP, <i>n</i> (%)	0 (0)	0 (0)	

EST: Endoscopic sphincterotomy; EPBD: Endoscopic papillary balloon dilation; EPLBD: Endoscopic papillary large balloon dilation; PEP: Post endoscopic retrograde cholangiopancreatography pancreatitis; CS: Colonoscopy.

Table 3 Factors influencing the endoscopic retrograde cholangiopancreatography procedural time

	Procedural time ≥ 70 min, <i>n</i> (yes/no)	Univariate analysis			Multivariate analysis		
		OR	95%CI	<i>P</i> value	OR	95%CI	<i>P</i> value
Age ≥ 76 yr	13/9	2.09	0.63–6.94	0.23			
Sex, male	17/20	0.34	0.06–1.98	0.23			
Period after B-II reconstruction ≥ 40	11/11	1.0	0.31–3.26	1.0			
Untreated papilla of Vater	21/21	1.0	0.06–17.1	1.0			
Antithrombotic drug use	3/4	0.71	0.14–3.63	0.68			
Periampullary diverticulum	1/3	0.30	0.03–3.15	0.32			
Bile duct stone	15/16	0.8	0.22–2.94	0.74			
Transverse diameter of largest stone ≥ 12.2 mm	7/8	0.77	0.18–3.21	0.72			
Number of stones ≥ 2	10/7	2.29	0.52–10.0	0.27			
CS group	17/10	4.08	1.11–5.0	0.035	3.97	1.05–15.0	0.04
EST	14/12	1.46	0.44–4.88	0.54			
EPBD or EPLBD	10/9	1.20	0.37–3.97	0.76			
Papilla of Vater access	20/19	1.58	0.24–10.5	0.64			
Stone clearance	8/8	1.0	0.24–4.2	1.0			
Stone destruction	6/3	2.67	0.52–13.7	0.24			
Procedural success	15/19	0.34	0.07–1.54	0.16	0.36	0.07–1.74	0.2

EST: Endoscopic sphincterotomy; EPBD: Endoscopic papillary balloon dilation; EPLBD: Endoscopic papillary large balloon dilation; CS: Colonoscopy; B-II: Billroth II.

multicenter studies are needed. Second, due to the retrospective nature of this study, ERCP procedures were not performed by specified endoscopists. However, ERCP was performed by pancreaticobiliary specialists who had experience performing at least 2000 ERCP procedures or by trainees under the guidance of these specialists. Therefore, the quality of the ERCP procedure was constant. Third, the exact cannulation time was not recorded. However, as described above, the scope was chosen randomly. Additionally, the patient characteristics, diameter or number of

Table 4 The upper bending angle of esophagogastroduodenoscopy was greater than that of colonoscopy

	EGDS group	CS group	P value
	GIF-Q240X	PCF-Q260AI/AL	
	GIF-Q260	PCF-PQ260L	
	GIF-Q260J	SIF-Q260	
Upper bending angle (degree)	210	180	
Duodenal direction and catheter direction (cross/parallel) ¹	11/3	8/15	0.02
Observation of papilla of Vater in the front, <i>n</i> (%) ²	11 (78.6)	1 (3.8)	< 0.01

The duodenal and catheter directions crossed more frequently in the esophagogastroduodenoscopy group than in the Colonoscopy group. The observation of the papilla of Vater papilla could easily be achieved by esophagogastroduodenoscopy.

¹The cases with unsuccessful biliary cannulation were excluded.

²The cases with unsuccessful papilla of Vater identification were excluded. EGDS: Esophagogastroduodenoscopy; CS: Colonoscopy.

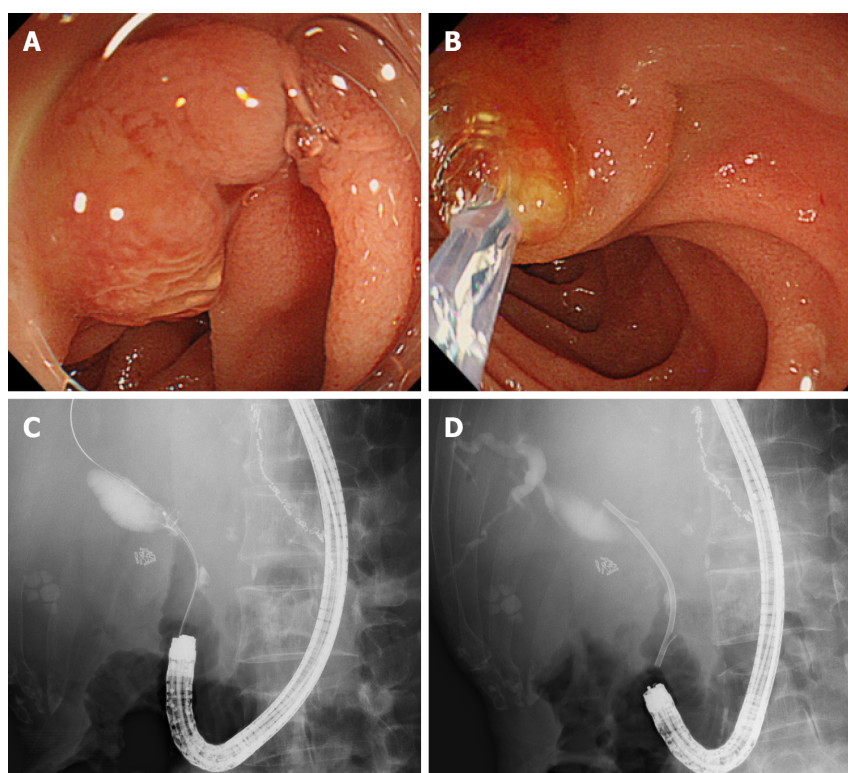


Figure 5 A case of treatment that was not successful by colonoscopy was successful by esophagogastroduodenoscopy. A: Cannulation to the papilla of Vater was not achieved because the papilla was difficult to observe in the front by colonoscopy; B: The papilla was observed in front by esophagogastroduodenoscopy, and cannulation was achieved; C: A common bile duct stricture caused by pancreatic cancer was observed by cholangiography; and D: A biliary stent was inserted.

stones, and factors related to ERCP were not significantly different between the two groups. Therefore, if EGDS is used for ERCP in B-II patients, the duration of the whole procedure, including insertion and cannulation, could be shortened.

Research conclusions

Compared to a longer scope, the esophagogastroduodenoscope shortened the procedural time of ERCP for patients who had undergone B-II reconstruction.

ARTICLE HIGHLIGHTS

Research background

Recently, with the advent of more advanced devices and endoscopic techniques, endoscopic retrograde cholangiopancreatography (ERCP) in Billroth II (B-II) patients has been increasingly performed. However, the procedures are difficult, and the techniques and strategies have not been defined.

Research motivation

The forward-viewing endoscope has been used for ERCP in B-II patients. By using the forward-viewing endoscope, ERCP in B-II patients was performed safely and as effectively as ERCP using a side-viewing endoscope. As forward-viewing endoscopes, esophagogastroduodenoscopy (EGDS) or colonoscopy (CS) is used for ERCP in B-II patients. However, which scope (EGDS or CS) should be used remains unknown.

Research objectives

To reveal the appropriate scope for ERCP in B-II patients.

Research methods

For the 44 included cases, this was the first ERCP procedure performed by EGDS or CS after B-II gastrectomy. These cases were divided into two groups: 17 cases of ERCP by EGDS (EGDS group) and 27 cases of ERCP by CS (CS group). The patient characteristics and ERCP procedures were compared between the EGDS and CS groups.

Research results

The procedural time was significantly shorter in the EGDS group than in the CS group. CS was an independent factor of a longer ERCP procedural time.

Research conclusions

Compared with CS, EGDS shortened the procedural time of ERCP for patients who had undergone B-II reconstruction.

Research perspectives

The results in this study could contribute to choosing an ERCP scope for patients who have undergone B-II reconstruction.

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Endoscopic ultrasound-guided fiducial marker placement in pancreatic cancer: A systematic review and meta-analysis

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Abstract

BACKGROUND

Pancreatic cancer (PC) mortality remains high despite advances in therapy. Combination chemoradiotherapy offers modest survival benefit over monotherapy with either. Fiducial markers serve as needed landmarks for image-guided radiotherapy (IGRT). Traditionally, these markers were placed surgically or percutaneously with limitations of each. Endoscopic ultrasound-guided placement overcomes these limitations.

AIM

To evaluate the safety, efficacy, and feasibility of endoscopic ultrasound (EUS)-guided fiducial placement for PC undergoing IGRT.

METHODS

Articles were searched in MEDLINE, PubMed, and Ovid journals. Pooling was conducted by fixed and random effects models. Heterogeneity was assessed using Cochran's Q test based upon inverse variance weights.

RESULTS

Initial search identified 1024 reference articles for EUS-guided fiducial placement in PC. Of these, 261 relevant articles were reviewed. Data was extracted from 11 studies ($n = 820$) meeting inclusion criteria. Pooled proportion of successful placement was 96.27% (95%CI: 95.35-97.81) with fiducial migration rates low at

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4.33% (95%CI: 2.45-6.71). Adverse event rates remained low, with overall pooled proportion of 4.85% (95%CI: 3.04-7.03).

CONCLUSION

EUS-guided placement of fiducial markers for IGRT of PC is safe, feasible, and efficacious. The ability to target deep structures under direct visualization while remaining minimally invasive are added benefits. Moreover, the ability to perform fine needle aspiration or celiac plexus neurolysis add value and increase patient-care efficiency. Whether EUS-guided fiducial placement improves outcomes in IGRT or offers any mortality benefits over traditional placement remains unknown and future studies are needed.

Key words: Endoscopic ultrasound; Pancreatic cancer; Fiducial marker; Image-guided radiotherapy; Systematic review; Meta-analysis

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Core tip: Historically, fiducial marker placement for pancreatic cancer has been performed surgically or percutaneously. The former is invasive and the latter is limited to superficial structures and lesions. Endoscopic ultrasound-guided fiducial placement for pancreatic cancer is a safe, efficacious, and feasible modality. It offers a minimally invasive approach that can target deep structures and lesions, and results in more efficient care delivery via the ability to perform additional procedures at the time of marker placement.

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INTRODUCTION

Pancreatic cancer (PC) is the fourth most common cause of cancer-related mortality among both genders in the United States, with pancreatic adenocarcinoma comprising the bulk. Of the nearly 57000 patients diagnosed annually, the majority will succumb to their disease^[1]. The poor prognosis of PC is attributed to its usually advanced stage at presentation, as well as local recurrence within 2 years in operable cases. Median survival among those undergoing surgical resection is 13 to 15 mo, and overall 5-year survival rates vary, but typically range from 3% to 25%^[2-6]. Depending upon the extent and location of disease, treatment options include surgical resection, chemotherapy, and radiation therapy. Chemotherapy and radiation therapy have been shown to improve both survival and quality of life in patients with advanced stages of disease, with combination therapy offering a modest improvement in survival over monotherapy^[7-11].

Image-guided radiotherapy (IGRT) allows for targeted application of radiation therapy using real-time imaging for precise delivery to affected tissue resulting in improved tumor control while sparing surrounding tissue^[12,13]. Stereotactic body radiotherapy is a form of IGRT in which multiple beams of radiation therapy can safely and effectively target a precise location, enabling high-dose radiation to a selective location while minimizing radiation where unnecessary^[14-16]. Given the soft tissue nature of the pancreas without reliable landmarks, the use of inert and implantable markers known as fiducials have served as landmarks allowing for tumor-tracking when placed in or near the tissue of interest. Placement of fiducials was previously limited to percutaneous placement by interventional radiology or operative placement by surgery^[17,18]. However, deep placement of fiducials percutaneously by interventional radiology may be limited by intervening structures, and operative placement by surgery is invasive, making endoscopic ultrasound-guided fiducial placement an ideal potential modality. EUS-guided fiducial placement permits targeting of deep structures and remains minimally invasive thereby reducing risk of complications. Additionally, Doppler imaging during EUS reduces the risk of

vascular penetration, and placement can be performed in close proximity under direct visualization. EUS-guided fiducial placement also offers the ability to perform other procedures during the same session. Patients presenting with imaging features suggestive of pancreatic malignancy can undergo fine needle aspiration (FNA) of the suspicious tissue for preliminary assessment or confirmation, followed by placement of fiducials thereby decreasing the interval between diagnosis and treatment^[19,20]. Furthermore, patients have tolerated same-session FNA, celiac plexus block to achieve pain control, as well as fiducial placement^[21].

Despite the relative safety of EUS-guided fiducial placement, minor potential complications are noted. A few studies have indicated a low rate of minor bleeding, abdominal pain, acute pancreatitis, elevated liver chemistries, and cholangitis^[22-25].

We aim to evaluate the feasibility, safety, and efficacy of EUS-guided fiducial placement for IGRT for PC.

MATERIALS AND METHODS

Study selection criteria

We solely included studies involving EUS-guided fiducial placement for intended IGRT for PC. We excluded abstracts without full text, studies involving purely extra-pancreatic fiducial marker placement, studies in languages other than English, and studies involving liquid fiducial markers.

Data collection and extraction

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement^[26] was utilized as a guide to our study design. As this study was a systematic review and meta-analysis, ethical approval was unnecessary. Databases searched included MEDLINE (through PubMed, an electronic search engine for published articles and Ovid), Medline non-indexed citations, old Medline, PubMed, Ovid journals, OVID Healthstar, American College of Physicians journal club, Google Scholar, Database of abstracts of Reviews of effectiveness, Cumulative Index for Nursing & Allied Health Literature, International Pharmaceutical Abstracts, and Cochrane Central Register of Controlled Trials. Our search included articles with parameters from January 1, 2000 to December 31, 2019. Terms used for search were Endoscopic ultrasound, PC, fiducial marker, image-guided radiation, stereotactic body radiation therapy. If there was unascertainable data from reviewed publications, corresponding study authors were contacted. Three authors (Patel JP, Puli SP, Revanur R) independently extracted the data into an abstraction form. Any divergences were resolved by mutual agreement. Cohen's κ ^[27] was used to quantify the agreement between the reviewers for the data.

Quality of studies

Various criteria have been employed to assess the quality of a study with control and treatment arms (*e.g.*, randomization, concealment of allocation, selection bias in the arms of the study, and blinding of outcome)^[28,29]. There is no consensus on assessment of studies without a control arm. These criteria, therefore, do not apply to studies without a control arm^[29]. Consequently, studies for this meta-analysis and systematic review were selected based on completeness of data and inclusion criteria. Completeness was defined as availability of data for pooled proportions with 95% confidence intervals.

Statistical analysis

Meta-analysis for the assessment and outcomes of EUS-guided fiducial marker placement in PC for anticipated IGRT was performed by calculating pooled estimates. Pooling was performed utilizing the Mantel-Haenszel method (fixed effects model) and DerSimonian Laird method (random effects model). Confidence intervals (CIs) were computed using the *F* distribution method^[30]. Forrest plots were constructed to demonstrate the point estimates in each study, with respect to the summary pooled estimate. The width of the point estimates in the Forrest plots corresponded the assigned weight for that study. For any 0 values, 0.5 was added as described by Cox^[31]. Based upon inverse variance weights, the heterogeneity of likelihood and diagnostic odds ratios were assessed utilizing Cochran's *Q* test^[32]. The Egger^[33] and Begg-Mazumdar^[34] bias indicators were utilized to evaluate the effect of publication and selection bias of the summary estimates. Funnel plots were generated for

assessment of interobserver variability utilizing the standard error and diagnostic odds ratio^[35,36].

RESULTS

Our initial search resulted in 1024 reference articles for endoscopic ultrasound-guided fiducial marker placement in PC for image-guided radiation therapy. Two hundred sixty one of these articles were reviewed, of which, 11 studies met inclusion criteria (Table 1) and underwent data extraction ($n = 820$). Of the 11 studies, nine included demographic information, with 524 males and 283 females with a mean age of 65.66 (SD: 4.15) years. A mean of 2.97 (SD: 1.06) fiducials were placed. The mean fiducial length and diameter were 6.55 (SD: 3.22) mm and 8.43 (SD: 0.24) mm. Pancreatic head and neck lesions were most frequently encountered ($n = 157$), followed by body and tail lesions ($n = 76$), and lastly uncinate process lesions ($n = 14$). The mean tumor size undergoing fiducial replacement was 34.6 (SD: 5.53) mm. Included studies were published as full texts. Our search results and methodology are outlined in the flow diagram labeled Figure 1.

Successful placement

Successful fiducial marker placement under EUS-guidance gave a pooled proportion of 96.27% (95%CI: 95.35-97.81) as shown in Figure 2A. Begg-Mazumdar bias indicator gave a Kendall's tau = -0.42 ($P = 0.07$), and Egger bias gave a value of -1.05 [95%CI: -2.07-(-0.02), $P = 0.05$].

Complete fiducial migration

Pooled proportion of fiducial marker migration was 4.33% (95%CI: 2.45-6.71) as shown in Figure 2B. Begg-Mazumdar bias indicator gave a Kendall's tau = 0.43 ($P = 0.24$), and Egger bias gave a value of 1.01 (95%CI: -3.85-2.41, $P = 0.12$).

Adverse events

Pooled proportion of adverse events was 4.85% (95%CI: 3.04-7.03) as demonstrated in Figure 2C. Begg-Mazumdar bias indicator gave a Kendall's tau = 0.47 ($P = 0.07$), and Egger bias gave a value of 0.49 (95%CI: -0.42-1.39, $P = 0.25$).

Figure 3 demonstrates funnel plot showing no significant publication bias. All pooled estimates calculated by fixed and random effects models yielded similar results. The change adjusted agreement analysis for data collected separately between reviewers gave a kappa value of 1.0.

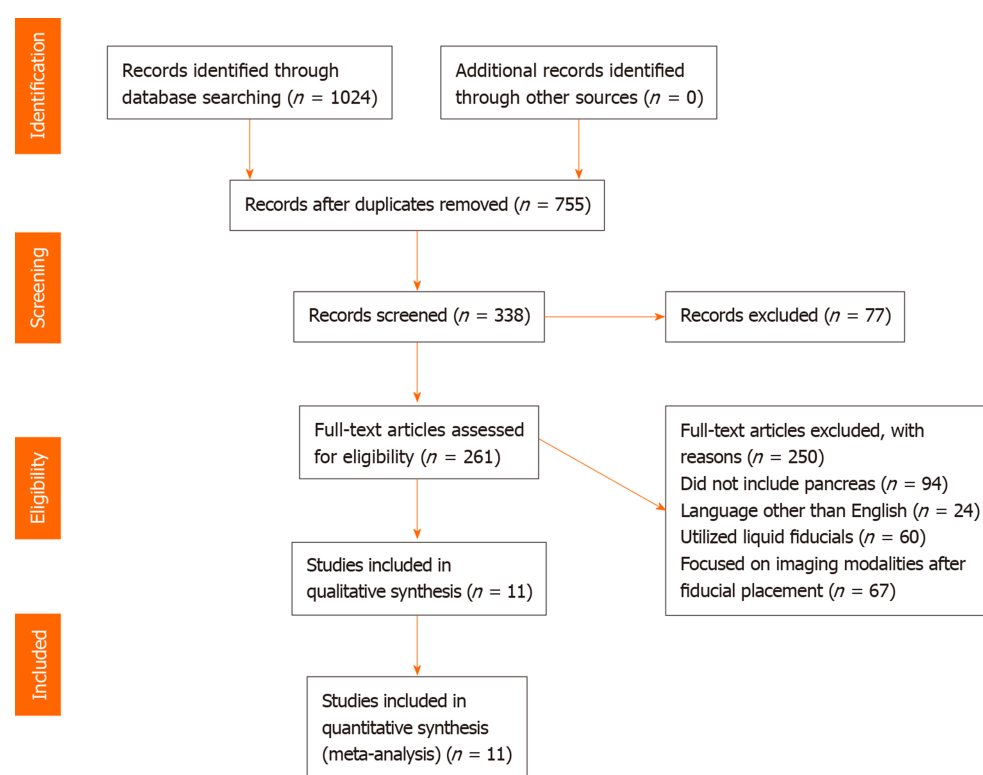
DISCUSSION

EUS-guided fiducial placement offers benefit over surgical or percutaneous placement due to ability to access deep structures and a variety of tissues, provide real-time high-resolution visualization near tissue of interest, and potentially decrease risk of peritoneal seeding^[37]. Although various factors can preclude successful placement, technical success rates are noted to range from 85% to 100%, with our meta-analysis revealing a pooled success rate of 96.2%. Novelty and lack of experience are two such factors that can impede successful placement. Park *et al*^[25] noted an initial learning curve as a barrier as all technical failures occurred in their first 12 cases, with no further failures in their subsequent 45 patients. Pishvaian *et al*^[22] and Sanders *et al*^[23] noted a limitation to be a history of pancreaticoduodenectomy resulting in inability to visualize tumor within the surgical bed. Additional challenges include transduodenal placement and fiducial delivery *via* 19-gauge needle in pancreatic head and uncinate process lesions but may be able to be overcome with a 22-gauge needle as it produces less rigidity and therefore results in ability to obtain more optimal positioning^[20,24,38].

Previously, fiducial placement was presumed to require specific placement and orientation with respect to the tissue of interest known as ideal fiducial geometry (IFG). Majumder *et al*^[39] evaluated success rate of endoscopically placed versus surgically placed fiducials with respect to attaining IFG as well as whether IFG was necessary to successfully undergo IGRT. They noted that surgical placement resulted in higher rates of attaining IFG, however, fiducial tracking success rates were higher in the EUS-guided group over the surgically placed group. This study further concluded that attaining IFG during fiducial placement was unnecessary for successful delivery

Table 1 Characteristics of included studies

Ref.	n	Mean age	No. male	No. female	Type of study
Pishvaian <i>et al</i> ^[22] , 2006	13	67.62	8	5	Prospective
Sanders <i>et al</i> ^[23] , 2010	51	73	29	22	Prospective
DiMaio <i>et al</i> ^[24] , 2010	30	63.2	19	11	Retrospective
Park <i>et al</i> ^[25] , 2010	57	67	29	28	Prospective
Varadarajulu <i>et al</i> ^[21] , 2010	9	57.67	4	5	Prospective
Khashab <i>et al</i> ^[19] , 2012	39	66.5	25	14	Retrospective
Fajardo <i>et al</i> ^[38] , 2013	23	63.13	13	10	Prospective
Majumder <i>et al</i> ^[39] , 2013	39	66.7	18	21	Retrospective
Choi <i>et al</i> ^[20] , 2014	32	66	21	11	Prospective
Dhadham <i>et al</i> ^[40] , 2016	188				Retrospective

**Figure 1** Flow diagram of our search results and methodology.

of radiation and tracking. Visibility of fiducials appears greater for traditional fiducials as compared to Visicoil fiducials^[19].

Fiducial migration can impede IGRT due to imprecise targeting or nonvisualization. Our meta-analysis shows a low rate of migration of 4.3%. Factors associated with migration include prior use of neoadjuvant chemotherapy resulting in tissue changes such as regression, as well post-procedural migration from post-procedure inflammation or movement within the tumor. Additionally, fiducial marker placement itself may introduce air bubbles into the target lesion at the time of insertion obscuring visualization and resulting in difficulty confirming successful placement. To overcome this, withdrawal of the stylet approximately seven to eight millimeters while backloading the fiducial and sealing in place with bone wax appears to prevent introduction of air bubbles^[20].

Adverse event rates were low with our meta-analysis demonstrating a rate of 4.8%. The most frequently encountered adverse event was mild procedural bleeding, and none required hospitalization or transfusion as a result. Mild pancreatitis was the next

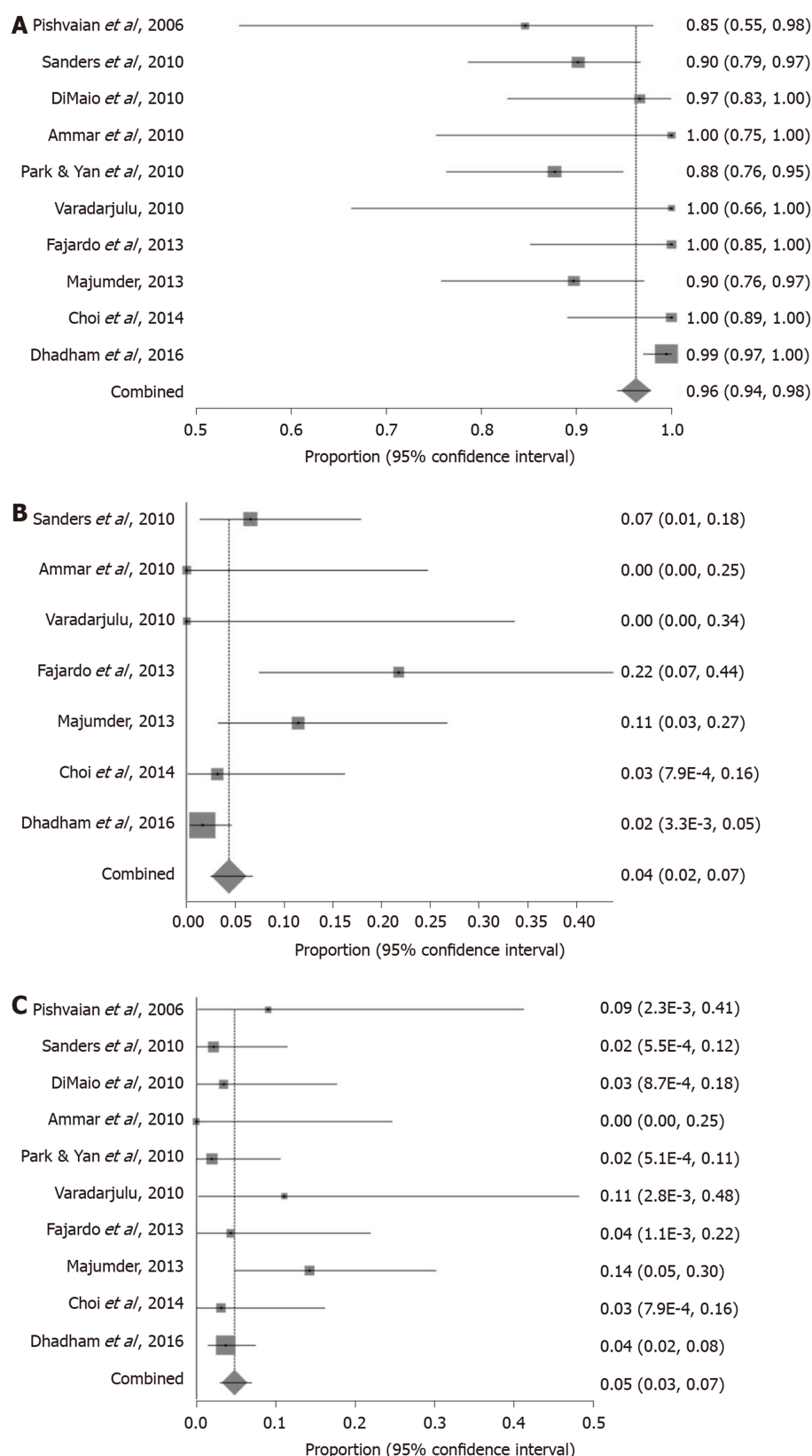


Figure 2 Proportion meta-analysis plot (fixed effects). A: Pooled proportion of endoscopic ultrasound-guided successful fiducial marker placement; B: Pooled proportion of fiducial migration; C: Pooled proportion of adverse events.

most commonly encountered adverse event, and all were treated with supportive care including fluid resuscitation, pain control, and pancreatic rest with subsequent discharge home within 48 h. As previously noted, an advantage of EUS-guided fiducial marker placement included the ability to perform multiple procedures under one session, though this theoretically may increase the likelihood of procedure related

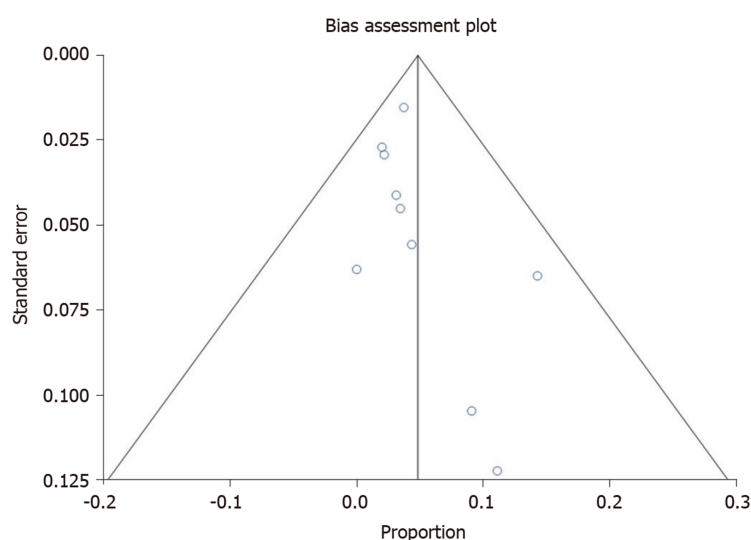


Figure 3 Bias assessment plot.

complications^[20].

All studies included in our meta-analysis were of prospective or retrospective case series'. Per our search, there were no identified randomized controlled trials on the subject. Consistency among studies was noted as they each consisted of initial fiducial marker placement and inherently had follow up for evaluation of adverse events when patients presented for follow up imaging for confirmation of successful placement. Telephone follow ups were also included. Additionally, nearly all studies provided characteristics of fiducial markers and needles used for placement, approach undertaken for placement, mean number of fiducial markers placed, tumor location, success and adverse event rates, as baseline patient characteristics. They demonstrated significant congruency with respect to their study designs, methods, and outcomes.

Our meta-analysis has a few limitations that are noteworthy. Different types of fiducials of variable diameters and lengths were used in the studies included which may impact visualization of fiducials for successful IGRT as well as affect migration rates. For the purposes of our study, we assumed no differences amongst the different fiducials exist. One study^[40] had a substantially larger sample size which can skew results. Additionally, retrospective studies were included in this meta-analysis which may result in selection bias. Furthermore, given the specific intent of our meta-analysis, there is some paucity with respect to subject volume as the total number of patients included in our study was 820. Lastly, there was variability amongst studies regarding inter-fiducial distance and tumor size which can affect successful placement, migration, and visibility.

Studies with statistically significant results are generally published and cited. Smaller studies may demonstrate larger treatment effects due to fewer differences than larger studies. This publication and selection bias may affect the summary estimates. This bias can be estimated by Egger bias indicators and Funnel plot construction. In this meta-analysis, both Egger bias and Begg-Mazumdar bias indicators were utilized and no statistically significant bias was shown. Additionally, no significant publication bias was demonstrated using Funnel plots.

In conclusion, survival rates for PC are abysmal and therapies that may help prolong survival are needed. IGRT offers a modest survival benefit over chemo or radiation therapy alone and is facilitated by fiducial markers allowing precise delivery of high dose radiation therapy. Our meta-analysis demonstrated that fiducial marker placement under EUS-guidance is safe, efficacious with lofty technical success rates, and associated with a low rate of adverse events. In addition, EUS-guided fiducial marker placement may offer higher rates of successful tumor tracking than surgically placed markers. The ability to obtain tissue for definitive diagnosis of PC and perform plexus block for pain control in the same session are added benefits not seen with other modes of fiducial marker delivery. Given the advantageous nature and favorable safety profile of EUS-guided fiducial marker placement, consideration should be given to this method of fiducial marker delivery for patients with PC who would benefit from radiotherapy as it may hasten diagnosis and improve quality of life. Further studies evaluating for improved outcomes in IGRT or for improved mortality rates are

needed.

ARTICLE HIGHLIGHTS

Research background

Fiducial marker placement for pancreatic cancer (PC) has demonstrated utility as a landmark to target radiotherapy with or without chemotherapy. Historically, these have been placed surgically or percutaneously, each with their own limitations. More recently, endoscopic ultrasound (EUS) guided placement has been undertaken.

Research motivation

PC remains a leading cause of cancer related mortality owing to its advanced stage at time of symptom development and subsequent inability to undergo surgery for definitive treatment. EUS has conferred diagnostic and therapeutic benefits with respect to tissue sampling and celiac plexus block. Given the inability to target deep structures with percutaneous fiducial marker placement and invasive nature of surgical fiducial marker placement, EUS has emerged as a potential marker placement modality that can overcome the aforementioned challenges.

Research objectives

We sought to evaluate the safety, efficacy, and feasibility of EUS-guided fiducial marker placement for PC patients anticipated to undergo radiotherapy *via* meta-analysis of available case series as no randomized clinical trials exist. The derived data has the potential to alter the clinical course of patients.

Research methods

Articles were searched in Medline, PubMed, and Ovid journals and ultimately, 11 studies met inclusion criteria and underwent data extraction ($n = 820$). Data extracted from included studies then underwent analysis by performing pooled estimates by Mantel-Haenszel (fixed effects model) and DerSimonian Laird method (random effects model). Confidence intervals (CIs) were computed using the F distribution method. Forrest plots were constructed to demonstrate the point estimates in each study, with respect to the summary pooled estimate. Heterogeneity was assessed using Cochran's Q test based upon inverse variance weights. The Egger and Begg-Mazumdar bias indicators were used to assess for publication and selection bias, and funnel plots were generated for assessment of interobserver variability.

Research results

Of the meta-analysis of 820 patients who underwent fiducial marker placement under EUS guidance, technical success of fiducial marker placement pooled proportion was 96.27% (95%CI: 95.35-97.81). EUS-guided placement was well tolerated with adverse event pooled proportion 4.85% (95%CI: 3.04-7.03). Given the need for the markers to serve as stationary landmarks to facilitate image-guided radiation therapy, post-procedural migration of fiducials is of significance. Pooled proportion of fiducial marker migration was 4.33% (95%CI: 2.45-6.71).

Research conclusions

Our meta-analysis demonstrated high technical success rates of EUS-guided fiducial placement, low rates of complete fiducial marker migration, and low adverse event rates demonstrating its utility as a fiducial marker placement modality. Further studies evaluating for improved outcomes in image-guided radiotherapy or improved modality are needed.

Research perspectives

EUS-guided fiducial placement is demonstrated to be a safe, efficacious, and feasible modality of marker placement. In addition, the ability to perform concomitant diagnostic procedures, such as fine needle biopsy, as well as therapeutic procedures, such as celiac plexus block, may hasten treatment and improve quality of life.

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Propofol vs midazolam sedation for elective endoscopy in patients with cirrhosis: A systematic review and meta-analysis of randomized controlled trials

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Abstract

BACKGROUND

Patients with cirrhosis frequently require sedation for elective endoscopic procedures. Several sedation protocols are available, but choosing an appropriate sedative in patients with cirrhosis is challenging.

AIM

To conduct a systematic review and meta-analysis to compare propofol and midazolam for sedation in patients with cirrhosis during elective endoscopic procedures in an attempt to understand the best approach.

METHODS

This systematic review and meta-analysis was conducted using the PRISMA guidelines. Electronic searches were performed using MEDLINE, EMBASE, Central Cochrane, LILACS databases. Only randomized control trials (RCTs) were included. The outcomes studied were procedure time, recovery time, discharge time, and adverse events (bradycardia, hypotension, and hypoxemia). The risk of bias assessment was performed using the Revised Cochrane Risk-of-Bias tool for randomized trials (RoB-2). Quality of evidence was evaluated by GRADEpro. The meta-analysis was performed using Review Manager.

PRISMA 2009 Checklist statement:

The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised in accordance with this checklist.

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**RESULTS**

The search yielded 3,576 records. Out of these, 8 RCTs with a total of 596 patients (302 in the propofol group and 294 in the midazolam group) were included for the final analysis. Procedure time was similar between midazolam and propofol groups (MD: 0.25, 95%CI: -0.64 to 1.13, $P = 0.59$). Recovery time (MD: -8.19, 95%CI: -10.59 to -5.79, $P < 0.00001$). and discharge time were significantly less in the propofol group (MD: -12.98, 95%CI: -18.46 to -7.50, $P < 0.00001$). Adverse events were similar in both groups (RD: 0.02, 95%CI: 0-0.04, $P = 0.58$). Moreover, no significant difference was found for bradycardia (RD: 0.03, 95%CI: -0.01 to 0.07, $P = 0.16$), hypotension (RD: 0.03, 95%CI: -0.01 to 0.07, $P = 0.17$), and hypoxemia (RD: 0.00, 95%CI: -0.04 to 0.04, $P = 0.93$). Five studies had low risk of bias, two demonstrated some concerns, and one presented high risk. The quality of the evidence was very low for procedure time, recovery time, and adverse events; while low for discharge time.

CONCLUSION

This systematic review and meta-analysis based on RCTs show that propofol has shorter recovery and patient discharge time as compared to midazolam with a similar rate of adverse events. These results suggest that propofol should be the preferred agent for sedation in patients with cirrhosis.

Key words: Sedation; Midazolam; Propofol; Cirrhosis; Endoscopic; Endoscopy; Meta-analysis

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Core tip: Patients with cirrhosis often require elective endoscopic procedures, but choosing an appropriate sedative is challenging. We performed a systematic review and meta-analysis of randomized controlled trials to compare propofol and midazolam for sedation in patients with cirrhosis during elective endoscopic procedures. We concluded propofol has shorter recovery and patient discharge time as compared to midazolam with a similar rate of adverse events, suggesting that propofol should be the preferred agent for sedation in patients with cirrhosis.

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INTRODUCTION

Cirrhosis is an advanced form of fibrosis that affects the liver with the destruction of the organ's lobular and vascular architecture^[1]. The progression of liver disease causes portal hypertension, which can lead to complications such as esophagogastric varices, portal hypertensive gastropathy, and gastric antral vascular ectasia (GAVE)^[2-11]. These patients often undergo diagnostic or therapeutic upper gastrointestinal endoscopy, and choosing an appropriate sedative is challenging. Sedation in this group of patients with underlying liver disease and their complications presents increased risks even when performed by well-trained personnel, mainly due to drug metabolism and interactions, baseline hemodynamics, and increased risk of adverse events. The recommended sedation level for elective endoscopies in patients with cirrhosis is mild to moderate that can be administered by anesthesiologists, endoscopists, or registered nurses^[12].

The most commonly used sedatives are usually benzodiazepine midazolam and short duration hypnotic agent propofol, while synthetic opioids can be added for their analgesic effect in some cases. Midazolam is the preferred benzodiazepine because of its short induction, recovery time, and amnesic properties^[13]. However, the half-life of midazolam can be prolonged in patients with cirrhosis, and midazolam can trigger

encephalopathy in these patients. Propofol does not need dose adjustment in patients with cirrhosis and has a faster onset of action, shorter effect, and faster recovery times^[13]. Many studies have compared propofol with midazolam for sedation in cirrhosis showing variable results. Therefore, we aimed to perform a systematic review and meta-analysis of randomized controlled trials (RCTs) to compare sedation with propofol and midazolam in patients with cirrhosis undergoing elective endoscopy.

MATERIALS AND METHODS

Protocol and registration

This systematic review was carried out in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA). The study was registered by The International Prospective Registry of Continuous Systematic Reviews of the National Institutes of Health Research (PROSPERO), under the code CRD42019137659 and was approved by the Scientific Ethics Committee of the Department of Gastroenterology of the Faculty of Medicine of the University of São Paulo.

Information sources and search

The search was carried out using MEDLINE (Pubmed); EMBASE; Cochrane Central Register of Randomized Controlled Clinical Trials/CENTRAL; and Latin-American and Caribbean Health Sciences Literature LILACS electronic databases from their date of inception to November 2019 with no language restriction. A gray literature search was also performed. The terms used for database search were "Sedation OR Sedations OR anesthesia OR Propofol OR Midazolam OR benzodiazepine" AND "Endoscopy OR endoscopic OR panendoscopy" AND "Cirrhosis OR liver OR hepatic."

Study selection, eligibility criteria, and data items

RCTs comparing propofol and midazolam for sedation during elective gastrointestinal endoscopy in patients with cirrhosis more than 18 years of age were included. Studies were excluded if they included patients without cirrhosis, patients with upper gastrointestinal bleeding, decompensated liver disease, neurological or psychiatric diseases; patients who used illicit drugs that could alter their central nervous system; patients that used drugs such as benzodiazepines, anti-depressants, antiepileptics, and patients with ASA class IV-V. Case series and studies that did not provide enough data for outcome analysis or full text were also excluded. The outcomes of our study were procedure time, recovery time, discharge time, and adverse events (bradycardia, hypotension, and hypoxemia).

Study selection and data collection process

All data were extracted from article texts, tables, and figures with any estimates made based on the presented data and figures. Two investigators independently reviewed each included article, and its eligibility was determined based on predetermined inclusion and exclusion criteria. Any discrepancy resolved by discussion and re-evaluation by senior authors. The following data were collected: Study model, the total number of included patients, gender, age, etiology of cirrhosis, Child-Turcotte-Pugh score, and adverse events related to the sedation.

Risk of bias in individual studies

The risk of bias in the studies was assessed using the Revised Cochrane Risk-of-Bias tool for randomized trials (RoB-2). We performed a complete analysis using RoB-2 for each of the outcomes in each selected study. In order to simplify the analysis, we assessed the overall risk of bias for each study using the same domains suggested in RoB-2.

Risk of bias across studies

We evaluated the randomized trials using the criteria from Bias Risk Assessment by the Cochrane Collaboration's tool - ROB2 - Risk of Bias^[14]. The tool analyzes the risk of bias by classifying it in five different domains: Randomization process, deviations in the intention of the intervention, loss of data on outcomes, methods of measuring outcomes, and selection of reported results. The risk of bias for each specific domain is categorized as "low risk," "some concerns," or "high risk" for each of the outcomes, according to the criteria described in detail in the Cochrane Handbook^[14].

Summary measures, synthesis of results and data analysis

GRADE (quality of evidence): The quality of evidence was assessed with the objective criteria of GRADE (Grading of Recommendations Assessment, Development, and Evaluation) for each of the pre-specified results and outcomes using the software GRADEpro - Guideline Development Tool (Mc Master University, 2015; Evidence Prime, Inc., Ontario, Canada). GRADE is a tool used to assess the quality of evidence-based on criteria that involve assessing the risk of bias, inconsistency, indirect evidence, imprecision, and publication bias. The evaluation of the risk of bias and the quality of the studies was carried out under the supervision of our statistical analysis team.

Statistical analysis: The metaanalysis was performed using RevMan 5 (Review Manager version 5.3.5 - Cochrane Collaboration, Oxford, United Kingdom). The risk of difference (RD) with a 95% confidence interval (CI) for dichotomous variables was calculated by using the Mantel-Haenszel Cochran method with the fixed-effects model. For continuous variables, we calculated the mean difference (MD) with 95%CI using random effect with inverse variance. The semi-quantitative values were reported as weighted mean with standard deviation determined by the number of patients in each study. All estimates were made based on an intention-to-treat analysis. Heterogeneity values were estimated according to Chi-square (χ^2) and Higgins method (I^2). Heterogeneity values greater than 50% were considered high. We used the fixed-effects model if the heterogeneity was < 50%. Absolute numbers, means, and standard deviations were used for data analysis. If the means and standard deviations were not reported, they were estimated using mathematical formulas (SP Hozo, B. Djulbegovic, I. Hozo). A *P* value of less than 0.05 was considered statistically significant.

RESULTS

Study selection

The initial search identified a total of 3576 citations. After eliminating duplicates, 1601 citations were selected for title and abstract review. Out of these, 54 studies were selected for full-text review. Eleven articles were then selected to examine for eligibility, out of which 3 were excluded because they were not RCTs. Finally, 8 studies^[15-22] were included in our meta-analysis (Figure 1).

Study characteristics

Eight RCTs with a total of 596 patients were included; 302 in the propofol group and 294 patients in the midazolam group. Individual study characteristics are summarized in Table 1. Four studies^[15-18] used sedation with only propofol or midazolam. The other four studies^[19-22] also used additional medications for sedation, such as opioid analgesic Pentazocine (Watanabe *et al*^[19]), fentanyl (Ahmed *et al*^[20] and Correia *et al*^[21]) and Meperidine in the midazolam group (Weston *et al*^[22]).

Risk of bias: Studies by Yoo *et al*^[18], Watanabe *et al*^[19], Ahmed *et al*^[20], Agrawal *et al*^[15], and Correia *et al*^[21] were considered low risk when globally assessed per outcome, while the studies by Khamaysi *et al*^[16] and Weston *et al*^[22] had some concerns, and the study by Riphaus *et al*^[17] had a high risk of bias (Figure 2).

GRADEpro: The estimated outcomes of procedure time, recovery time, and adverse events showed very low quality of evidence, and discharge time showed low quality of evidence (Figure 3).

Results of individual studies and synthesis of results

Procedure time: Seven studies^[15-17,19-22] with a total of 556 patients (282 propofol group and 274 midazolam group) reported procedure time. No statistical difference was found between the propofol and midazolam groups (MD: 0.25, 95%CI: -0.64 to 1.13, *P* = 0.59) (Figure 4).

Recovery time: Six studies^[15-18,20,22] with a total of 363 patients (191 in the propofol group and 172 in the midazolam group) reported recovery time after sedation. The recovery time was significantly higher in the midazolam group (MD: -8.19, 95%CI: -10.59 to -5.79, *P* < 0.00001) (Figure 5).

Discharge time: Three studies^[16,20,22] with a total of 181 patients (91 in the propofol group and 90 in the midazolam group) reported discharge time after sedation. The

Table 1 Characteristics of included studies

Ref.	Study type	Inclusion criteria and outcomes	Medication	Intervention
Yoo <i>et al</i> ^[18] , 2019, South Korea	RCT	Inclusion: Patients aged 19 to 75 yr for evaluation of portal hypertension; ASA I-III; Child-Turcotte-Pugh A, B, and C. Outcomes: Exacerbation of MHE, adverse events and discharge time; suggestive satisfaction measurements.	Propofol (20)	Propofol: 0.5 mg/kg in patients < 65 yr old or with body weight > 55 kg. In patients older than 65 yr and with body weight < 55 kg, the initial dose was 50% lower.
			Midazolam (20)	Midazolam: 0.03 mg/kg or 2 mg if the patient is < 65 yr old or with a body weight > 55 kg. In patients older than 65 yr and with body weight under 55 kg, the initial dose was 20% lower.
			Midazolam and propofol (20)	Midazolam: 0.03 mg/kg or 2 mg; Propofol: 20 mg. If the patient is > 65 yr old or has a body weight < 55 kg, the midazolam and propofol doses were respectively 20% and 50% lower.
Watanabe <i>et al</i> ^[19] , 2018, Japan	RCT	Inclusion: Patients aged 20 to 80 yr, hepatic cirrhosis for the treatment of sclerosis, primary prophylaxis, Child-Turcotte-Pugh A and B. Outcomes: Exacerbation of MHE, patient and operator satisfaction, and adverse events.	Propofol (11)	Pentazocine 15 mg + Propofol 1% 20 mg IV followed by BIC of 3-5 mg/kg/h. In case of body movements or discomfort, 20 mg of Propofol (IV) was administered.
			Midazolam (12)	Pentazocine 15 mg + midazolam 2.5-5 mg. In case of body movement or signs of discomfort, an IV infusion with an additional 2.5 mg of midazolam was administered.
Ahmed <i>et al</i> ^[20] , 2017, Egypt	RCT	Inclusion: Patients aged 40 to 60 yr, Child-Turcotte-Pugh B or C, patients willing to be part of the study. Outcomes: Procedure duration, recovery time, discharge time, sedation scores, and adverse events.	Propofol (50)	Propofol 1 mg/kg + 0.5 mcg/kg IV until a satisfactory level of sedation is reached. An additional dose of 0.2 mg/kg of propofol was administered in case of discomfort.
			Midazolam (50)	Midazolam 3 mg IV + fentanyl 0.5 mcg/kg until a satisfactory level of sedation is reached. A supplementary dose of 1 mg of midazolam was administered in case of an unsatisfactory level of sedation.
Agrawal <i>et al</i> ^[15] , 2012, India	RCT	Inclusion: Patients aged 18 to 70 yr, hepatic cirrhosis confirmed and staged by Child-Turcotte-Pugh A and B, MELD, ASA I-III. Outcomes: Deterioration of psychometric tests before and after the examination, critical flicker frequency before and after, adverse events.	Propofol (40)	Propofol 0.5-1 mg IV, followed by an additional bolus if necessary.
			Midazolam (42)	Midazolam 0.5 - 1 mg IV, with an increasing dosage every 1-3 min, until a satisfactory level of sedation is reached.
			No-sedation (45)	
Correia <i>et al</i> ^[21] , 2011, Brazil	RCT	Inclusion: Patients aged 18 to 75 yr, with hepatic cirrhosis, Child-Turcotte-Pugh A, B or C, ASA I-III. Outcomes: Procedure duration, discharge time, recovery time, and adverse events.	Propofol (100)	Midazolam 0.05 mg/kg with a dosage of 1 mg every 2 min, if necessary, up to a maximum dose of 0.1 mg/kg or 10 mg + 50 mcg of fentanyl.
			Midazolam (110)	Propofol 0.25 mg/kg with a dosage of 20-30 mg, if necessary, every 30-60 s up to a maximum dose of 400 mg + fentanyl 50 mcg.
Khamaysi <i>et al</i> ^[16] , 2011, Israel	RCT	Inclusion: Compensated liver cirrhosis, Child-Turcotte-Pugh A and B. Outcomes: Sub-clinical hepatic encephalopathy before and after, procedure duration, induction time, recovery time, discharge time, adverse events.	Propofol (31)	Propofol: 30-50 mg followed by repeated dosages of 10-20 mg at intervals of 15 s, at the endoscopist's discretion, up to a 70-100 mg dose, considering the level of satisfactory sedation.
			Midazolam (30)	Midazolam: (0.5-1.0 mg) administered by intravenous bolus injection, with incremental dosages at intervals of approximately 1 to 3 min until a satisfactory level of sedation for the procedure was reached (variation of 3-6 mg).

Riphaus <i>et al</i> ^[17] , 2009, Germany	RCT	Inclusion: Patients over 18 yr old diagnosed with hepatic cirrhosis, Child-Turcotte-Pugh A, B and C, without using benzodiazepine or antiepileptics, ASA I-III. Control group: Non-cirrhotic. Outcomes: Acute deterioration of minimal encephalopathy before and after sedation, procedure duration, recovery time, and adverse events.	Control/No-sedation (30)	
			Propofol (40)	Propofol: 40 mg of propofol 1% or 60 mg in patients weighing 70 kg; an extra dose of 10 mg was administered if necessary.
Weston <i>et al</i> ^[22] , 2003, United States	RCT	Inclusion: Patients over 18 yr old, confirmed hepatic cirrhosis, Child-Turcotte-Pugh A and B, ASA I-II. Outcomes: Procedure duration, recovery time, discharge time, and adverse events.	Midazolam (20)	Midazolam: 2.5 mg IV, with repeated doses administered to ensure satisfactory sedation within a limit of 7.5 mg total.
			Control/No-sedation (20)	
			Propofol (10)	Propofol: 30-50 mg IV, followed by a 10-20 mg dosage every 15 s, at the discretion of an endoscopist or nurse, until a satisfactory level of sedation is reached.
			Midazolam (10)	Midazolam: 0.5-1 mg + meperidine (12.5-25 mg), with an additional dosage every 1-3 min if necessary.

MHE: Minimal hepatic encephalopathy; MELD: Model for End-Stage Liver Disease.

discharge was significantly lower in the propofol group compared to midazolam (MD: -12.98, 95%CI: -18.46 to -7.50, $P < 0.00001$) (Figure 6).

Adverse events: All included studies^[15-22] reported the incidence of adverse events related to sedation during upper gastrointestinal endoscopy (bradycardia, hypotension, and hypoxemia).

Adverse events were similar in both groups (RD: 0.02, 95%CI: 0-0.04, $P = 0.58$). Also, no significant difference was found when comparing each adverse event individually (Figure 7).

Bradycardia: Eight studies^[15-22] with a total of 596 patients (302 in the propofol group and 294 in the midazolam group) reported the incidence of bradycardia related to sedation during upper gastrointestinal endoscopy. Increase incidence of bradycardia was seen in patients receiving midazolam for sedation; however, the difference was not statistically significant (RD: 0.03, 95%CI: -0.01 to 0.07, $P = 0.16$).

Hypotension: All studies^[15-22] reported the incidence of hypotension related to sedation during upper gastrointestinal endoscopy. An increase in the incidence of hypotension was seen with the use of midazolam; however, it was not statistically significant (RD: 0.03, 95%CI: -0.01 to 0.07, $P = 0.17$).

Hypoxemia: All eight studies^[15-22] reported the incidence of hypoxemia related to sedation. No statistically significant difference was found between groups (RD: 0.00, 95%CI: -0.04 to 0.04, $P = 0.93$).

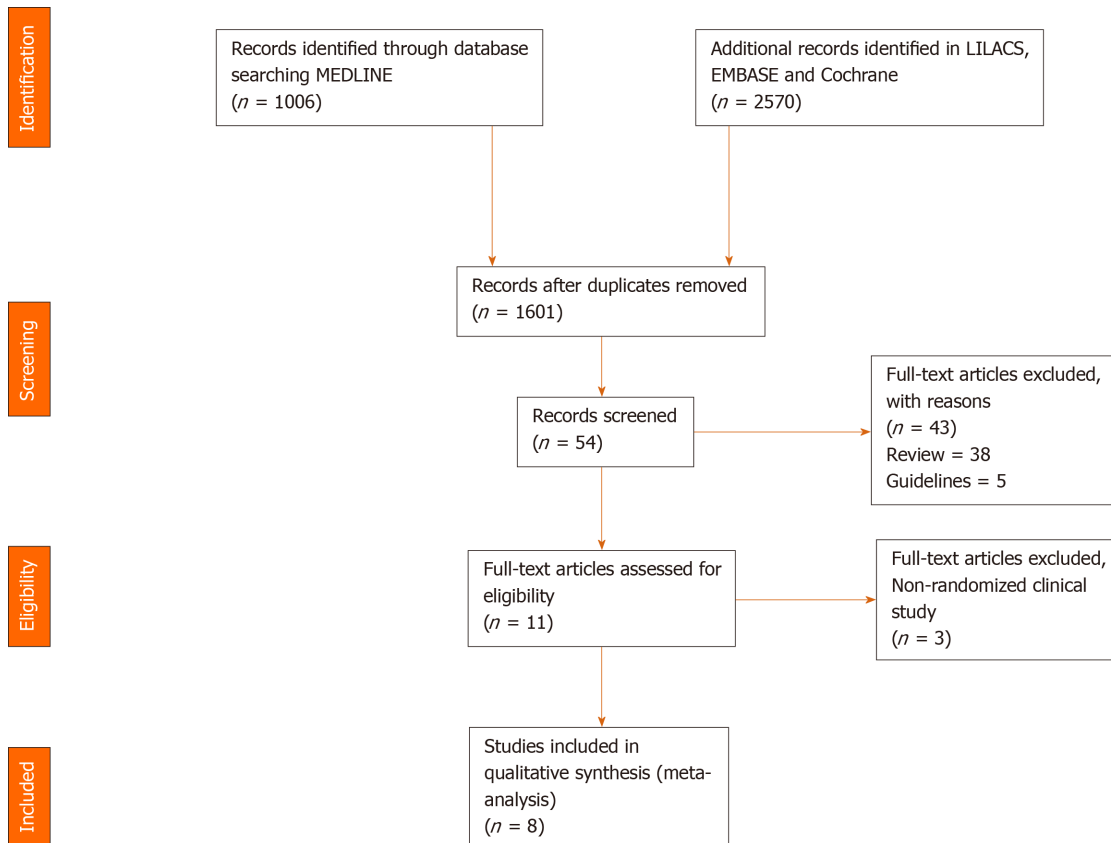


Figure 1 Flow chart of study selection. Cochrane CENTRAL: Cochrane Central Register of Controlled Trials; Propofol vs midazolam sedation for elective endoscopy in patients with cirrhosis.

DISCUSSION

Historically endoscopy was performed without sedation, which can be painful and uncomfortable for patients^[23]. Over time, the application of topical anesthesia was introduced, and some countries still only use topical anesthesia because of low cost, patient preference, or institutional availability^[24-26]. Administration of analgesics and intravenous sedation during endoscopy was a significant breakthrough worldwide, for both physicians and patients alike because of several advantages such as patient comfort, reduced discharge time, and early recovery after the procedure^[27-29]. These can be used either alone or in combination for a synergetic effect to comfortably perform the procedure while maintaining an adequate level of sedation. Sedation in endoscopy is safe when we correctly select, individualize, and optimize the medicine dosage for each type of patient. One of the primary considerations is patient comorbidities, including hepatic dysfunction- which can lead to difficulty in clearance, recirculation, and increased half-life of drugs^[30-36]. Sedation during endoscopy in patients with hepatic dysfunction was highlighted in 1975 when benzodiazepine use was compared in patients with and without liver abnormalities. Patients with cirrhosis can have alterations in the metabolism of benzodiazepines, which can result in impaired psychomotor function and increased recovery time; therefore, it was suggested to use benzodiazepines with caution^[31,37-39]. Whereas, short-duration hypnotic agent propofol does not need dose adjustment in patients with cirrhosis and has a faster onset of action, shorter effect, and quick recovery time^[13].

We studied the optimal approach for sedation during an elective upper gastrointestinal endoscopy in patients with cirrhosis. In our analysis, we included 8 RCTs^[15-22] all with adequate designs, with a total of 596 patients. Our analysis showed that propofol had a faster recovery and discharge time. However, procedure time and adverse events were similar between propofol and midazolam group. Our results are consistent with the previous metanalysis by Tsai *et al.*^[40]; however, we included three more recent RCTs as well. Despite our study population only composed of patients with liver cirrhosis, our results are similar to a recent meta-analysis by Delgado *et al.*^[41] showing that propofol to be a better approach during upper GI endoscopy for all patients. The use of propofol for endoscopy in patients with cirrhosis has been

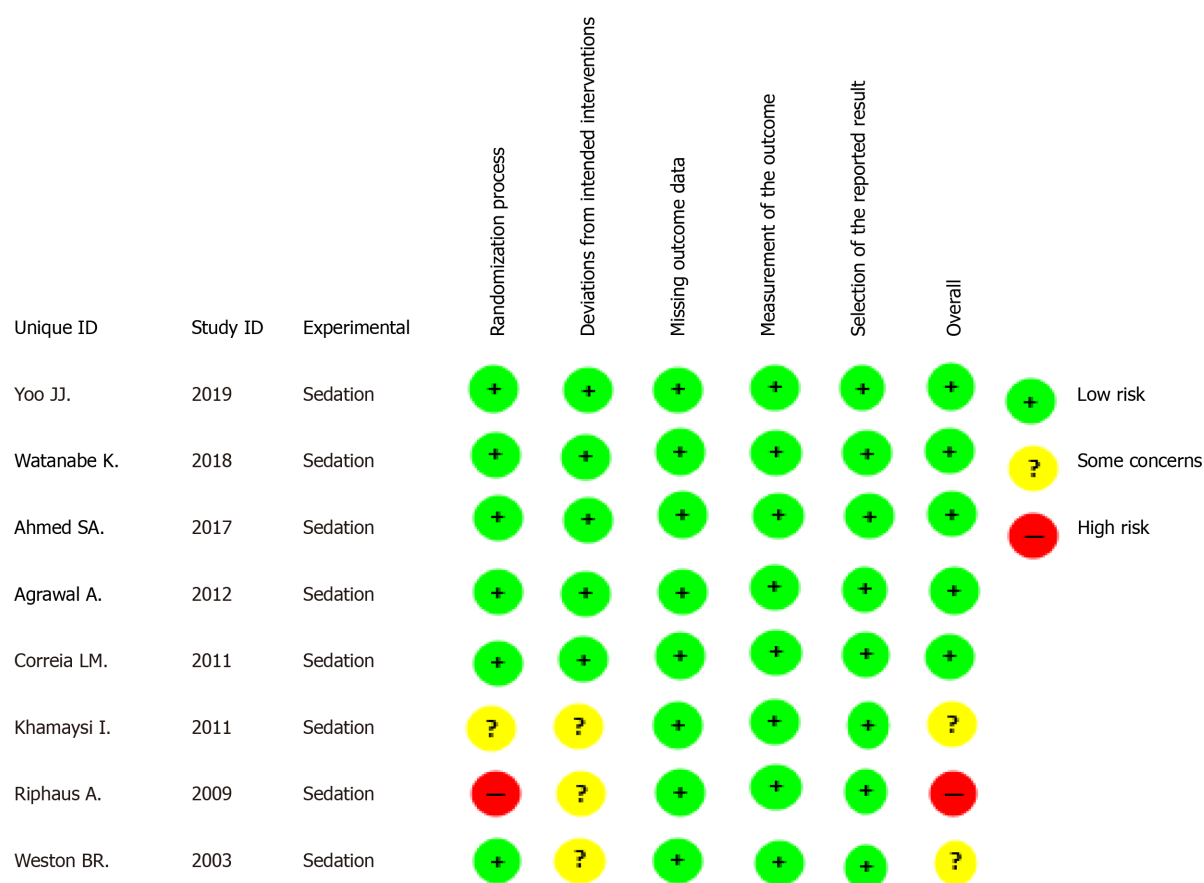


Figure 2 Overall risk of bias.

increasing; however, one of the limitations for widespread use is that propofol is restricted mostly to anesthesiologists in some countries^[42-47].

Seven RCTs were included^[15-17,19-22] in our analysis for procedure time, and we found no statistical difference between midazolam and propofol. Five diagnostic and therapeutic procedures studies^[15-17,20,22] showed shorter procedure time for the midazolam group; however, 2 RCTs^[19,21], including therapeutic procedures, showed shorter procedure time for the propofol group. The study by Agrawal *et al*^[15] also included patients without any sedation and showed a shorter procedure time in the sedation group, likely due to a reduction in the discomfort that patients felt during endoscopy without sedation. All 6 RCTs^[15-18,20,22] evaluating recovery time demonstrated a faster recovery time when using propofol compared to midazolam. Therefore, a statistically significant difference in recovery time was found in the metaanalysis favoring the propofol group, although the methods to assess recovery varied slightly in studies. Three RCTs^[15,16,22] used blood pressure and heart rate parameters within 20% of the baseline, oxygen saturation greater than 90% in ambient air, ability to tolerate oral fluids, and bedside support capacity without help or regaining basal function. While Yoo *et al*^[18] and Ahmed *et al*^[20] evaluated patients for recovery using blood pressure, pulse oxymetry, and heart rate parameters. Different from other studies, Riphaus *et al*^[17] used the post-anesthesia recovery score (PARS) which consists of five parameters (1) activity (inability to move the limbs, ability to move two or four limbs with or without command); (2) respiration (evidence of apnea, labored breathing, or normal breathing pattern); (3) circulation (blood pressure compared with baseline: $\pm 50\%$ to baseline, $\pm 20\%$ to 50% compared to baseline, $\pm 20\%$ to baseline); (4) consciousness (non-arousable, arousable, or fully awake); and (5) skin color (cyanotic, pink, or normal). 0, 1 or 2 points are given for each parameter, and complete recovery is indicated by the maximum PARS of 10 points. Our metaanalysis, including 3 RCTs^[16,20,22], showed that propofol was associated with a faster discharge time than midazolam. Khamaysi *et al*^[16] and Weston *et al*^[22] showed results favoring propofol. While Ahmed *et al*^[20] showed no difference in discharge time between propofol and midazolam.

Many adverse events in endoscopy are related to sedation. Our study found no

Propofol <i>vs</i> midazolam sedation for elective endoscopy in patients with cirrhosis. A systematic review and meta-analysis of randomized controlled trials					
Patient or population: Elective endoscopy in a patient with cirrhosis propofol versus midazolam: A systematic review and meta-analysis					
Setting:					
Intervention: Propofol					
Comparison: Midazolam					
Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95%CI)	Anticipated absolute effects	
				Risk with midazolam	Risk difference with propofol
Procedure time	556 (7 RCTs ^[15-17,19-22])	⊕○○○ Very low ^{a,b,c}	-	The mean procedure time was 0	MD 0.25 higher (0.64 lower to 1.13 higher)
Recovery time	363 (6 RCTs ^[15-18,20,22])	⊕○○○ Very low ^{b,d}	-	The mean recovery time was 0	MD 8.19 lower (10.59 lower to 5.79 lower)
Discharge time	181 (3 RCTs ^[16,20,22])	⊕⊕○○ Low ^{b,e}	-	The mean discharge time was 0	MD 12.98 lower (18.46 lower to 7.5 lower)
Adverse Events	1788 (8 RCTs ^[15-22])	⊕○○○ Very low ^{c,f}	Not estimable	53 per 1.000	53 fewer per 1.000 (53 fewer to 53 fewer)
Adverse Events - Bradycardia	596 (8 RCTs ^[15-22])	⊕○○○ Very low ^{c,f}	Not estimable	44 per 1.000	44 fewer per 1.000 (44 fewer to 44 fewer)
Adverse Events - Hypotension	596 (8 RCTs ^[15-22])	⊕○○○ Very low ^{c,f}	Not estimable	48 per 1.000	48 fewer per 1.000 (48 fewer to 48 fewer)
Adverse Events - Hypoxemia	596 (8 RCTs ^[15-22])	⊕○○○ Very low ^{c,f}	Not estimable	68 per 1.000	68 fewer per 1.000 (68 fewer to 68 fewer)
*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI).					
GRADE Working Group grades of evidence					
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect					
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different					
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect					
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect					

CI: Confidence interval; MD: Mean difference

Explanations

- a. Riphaus A, 2009 risk of bias high. Khamaysi, 2011 and Weston BR. 2003 some concerns.
- b. High heterogeneity.
- c. Non significant difference.
- d. Riphaus A 2009, Risk of bias high. Khamaysi, 2011 and Weston BR. 2003, risk bias some concerns.
- e. Khamaysi, 2011 and Weston BR. 2003, Risk of bias some concerns.
- f. Riphaus A, 2009 risk of bias high in (Bradycardia, Hypotension and Hypoxemia).

Figure 3 GRADEpro. Propofol *vs* midazolam sedation for elective endoscopy in patients with cirrhosis. A systematic review and meta-analysis of randomized controlled trials. ^aRiphaus A, 2009 risk of bias high. Khamaysi, 2011 and Weston BR. 2003 some concerns. ^bHigh heterogeneity. ^cNon significant difference. ^dRiphaus A 2009, Risk of bias high. Khamaysi, 2011 and Weston BR. 2003, risk bias some concerns. ^eKhamaysi, 2011 and Weston BR. 2003, Risk of bias some concerns. ^fRiphaus A, 2009 risk of bias high in (Bradycardia, Hypotension and Hypoxemia). CI: Confidence interval; MD: Mean difference.

statistical difference when comparing adverse events related to the use of propofol and

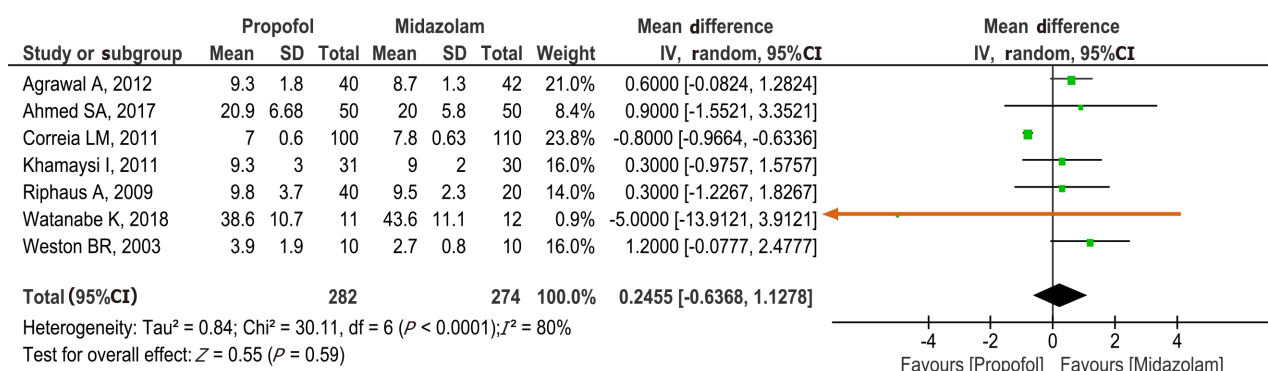


Figure 4 Forest plot comparing procedure time between propofol and midazolam group for sedation during elective upper gastrointestinal endoscopy in patients with cirrhosis.

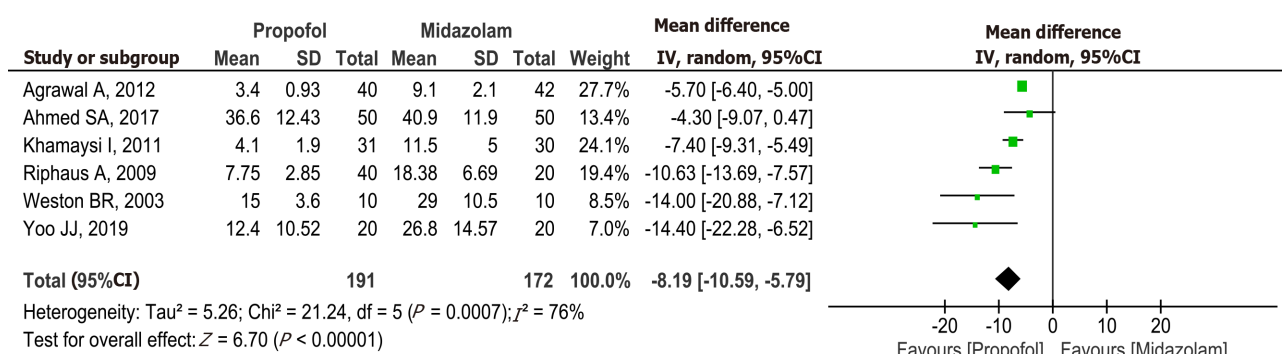


Figure 5 Forest plot comparing recovery time between propofol and midazolam group for sedation during elective upper gastrointestinal endoscopy in patients with cirrhosis.

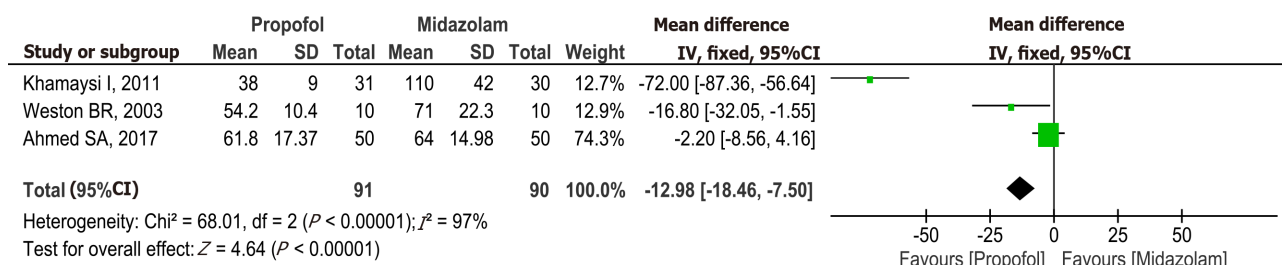


Figure 6 Forest plot comparing discharge time between propofol and midazolam group for sedation during elective upper gastrointestinal endoscopy in patients with cirrhosis.

midazolam. Our results were similar to a retrospective study^[30] of 1667 patients with cirrhosis, which showed no difference in adverse events between midazolam plus fentanyl *vs* propofol sedation for endoscopy. Another recent multicenter cross-sectional study^[48] that included 9007 endoscopic procedures in patients with cirrhosis reported that adverse events were infrequent and cardiovascular adverse events were related to unfit patients and those requiring general anesthesia. Cardiopulmonary adverse events in our study were mainly seen in 3 RCTs^[17,20,21], which included endoscopic therapeutic procedures (varices treatment) likely because of the prolonged procedure time and the need for higher sedation dose for patient comfort. Given the significance of cardiopulmonary adverse events with sedation, we further evaluated adverse events like bradycardia, hypotension, and hypoxemia individually.

In our meta-analysis, there was no difference in the incidence of bradycardia between propofol and midazolam. Bradycardia was described as a heart rate (HR) < 50 in most studies^[16,17,20,22], HR < 45 by Watanabe *et al*^[19], 25% decrease in initial HR or HR < 55 bpm by Correia *et al*^[21] and a 20% decrease in initial HR by Agrawal *et al*^[15] Patients in

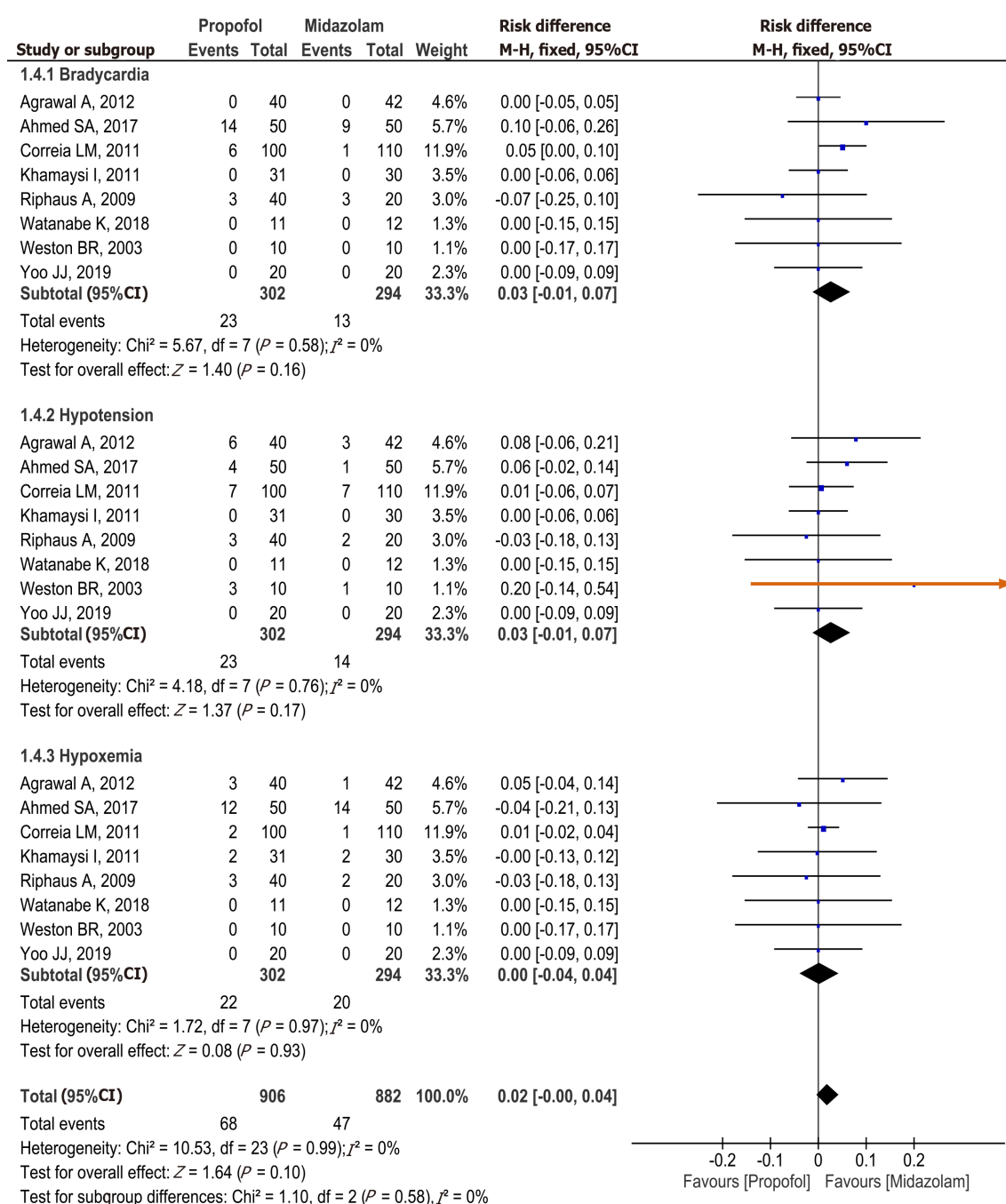


Figure 7 Forest plot comparing adverse events between propofol and midazolam group for sedation during elective upper gastrointestinal endoscopy in patients with cirrhosis.

only one study (Ahmed *et al*^[20]) were administered atropine 0.3 mg IV to control bradycardia. Hypotension with propofol is well recognized due to a reduction in systemic vascular reduction and depression of myocardial contractility. In our analysis, Agrawal *et al*^[15] and Weston *et al*^[22] notably used high doses of propofol, which could potentially result in the development of hypotension. However, in our analysis, we did not find any difference in the incidence of hypotension between propofol and midazolam. The included studies used various parameters to define hypotension. Agrawal *et al*^[15] defined a blood pressure < 20% of the baseline, while Correia *et al*^[21] considered a 20% decrease in MAP or a systolic blood pressure < 90 mmHg or a diastolic blood pressure < 50 mmHg as hypotension. Khamaysi *et al*^[16], Riphaus *et al*^[17], and Weston *et al*^[22] considered a systolic blood pressure < 90 mmHg as hypotension. Ahmed *et al*^[20] considered a decrease in mean arterial pressure (MAP) of 20 mmHg from baseline as hypotension and administered ephedrine 10 mg and Ringer's lactate 5 mL/kg when it occurred. Watanabe *et al*^[19] considered a systolic blood pressure < 80 mmHg as hypotension. Unlike other studies, Yoo *et al*^[18] did not

report any hypotension in both groups. Similarly, there was no difference in the incidence of hypoxemia seen in the propofol and midazolam group, although the definition of hypoxemia varied in studies. In most included studies^[15-17,19-21], hypoxemia was defined as oxygen saturation of less than 90%. Weston *et al*^[22] considered an oxygen saturation < 85% as hypoxemia and also measured hypoventilation if the respiratory rate was < 8 breaths per minute or by using a capnograph. Yoo *et al*^[18] did not specify the values for hypoxemia, or if the patients were receiving oxygen. Seven studies^[15-17,19-22] reported the use of oxygen through the nasal cannula at a rate of 2 to 5 L/min with an increase if necessary.

Hepatic encephalopathy is a multifaceted disorder in patients with cirrhosis and more evident in patients with high Child-Turcotte-Pugh and MELD scores. Benzodiazepines can particularly exacerbate hepatic encephalopathy after endoscopy in some patients^[49,50], while the risk of encephalopathy reported with propofol is relatively low. Studies by Khamaysi *et al*^[16], Riphaus *et al*^[17] and Agrawal *et al*^[15] included in our analysis reported that the risk of exacerbating minimal hepatic encephalopathy was less in the propofol group compared to midazolam. However, studies by Watanabe *et al*^[19] and Yoo *et al*^[18] did not present a statistically significant difference in minimal hepatic encephalopathy, with the latter using a software ("Stroop") for testing. In our meta-analysis, we could not quantitatively estimate the incidence of hepatic encephalopathy after sedation with propofol or midazolam since it was not uniformly reported. Five RCTs^[15-19] that evaluated change in cognition used different tests to assess minimal hepatic encephalopathy prior to and after endoscopy without time standardization. Some of the tests described in the literature^[16,17,19] to assess hepatic encephalopathy are Number Connection Tests (NCT), test and combination of psychometric^[15], Portosystemic Encephalopathy (PSE)^[17] Psychometric tests and Critical Flicker Frequency (CFF)^[15], Cognitive Function Score (CFS)^[16], Digital Symbol Tests (DST)^[15], Line Tracing Tests (LTT)^[15], Serial Dotting Tests (SDT)^[15], and a test using the app "Stroop"^[18] (limitation in patients of advanced age, low education level, and high MELD).

Despite our rigorous meta-analysis, including only RCTs, our study has several limitations. The quality of our systematic review and meta-analysis is inherently limited by the quality of the included studies. A high degree of statistical heterogeneity was found in some of our estimates. The included studies had patients with different Child-Turcotte-Pugh scores (A-B, B-C, and A-B-C). The doses of sedation used in studies were not consistent. Higher sedation doses of propofol and midazolam were used in the studies by Watanabe *et al*^[19], Ahmed *et al*^[20], Agrawal *et al*^[15], Correia *et al*^[21], Khamaysi *et al*^[16], Riphaus *et al*^[17], and Weston *et al*^[22] as compared to the doses used in the study by Yoo *et al*^[18]. This variance in doses was likely related to differences in BMI, height, and ethnicity of the patients included in these studies^[18]. Additionally, some studies also used synthetic analgesics. We could not quantitatively estimate the minimal hepatic encephalopathy after sedation since the tests used in the included studies to assess hepatic encephalopathy were not uniform.

In conclusion, propofol has faster recovery time and a shorter patient discharge time compared with midazolam, with similar adverse events. Therefore, propofol should be the preferred agent for sedation in patients with cirrhosis undergoing upper gastrointestinal endoscopy.

ARTICLE HIGHLIGHTS

Research background

Administration of analgesics and intravenous sedation during endoscopy in patients with cirrhosis has several advantages such as patient comfort, reduced discharge time, and early recovery after the procedure. However, proper selection of sedative medications is essential because of the risk of complications mainly due to underlying hepatic dysfunction- which can lead to difficulty in clearance, recirculation, and increased half-life of drugs.

Research motivation

Many diagnostic or therapeutic upper gastrointestinal endoscopy procedures are often performed in cirrhosis, but choosing effective and safe sedative medications can be a real challenge. Therefore, we wanted to compare commonly used sedation protocols in an attempt to understand the best approach.

Research objectives

To perform a systematic review and meta-analysis of Randomized Controlled Trials comparing sedation with propofol and midazolam in patients with cirrhosis undergoing elective endoscopy.

Research methods

We performed a systematic review and meta-analysis using the PRISMA guidelines. Electronic searches were performed using MEDLINE, EMBASE, Central Cochrane, LILACS databases. Only randomized control trials (RCTs) were included. The outcomes studied were procedure time, recovery time, discharge time, and adverse events (bradycardia, hypotension, and hypoxemia).

Research results

Eight randomized clinical trials were included in the final analysis with a total of 596 patients, of whom 302 belonged to the propofol group and 294 to the midazolam group. Procedure time was similar between midazolam and propofol groups; however, the recovery time and discharge time were significantly less in the propofol group. Adverse events were similar in both groups, and no significant difference was found in rates of bradycardia, hypotension, and hypoxemia.

Research conclusions

Our study showed that propofol has shorter recovery and patient discharge time as compared to midazolam with a similar rate of adverse events. These results suggest that propofol should be the preferred agent for sedation in patients with cirrhosis.

Research perspectives

Sedation medications used during endoscopy can differ in outcomes in patients with cirrhosis. Randomized control trials comparing outcomes and adverse events of multiple sedation protocols in patients with cirrhosis should be carried out in the future.

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