ISSN 1948-5190 (online)

World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2022 December 16; 14(12): 739-794

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Endoscopy

Contents

Monthly Volume 14 Number 12 December 16, 2022

World Journal of Gastrointestinal Endoscopy

Monthly Volume 14 Number 12 December 16, 2022

Contents

NAME OF JOURNAL

World Journal of Gastrointestinal Endoscopy

ISSN

ISSN 1948-5190 (online)

LAUNCH DATE

October 15, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Anastasios Koulaouzidis, Bing Hu, Sang Chul Lee, Joo Young Cho

EDITORIAL BOARD MEMBERS

https://www.wjgnet.com/1948-5190/editorialboard.htm

PUBLICATION DATE

December 16, 2022

COPYRIGHT

© 2022 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS

https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS

https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT

https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE

https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS

https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION

https://www.f6publishing.com

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Endosc 2022 December 16; 14(12): 739-747

DOI: 10.4253/wjge.v14.i12.739

ISSN 1948-5190 (online)

OPINION REVIEW

Role of multidetector computed tomography angiography in non-variceal upper gastrointestinal bleeding: A comprehensive review

Alberto Martino, Marco Di Serafino, Lucio Amitrano, Luigi Orsini, Lorena Pietrini, Rossana Martino, Antonella Menchise, Luca Pignata, Luigia Romano, Giovanni Lombardi

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Elsayed MO, United Kingdom; Tatlıparmak AC, Turkey

Received: September 27, 2022
Peer-review started: September 27, 2022
First decision: October 20, 2022
Revised: October 30, 2022
Accepted: November 9, 2022
Article in press: November 9, 2022
Published online: December 16, 2022

Alberto Martino, Lucio Amitrano, Luigi Orsini, Lorena Pietrini, Rossana Martino, Antonella Menchise, Giovanni Lombardi, Department of Gastroenterology and Digestive Endoscopy, AORN "Antonio Cardarelli", Napoli 80131, Italy

Marco Di Serafino, Luigia Romano, Department of General and Emergency Radiology, AORN "Antonio Cardarelli", Napoli 80131, Italy

Luca Pignata, Department of Clinical Medicine and Surgery, Gastroenterology and Hepatology Unit, University of Naples "Federico II", Napoli 80131, Italy

Corresponding author: Alberto Martino, MD, Staff Physician, Department of Gastroenterology and Digestive Endoscopy, AORN "Antonio Cardarelli", 9 Via Antonio Cardarelli, Napoli 80131, Italy. albertomartinomd@gmail.com

Abstract

Non-variceal upper gastrointestinal bleeding (NVUGIB) is a common gastroenterological emergency associated with significant morbidity and mortality. Upper gastrointestinal endoscopy is currently recommended as the gold standard modality for both diagnosis and treatment, with computed tomography traditionally playing a limited role in the diagnosis of acute NVUGIB. Following the introduction of multidetector computed tomography (MDCT), this modality is emerging as a promising tool in the diagnosis of NVUGIB. However, to date, evidence concerning the role of MDCT in the NVUGIB diagnosis is still lacking. The aim of our study was to review the current evidence concerning the role of MDCT in the diagnosis of acute NVUGIB.

Key Words: Gastrointestinal bleeding; Upper gastrointestinal bleeding; Non-variceal upper gastrointestinal bleeding; Computed tomography; Multidetector computed tomography; Multidetector computed tomography angiography

Core Tip: Upper gastrointestinal endoscopy is currently recommended as the first-line technique for diagnosis and treatment of non-variceal upper gastrointestinal bleeding (NVUGIB). Conversely, computed tomography has a limited role in the diagnosis of acute NVUGIB. However, following the introduction of multidetector computed tomography (MDCT), this modality is emerging as a promising tool in the diagnosis of NVUGIB. Nevertheless, to date, evidence concerning the role of MDCT in the NVUGIB diagnosis is still lacking. Our study aimed to review the current evidence concerning the role of MDCT in the diagnosis of acute NVUGIB.

Citation: Martino A, Di Serafino M, Amitrano L, Orsini L, Pietrini L, Martino R, Menchise A, Pignata L, Romano L, Lombardi G. Role of multidetector computed tomography angiography in non-variceal upper gastrointestinal bleeding: A comprehensive review. *World J Gastrointest Endosc* 2022; 14(12): 739-747
URL: https://www.wjgnet.com/1948-5190/full/v14/i12/739.htm
DOI: https://dx.doi.org/10.4253/wjge.v14.i12.739

INTRODUCTION

Acute upper gastrointestinal bleeding (UGIB) is the most common gastroenterological emergency with an annual incidence of 40-150/100000 population[1-3]. It is defined as hemorrhage occurring from a source located proximal to the ligament of Treitz. Based on the etiology, it is usually classified as variceal and non-variceal upper gastrointestinal bleeding (NVUGIB), with peptic ulcers, neoplasms and Mallory-Weiss syndrome being the most common causes of NVUGIB[1,2,4].

Despite marked advances in the management of acute UGIB, its mortality rate is still high ranging from 8% to 14%[5-7], and increasing up to 40% in high-risk patients[8].

Following hemodynamic stabilization, esophagogastroduodenoscopy (EGD) is currently recommended as the first-line diagnostic procedure in NVUGIB patients, allowing for simultaneous localization, characterization and hemostatic treatment in the majority of bleeding lesions[9-11]. The reported EGD sensitivity and specificity for UGIB are 92%-98% and 30%-100%, respectively[3]. However, EGD often fails to identify the exact bleeding site in case of massive UGIB (> 1 mL/min), being non-diagnostic in 10% of cases of UGIB[3,12]. Furthermore, Vreeburg *et al*[13] reported unsuccessful diagnosis at first endoscopy in 24% of acute UGIB patients, with endoscopic view impairment for excessive blood or clots in 15% of cases.

As opposed to acute lower gastrointestinal bleeding[14-16], computed tomography (CT) has currently a limited role in the diagnosis of acute UGIB and its routine adoption in the setting of acute NVUGIB is not recommended[9-11]. However, the introduction of multidetector CT (MDCT) technology has led to increased image resolution and markedly decreased scanning time, thus allowing the identification of contrast medium (CM) extravasation into the bowel lumen before contrast medium dilution. Furthermore, the ability of helical CT to detect active gastrointestinal bleeding may exceed the lower limit of 0.5 mL/min reported for mesenteric angiography and may approach the 0.2 mL/min limit of 99mTc-red blood cell scintigraphy[17]. Thus, recently, MDCT has been increasingly adopted in the diagnostic approach of most vascular diseases, and a promising role of this technique in the NVUGIB diagnosis has been suggested[18,19]. Anyway, evidence regarding the value of MDCT in NVUGIB is still limited. The aim of our study was to extensively review the current evidence with regard to the role of MDCT in the diagnosis of acute NVUGIB.

LITERATURE SEARCH

We performed a comprehensive literature search of the PubMed (MEDLINE) and EMBASE electronic databases up to July 2022, in order to identify relevant studies evaluating the role of MDCT in the diagnosis of acute NVUGIB. The medical search strategy used the terms "computed tomography", "CT", "computed tomography angiography", "CTA", "multidetector computed tomography", "MDCT", "non-variceal upper gastrointestinal bleeding", and "non-variceal upper gastrointestinal haemorrhage" in various combinations, using the Boolean operators AND, OR, and NOT. Search strategy was limited to human studies and articles written in English. Meeting abstracts, individual case reports, case series (< 5 cases), review articles, position papers, editorials, commentaries, and book chapters were excluded from our review. The reference lists of pertinent identified studies and related review articles were carefully hand-searched in order to obtain any additional eligible studies.

ROLE OF MDCT IN NVUGIB

Evidence

A total of 9 studies were included in our final analysis[20-28]. All but 3 prospective studies[20,24,25] were retrospective[21-23,26-28]. With the exception of one study comparing enhanced and unenhanced MDCT[26], in all of the remnant studies intravenous contrast-enhanced MDCT scan with at least an arterial phase acquisition was evaluated[20-25,27,28]. No CM was orally administered in any of the included studies. Main characteristics of the included studies in which MDCT was adopted in the diagnosis of acute NVUGIB are summarized in Table 1. Figures 1-3 show three cases of severe NVUGIB in which MDCT was performed immediately after EGD, providing bleeding etiology identification and thus guiding further treatment.

In 2006, Yoon *et al*[20] first prospectively evaluated the role of arterial phase MDCT in 7 patients admitted for acute massive NVUGIB in whom endoscopic examination or hemostasis failed. A high accuracy of MDCT for the detection and localization of the bleeding sites was showed.

Later on, in a small retrospective case series MDCT was able to detect the bleeding source in all cases and to identify the bleeding etiology in 9 out of 10 cases. Of note, CT provided a diagnosis in 6 patients after negative findings at angiography (n = 2) and endoscopy (n = 4). In the remaining 4 patients, CT was the initial imaging method providing a diagnosis in all 4, and no further diagnostic work-up was performed. Moreover, CM extravasation was detected in all patients with acute severe NVUGIB (7/10) and the identified NVUGIB etiology mainly included rare causes of massive NVUGIB (aortoduodenal fistula, n = 4 and arterial pseudoaneurysm, n = 4, and arteriobiliary fistula, n = 1), requiring non-endoscopic treatment[21].

In 2008, Jaeckle *et al*[22] retrospectively reported the efficacy of MDCT in 10 UGIB patients in whom upper endoscopy failed to reveal the bleeding source. In 9 out of 10 patients MDCT was able to localize the bleeding site, while active bleeding was showed in 5 cases. In the only false-negative finding, angiographic and endoscopic follow-up revealed duodenal invasion of a small pancreatic carcinoma with duodenal bleeding.

Later on, a high MDCT accuracy for the detection of acute UGIB was reported in a small retrospective case series. Of note, MDCT criteria for acute GIB not only included the identification of active CM extravasation within bowel lumen, but also the detection of mass or pathologic vessel[23].

Subsequently, a small prospective study from Italy reported an excellent sensitivity of MDCT in identifying bleeding site and etiology (100.0% and 90.9%, respectively, compared with 72.7% and 54.5%, respectively, of endoscopy). Of note, patients in whom bleeding stopped after the operative endoscopy were not included in the study, whereas EGD failure was observed in 5 out of 11 of the included patients[24].

In 2012, Sun *et al*[25] prospectively evaluated the role of tri-phasic MDCT as the initial diagnostic investigation in patients with both severe and mild acute UGIB. As similarly previously reported, criteria for positive CT were not limited to the presence of active CM extravasation within bowel lumen, but also included identification of abnormal bowel mucosal enhancement, vascular malformation, abnormally enhancing polyp or diverticulum, or tumor. MDCT was shown to be a highly accurate first-line screening modality for both detection and localization of UGIB, effectively guiding further management. However, interestingly, no CM extravasation was observed in any of the included patients with mild UGIB[25].

Subsequently, the usefulness of MDCT prior to urgent endoscopy was confirmed in a similar large retrospective study. Indeed, pre-operative MDCT showed a diagnostic accuracy for the bleeding origin detection of 57.8% (130 of 227 patients) and 19.4% (20 of 103 patients) for the enhanced and unenhanced MDCT groups, respectively, among expert radiologists. To be mentioned, the authors excluded from their study patients in whom other therapeutic modalities, such as angiography or surgery, were performed rather than urgent endoscopy due to MDCT results. Finally, the average time needed for endoscopic detection of bleeding origin in the MDCT-positive group was significantly faster (88.1 s) than that in the MDCT-negative group (155.8 s) among patients who underwent the enhanced MDCT scan ($P \leq 0.05$)[26].

Conversely, a recent large retrospective study showed that MDCT prior to endoscopy has a significantly low sensitivity for the identification of UGIB site and etiology, as compared with endoscopy. However, of note, the study did not include cases in whom EGD failed, or the endoscopic diagnosis was other than ulcer, varices, or cancer. Moreover, unstable patients were also excluded. As stated by the authors, all of the included patients were affected by mild UGIB, thus massive and rare and causes of acute UGIB were excluded from this study[27].

Intriguingly, Jono *et al*[28] compared CT findings with two well validated clinical scores to predict mortality, rebleeding and need for endoscopic therapy in NVUGIB patients. In all patients CT was performed prior to upper endoscopy. Although upper gastrointestinal (UGI) hemorrhage and UGI wall findings on CT scan were not significant in predicting mortality and rebleeding, the first CT finding better predicted the need for endoscopic therapy than both clinical Rockall score (adjusted odds ratio 10.10) and Glasgow Blatchford score (adjusted odds ratio 10.70)[28].

Table 1 Summary of studies reporting on the role of multidetector computed tomography in the diagnosis of acute Non-variceal upper gastrointestinal bleeding

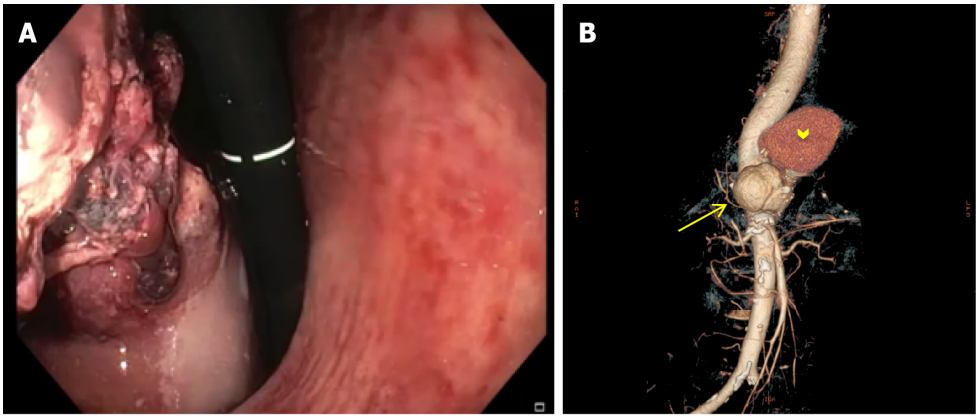
Ref.	Study design	Patients, *n*	Type of CT	Inclusion criteria	Exclusion criteria	Criteria for positive CT	Reference standard	Study aim	Results
Yoon *et al*[20], 2006	P	7	4-MDCT	Patients with massive UGIB in whom endoscopic examination or hemostasis failed	-	Active GIB: Extravasation of CM with attenuation> 90 HU within bowel lumen	Angiography	Accuracy of MDCT for detection and localization of acute massive UGIB	GIB detection: TP: 4/7, FN: 2/7, FP: 1/7, TN: 0/7, GIB localization: TP: 7/7
Scheffel *et al*[21], 2007	R	10	4-, 16-, or 64-MDCT	Patients with UGIB who underwent CT in the acute phase of hemorrhage	-	Acute GIB: Active extravasation of CM within bowel lumen; or extravasated CM with attenuation > 90 HU	Surgery, angiography, endoscopy, or pathology	Ability of MDCT to identify source and etiology of acute UGIB	GIB detection: 10/10; GIB etiology identification: 9/10
Jaeckle *et al*[22], 2008	R	10	16- or 40-MDCT	Patients with UGIB in whom endoscopic examination failed to identify the bleeding source	Serum creatinine > 250 μmol/L; or iodinated CM allergy	Active GIB: Active extravasation of CM with attenuation > 90 HU within bowel lumen; or collection of hyperdense intraluminal blood with attenuation > 90 HU	Endoscopy, angiography and/or surgery	Accuracy of MDCT for detection and localization of acute UGIB	GIB detection: TP: 9/10; FN: 1/10; GIB localization: TP: 9/10; FN: 1/10
Fung *et al*[23], 2008	R	6	64-MDCT	Patients with UGIB who underwent angiography	-	Acute GIB: Mass, abnormal vessel, or active extravasation of CM within bowel lumen	Angiography	Accuracy of MDCT for detection of acute UGIB	TP: 6/6
Frattaroli *et al*[24], 2009	P	11 (1 VUGIB)	16-MDCT	Patients with severe acute UGIB following endoscopy	Hemodynamicinstability; non-severe, intermittent, or chronic GIB; or effective endoscopic hemosthasis	Acute GIB: Active extravasation of CM within bowel lumen	Endoscopy, angiography, surgery, or post-mortem findings	Ability of MDCT to identify UGIB site and etiology	GIB site identification: Sensitivity 100% (*vs* 72.7% of endoscopy); GIB etiology identification: Sensitivity 90.9% (*vs* 54.5% of endoscopy)
Sun *et al* [25], 2012	P	33	16-, 64-, or dual-source MDCT	Patients with acute UGIB who underwent; MDCT as the initial diagnostic examination	Iodinated CM allergy; pregnancy; or serum creatinine > 2.0 mg/dL	Active GIB: Active extravasation of CM with attenuation > 90 HU within bowel lumen; focal or segmental abnormal bowel mucosal enhancement; presence of a vascular malformation; polyp or diverticulum with abnormal enhancement; or tumor	Endoscopy, angiography, surgery, or pathology	Accuracy of MDCT for detection of active UGIB	TP: 25/33; FN: 3/33; TN: 5/33
Miyaoka *et al*[26],	R	330	64-MDCT	Patients with acute UGIB	Patients who underwent other therapeutic	Active GIB: Extravasation of	Endoscopy	Accuracy of MDCT for	Enhanced MDCT: 57.8%

2014				who underwent MDCT prior to urgent endoscopy	modalities rather than urgent endoscopy due to MDCT findings	CM within bowel lumen; possible bleeding: Wall thickening; focal wall enhancement; masses, varices, and aneurysms, with or without the intraluminal high-attenuation substance		detection of acute UGIB origin	(130/227); unenhanced MDCT: 19.4% (20/103)
Jono *et al* [28], 2019	R	386	16- or 64-MDCT	Patients with NVUGIB who underwent MDCT prior to urgent endoscopy	VUGIB; or no CT exam	UGI hemorrhage: Yes or no; UGI wall change: Concavity or hypertrophy	Endoscopy	OR of risks scores based on clinical data and CT findings for predicting mortality, rebleeding and need for endoscopic therapy in NVUGIB	UGI hemorrhage: Not significant in predicting mortality and rebleeding, but significant in predicting need for endoscopic therapy (OR 10.1 for RS and 10.70 for GBS); UGI wall change: Not significant in predicting mortality, rebleeding and need for endoscopic therapy
Kim *et al* [27], 2022	R	269 (53 VUGIB)	64-MDCT	Patients with acute UGIB who underwent MDCT prior to endoscopy	Execution of endoscopy 24 h after admission; endoscopic examination failure; LGIB; acute or chronic kidney injure; or iodinated CM allergy	Active bleeding: Active extravasation of CM within bowel lumen; recent bleeding: Hemorrhagic content, suspicious hematoma, and blood clots	Endoscopy	Accuracy of MDCT for identification of status, location, and etiology of UGIB	Bleeding status identification: 32.9% (active bleeding); 27.4% (recent bleeding); 94.8% (no bleeding); bleeding location identification: 60.9% (esophagus), 60.6% (stomach), 50.9% (duodenum); bleeding etiology identification: 58.3% (ulcerative bleeding), 65.9% (cancerous bleeding), 56.6% (variceal bleeding)

CT: Computed tomography; MDCT: Multidetector-row computed tomography; UGIB: Upper gastrointestinal bleeding; GIB: Gastrointestinal bleeding; CM: Contrast medium; HU: Hounsfield units; TP: True positive; FN: False negative; FP: False positive; TN: True negative; VUGIB: Variceal upper gastrointestinal bleeding; UGI: Upper gastrointestinal; OR: Odds ratio; RS: Rockall score; GBS: Glasgow-Blatchford score; LGIB: Lower gastrointestinal bleeding.

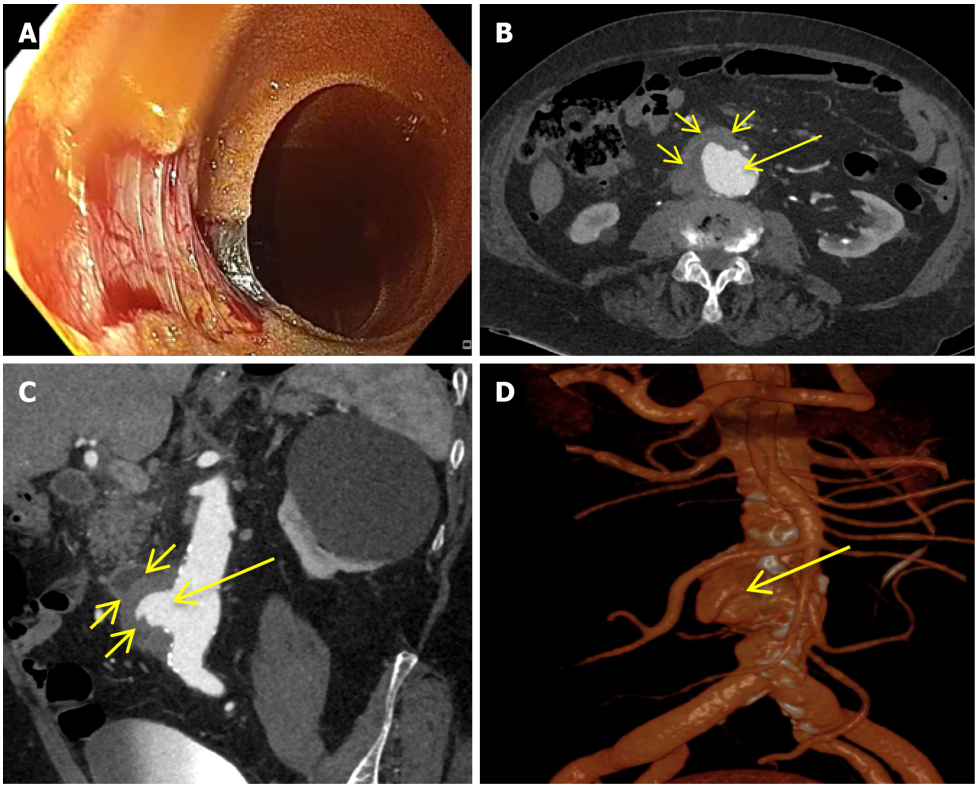
CONCLUSION

EGD is currently recommended as the first-line modality for both diagnosis and treatment of NVUGIB, with MDCT playing only a limited role in the diagnosis of NVUGIB[9-11]. However, endoscopy may fail to identify the source of UGIB, especially in case of massive hemorrhage. Furthermore, although rare, various unusual cause of UGIB may not be properly diagnosed by endoscopy and require solely endovascular or surgical treatment[29-31]. MDCT has been suggested to be a promising non-invasive, fast and widely available diagnostic tool in the diagnosis of NVUGIB, with reported high diagnostic accuracy for both detection and localization of bleeding, especially among patients with severe hemorrhage[32]. Moreover, MDCT is capable to identify the bleeding etiology, representing the gold standard diagnostic modality for most of the unusual causes of NVUGIB. Finally, as opposed to endoscopy, MDCT is capable to accurately evaluate the bleeding lesion, providing information to extraluminal abnormalities, feeding and draining vessels, and its anatomical relationship to



DOI: 10.4253/wjge.v14.i12.739 **Copyright** ©The Author(s) 2022.

Figure 1 Severe non-variceal upper gastrointestinal bleeding due to primary aorto-gastric fistula. A: Retroflexed endoscopic view showing gastric bulging mass partially covered by blood clots, originating from the fundus and extending to the posterior wall of the proximal body; B: Three-dimensional computed tomography angiography showing ruptured thoracoabdominal aortic aneurysm (arrow), retained by a periaortic hematoma (arrowhead).

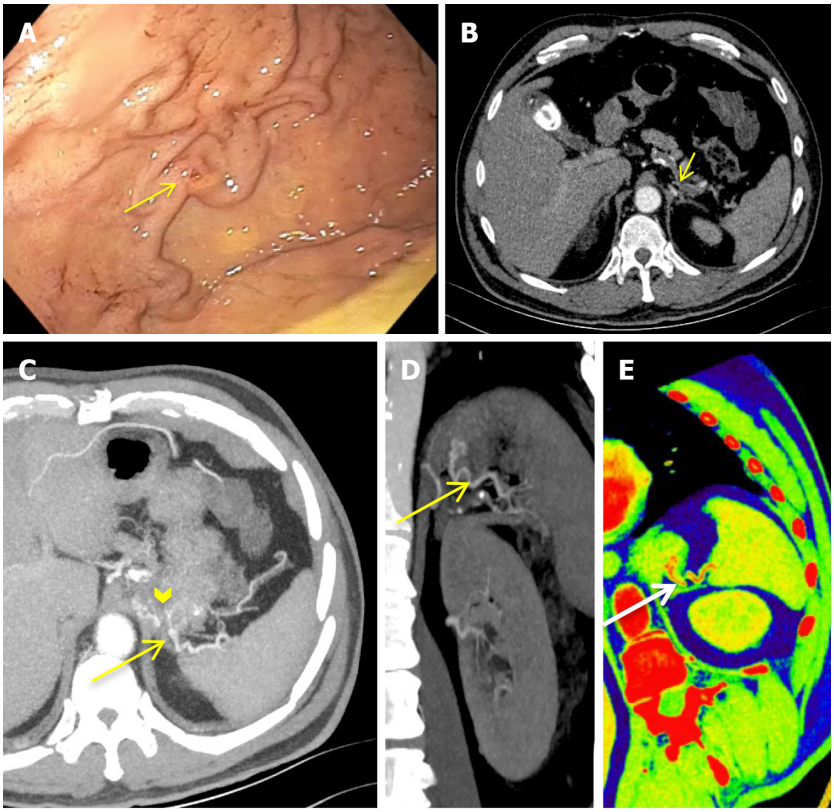


DOI: 10.4253/wjge.v14.i12.739 **Copyright** ©The Author(s) 2022.

Figure 2 Severe non-variceal upper gastrointestinal bleeding due to primary aorto-duodenal fistula. A: Esophagogastroduodenoscopy showing a large pulsating wall defect of the third duodenal portion; B-D: Axial computed tomography artery phase (B), coronal-oblique maximum intensity projection artery phase (C) and three-dimensional volume rendering reconstruction (D) showing a large outpouching from the right anterolateral wall of the abdominal aorta (B-D; long arrow) at the level of the third duodenal portion with loss of interface fat plane (B and C; short arrows), in the absence of neither air bubble within the aortic lumen and wall nor contrast medium extravasation into the duodenal lumen.

surrounding structures. Thus, MDCT has the potential to stratify patients who need earlier treatment and to assist clinicians in planning further safe, effective and tailored treatment, whether it is endoscopic, endovascular, and/or surgical.

In our opinion, MDCT angiography plays a primary role in NVUGIB patients in whom endoscopic examination fails to identify and/or to properly treat the bleeding lesion. Furthermore, in case of uncertain etiologic diagnosis at endoscopy, MDCT should be performed before treatment. Finally, across referral centers, MDCT angiography may play a role as first-line diagnostic modality in NVUGIB, especially among patients admitted for severe bleeding. Indeed, it may easily identify the bleeding



DOI: 10.4253/wjge.v14.i12.739

Figure 3 Severe non variceal upper gastrointestinal bleeding due to gastric submucosal arterial collaterals secondary to splenic artery thrombosis. A: Retroflexed endoscopic view of the gastric fundus showing varicose-shaped submucosal vessels with a small erosion (arrow); B-E: Axial computed tomography dual-energy arterial phase (B) with maximum intensity projection artery phase reconstruction on axial (C) and coronal (D) multiplanar view and oblique-coronal colorimetric low keV (E) showing splenic artery thrombosis (B: short arrow) with an arterial cluster at the gastric fundus (C: arrowhead) arising from splenic artery collateral vessels (C-E: long arrow).

status, addressing the timing of treatment, and provide an etiological diagnosis of the bleeding lesion, thereby strictly directing further safe and effective management. Finally, in case of failure of endoscopic hemosthasis, emergent endovascular or surgical treatment could be directly, safely and effectively performed by the pre-alerted interventional radiologist or surgeon. However, further large prospective studies in high-volume referral centers are needed to clarify the role of MDCT in NVUGIB, especially as first-line diagnostic tool in patients affected by severe acute NVUGIB. High morbidity and mortality still associated with acute NVUGIB justify active research in this field.

ACKNOWLEDGEMENTS

We are grateful to Velia De Magistris for English editing.

FOOTNOTES

Author contributions: Martino A, Di Serafino M, and Amitrano L designed research and wrote, edited, and finalized the text; Martino A, Di Serafino M, Orsini L, Pietrini L, Martino R, Menchise A, and Pignata L performed literature search and analyzed the data; Romano L and Lombardi G reviewed the paper for important intellectual content.

Conflict-of-interest statement: No conflict of interest to declare.

Country/Territory of origin: Italy

ORCID number: Alberto Martino 0000-0002-8759-6518; Marco Di Serafino 0000-0001-6972-1859; Luigi Orsini 0000-0001-7029-3994; Luigia Romano 0000-0002-5201-547X; Giovanni Lombardi 0000-0002-5957-3132.

Corresponding Author's Membership in Professional Societies: Associazione Italiana Gastroenterologi ed endoscopisti digestivi Ospedalieri; Società Italiana Endoscopia Digestiva.

S-Editor: Chen YL
L-Editor: A
P-Editor: Chen YL

REFERENCES

1 **Laine L**, Yang H, Chang SC, Datto C. Trends for incidence of hospitalization and death due to GI complications in the United States from 2001 to 2009. *Am J Gastroenterol* 2012; **107**: 1190-5; quiz 1196 [PMID: 22688850 DOI: 10.1038/ajg.2012.168]
2 **Wuerth BA**, Rockey DC. Changing Epidemiology of Upper Gastrointestinal Hemorrhage in the Last Decade: A Nationwide Analysis. *Dig Dis Sci* 2018; **63**: 1286-1293 [PMID: 29282637 DOI: 10.1007/s10620-017-4882-6]
3 **Lee EW**, Laberge JM. Differential diagnosis of gastrointestinal bleeding. *Tech Vasc Interv Radiol* 2004; **7**: 112-122 [PMID: 16015555 DOI: 10.1053/j.tvir.2004.12.001]
4 **Hearnshaw SA**, Logan RF, Lowe D, Travis SP, Murphy MF, Palmer KR. Acute upper gastrointestinal bleeding in the UK: patient characteristics, diagnoses and outcomes in the 2007 UK audit. *Gut* 2011; **60**: 1327-1335 [PMID: 21490373 DOI: 10.1136/gut.2010.228437]
5 **Sanders DS**, Perry MJ, Jones SG, McFarlane E, Johnson AG, Gleeson DC, Lobo AJ. Effectiveness of an upper-gastrointestinal haemorrhage unit: a prospective analysis of 900 consecutive cases using the Rockall score as a method of risk standardisation. *Eur J Gastroenterol Hepatol* 2004; **16**: 487-494 [PMID: 15097042 DOI: 10.1097/00042737-200405000-00009]
6 **van Leerdam ME**, Vreeburg EM, Rauws EA, Geraedts AA, Tijssen JG, Reitsma JB, Tytgat GN. Acute upper GI bleeding: did anything change? *Am J Gastroenterol* 2003; **98**: 1494-1499 [PMID: 12873568 DOI: 10.1111/j.1572-0241.2003.07517.x]
7 **Nahon S**, Hagège H, Latrive JP, Rosa I, Nalet B, Bour B, Faroux R, Gower P, Arpurt JP, Denis J, Henrion J, Rémy AJ, Pariente A; Groupe des Hémorragies Digestives Hautes de l'ANGH. Epidemiological and prognostic factors involved in upper gastrointestinal bleeding: results of a French prospective multicenter study. *Endoscopy* 2012; **44**: 998-1008 [PMID: 23108771 DOI: 10.1055/s-0032-1310006]
8 **Walker TG**. Acute gastrointestinal hemorrhage. *Tech Vasc Interv Radiol* 2009; **12**: 80-91 [PMID: 19853226 DOI: 10.1053/j.tvir.2009.08.002]
9 **Laine L**, Barkun AN, Saltzman JR, Martel M, Leontiadis GI. ACG Clinical Guideline: Upper Gastrointestinal and Ulcer Bleeding. *Am J Gastroenterol* 2021; **116**: 899-917 [PMID: 33929377 DOI: 10.14309/ajg.0000000000001245]
10 **Gralnek IM**, Stanley AJ, Morris AJ, Camus M, Lau J, Lanas A, Laursen SB, Radaelli F, Papanikolaou IS, Cúrdia Gonçalves T, Dinis-Ribeiro M, Awadie H, Braun G, de Groot N, Udd M, Sanchez-Yague A, Neeman Z, van Hooft JE. Endoscopic diagnosis and management of nonvariceal upper gastrointestinal hemorrhage (NVUGIH): European Society of Gastrointestinal Endoscopy (ESGE) Guideline - Update 2021. *Endoscopy* 2021; **53**: 300-332 [PMID: 33567467 DOI: 10.1055/a-1369-5274]
11 **Sung JJ**, Chiu PW, Chan FKL, Lau JY, Goh KL, Ho LH, Jung HY, Sollano JD, Gotoda T, Reddy N, Singh R, Sugano K, Wu KC, Wu CY, Bjorkman DJ, Jensen DM, Kuipers EJ, Lanas A. Asia-Pacific working group consensus on non-variceal upper gastrointestinal bleeding: an update 2018. *Gut* 2018; **67**: 1757-1768 [PMID: 29691276 DOI: 10.1136/gutjnl-2018-316276]
12 **Lieberman D**. Gastrointestinal bleeding: initial management. *Gastroenterol Clin North Am* 1993; **22**: 723-736 [PMID: 7905862]
13 **Vreeburg EM**, Snel P, de Bruijne JW, Bartelsman JF, Rauws EA, Tytgat GN. Acute upper gastrointestinal bleeding in the Amsterdam area: incidence, diagnosis, and clinical outcome. *Am J Gastroenterol* 1997; **92**: 236-243 [PMID: 9040198]
14 **Triantafyllou K**, Gkolfakis P, Gralnek IM, Oakland K, Manes G, Radaelli F, Awadie H, Camus Duboc M, Christodoulou D, Fedorov E, Guy RJ, Hollenbach M, Ibrahim M, Neeman Z, Regge D, Rodriguez de Santiago E, Tham TC, Thelin-Schmidt P, van Hooft JE. Diagnosis and management of acute lower gastrointestinal bleeding: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2021; **53**: 850-868 [PMID: 34062566 DOI: 10.1055/a-1496-8969]
15 **Strate LL**, Gralnek IM. ACG Clinical Guideline: Management of Patients With Acute Lower Gastrointestinal Bleeding. *Am J Gastroenterol* 2016; **111**: 459-474 [PMID: 26925883 DOI: 10.1038/ajg.2016.41]
16 **Oakland K**, Chadwick G, East JE, Guy R, Humphries A, Jairath V, McPherson S, Metzner M, Morris AJ, Murphy MF, Tham T, Uberoi R, Veitch AM, Wheeler J, Regan C, Hoare J. Diagnosis and management of acute lower gastrointestinal bleeding: guidelines from the British Society of Gastroenterology. *Gut* 2019; **68**: 776-789 [PMID: 30792244 DOI: 10.1136/gutjnl-2018-317807]
17 **Kuhle WG**, Sheiman RG. Detection of active colonic hemorrhage with use of helical CT: findings in a swine model. *Radiology* 2003; **228**: 743-752 [PMID: 12954894 DOI: 10.1148/radiol.2283020756]
18 **Napoli A**, Fleischmann D, Chan FP, Catalano C, Hellinger JC, Passariello R, Rubin GD. Computed tomography angiography: state-of-the-art imaging using multidetector-row technology. *J Comput Assist Tomogr* 2004; **28** Suppl 1: S32-

S45 [PMID: 15258492 DOI: 10.1097/01.rct.0000120859.80935.10]
19 **Wu LM**, Xu JR, Yin Y, Qu XH. Usefulness of CT angiography in diagnosing acute gastrointestinal bleeding: a meta-analysis. *World J Gastroenterol* 2010; **16**: 3957-3963 [PMID: 20712058 DOI: 10.3748/wjg.v16.i31.3957]
20 **Yoon W**, Jeong YY, Shin SS, Lim HS, Song SG, Jang NG, Kim JK, Kang HK. Acute massive gastrointestinal bleeding: detection and localization with arterial phase multi-detector row helical CT. *Radiology* 2006; **239**: 160-167 [PMID: 16484350 DOI: 10.1148/radiol.2383050175]
21 **Scheffel H**, Pfammatter T, Wildi S, Bauerfeind P, Marincek B, Alkadhi H. Acute gastrointestinal bleeding: detection of source and etiology with multi-detector-row CT. *Eur Radiol* 2007; **17**: 1555-1565 [PMID: 17171511 DOI: 10.1007/s00330-006-0514-9]
22 **Jaeckle T**, Stuber G, Hoffmann MH, Jeltsch M, Schmitz BL, Aschoff AJ. Detection and localization of acute upper and lower gastrointestinal (GI) bleeding with arterial phase multi-detector row helical CT. *Eur Radiol* 2008; **18**: 1406-1413 [PMID: 18351347 DOI: 10.1007/s00330-008-0907-z]
23 **Fung HS**, Kwok PC, Lau S, Wong WK, Chan SCH. 64-slice multi-detector computed tomography for detection of acute gastrointestinal bleeding. *J HK Coll Radiol* 2008; **11**: 13-18
24 **Frattaroli FM**, Casciani E, Spoletini D, Polettini E, Nunziale A, Bertini L, Vestri A, Gualdi G, Pappalardo G. Prospective study comparing multi-detector row CT and endoscopy in acute gastrointestinal bleeding. *World J Surg* 2009; **33**: 2209-2217 [PMID: 19653032 DOI: 10.1007/s00268-009-0156-6]
25 **Sun H**, Jin Z, Li X, Qian J, Yu J, Zhu F, Zhu H. Detection and localization of active gastrointestinal bleeding with multidetector row computed tomography angiography: a 5-year prospective study in one medical center. *J Clin Gastroenterol* 2012; **46**: 31-41 [PMID: 22064550 DOI: 10.1097/MCG.0b013e31823337ee]
26 **Miyaoka Y**, Amano Y, Ueno S, Izumi D, Mikami H, Yazaki T, Okimoto E, Sonoyama T, Ito S, Fujishiro H, Kohge N, Imaoka T. Role of enhanced multi-detector-row computed tomography before urgent endoscopy in acute upper gastrointestinal bleeding. *J Gastroenterol Hepatol* 2014; **29**: 716-722 [PMID: 24224950 DOI: 10.1111/jgh.12447]
27 **Kim D**, Kim JH, Ko DR, Min IK, Choi A, Beom JH. Usefulness of contrast-enhanced multi-detector computed tomography in identifying upper gastrointestinal bleeding: A retrospective study of patients admitted to the emergency department. *PLoS One* 2022; **17**: e0266622 [PMID: 35390082 DOI: 10.1371/journal.pone.0266622]
28 **Jono F**, Iida H, Fujita K, Kaai M, Kanoshima K, Ohkuma K, Nonaka T, Ida T, Kusakabe A, Nakamura A, Koyama S, Nakajima A, Inamori M. Comparison of computed tomography findings with clinical risks factors for endoscopic therapy in upper gastrointestinal bleeding cases. *J Clin Biochem Nutr* 2019; **65**: 138-145 [PMID: 31592208 DOI: 10.3164/jcbn.18-115]
29 **Parikh K**, Ali MA, Wong RC. Unusual Causes of Upper Gastrointestinal Bleeding. *Gastrointest Endosc Clin N Am* 2015; **25**: 583-605 [PMID: 26142040 DOI: 10.1016/j.giec.2015.02.009]
30 **Munteanu L**, Iancu I, Breazu C, Cioltean C, Brânzilă S, Odainii A, Furda P, Bocşe H, Herdean A, Bartoş D, Bartoş A. Rare Causes of Gastrointestinal Bleeding: Focus on Pancreatic Pathology and Visceral Artery Aneurysms. *Chirurgia (Bucur)* 2021; **116**: S5-S15 [PMID: 35274607]
31 **Di Serafino M**, Iacobellis F, Schillirò ML, Dell'Aversano Orabona G, Martino A, Bennato R, Borzelli A, Oliva G, D'Errico C, Pezzullo F, Barbuto L, Ronza R, Ponticiello G, Corvino F, Giurazza F, Lombardi G, Niola R, Romano L. The Role of CT-Angiography in the Acute Gastrointestinal Bleeding: A Pictorial Essay of Active and Obscure Findings. *Tomography* 2022; **8**: 2369-2402 [PMID: 36287797 DOI: 10.3390/tomography8050198]
32 **British Society of Gastroenterology Endoscopy Committee**. Non-variceal upper gastrointestinal haemorrhage: guidelines. *Gut* 2002; **51** Suppl 4: iv1-iv6 [PMID: 12208839 DOI: 10.1136/gut.51.suppl_4.iv1]

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Endosc 2022 December 16; 14(12): 748-758

DOI: 10.4253/wjge.v14.i12.748

ISSN 1948-5190 (online)

MINIREVIEWS

Endoscopic ultrasound-guided diagnosis and treatment of gastric varices

Jian Yang, Yan Zeng, Jun-Wen Zhang

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Balaban DV, Romania; Pantelis AG, Greece

Received: September 13, 2022
Peer-review started: September 13, 2022
First decision: October 17, 2022
Revised: October 25, 2022
Accepted: November 21, 2022
Article in press: November 21, 2022
Published online: December 16, 2022

Jian Yang, Jun-Wen Zhang, Department of Gastroenterology, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China

Yan Zeng, Department of Psychology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing 400010, China

Corresponding author: Jun-Wen Zhang, MD, Chief Doctor, Professor, Department of Gastroenterology, The First Affiliated Hospital of Chongqing Medical University, No. 1 Youyi Road, Yuzhong District, Chongqing 400016, China. 959308413@qq.com

Abstract

Gastric varices (GV) represent a common and severe complication in patients with portal hypertension, commonly seen in patients with cirrhosis and severe pancreatic disease. Endoscopic ultrasonography is a safe and efficacious approach that can perform real-time ultrasonic scanning and intervention for the gastrointestinal submucosa, portal vein and its tributaries, and collateral circulations during direct endoscopic observation. Recently, various studies have been published about endoscopic ultrasound (EUS)-guided management of GV, mainly including diagnosis, treatment, and prognostic analysis. This article reviews published articles and guidelines to present the development process and current management of EUS-guided GV procedures.

Key Words: Endoscopic ultrasound; Diagnosis; Treatment; Gastric varices

Core Tip: Gastric varices (GV) are a common and severe complication in patients with portal hypertension, and GV bleed more severely with a higher mortality rate than esophageal varices. With increased applications in GV management, endoscopic ultrasound (EUS) has demonstrated diagnosis and treatment benefits, particularly in cases of refractory bleeding or those unsuitable for conventional therapies by preoperative assessments, and thus enriches originally-limited options. The advantages of EUS exist throughout the process, from diagnosis, preoperative assessment, treatment, and efficacy evaluation to follow-up in GV patients. This article reviews published articles and guidelines to present the recent EUS-guided management of GV.

Citation: Yang J, Zeng Y, Zhang JW. Endoscopic ultrasound-guided diagnosis and treatment of gastric varices. *World J Gastrointest Endosc* 2022; 14(12): 748-758
URL: https://www.wjgnet.com/1948-5190/full/v14/i12/748.htm
DOI: https://dx.doi.org/10.4253/wjge.v14.i12.748

INTRODUCTION

Gastric varices (GV) represent complex and heterogeneous collections of vascular shunts between the portal splenic venous system and systemic veins in the abdomen and chest[1]. GV are a common and severe complication in patients with portal hypertension (PH). Patients with chronic liver and pancreatic diseases are at risk of developing PH. Compared with esophageal varices (EV), GV bleed in significantly fewer patients but more severely with a higher mortality rate[2]. Despite decades of advances in diagnosing and treating procedures, managing GV bleeding in patients with PH remains a unique clinical challenge. Accurately detecting PH and GV are critical in managing PH[3]. However, conventional gastroscopy cannot effectively observe small GV and portal vein (PV) and their tributaries, not to mention its disability for real-time venous blood flow visualization during and after endoscopic procedures. Meanwhile, effective treatment options for GV bleeding used to be limited. Even in patients undergoing emergency endoscopic treatment such as emergency ligation, rebleeding and mortality rates are still non-negligible[4]. With increased applications in GV management[5-7], endoscopic ultrasound (EUS) has demonstrated diagnostic and therapeutical benefits and enriches originally-limited options. By comprehensively performing an electronic literature search of Medline/PubMed, Embase, *Reference Citation Analysis* (*RCA*) databases, and Web of Science databases from inception to September 10, 2022, we review published articles and guidelines to present the development process and current management of EUS-guided GV procedures.

CLASSIFICATION

Varied endoscopic classifications exist for GV[8], among which Sarin classification is the most commonly used. According to Sarin classification, GV exist in four types, including isolated GV type 1 (IGV1), IGV2, gastroesophageal varices type 1 (GOV1), and GOV2. The Sarin classification was based on the location of GV and their relationship with EV[2], while another one, the Hashizome classification, focuses on the form, location, and color of GV[9]. Even though few EUS-based GV classifications have been reported, esophagogastric varices were once investigated and classified into three types according to the vascular structures and locations, including the esophageal type, esophagogastric type, and solitary gastric type[10]. Another research in patients with cirrhosis proposed a new classification criterion for GV, which included three types of GV sizes and gastric wall abnormalities, respectively[11].

EPIDEMIOLOGY

According to anatomic location, GV are classified as gastroesophageal or isolated GV, and the reported incidence of GV varies in patients with PH (2%-70%)[12]. The most common GV type is the lesser curve varix, which is also classified as type 1 GOV (GOV1, Sarin classification)[2]. GV makes up about 10%-20% of all types of varices[2,13]. Previous studies have demonstrated that GV bleeding could happen at lower portal pressures when compared to esophageal varices[14,15], and the cumulative risk for GV bleeding in patients with PH at 1, 3, and 5 years has been reported to be as high as 16%, 36%, and 44%, respectively[16]. Acute GV bleeding is one of the leading causes of death in cirrhotic patients, even in patients who have undergone N-butyl-cyanoacrylate (NBC) injections. A retrospective study of 132 patients documented a 16.7% mortality rate within 6 wk after NBC injection treatment[17]. Left-sided PH (LSPH) accounts for approximately 5% of extrahepatic PH cases and is characterized by isolated GV [18]. In patients with LSPH due to pancreatic disease, GV bleeding has been reported in approximately 8% to 15% of patients[19,20].

DIAGNOSIS

EUS combines ultrasound imaging and traditional endoscopy to obtain real-time ultrasound images and provide detailed information about the gastrointestinal tract and the surrounding organs and vessels. EUS technology has enabled endoscopists to break through the observing limitation inside the digestive tract and greatly enriched the diagnosis and differential diagnosis of GV. The combination of EUS with

color or flow Doppler techniques facilitates better identification and monitoring of GV.

Accurate identification

EUS and mini-probes have played a revolutionary part in GV identification. High-frequency mini-probes can increase the sensitivity in identifying the minimal or initial varices and thus are beneficial for early diagnosis of esophageal varices and GV[21]. EUS could assess both the intraluminal and extraluminal varices in cirrhotic patients and therefore improve the management of PH[22]. Linear or radial EUS should be recommended to distinguish GV from other causes of prominent gastric folds, especially in cases with no evidence of PH or cirrhosis, as reported in patients with gastrointestinal stromal tumor or mucosa-associated lymphoid tissue lymphoma[23,24]. PH and splenic vein thrombosis remain the leading causes of GV bleeding. Accurate identification of PH is essential in managing patients with cirrhosis and pancreatic disease and preventing complications, including gastrointestinal bleeding. The endoscopic diagnosis of PH by conventional gastroscopy is mainly based on the visualization of bluish dilated tortuous varices, while GOV are not present in approximately 60% of patients with PH[25]. GV is located in a deeper submucosa than EV and is, therefore, difficult to differentiate from other causes of prominent gastric folds by conventional endoscopy. However, even blood flow in small varices not diagnosed by gastroscopy can be visualized by color Doppler endoscopic ultrasonography (CD-EUS), and the minimum diameter of varices detected was 2 mm in the 1990s[26]. Real-time portal pressures and liver biopsies can be acquired during one EUS procedure, so EUS has recently become increasingly popular in patients suspected of having PH or liver cirrhosis[27]. Therefore, EUS is a practical approach for differentiating PH from other related diseases.

Preprocedural evaluation

Predictors of GV bleeding include fundal varices, large varices (> 5 mm), red color signs, and Child-Pugh C class[28]. EUS can determine the bleeding risk of GV patients and facilitate timely therapeutic intervention for high-risk patients without active bleeding. EUS and high-frequency mini-probes can accurately measure the variceal radius and wall thickness, which supports subsequent identification of patients at risk for variceal bleeding[29,30]. In addition, estimating the presence of GV in patients with massive active gastrointestinal bleeding is distressing, while CD-EUS can help better confirm GV, determine accessibility, and select a suitable treatment plan in these cases. CD-EUS and EUS-guided angiography can also assess the primary feeding vein system of GV, fluid dynamics, and gastrorenal shunts[31,32], which is of great significance for the subsequent treatment selection and the reduction of postoperative complications. More importantly, EUS-guided evaluation is a reproducible and non-invasive approach.

Therapeutic evaluation

EUS procedures have been proven effective in assessing GV obliteration and identifying perforated veins, thus improving real-time monitoring and repeated injection management[5,8,33]. A prospective cohort study of 102 patients concluded that red signs, variceal size, and presence of para-gastric veins indicated a high risk of GV rebleeding after endoscopic therapy, all of which were identifiable by EUS [34]. EUS can visualize the altered ultrasonic echo immediately during endoscopic treatments, and the disappearance of the original blood flow verified by CD-EUS was thought to be one indicator of real-time therapeutic efficacy[26]. Meanwhile, alterations of variceal radius and wall thickness assessed by EUS also predicted endoscopic and pharmacological efficacy[30]. CD-EUS allows assessments of vascular blood flow and possible morphologic or hemodynamic changes after endoscopic treatment. A prospective observational study of 30 patients demonstrated that feeder vessels of GV could be identified during endoscopic procedures, and GV would disappear immediately after targeted injections of these feeding vessels[35]. Furthermore, follow-up EUS after obliteration helps to identify the remaining flow in the perforating vein and decide whether to repeat endoscopic procedures to reduce the possibility of postoperative bleeding[36]. Previous studies have demonstrated severe peri-EV and large perforating EV detected by a 20 MHz mini-probe as valuable indicators for EV recurrence after endoscopic injection sclerotherapy[37]; in addition, biweekly EUS monitoring could identify requirements for repeated NBC injection and decrease recurrent bleeding rates (18.5% *vs* 44.7%, P = 0.0053) in cirrhotic patients with bleeding GV[5]. Precise obliteration assessment of targeted GV contributes to reducing injection doses and related fatal embolization, which is a way safer and more objective than traditional estimation only by GV "hardening" after injection.

Treatment

Interventional EUS procedures have undergone tremendous development over the past three decades. EUS technology has evolved rapidly from a diagnostic tool to a promising therapeutic modality in patients with GV. Acute GV bleeding in patients with PH is a severe medical emergency, and the immediate therapeutic goals are to control bleeding, prevent early recurrence (within 5 d), and reduce 6-wk mortality[38,39]. Direct endoscopic cyanoacrylate injection is recommended as the first-line therapy for GV bleeding. Meanwhile, other injection procedures with the aid of EUS are increasingly performed due to their safety, efficiency, and accuracy[31]. EUS-guided injection procedures in GV patients

included EUS-glue, EUS-coil, EUS-coil & glue, EUS-thrombin, EUS-coil & thrombin, and EUS-coil & gelatin[5,7,31,40]. Previous studies have reported that EUS-guided injection has a significantly lower rebleeding rate (8.8% *vs* 23.7%, $P = 0.045$) and requires a smaller amount of cyanoacrylate (2.0 ± 0.8 mL *vs* 3.3 ± 1.3 mL, $P < 0.001$) compared to direct injection in a randomized controlled trial[41]. A meta-analysis of 851 GV patients in 23 studies revealed that EUS-guided GV procedures demonstrated superior clinical efficacy than conventional endoscopic glue injection in obliteration, recurrence, and long-term rebleeding, which increasingly emphasizes the advantages of EUS-guided procedures in GV [42].

EUS-guided sclerotherapy

Endoscopic sclerotherapy has been reported effective in treating bleeding varices and preventing the first variceal bleeding[43]. However, endoscopic sclerotherapy demonstrated less effectiveness in GV than in EV. Commonly used sclerosants include ethanolamine oleate (EO), glucose solutions, sodium tetradecyl, and acetic acid[44]. Larger injection doses are contemplated to avoid reduced efficacy caused by the early flush of injected sclerosants, but massive sclerosant injections may cause serious complications such as gastric necrosis and perforation[45]. In a prospective study of 92 consecutive, nonrandomized patients with variceal bleeding, it was concluded that endoscopic sclerotherapy only demonstrated temporary control of GV bleeding, and the high incidence of severe early rebleeding required alternative treatments or modified sclerotherapy techniques[46]. Balloon-occluded endoscopic sclerotherapy has been demonstrated as an effective and safe prophylactic treatment for high-risk GV with significantly reduced sclerotherapy volume in a prospective, randomized, comparative clinical trial, and this procedure can even be used in patients without gastrorenal shunts[47]. In contrast, EUS-guided sclerotherapy can offer a real-time observation during GV injection and reduce sclerosant dosage as well as complications by accurately injecting an appropriate amount of sclerosant into the target location. Meanwhile, EUS-guided sclerotherapy showed a lower recurrence rate and more extended recurrence than conventional sclerotherapy in a randomized controlled trial of 50 patients with cirrhosis and varices[48]. However, considering that the survival disadvantage from EO injection therapy was partially related to its lower hemostasis rate (55% *vs* 88%, $P = 0.023$) and higher early bleeding rates[49], experts believe that cyanoacrylate is superior to EO in treating GV bleeding.

EUS-guided tissue adhesive injection

EUS-guided tissue adhesive injection is to inject tissue adhesive into the targeted GV *via* a fine-needle aspiration (FNA) device. Three leading tissue adhesives used in endoscopic injections are NBC, 2-octyl-cyanoacrylate, and NBC plus methacryloxysulfolane[50], among which NBC is the most commonly employed agent, and it has been proved to have faster and firmer obliteration efficacy in GV than other alternatives, such as thrombin, absorbable gelatin sponge (AGS), and alcohol[51]. Endoscopic therapy with NBC is recommended for acute bleeding from IGV and those GOV2 that extend beyond the cardia [38]. Direct injection of tissue adhesives in GV patients was first reported by Soehendra *et al*[52] in 1986, which resulted in definitive hemostasis. Many years later, EUS-guided cyanoacrylate injection was reported with technical success in five GV patients[31]. Since then, numerous studies have been conducted using EUS-guided cyanoacrylate injection procedures[36,53]. EUS visualization of GV may improve hemostasis efficacy due to precise targeting and real-time obliteration confirmation while remaining less affected by blood; therefore, EUS-guided procedures seem more suitable in active bleeding with no need for gastric rinsing[54]. Even though endoscopic injection therapy has been proven minimally invasive and effective[55], these procedures with sclerosants or glue may cause severe complications occurring neither in EUS injections nor traditional injections, including systemic embolization, fever, pain, and recurrent bleeding[13,56]. Due to the potential presence of right-to-left shunts, traditional tissue adhesive injections may lead to fatal multiple systemic embolisms, so extreme caution was recommended for cyanoacrylate injection in adolescents with PH of unknown origin[57]. Therefore, reducing cyanoacrylate-related complications has always been one of the research hotspots, while the critical point of reducing complications is to minimize the injection dose effectively. Consequently, the Clip-assisted cyanoacrylate injection procedure was reported to be safe, convenient, and efficacious in treating GV with concomitant gastrorenal shunt[58], and our center has recently recorded a modified EUS-guided selective NBC injection procedure in an LSPH patient with good hemostasis efficacy and no post-operational gastrointestinal bleeding and ectopic embolism due to reduced injection dosage[59]. In addition, many details of EUS-guided injection procedures remain to be further explored, for example, 19- or 22-gauge needles have been used and reported without comparison in previous studies[36,53], and there is still no consensus on the exact EUS-guided tissue adhesive injection procedure.

EUS-guided coil embolization

EUS-guided coil embolization is to inject coils into the targeted blood vessels through EUS to interrupt the blood supply and thus achieve hemostasis. These coils are made up of light metal alloy and synthetic fibers, and they can obliterate GV with fewer embolization complications than those caused by tissue adhesive. EUS-guided coil embolization was first reported in a case report of successful hemostasis in refractory ectopic variceal bleeding[60], which provided a new idea for GV therapy. EUS-

guided coil embolization in GV patients was reported shortly thereafter[61]. In the above study, the target site for puncture and coil placement was modified from GV to its perforating feeding vein, successfully blocking blood flow and reducing the number of coils[61]. Surprisingly, a follow-up study found that EUS-guided coil embolization could achieve GV disappearance in most patients with only one endoscopic intervention[36]. Although EUS-guided coil therapy appeared superior in treating GV due to a higher technical success rate, fewer endoscopies, and a lower complication rate and reintervention rate[36,40], it remains to be determined whether the EUS-guided coil or tissue adhesive injection procedure is preferred. Coil migrating from the targeted varices and significant bleeding from the puncture site were both observed in previous studies[62,63]. Moreover, since the advantages of reduced endoscopic interventions and recurrent bleeding rates in EUS-guided coil embolization procedure comes at the expense of multiple coil placement and additional risks of radiation exposure, EUS-guided coil injection was believed to be significantly more expensive, technically more demanding, and not viable in many patients by some experts[64].

EUS-guided coil embolization combined with tissue adhesive injection

Despite EUS-guided tissue adhesive injection being reported to improve accuracy compared with conventional procedures, postprocedural ectopic embolization and other complications were still disturbing. Meanwhile, although EUS-guided coil embolization demonstrated a relatively low probability of ectopic embolism, unsatisfactory hemostasis still existed in some patients. Both these approaches have their advantages and disadvantages. Since embolizations caused by cyanoacrylate were thought to be mainly related to the injection volume, reducing the injection dose has become a key to breakthrough. Coils with attached synthetic fibers may decrease the injected glue dosage (1 mL less per patient than that in the conventional procedure), thereby reducing the incidence of ectopic embolism while achieving equal obliteration efficacy[65]. This new method combines EUS-guided tissue adhesive injection and coil embolization to achieve complementary advantages and satisfactory effectiveness. In the same study, transesophageal injection access from the distal esophagus to the fundus was first introduced and has demonstrated many benefits, including avoiding the difficulty of retroflexing the endoscope, no hindrance caused by blood in the stomach, and no disruption of the gastric mucosa overlying GV[65]. Moreover, an observational study of GV patients revealed a 100% technical success rate and 96.6% complete variceal obliteration rate in the EUS-guided coil and cyanoacrylate embolization procedure[35]. In a retrospective study of 152 patients with GV, 125 patients underwent EUS-guided combined injection of coils and cyanoacrylate glue, with a mean number of 1.4 coils (range 1-4) and 2 mL (range 0.5-6) cyanoacrylate per patient; after a mean follow-up of 436 d, only 4 (3%) patients presented with mild delayed upper GI bleeding due to coil/glue extrusion[66]. Furthermore, compared with EUS-guided coil injection alone, EUS-guided coil embolization combined with tissue adhesive injection demonstrated a higher variceal occlusion rate (86.7% *vs* 13.3%, $P < 0.001$), lower postoperative rebleeding rate (3.3% *vs* 20%, $P = 0.04$), and lower reintervention rate (16.7% *vs* 40%, $P = 0.01$)[7]. A meta-analysis of 536 patients concluded that EUS combination therapy with coil embolization and cyanoacrylate injection appeared to be preferred for GV over EUS-based monotherapy among a variety of EUS-guided therapies available due to its lower adverse event rates compared to cyanoacrylate alone (10% *vs* 21%, $P < 0.001$) and similar rates compared to coil embolization alone (10% *vs* 3%, $P = 0.057$)[67]. Although the above studies supported the superiority of EUS-guided combined injection of coils and cyanoacrylate glue over the application of coils or cyanoacrylate glue alone[7,65,66], there is still a lack of evidence of optimal coil numbers and mid-long term complications. Moreover, some experts believe that standard endoscopic cyanoacrylate injections are easier to perform and more accessible for endoscopists worldwide. In contrast, EUS-guided joint injections are more challenging and time-consuming and thus may be more beneficial for only a few selected and severe GV cases[68].

Other EUS-guided injections

Due to numerous complications after routine tissue adhesive injections[13,56,57], several studies have reported alternatives to cyanoacrylate, which included AGS, thrombin, EO. AGS is a type of purified collagen with liquefaction ability and thus appears not associated with post-injection ulcerations. EUS-guided coil embolization and AGS was reported to be a novel alternative to cyanoacrylate with high clinical success rates and low risk for complications in treating bleeding GV in a retrospective review[40,69]. Some experts have also suggested human thrombin as a simple and practical alternative to tissue adhesives due to fewer complications[70,71], but thrombin demonstrated inferior GV obliteration efficacy than cyanoacrylate. Another case series reported successful hemostatic efficacy in a follow-up period of 57 mo after EUS-guided coil deployment with sclerosant (EO). The authors believed that both isolated GV and their feeding veins would be reliably obliterated after this procedure[72]. However, most of these studies compared their EUS-guided injection procedures only with conventional cyanoacrylate injections but not with EUS-guided cyanoacrylate injections, and thus further research with more patients is still needed.

EUS-guided endovascular treatments

Transjugular intrahepatic portosystemic shunt (TIPS) has been proven effective in reducing portal

venous pressure and is especially recommended in patients with persistent variceal bleeding uncontrolled by endoscopic and medical therapy and postoperative rebleeding within 5 d[38]. Nevertheless, TIPS could increase risks for patients with congestive heart failure, pulmonary hypertension, advanced cirrhosis, or hepatic encephalopathy[73]. EUS techniques offer real-time visualizations of various vascularity without radiation exposure and promising alternatives for endovascular therapy, such as EUS-guided intrahepatic portosystemic shunt (EIPS), EUS-guided portal pressure gradient (EUS-PPG), and EUS-guided partial splenic embolization (PSE). Compared with traditional puncture of the PV branch from the hepatic vein, a technically challenging procedure with serious complications, EUS guidance can directly confirm the vascular flow after stent deployment and expansion[74]. EIPS was recommended due to the advantages of non-transjugular access and reduced vascular injuries. EUS-guided portal venography with carbon dioxide using a 25 gauge FNA needle was reported feasible, technically simple, and safe in a porcine model a decade and a half ago[75]. Two years later, EIPS creation was reported to be a valuable alternative to conventional TIPS in a live porcine model with normal PV pressure[76]. After that, EIPS with direct portal pressure measurements proved a novel alternative to TIPS in a study of five Yorkshire pigs[74]. In a pilot study that enrolled 28 patients with liver diseases, EUS-PPG procedures demonstrated promising safety, availability, and simplicity in managing patients with liver disease[77]. Recently, EUS-PPG with a 22-gauge FNA needle demonstrated accuracy and security as an alternative to hepatic venous pressure gradient mea-surements in a prospective study of 12 patients with hepatic sinusoidal obstruction syndrome or Budd-Chiari syndrome[6]. However, the major limitation of these two studies was the exclusion of patients with increased bleeding risks (patients with an international normalized ratio > 1.5 or platelet count < 50 were excluded)[6,77]. These above EUS technologies are gradually transitioning from animal models to patients. Meanwhile, EUS-guided PSE was first reported in a patient with alcoholic cirrhosis and variceal bleeding as an alternative procedure for preventing recurrent GV bleeding and hypersplenism [78]. EUS-guided coil implantation and following glue injection were performed in isolated collateral outside the gastric wall in a perigastric location to achieve vascular embolization; reduced GV was confirmed by follow-up endoscopy, and authors believed that the access to the splenic artery through the gastric wall has the advantage of a shorter puncture path[78]. Despite all these developments in EUS-guided endovascular treatments, more data are yet demanded to compare EUS-guided and radiation-guided endovascular therapies.

LIMITATIONS

Although increased utilizations have demonstrated promising benefits of EUS-guided procedures, and some experts claim them as first-line strategies[11], EUS-guided interventions are not yet one of the routine endoscopic procedures for GV patients and are just recommended after failures of conventional therapies. Meanwhile, limited EUS-based GV classifications exist, and most GV are classified by endoscopic criteria. Moreover, there is still a lack of acknowledged standards for EUS-guided procedures and their roles in primary prophylaxis, acute hemorrhage, and secondary prophylaxis in GV patients, and most studies are retrospective and nonrandomized with small numbers of GV patients. As such, limited data are available to evaluate the mid-long term efficacy and safety of various EUS-guided treatments. Further prospective randomized trials and guidelines are still needed to optimize EUS-guided procedures in GV. Furthermore, numerous treatment options exist for GV, among which EUS-guided procedures are mainly performed in tertiary care centers due to the limited availability of EUS and well-trained specialists[27]. Under such circumstances, TIPS and balloon-occlusion retrograde transvenous obliteration were still the central and practical options for salvage therapies in patients with refractory variceal bleeding. Additionally, most previous studies focused on investigating the advantages of EUS-guided procedures over traditional endoscopic ones, while direct comparisons between diverse EUS-guided approaches are still limited.

CONCLUSION

EUS-guided diagnoses and treatments have recently emerged as convenient diagnostic procedures and promising hemostatic interventions for GV (Table 1), particularly in cases of refractory bleeding or those unsuitable for conventional therapies by preoperative assessment. EUS procedures have already proved capable of effective real-time visualization, accurate identification, and perioperative assessment in GV. Meanwhile, various EUS-guided GV injection approaches and highly effective endovascular procedures, such as EUS-guided coil embolization combined with tissue adhesive injection, EIPS, and EUS-guided PSE, have demonstrated encouraging clinical outcomes and developmental potentials. These EUS-guided diagnoses and treatments are currently recommended for patients with appropriate affordability, disease severity, and collateral pathway anatomy in advanced EUS centers. Additionally, multidisciplinary discussion team recommendations could provide preferable personalized management and a remarkably reduced rebleeding risk[22].

Table 1 Endoscopic ultrasound-guided diagnosis and treatment of gastric varices

EUS application	Potential benefits	Areas of concern	Ref.
Diagnosis			
Accurate identification	Improving diagnostic sensitivity and differential diagnosis; real-time	-	[21-27]
Preprocedural evaluation	Predicting bleeding risk and determining treatment; reproducible and non-invasive	-	[29-32]
Therapeutic evaluation	Improving real-time monitoring and repeated injection management; safer and more objective	-	[5,8,26,33-36]
Treatment			
EUS-guided sclerotherapy	Reducing injection dose, complications, and recurrence	Inferior to cyanoacrylate	[47-49]
EUS-guided tissue adhesive injection	Reducing injection dose, rebleeding rate and complications; faster and more firmly	Lack of recommended procedures and comparison among different needles	[36,41,42,51,54-59]
EUS-guided coil embolization	Improving technical success and reducing interventions and complications	Additional radiation exposure; expensive; technically demanding	[36,40,60-64]
EUS-guided coil embolization combined with tissue adhesive injection	Improving variceal occlusion, reducing rebleeding and reinterventions	Not clear about optimal coil numbers; technically challenging and time-consuming	[7,35,65-68]
Other EUS-guided injections	Novel alternatives; high clinical success rates with low risk for complications	Inferior variceal obliteration efficacy; lack of controlled studies	[40,69-72]
EUS-guided endovascular treatments	No radiation exposure; shorter puncture path; promising alternatives	Lack of controlled studies	[6,74-78]

EUS: Endoscopic ultrasound.

In conclusion, EUS technique advantages exist throughout the process, from diagnosis, preoperative assessment, treatment, and efficacy evaluation to follow-up in GV patients, and thus it is worthy of further research and promotion. EUS application by skilled EUS experts in proper GV patients at the right time will improve their diagnosis, efficacy, and whole GV management.

FOOTNOTES

Author contributions: Yang J and Zeng Y contributed equally to this work. Yang J, Zeng Y, and Zhang JW designed the study; Yang J and Zeng Y performed the literature search, analyzed the data, and wrote the manuscript; and all authors have read and approved the final manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Country/Territory of origin: China

ORCID number: Jian Yang 0000-0001-8170-0727; Yan Zeng 0000-0003-4935-1306; Jun-Wen Zhang 0000-0003-2911-598X.

S-Editor: Wang JJ
L-Editor: Wang TQ
P-Editor: Wang JJ

REFERENCES

1 **Henry Z**, Patel K, Patton H, Saad W. AGA Clinical Practice Update on Management of Bleeding Gastric Varices: Expert Review. *Clin Gastroenterol Hepatol* 2021; **19**: 1098-1107.e1 [PMID: 33493693 DOI: 10.1016/j.cgh.2021.01.027]
2 **Sarin SK**, Lahoti D, Saxena SP, Murthy NS, Makwana UK. Prevalence, classification and natural history of gastric varices:

a long-term follow-up study in 568 portal hypertension patients. *Hepatology* 1992; **16**: 1343-1349 [PMID: 1446890 DOI: 10.1002/hep.1840160607]
3 **Hammoud GM**, Ibdah JA. Utility of endoscopic ultrasound in patients with portal hypertension. *World J Gastroenterol* 2014; **20**: 14230-14236 [PMID: 25339809 DOI: 10.3748/wjg.v20.i39.14230]
4 **Augustin S**, Altamirano J, González A, Dot J, Abu-Suboh M, Armengol JR, Azpiroz F, Esteban R, Guardia J, Genescà J. Effectiveness of combined pharmacologic and ligation therapy in high-risk patients with acute esophageal variceal bleeding. *Am J Gastroenterol* 2011; **106**: 1787-1795 [PMID: 21625271 DOI: 10.1038/ajg.2011.173]
5 **Lee YT**, Chan FK, Ng EK, Leung VK, Law KB, Yung MY, Chung SC, Sung JJ. EUS-guided injection of cyanoacrylate for bleeding gastric varices. *Gastrointest Endosc* 2000; **52**: 168-174 [PMID: 10922086 DOI: 10.1067/mge.2000.107911]
6 **Zhang W**, Peng C, Zhang S, Huang S, Shen S, Xu G, Zhang F, Xiao J, Zhang M, Zhuge Y, Wang L, Zou X, Lv Y. EUS-guided portal pressure gradient measurement in patients with acute or subacute portal hypertension. *Gastrointest Endosc* 2021; **93**: 565-572 [PMID: 32615178 DOI: 10.1016/j.gie.2020.06.065]
7 **Robles-Medranda C**, Oleas R, Valero M, Puga-Tejada M, Baquerizo-Burgos J, Ospina J, Pitanga-Lukashok H. Endoscopic ultrasonography-guided deployment of embolization coils and cyanoacrylate injection in gastric varices versus coiling alone: a randomized trial. *Endoscopy* 2020; **52**: 268-275 [PMID: 32126576 DOI: 10.1055/a-1123-9054]
8 **Abby Philips C**, Sahney A. Oesophageal and gastric varices: historical aspects, classification and grading: everything in one place. *Gastroenterol Rep (Oxf)* 2016; **4**: 186-195 [PMID: 27324725 DOI: 10.1093/gastro/gow018]
9 **Hashizume M**, Kitano S, Yamaga H, Koyanagi N, Sugimachi K. Endoscopic classification of gastric varices. *Gastrointest Endosc* 1990; **36**: 276-280 [PMID: 2365213 DOI: 10.1016/s0016-5107(90)71023-1]
10 **Nakamura H**, Inoue H, Kawano T, Goseki N, Endo M, Sugihara K. Selection of the treatment for esophagogastric varices. Analyses of collateral structures by endoscopic ultrasonography. *Surg Endosc* 1992; **6**: 228-234 [PMID: 1465729 DOI: 10.1007/BF02498809]
11 **Boustière C**, Dumas O, Jouffre C, Letard JC, Patouillard B, Etaix JP, Barthélémy C, Audigier JC. Endoscopic ultrasonography classification of gastric varices in patients with cirrhosis. Comparison with endoscopic findings. *J Hepatol* 1993; **19**: 268-272 [PMID: 8301060 DOI: 10.1016/s0168-8278(05)80581-1]
12 **Sarin SK**, Kumar A. Gastric varices: profile, classification, and management. *Am J Gastroenterol* 1989; **84**: 1244-1249 [PMID: 2679046]
13 **Bazarbashi AN**, Ryou M. Gastric variceal bleeding. *Curr Opin Gastroenterol* 2019; **35**: 524-534 [PMID: 31577562 DOI: 10.1097/MOG.0000000000000581]
14 **Tripathi D**, Therapondos G, Jackson E, Redhead DN, Hayes PC. The role of the transjugular intrahepatic portosystemic stent shunt (TIPSS) in the management of bleeding gastric varices: clinical and haemodynamic correlations. *Gut* 2002; **51**: 270-274 [PMID: 12117893 DOI: 10.1136/gut.51.2.270]
15 **Watanabe K**, Kimura K, Matsutani S, Ohto M, Okuda K. Portal hemodynamics in patients with gastric varices. A study in 230 patients with esophageal and/or gastric varices using portal vein catheterization. *Gastroenterology* 1988; **95**: 434-440 [PMID: 3391371 DOI: 10.1016/0016-5085(88)90501-x]
16 **Kim T**, Shijo H, Kokawa H, Tokumitsu H, Kubara K, Ota K, Akiyoshi N, Iida T, Yokoyama M, Okumura M. Risk factors for hemorrhage from gastric fundal varices. *Hepatology* 1997; **25**: 307-312 [PMID: 9021939 DOI: 10.1053/jhep.1997.v25.pm0009021939]
17 **Teng W**, Chen WT, Ho YP, Jeng WJ, Huang CH, Chen YC, Lin SM, Chiu CT, Lin CY, Sheen IS. Predictors of mortality within 6 weeks after treatment of gastric variceal bleeding in cirrhotic patients. *Medicine (Baltimore)* 2014; **93**: e321 [PMID: 25546678 DOI: 10.1097/MD.0000000000000321]
18 **Köklü S**, Coban S, Yüksel O, Arhan M. Left-sided portal hypertension. *Dig Dis Sci* 2007; **52**: 1141-1149 [PMID: 17385040 DOI: 10.1007/s10620-006-9307-x]
19 **Pandey V**, Patil M, Patel R, Chaubal A, Ingle M, Shukla A. Prevalence of splenic vein thrombosis and risk of gastrointestinal bleeding in chronic pancreatitis patients attending a tertiary hospital in western India. *J Family Med Prim Care* 2019; **8**: 818-822 [PMID: 31041207 DOI: 10.4103/jfmpc.jfmpc_414_18]
20 **Liu Q**, Song Y, Xu X, Jin Z, Duan W, Zhou N. Management of bleeding gastric varices in patients with sinistral portal hypertension. *Dig Dis Sci* 2014; **59**: 1625-1629 [PMID: 24500452 DOI: 10.1007/s10620-014-3048-z]
21 **Bocus P**, Ceolin M, Battaglia G. Endoscopic ultrasonography (EUS) in portal hypertension. *Minerva Med* 2007; **98**: 431-436 [PMID: 17921962]
22 **Tseng Y**, Ma L, Lv M, Luo T, Liu C, Wei Y, Zhou J, Yan Z, Xu P, Hu G, Ding H, Ji Y, Chen S, Wang J. The role of a multidisciplinary team in the management of portal hypertension. *BMC Gastroenterol* 2020; **20**: 83 [PMID: 32245413 DOI: 10.1186/s12876-020-01203-4]
23 **Jonason DE**, Linden M, Trikudanathan G. Mucosa-Associated Lymphoid Tissue Lymphoma Masked as Gastric Varices With Acute Upper Gastrointestinal Bleeding: A Case Report. *Cureus* 2022; **14**: e26424 [PMID: 35911343 DOI: 10.7759/cureus.26424]
24 **Wong RC**, Farooq FT, Chak A. Endoscopic Doppler US probe for the diagnosis of gastric varices (with videos). *Gastrointest Endosc* 2007; **65**: 491-496 [PMID: 17321253 DOI: 10.1016/j.gie.2006.11.017]
25 **Groszmann RJ**, Garcia-Tsao G, Bosch J, Grace ND, Burroughs AK, Planas R, Escorsell A, Garcia-Pagan JC, Patch D, Matloff DS, Gao H, Makuch R; Portal Hypertension Collaborative Group. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. *N Engl J Med* 2005; **353**: 2254-2261 [PMID: 16306522 DOI: 10.1056/NEJMoa044456]
26 **Iwase H**, Suga S, Morise K, Kuroiwa A, Yamaguchi T, Horiuchi Y. Color Doppler endoscopic ultrasonography for the evaluation of gastric varices and endoscopic obliteration with cyanoacrylate glue. *Gastrointest Endosc* 1995; **41**: 150-154 [PMID: 7721004 DOI: 10.1016/s0016-5107(05)80599-1]
27 **Mann R**, Goyal H, Perisetti A, Chandan S, Inamdar S, Tharian B. Endoscopic ultrasound-guided vascular interventions: Current insights and emerging techniques. *World J Gastroenterol* 2021; **27**: 6874-6887 [PMID: 34790012 DOI: 10.3748/wjg.v27.i40.6874]
28 **Ryan BM**, Stockbrugger RW, Ryan JM. A pathophysiologic, gastroenterologic, and radiologic approach to the management of gastric varices. *Gastroenterology* 2004; **126**: 1175-1189 [PMID: 15057756 DOI:

10.1053/j.gastro.2004.01.058]
29 **Schiano TD**, Adrain AL, Cassidy MJ, McCray W, Liu JB, Baranowski RJ, Bellary S, Black M, Miller LS. Use of high-resolution endoluminal sonography to measure the radius and wall thickness of esophageal varices. *Gastrointest Endosc* 1996; **44**: 425-428 [PMID: 8905362 DOI: 10.1016/s0016-5107(96)70093-7]
30 **Escorsell A**, Bordas JM, Feu F, García-Pagán JC, Ginès A, Bosch J, Rodés J. Endoscopic assessment of variceal volume and wall tension in cirrhotic patients: effects of pharmacological therapy. *Gastroenterology* 1997; **113**: 1640-1646 [PMID: 9352867 DOI: 10.1053/gast.1997.v113.pm9352867]
31 **Romero-Castro R**, Pellicer-Bautista FJ, Jimenez-Saenz M, Marcos-Sanchez F, Caunedo-Alvarez A, Ortiz-Moyano C, Gomez-Parra M, Herrerias-Gutierrez JM. EUS-guided injection of cyanoacrylate in perforating feeding veins in gastric varices: results in 5 cases. *Gastrointest Endosc* 2007; **66**: 402-407 [PMID: 17643723 DOI: 10.1016/j.gie.2007.03.008]
32 **Romero-Castro R**, Jimenez-Garcia VA, Irisawa A, Carmona-Soria I, Caunedo-Alvarez A, Teoh AYB, Giovannini M. Anatomic and hemodynamic findings during endoscopic ultrasound-guided angiography of gastric varices: a note of caution for endoscopic ultrasound-guided therapy. *Endoscopy* 2022 [PMID: 35913065 DOI: 10.1055/a-1884-9245]
33 **Tayyem O**, Bilal M, Samuel R, Merwat SK. Evaluation and management of variceal bleeding. *Dis Mon* 2018; **64**: 312-320 [PMID: 29525376 DOI: 10.1016/j.disamonth.2018.02.001]
34 **Ma L**, Tseng Y, Luo T, Wang J, Lian J, Tan Q, Li F, Chen S. Risk stratification for secondary prophylaxis of gastric varices due to portal hypertension. *Dig Liver Dis* 2019; **51**: 1678-1684 [PMID: 31202610 DOI: 10.1016/j.dld.2019.05.020]
35 **Robles-Medranda C**, Valero M, Nebel JA, de Britto Junior SR, Puga-Tejada M, Ospina J, Muñoz-Jurado G, Pitanga-Lukashok H. Endoscopic-ultrasound-guided coil and cyanoacrylate embolization for gastric varices and the roles of endoscopic Doppler and endosonographic varicealography in vascular targeting. *Dig Endosc* 2019; **31**: 283-290 [PMID: 30449033 DOI: 10.1111/den.13305]
36 **Romero-Castro R**, Ellrichmann M, Ortiz-Moyano C, Subtil-Inigo JC, Junquera-Florez F, Gornals JB, Repiso-Ortega A, Vila-Costas J, Marcos-Sanchez F, Muñoz-Navas M, Romero-Gomez M, Brullet-Benedi E, Romero-Vazquez J, Caunedo-Alvarez A, Pellicer-Bautista F, Herrerias-Gutierrez JM, Fritscher-Ravens A. EUS-guided coil *vs* cyanoacrylate therapy for the treatment of gastric varices: a multicenter study (with videos). *Gastrointest Endosc* 2013; **78**: 711-721 [PMID: 23891417 DOI: 10.1016/j.gie.2013.05.009]
37 **Irisawa A**, Saito A, Obara K, Shibukawa G, Takagi T, Shishido H, Sakamoto H, Sato Y, Kasukawa R. Endoscopic recurrence of esophageal varices is associated with the specific EUS abnormalities: severe periesophageal collateral veins and large perforating veins. *Gastrointest Endosc* 2001; **53**: 77-84 [PMID: 11154493 DOI: 10.1067/mge.2001.108479]
38 **de Franchis R**; Baveno VI Faculty. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. *J Hepatol* 2015; **63**: 743-752 [PMID: 26047908 DOI: 10.1016/j.jhep.2015.05.022]
39 **Garcia-Tsao G**, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. *Hepatology* 2017; **65**: 310-335 [PMID: 27786365 DOI: 10.1002/hep.28906]
40 **Bazarbashi AN**, Wang TJ, Jirapinyo P, Thompson CC, Ryou M. Endoscopic Ultrasound-Guided Coil Embolization With Absorbable Gelatin Sponge Appears Superior to Traditional Cyanoacrylate Injection for the Treatment of Gastric Varices. *Clin Transl Gastroenterol* 2020; **11**: e00175 [PMID: 32677809 DOI: 10.14309/ctg.0000000000000175]
41 **Bick BL**, Al-Haddad M, Liangpunsakul S, Ghabril MS, DeWitt JM. EUS-guided fine needle injection is superior to direct endoscopic injection of 2-octyl cyanoacrylate for the treatment of gastric variceal bleeding. *Surg Endosc* 2019; **33**: 1837-1845 [PMID: 30259158 DOI: 10.1007/s00464-018-6462-z]
42 **Mohan BP**, Chandan S, Khan SR, Kassab LL, Trakroo S, Ponnada S, Asokkumar R, Adler DG. Efficacy and safety of endoscopic ultrasound-guided therapy versus direct endoscopic glue injection therapy for gastric varices: systematic review and meta-analysis. *Endoscopy* 2020; **52**: 259-267 [PMID: 32028533 DOI: 10.1055/a-1098-1817]
43 **Svoboda P**, Kantorová I, Ochmann J, Kozumplík L, Marsová J. A prospective randomized controlled trial of sclerotherapy *vs* ligation in the prophylactic treatment of high-risk esophageal varices. *Surg Endosc* 1999; **13**: 580-584 [PMID: 10347295 DOI: 10.1007/s004649901045]
44 **Philips CA**, Ahamed R, Rajesh S, George T, Mohanan M, Augustine P. Beyond the scope and the glue: update on evaluation and management of gastric varices. *BMC Gastroenterol* 2020; **20**: 361 [PMID: 33126847 DOI: 10.1186/s12876-020-01513-7]
45 **Sugawa C**. Perforation after endoscopic injection sclerotherapy for bleeding gastric varices. Surg Endosc 8: 1221-1222. *Surg Endosc* 1994; **8**: 1257 [PMID: 7809820 DOI: 10.1007/BF00591067]
46 **Trudeau W**, Prindiville T. Endoscopic injection sclerosis in bleeding gastric varices. *Gastrointest Endosc* 1986; **32**: 264-268 [PMID: 3488937 DOI: 10.1016/s0016-5107(86)71843-9]
47 **Shiba M**, Higuchi K, Nakamura K, Itani A, Kuga T, Okazaki H, Fujiwara Y, Arakawa T. Efficacy and safety of balloon-occluded endoscopic injection sclerotherapy as a prophylactic treatment for high-risk gastric fundal varices: a prospective, randomized, comparative clinical trial. *Gastrointest Endosc* 2002; **56**: 522-528 [PMID: 12297768 DOI: 10.1067/mge.2002.127410]
48 **de Paulo GA**, Ardengh JC, Nakao FS, Ferrari AP. Treatment of esophageal varices: a randomized controlled trial comparing endoscopic sclerotherapy and EUS-guided sclerotherapy of esophageal collateral veins. *Gastrointest Endosc* 2006; **63**: 396-402; quiz 463 [PMID: 16500386 DOI: 10.1016/j.gie.2005.10.039]
49 **Oho K**, Iwao T, Sumino M, Toyonaga A, Tanikawa K. Ethanolamine oleate versus butyl cyanoacrylate for bleeding gastric varices: a nonrandomized study. *Endoscopy* 1995; **27**: 349-354 [PMID: 7588347 DOI: 10.1055/s-2007-1005712]
50 **ASGE Technology Committee**, Bhat YM, Banerjee S, Barth BA, Chauhan SS, Gottlieb KT, Konda V, Maple JT, Murad FM, Pfau PR, Pleskow DK, Siddiqui UD, Tokar JL, Wang A, Rodriguez SA. Tissue adhesives: cyanoacrylate glue and fibrin sealant. *Gastrointest Endosc* 2013; **78**: 209-215 [PMID: 23867370 DOI: 10.1016/j.gie.2013.04.166]
51 **Sarin SK**, Jain AK, Jain M, Gupta R. A randomized controlled trial of cyanoacrylate versus alcohol injection in patients with isolated fundic varices. *Am J Gastroenterol* 2002; **97**: 1010-1015 [PMID: 12003381 DOI: 10.1111/j.1572-0241.2002.05622.x]

52 **Soehendra N**, Nam VC, Grimm H, Kempeneers I. Endoscopic obliteration of large esophagogastric varices with bucrylate. *Endoscopy* 1986; **18**: 25-26 [PMID: 3512261 DOI: 10.1055/s-2007-1013014]

53 **Gonzalez JM**, Giacino C, Pioche M, Vanbiervliet G, Brardjanian S, Ah-Soune P, Vitton V, Grimaud JC, Barthet M. Endoscopic ultrasound-guided vascular therapy: is it safe and effective? *Endoscopy* 2012; **44**: 539-542 [PMID: 22389233 DOI: 10.1055/s-0031-1291609]

54 **Gubler C**, Bauerfeind P. Safe and successful endoscopic initial treatment and long-term eradication of gastric varices by endoscopic ultrasound-guided Histoacryl (N-butyl-2-cyanoacrylate) injection. *Scand J Gastroenterol* 2014; **49**: 1136-1142 [PMID: 24947448 DOI: 10.3109/00365521.2014.929171]

55 **Chevallier O**, Guillen K, Comby PO, Mouillot T, Falvo N, Bardou M, Midulla M, Aho-Glélé LS, Loffroy R. Safety, Efficacy, and Outcomes of N-Butyl Cyanoacrylate Glue Injection through the Endoscopic or Radiologic Route for Variceal Gastrointestinal Bleeding: A Systematic Review and Meta-Analysis. *J Clin Med* 2021; **10** [PMID: 34070534 DOI: 10.3390/jcm10112298]

56 **Lim YS**. Practical approach to endoscopic management for bleeding gastric varices. *Korean J Radiol* 2012; **13** Suppl 1: S40-S44 [PMID: 22563286 DOI: 10.3348/kjr.2012.13.S1.S40]

57 **Saracco G**, Giordanino C, Roberto N, Ezio D, Luca T, Caronna S, Carucci P, De Bernardi Venon W, Barletti C, Bruno M, De Angelis C, Musso A, Repici A, Suriani R, Rizzetto M. Fatal multiple systemic embolisms after injection of cyanoacrylate in bleeding gastric varices of a patient who was noncirrhotic but with idiopathic portal hypertension. *Gastrointest Endosc* 2007; **65**: 345-347 [PMID: 17141231 DOI: 10.1016/j.gie.2006.07.009]

58 **Zhang M**, Li P, Mou H, Shi Y, Tuo B, Jin S, Sun R, Wang G, Ma J, Zhang C. Clip-assisted endoscopic cyanoacrylate injection for gastric varices with a gastrorenal shunt: a multicenter study. *Endoscopy* 2019; **51**: 936-940 [PMID: 31378856 DOI: 10.1055/a-0977-3022]

59 **Yang J**, Zeng Y, Zhang JW. Modified endoscopic ultrasound-guided selective N-butyl-2-cyanoacrylate injections for gastric variceal hemorrhage in left-sided portal hypertension: A case report. *World J Clin Cases* 2022; **10**: 6254-6260 [PMID: 35949826 DOI: 10.12998/wjcc.v10.i18.6254]

60 **Levy MJ**, Wong Kee Song LM, Kendrick ML, Misra S, Gostout CJ. EUS-guided coil embolization for refractory ectopic variceal bleeding (with videos). *Gastrointest Endosc* 2008; **67**: 572-574 [PMID: 17997404 DOI: 10.1016/j.gie.2007.06.063]

61 **Romero-Castro R**, Pellicer-Bautista F, Giovannini M, Marcos-Sánchez F, Caparros-Escudero C, Jiménez-Sáenz M, Gomez-Parra M, Arenzana-Seisdedos A, Leria-Yebenes V, Herrerias-Gutiérrez JM. Endoscopic ultrasound (EUS)-guided coil embolization therapy in gastric varices. *Endoscopy* 2010; **42** Suppl 2: E35-E36 [PMID: 20073010 DOI: 10.1055/s-0029-1215261]

62 **Fujii-Lau LL**, Law R, Wong Kee Song LM, Gostout CJ, Kamath PS, Levy MJ. Endoscopic ultrasound (EUS)-guided coil injection therapy of esophagogastric and ectopic varices. *Surg Endosc* 2016; **30**: 1396-1404 [PMID: 26139494 DOI: 10.1007/s00464-015-4342-3]

63 **Khoury T**, Massarwa M, Daher S, Benson AA, Hazou W, Israeli E, Jacob H, Epstein J, Safadi R. Endoscopic Ultrasound-Guided Angiotherapy for Gastric Varices: A Single Center Experience. *Hepatol Commun* 2019; **3**: 207-212 [PMID: 30766958 DOI: 10.1002/hep4.1289]

64 **Levy MJ**, Wong Kee Song LM. EUS-guided angiotherapy for gastric varices: coil, glue, and sticky issues. *Gastrointest Endosc* 2013; **78**: 722-725 [PMID: 24120335 DOI: 10.1016/j.gie.2013.07.004]

65 **Binmoeller KF**, Weilert F, Shah JN, Kim J. EUS-guided transesophageal treatment of gastric fundal varices with combined coiling and cyanoacrylate glue injection (with videos). *Gastrointest Endosc* 2011; **74**: 1019-1025 [PMID: 21889139 DOI: 10.1016/j.gie.2011.06.030]

66 **Bhat YM**, Weilert F, Fredrick RT, Kane SD, Shah JN, Hamerski CM, Binmoeller KF. EUS-guided treatment of gastric fundal varices with combined injection of coils and cyanoacrylate glue: a large U.S. experience over 6 years (with video). *Gastrointest Endosc* 2016; **83**: 1164-1172 [PMID: 26452992 DOI: 10.1016/j.gie.2015.09.040]

67 **McCarty TR**, Bazarbashi AN, Hathorn KE, Thompson CC, Ryou M. Combination therapy *versus* monotherapy for EUS-guided management of gastric varices: A systematic review and meta-analysis. *Endosc Ultrasound* 2020; **9**: 6-15 [PMID: 31417066 DOI: 10.4103/eus.eus_37_19]

68 **Lo GH**. Should we pursue high obliteration rate or high hemostatic rate in the therapy of gastric varices? *Endoscopy* 2020; **52**: 709 [PMID: 32722839 DOI: 10.1055/a-1167-8274]

69 **Bazarbashi AN**, Wang TJ, Thompson CC, Ryou M. Endoscopic ultrasound-guided treatment of gastric varices with coil embolization and absorbable hemostatic gelatin sponge: a novel alternative to cyanoacrylate. *Endosc Int Open* 2020; **8**: E221-E227 [PMID: 32010757 DOI: 10.1055/a-1027-6708]

70 **Heneghan MA**, Byrne A, Harrison PM. An open pilot study of the effects of a human fibrin glue for endoscopic treatment of patients with acute bleeding from gastric varices. *Gastrointest Endosc* 2002; **56**: 422-426 [PMID: 12196788 DOI: 10.1016/s0016-5107(02)70054-0]

71 **Smith MR**, Tidswell R, Tripathi D. Outcomes of endoscopic human thrombin injection in the management of gastric varices. *Eur J Gastroenterol Hepatol* 2014; **26**: 846-852 [PMID: 24892515 DOI: 10.1097/MEG.0000000000000119]

72 **Irisawa A**, Shibukawa G, Hoshi K, Yamabe A, Sato A, Maki T, Yoshida Y, Yamamoto S, Obara K. Endoscopic ultrasound-guided coil deployment with sclerotherapy for isolated gastric varices: Case series of feasibility, safety, and long-term follow-up. *Dig Endosc* 2020; **32**: 1100-1104 [PMID: 32147871 DOI: 10.1111/den.13666]

73 **Sankar K**, Moore CM. Transjugular Intrahepatic Portosystemic Shunts. *JAMA* 2017; **317**: 880 [PMID: 28245324 DOI: 10.1001/jama.2016.20899]

74 **Schulman AR**, Ryou M, Aihara H, Abidi W, Chiang A, Jirapinyo P, Sakr A, Ajeje E, Ryan MB, Thompson CC. EUS-guided intrahepatic portosystemic shunt with direct portal pressure measurements: a novel alternative to transjugular intrahepatic portosystemic shunting. *Gastrointest Endosc* 2017; **85**: 243-247 [PMID: 27468858 DOI: 10.1016/j.gie.2016.07.041]

75 **Giday SA**, Ko CW, Clarke JO, Shin EJ, Magno P, Jagannath SB, Buscaglia JM, Kantsevoy SV. EUS-guided portal vein carbon dioxide angiography: a pilot study in a porcine model. *Gastrointest Endosc* 2007; **66**: 814-819 [PMID: 17905028 DOI: 10.1016/j.gie.2007.05.056]

76 **Buscaglia JM**, Dray X, Shin EJ, Magno P, Chmura KM, Surti VC, Dillon TE, Ducharme RW, Donatelli G, Thuluvath PJ, Giday SA, Kantsevoy SV. A new alternative for a transjugular intrahepatic portosystemic shunt: EUS-guided creation of an intrahepatic portosystemic shunt (with video). *Gastrointest Endosc* 2009; **69**: 941-947 [PMID: 19327481 DOI: 10.1016/j.gie.2008.09.051]

77 **Huang JY**, Samarasena JB, Tsujino T, Lee J, Hu KQ, McLaren CE, Chen WP, Chang KJ. EUS-guided portal pressure gradient measurement with a simple novel device: a human pilot study. *Gastrointest Endosc* 2017; **85**: 996-1001 [PMID: 27693644 DOI: 10.1016/j.gie.2016.09.026]

78 **Chen Q**, Li Z, Yang Y, Yan W, Cheng B, Yuan Y, Zhang ZG. Partial splenic embolization through endoscopic ultrasound-guided implantation of coil as a potential technique to treat portal hypertension. *Endoscopy* 2021; **53**: E40-E41 [PMID: 32483779 DOI: 10.1055/a-1174-5590]

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Endosc 2022 December 16; 14(12): 759-768

DOI: 10.4253/wjge.v14.i12.759

ISSN 1948-5190 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Effectiveness of early colonoscopy in patients with colonic diverticular hemorrhage: A single-center retrospective cohort study

Chikamasa Ichita, Sayuri Shimizu, Akiko Sasaki, Chihiro Sumida, Takashi Nishino, Karen Kimura

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Fusaroli P, Italy; Teramoto-Matsubara OT, Mexico

Received: October 11, 2022
Peer-review started: October 11, 2022
First decision: October 26, 2022
Revised: November 1, 2022
Accepted: November 22, 2022
Article in press: November 22, 2022
Published online: December 16, 2022

Chikamasa Ichita, Akiko Sasaki, Chihiro Sumida, Takashi Nishino, Karen Kimura, Department of Gastroenterology Medicine Center, Shonan Kamakura General Hospital, Kamakura 247-8533, Kanagawa, Japan

Chikamasa Ichita, Sayuri Shimizu, Department of Health Data Science, Yokohama City University, Yokohama 236-0027, Kanagawa, Japan

Corresponding author: Chikamasa Ichita, MD, Doctor, Department of Gastroenterology Medicine Center, Shonan Kamakura General Hospital, 1370-1, Okamoto, Kamakura 247-8533, Kanagawa, Japan. ichikamasa@yahoo.co.jp

Abstract

BACKGROUND

Current guidelines recommend colonoscopy within 24 h for acute lower gastrointestinal bleeding; however, the evidence in support for colonic diverticular hemorrhage (CDH) indications remains insufficient.

AIM

To investigate the effectiveness of early colonoscopy on the length of hospital stay for CDH patients.

METHODS

We conducted a single-center retrospective cohort study. Patients who underwent colonoscopy within 24 h of presentation (early group) were compared with those who underwent colonoscopy beyond 24 h of presentation (elective group). The primary outcome was the length of hospital stay, and secondary outcomes were the identification of stigmata of recent hemorrhage (SRH), rebleeding, red blood cell transfusion more than 4 units, and interventional radiology and abdominal surgery after colonoscopy.

RESULTS

We identified 574 CDH cases. Patients were divided into the early (n = 328) and elective (n = 226) groups. After propensity score matching, 191 pairs were generated. The length of hospital stay did not significantly differ between the two groups (early group *vs* elective group; median, 7 *vs* 8 d; P = 0.10). The early group had a significantly high identification of SRH (risk difference, 11.6%; 95%CI: 2.7 to 20.3; P = 0.02). No significant differences were found in the rebleeding (risk difference, 4.7%; 95%CI: -4.1 to 13.5; P = 0.35), red blood cell transfusion more

than 4 units (risk difference, 1.6%; 95%CI: -7.5 to 10.6; P = 0.82), and interventional radiology and abdominal surgery rate after colonoscopy (risk difference, 0.5%; 95%CI: -2.2 to 3.2; P = 1.00).

CONCLUSION
Early colonoscopy within 24 h, on arrival for CDH, could not improve the length of hospital stay.

Key Words: Colonic diverticular hemorrhage; Colonic diverticular bleeding; Diverticular hemorrhage; Diverticular bleeding; Early colonoscopy; Colonoscopy

Core Tip: Current guidelines recommend colonoscopy within 24 h for acute lower gastrointestinal bleeding; however, the evidence in support for colonic diverticular hemorrhage (CDH) indications remains insufficient. We investigate the effectiveness of early colonoscopy on the length of hospital stay for CDH. The purpose of the study was to compare the length of hospital stay for CDH by dividing patients into two groups: An early group who underwent colonoscopy within 24 h and an elective group who underwent colonoscopy beyond 24 h and analysis was performed using propensity score matching. Early colonoscopy did not improve the length of hospital stay.

Citation: Ichita C, Shimizu S, Sasaki A, Sumida C, Nishino T, Kimura K. Effectiveness of early colonoscopy in patients with colonic diverticular hemorrhage: A single-center retrospective cohort study. *World J Gastrointest Endosc* 2022; 14(12): 759-768
URL: https://www.wjgnet.com/1948-5190/full/v14/i12/759.htm
DOI: https://dx.doi.org/10.4253/wjge.v14.i12.759

INTRODUCTION

Among cases of acute lower gastrointestinal bleeding (ALGIB), colonic diverticular hemorrhage (CDH) is the most common, accounting for more than 60% of cases[1,2]. The clinical presentation of diverticular hemorrhage is usually hematochezia without fever or abdominal pain[3], and the diagnosis can be made with computed tomography (CT) findings, but colonoscopy is recommended for a definitive diagnosis [4,5].

Although various studies, including randomized controlled trials (RCTs)[6-9], have shown that current guidelines recommend colonoscopy within 24 h for ALGIB[2,4,5], no clear evidence has been established for CDH alone. The percentage of spontaneous hemostasis for CDH was as high as 60%-90% [2,10-12], while the prevalence of rebleeding was reported to be as high as 13%-48%[13]. Even if the source of bleeding is identified by early colonoscopy, it is unclear whether early colonoscopy reduces hospital stay.

Emergency colonoscopy is often difficult to perform because of colon preparation and personnel availability for the procedure. The purpose of this study was to determine whether early colonoscopy for diverticular hemorrhage improves hospital stay.

MATERIALS AND METHODS

Study design

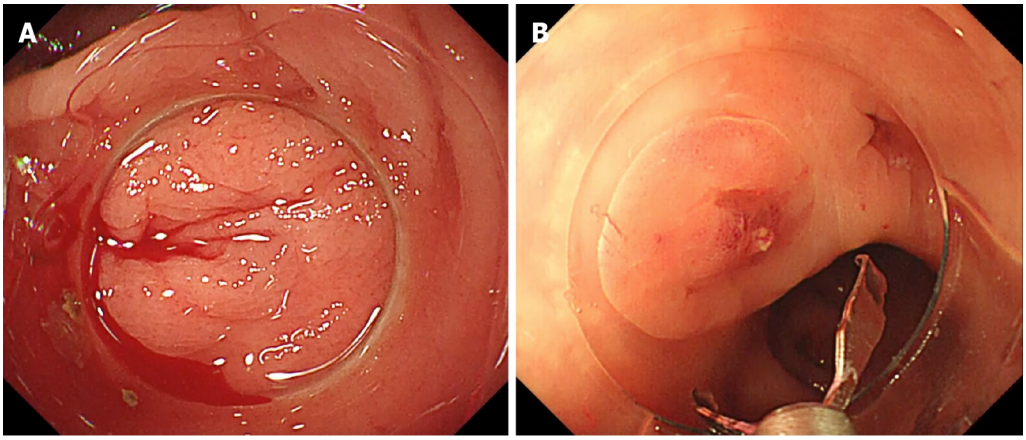
This was a single-center, retrospective cohort study.

Patient selection

We included patients who presented to Shonan Kamakura General Hospital with hematochezia and underwent colonoscopy with a diagnosis of diverticular hemorrhage over a 5-year period from January 2017 to December 2021. Colonic diverticular hemorrhage was defined as 1) When the stigmata of recent hemorrhage (SRH) were found in the diverticulum[14] (Figures 1 and 2) When the colonoscopic findings ruled out diseases other than CDH.

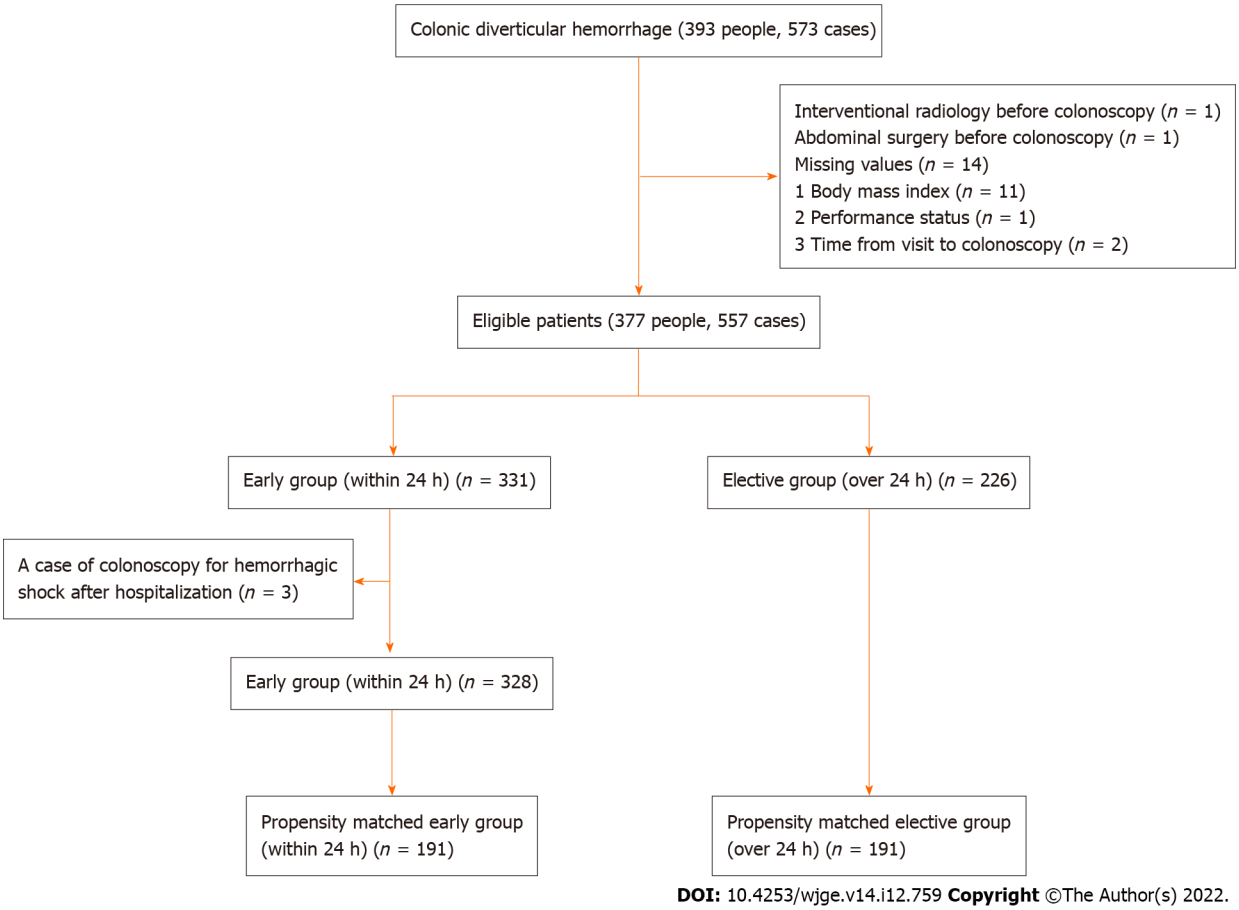
Exposure

Patients were divided into early and elective groups. The early group was defined as patients who underwent colonoscopy within 24 h of arrival and the elective group was defined as patients who underwent colonoscopy beyond 24 h of arrival.



DOI: 10.4253/wjge.v14.i12.759 **Copyright** ©The Author(s) 2022.

Figure 1 Image of Stigmata of recent hemorrhage. A: Active bleeding; B: Non-bleeding visible vessel.



DOI: 10.4253/wjge.v14.i12.759 **Copyright** ©The Author(s) 2022.

Figure 2 Patient flow.

Exclusion criteria

Patients who underwent interventional radiology (IVR) or abdominal surgery prior to colonoscopy were excluded. Patients for which variables could not be obtained, such as time from visit to colonoscopy, were also excluded. Patients who presented without hemorrhagic shock but developed hemorrhagic shock during follow-up and were allocated to the early colonoscopy group were excluded because they were allocated to the early colonoscopy group due to deterioration of their condition, which may have disadvantaged the early group.

Variables and outcomes

Variables included age, sex, body mass index, smoking history, Eastern Cooperative Oncology Group

performance status (PS) over 3[15], comorbidities (hypertension, diabetes mellites, coronary artery disease, chronic kidney disease, hemodialysis), and the use of medications (antithrombotics and non-steroidal anti-inflammatory drugs, shock vitality at presentation, contrast CT findings, and blood sampling data (hemoglobin under 10 g/dL and platelet under 10000 /μL). Body mass index was categorized as underweight (< 18.5), normal weight (18.5-24.9), overweight (25-29.9), and obese (≥ 30). Smoking history was categorized as current, past, never, or no information. PS was determined by the condition of the patient at the time of the visit. Comorbidities were ascertained from the patient's medical history and medications at the time of presentation, and creatinine over 1.5 mg/dL was defined as chronic kidney disease. Antithrombotics use was defined as the prescription of aspirin, thienopyridine, warfarin, and direct oral anticoagulants. Shock vitality was defined as a shock index over 1 at presentation[16]. Contrast CT findings were classified as: (1) With an extravascular leak; (2) without an extravascular leak; or (3) without contrast CT, according to the contrast CT taken at the time of presentation. Extravascular leakage was defined as leakage of contrast medium into the colon at least in the delayed phase.

The primary outcome was the length of hospital stay. Secondary outcomes included the identification percentage of SRH[14], rebleeding, red blood cell transfusion more than 4 units, and the IVR and abdominal surgery after colonoscopy. IVR and abdominal surgery were defined as those performed to control diverticular bleeding or to control colonoscopy-related complications. The observation period for the outcome was during hospitalization.

Statistical analysis

We performed a propensity score matching analysis between the early and elective groups. This method can minimize the effect of selection bias and imbalances in patient backgrounds between the groups [17]. We estimated propensity scores with a logistic regression using early colonoscopy as a dependent variable and all covariates as independent variables. A one-to-one propensity score matching was performed utilizing the nearest neighbor method without replacement. The caliper width was set at 20% of the standard deviation of the propensity scores on the logit scale. Balances in baseline variables using standardized mean differences were also examined and values of < 0.1 were considered balanced[17].

In addition, two analyses were performed as sensitivity analyses. First, we performed an analysis in which the time to exposure was changed. The group with a time from visit to a colonoscopy of fewer than 12 h was defined as the early group (< 12 h), and the group with a time of 12 h or more was defined as the elective group (≥ 12 h). Propensity score matching was used for analysis in the same approach as in the main analysis. Second, we performed a multivariate analysis using the same covariates. We performed multivariable linear regression analyses for the length of hospital stay and performed multivariable logistic regression analyses for the identification of SRH, rebleeding, red blood cell transfusions more than 4 units, and IVR and abdominal surgery after colonoscopy.

Continuous variables are reported using medians and interquartile ranges, and categorical variables are reported using numbers and percentages. Continuous variables were compared using Mann-Whitney U tests and categorical variables were compared using chi-square tests. The risk difference with 95% confidence intervals (CI) was calculated for binary outcomes. We also calculated odds ratios (ORs) and their 95%CIs in the multivariable analysis. The two-sided significance level for all tests was $P < 0.05$. All analyses were performed using EZR version 1.55[18], a package for R statistical software (https://www.r-project.org/). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

Ethics

All procedures were performed in accordance with the ethical standards established in the 1964 Declaration of Helsinki and its later amendments. The study was reviewed and approved by the institutional review board of the Future Medical Research Center Ethical Committee (IRB No. TGE01304-024). Due to the observational study based on medical records without using samples taken from the human body, informed consent was obtained from all participants through the opt-out method on our hospital website.

RESULTS

During the study period, 573 CDH cases were identified. After applying the defined exclusion criteria, 557 cases were included in the present study. The patients were divided into the early (n = 328) and elective (n = 226) groups. One-to-one propensity score matching created 191 pairs of patients (Figure 2).

Baseline characteristics of eligible patients before and after propensity score matching are provided in Table 1. Before propensity score matching, sex, smoking history, shock vitals at presentation, and contrast CT findings were unbalanced, especially contrast CT findings were highly unbalanced. After propensity score matching, the baseline characteristics of both groups were nearly balanced.

Table 1 Patient background before and after propensity score matching

	Before propensity score matching			After propensity score matching		
	Early group (< 24 h)	Elective group (≥ 24 h)	SMD	Early group (< 24 h)	Elective group (≥ 24 h)	SMD
Variables	***n* = 328**	***n* = 226**		***n* = 191**	***n* = 191**	
Age, yr, median (IQR)	79.0 (71.0–84.0)	79.0 (72.3–84.0)	0.047	78.0 (70.0–84.0)	79.0 (71.5–84.0)	0.057
Male, *n* (%)	220 (67.1)	135 (59.7)	0.153	132 (69.1)	126 (66.0)	0.067
Body mass index, *n* (%)			0.087			0.094
< 18.5	46 (14.0)	18 (8.0)		15 (7.9)	18 (9.4)	
18.5-24.9	210 (64.0)	153 (67.7)		124 (64.9)	128 (67.0)	
25-29.9	76 (23.2)	76 (23.2)		45 (23.6)	39 (20.4)	
≥ 30	12 (3.7)	9 (4.0)		3 (1.6)	4 (2.1)	
Smoking			0.162			0.075
Current, *n* (%)	45 (13.7)	25 (11.1)		23 (12.0)	24 (12.6)	
Past, *n* (%)	104 (31.7)	64 (28.3)		64 (33.5)	58 (30.4)	
Never, *n* (%)	169 (51.5)	133 (58.8)		101 (52.9)	105 (55.0)	
No information, *n* (%)	10 (3.0)	4 (1.8)		3 (1.6)	4 (2.1)	
Performance status ≥ 3, *n* (%)	34 (10.4)	20 (8.8)	0.051	15 (7.9)	20 (10.5)	0.091
Comorbidities						
Hypertension, *n* (%)	210 (64.0)	152 (67.3)	0.051	124 (64.9)	122 (63.9)	0.022
Diabetes mellitus, *n* (%)	67 (20.4)	51 (22.6)	0.052	41 (21.5)	37 (19.4)	0.052
Coronary artery disease, *n* (%)	92 (28.0)	67 (29.6)	0.035	63 (33.0)	57 (29.8)	0.068
Chronic kidney disease, *n* (%)	33 (10.1)	28 (12.4)	0.074	22 (11.5)	25 (13.1)	0.048
Hemodialysis, *n* (%)	2 (0.6)	5 (2.2)	0.136	2 (1.0)	4 (2.1)	0.084
Medication						
Antithrombotics, *n* (%)	123 (37.5)	80 (35.4)	0.044	79 (41.4)	68 (35.6)	0.119
NSAIDs, *n* (%)	14 (4.3)	14 (6.2)	0.087	8 (4.2)	9 (4.7)	0.025
Shock vitality at presentation, *n* (%)	28 (8.5)	12 (5.3)	0.127	9 (4.7)	12 (6.3)	0.069
Contrast CT findings			0.811			0.027
With an extravascular leak, *n* (%)	129 (39.3)	17 (7.5)		17 (8.9)	17 (8.9)	
Without an extravascular leak, *n* (%)	159 (48.5)	170 (75.2)		138 (72.3)	140 (73.3)	
Without contrast CT, *n* (%)	40 (12.2)	39 (17.3)		36 (18.8)	34 (17.8)	
Blood sampling data						
Hemoglobin < 10 g/dL, *n* (%)	84 (25.6)	61 (27.0)	0.031	54 (28.3)	51 (26.7)	0.035
Platelet < 10000 /μL, *n* (%)	4 (1.2)	3 (1.3)	0.01	2 (1.0)	2 (1.0)	< 0.001

CT: Computed tomography; SMD: Standardized mean difference; IQR: interquartile range; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs.

Table 2 shows outcomes after propensity score matching. Length of hospital stay did not significantly differ between the two groups (early group *vs* elective group; median, 7 *vs* 8 d; $P = 0.10$). Among the secondary outcomes, the identification percentage of SRH was significantly higher in the early group (32.5% in the early group *vs* 20.9% in the elective group; risk difference, 11.6%; 95%CI: 2.7 to 20.3; $P = 0.02$). The rebleeding (28.8% *vs* 24.1%, respectively; risk difference, 4.7%; 95%CI: -4.1 to 13.5; $P = 0.35$), red blood cell transfusions more than 4 units (29.3% *vs* 27.7%, respectively; risk difference, 1.6%; 95%CI: -7.5 to 10.6; $P = 0.82$), and IVR and abdominal surgery after colonoscopy (2.1% *vs* 1.6%, respectively; risk difference, 0.5%; 95%CI: -2.2 to 3.2; $P = 1.00$) were not significantly different between the two groups.

Table 2 Outcomes of the main analysis

Outcomes	Early group (< 24 h)	Elective group (≥ 24 h)	Difference (95%CI)	*P* value
Primary outcome				
Length of hospital stay, days, median (IQR)	7 (7–9)	8 (7– 9.5)		0.10
Secondary outcomes				
Identification of stigmata of recent hemorrhage (%)	32.5 (62/191)	20.9 (40/191)	11.6 (2.7 to 20.3)	0.02
Rebleeding (%)	28.8 (55/191)	24.1 (46/191)	4.7 (-4.1 to 13.5)	0.35
Red blood cell transfusion ≥ 4 units (%)	29.3 (56/191)	27.7 (53/191)	1.6 (-7.5 to 10.6)	0.82
Interventional radiology and abdominal surgery (%)	2.1 (4/191)	1.6 (3/191)	0.5 (-2.2 to 3.2)	1.00

CI: Confidence interval; IQR: Interquartile range.

The results of the sensitivity analysis adopted 12 h as the exposure time, which was similar to those of the main analysis, however, the identification of SRH was different from that of the main analysis, and the superiority of early colonoscopy could not be demonstrated (Table 3). Sensitivity analyses with multivariate analysis showed similar results to the main analysis (Table 4).

DISCUSSION

The results of this study showed no significant difference in the length of hospital stay between early colonoscopy within 24 h and elective colonoscopy. Sensitivity analyses also showed similar results, indicating the robustness of the results. In contrast, the identification percentage of SRH, although a sensitivity analysis adopting an exposure time of 12 h did not show any advantage, was significantly higher in the early group. However, early colonoscopy did not indicate significant differences in rebleeding, red blood cell transfusion more than 4 units, and IVR and abdominal surgery after colonoscopy.

The randomized control trial (RCT) investigating the benefit of early colonoscopy, which currently has the most robust evidence, is a multicenter study published in 2020[9]. In this RCT, they found an increased identification percentage of SRH in the early group, but no significant difference in the rebleeding or length of hospital stay. Similar to our study, they were unable to demonstrate the benefit of early colonoscopy within 24 h. Although we did not recognize any RCTs that investigated the usefulness of early colonoscopy for CDH because definitive diagnosis is difficult to make before colonoscopy, we did recognize a large, receipt-based observational study in the United States (n = 20,100)[19]. In this United States study, early colonoscopy within 24 h also increased rebleeding and readmission. Some of the results indicated a disadvantage of early colonoscopy. There may be several reasons for this result. In case of the receipt database study: (1) It was difficult to obtain important information such as imaging information; (2) It did not ensure accurate diagnosis; and (3) It was difficult to obtain information on an hourly scale. In the present study: (1) Although various confounding factors can be compensated for with surrogate markers, confounding factors such as extravascular leakage findings on contrast CT could not be adequately addressed, which was important in this study; and (2) The accuracy of the diagnosis itself is likely to be unclear for diseases for which validation studies are insufficient. In such cases, the diagnosis may be incorrect if factors other than ICD-10 codes are not used appropriately. The Receipt Database Study can provide data on a daily scale, but it is difficult to provide data on an hourly scale. If the procedure was performed on the same day of admission, the range would be from 0 to 47 h, depending on the time at which the patient was admitted to the hospital. Few studies have evaluated the appropriate colonoscopy time for CDH. Although the present study was an observational study conducted at a single institution, the covariates were appropriately selected and adjusted, and robustness was demonstrated in the sensitivity analysis.

A possible reason for a prolonged length of hospital stay despite the identification of the source of bleeding in our study is the high rebleeding. Table 5 shows the hemostatic methods used in endoscopic hemostasis at the time of the main analysis of this study. In this study, the most common method of hemostasis in both the early and elective groups was the zipper clipping method. As shown in Table 6, the rebleeding of the zipper clipping method was considerably higher than that of other hemostatic techniques. In contrast, the direct clipping method and endoscopic band ligation (EBL) method have a significantly lower rebleeding (direct clipping method *vs* zippier clipping method *vs* EBL method; 9.3% *vs* 45.1% *vs* 10.3%). Especially for the EBL method, its low rebleeding and safety have been reported in recent years[20-24]. The general adoption of these hemostatic methods could improve rebleeding and shorten hospital stays. The number of EBL method cases in this study was inadequate because we

Table 3 Results of sensitivity analysis for a colonoscopy exposure time of 12 h

Outcomes	Early group (< 12 h)	Elective group (≥ 12 h)	Difference (95%CI)	*P* value
Primary outcome				
Length of hospital stay, median (IQR)	7 (6–9)	8 (7– 9)		0.09
Secondary outcomes				
Identification of stigmata of recent hemorrhage (%)	40.8 (51/125)	33.6 (42/125)	7.2 (-4.7 to 19.1)	0.30
Rebleeding (%)	37.6 (47/125)	25.6 (32/125)	12.0 (0.6 to 23.4)	0.06
Red blood cell transfusion ≥ 4 units (%)	30.4 (38/125)	28.8 (36/125)	1.6 (-9.7 to 12.9)	0.89
Interventional radiology and abdominal surgery (%)	2.4 (3/125)	3.2 (4/125)	-0.8 (-4.9 to 3.3)	0.74

CI: Confidence interval; IQR: Interquartile range.

Table 4 Results of sensitivity analysis using multivariate analysis

Primary outcome	Coefficient (95%CI)	*P* value
Length of hospital stay	0.08 (-0.71 to 0.87)	0.84
Secondary outcomes	Odds ratio (95%CI)	*P* value
Identification of stigmata of recent hemorrhage	1.76 (1.14–2.70)	0.01
Rebleeding	1.21 (0.78–1.86)	0.39
Red blood cell transfusion ≥ 4 units	0.91 (0.55–1.50)	0.71
Interventional radiology and abdominal surgery	0.93 (0.23–3.78)	0.92

CI: Confidence interval.

Table 5 Different hemostatic methods in the main analysis

Hemostatic method	Early group (< 24 h)	Elective group (≥ 24 h)	*P* value
Direct clipping method, *n* (%)	17/60 (28.3)	9/40 (22.5)	0.794
Zipper clipping, method, *n* (%)	30/60 (50.0)	21/40 (52.5)	
Endoscopic band ligation method, *n* (%)	13/60 (21.7)	10/40 (25.0)	

Table 6 Rebleeding rates by hemostatic methods, *n* (%)

Hemostatic method	Direct clipping method (*n* = 43)	Zipper clipping method (*n* = 82)	Endoscopic band ligation method (*n* = 47)
Rebleeding	4 (9.3)	37 (45.1)	5 (10.6)

adopted the EBL method in 2020. Further studies will be conducted in the future.

Limits of the study

There are several limitations associated with our study that should be noted. First, this is a single-center study, and generalizability to outside institutions is insufficient. Second, the localization of diverticula and the frequency of CDH are different among racial groups. It is unclear whether the Asian data can be applied to other races[25-28]. Third, the benefits of colonoscopy for CDH are not only potential in terms of reduced hospital stay associated with the colonoscopic hemostasis, but also an important factor in confirming the diagnosis. It should be noted that this study did not consider the benefits of the diagnostic factor.

Finally, this study focused on the time period from hospital visit to colonoscopy, not from the onset of hematochezia to colonoscopy. Therefore, the time period from the onset of hematochezia to colonoscopy may have differed from the actual time.

CONCLUSION

In conclusion, our study showed that early colonoscopy within 24 h did not improve the length of hospital stay for CDH. Early colonoscopy may not be necessary for all cases of CDH.

ARTICLE HIGHLIGHTS

Research background

Appropriate timing of colonoscopy for colonic diverticular hemorrhage is not well evidenced.

Research motivation

The motivation for this study is to investigate whether within 24 h is an appropriate timing for colonoscopy for colonic diverticular hemorrhage.

Research objectives

We aimed to compare the length of hospital stay for colonoscopy for colonic diverticular hemorrhage by dividing patients into two groups: early groups (within 24 h) and elective colonoscopy (after 24 h).

Research methods

A single-center retrospective study over 5 years compared the two groups using propensity score matching.

Research results

Early colonoscopy within 24 h did not significantly improve hospital stay.

Research conclusions

Early colonoscopy within 24 h for colonic diverticular hemorrhage may not improve length of hospital stay.

Research perspectives

Further research is needed to determine which patients really need early colonoscopy.

ACKNOWLEDGEMENTS

We would like to express our gratitude to the Gastroenterology Medicine Center, the Emergency Department, and the Surgery Department of Shonan Kamakura General Hospital, who were involved in the patient care.

FOOTNOTES

Author contributions: Ichita C, Shimizu S, Sasaki A, Sumida C, Nishino T, and Kimura K contributed equally to this work; Ichita C contributed to the planning, data gathering, literature review, writing and editing of this article; Shimizu S provided epidemiological advice and reviewed for statistical analysis; Sasaki A, Sumida C, Nishino T, and Kimura K provided professional suggestions in the conduct of the study; all authors commented on draft versions and approved the final version of the manuscript.

Institutional review board statement: The study was reviewed and approved by the institutional review board of the Future Medical Research Center Ethical Committee (IRB No. TGE01304-024).

Informed consent statement: Due to the observational study based on medical records without using samples taken from the human body, informed consent was obtained from all participants through the opt-out method on our hospital website.

Conflict-of-interest statement: All the authors have no conflicts of interest directly relevant to the content of this article.

Data sharing statement: The original anonymous dataset is available on request from the corresponding author at ichikamasa@yahoo.co.jp.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was

prepared and revised according to the STROBE Statement—checklist of items.

Country/Territory of origin: Japan

ORCID number: Chikamasa Ichita 0000-0001-9210-7371; Sayuri Shimizu 0000-0003-0661-1171; Akiko Sasaki 0000-0003-4219-554X; Chihiro Sumida 0000-0002-4616-6407; Takashi Nishino 0000-0002-6717-1096; Karen Kimura 0000-0001-8165-1777.

S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

REFERENCES

1 **Nagata N**, Kobayashi K, Yamauchi A, Yamada A, Omori J, Ikeya T, Aoyama T, Tominaga N, Sato Y, Kishino T, Ishii N, Sawada T, Murata M, Takao A, Mizukami K, Kinjo K, Fujimori S, Uotani T, Fujita M, Sato H, Suzuki S, Narasaka T, Hayasaka J, Funabiki T, Kinjo Y, Mizuki A, Kiyotoki S, Mikami T, Gushima R, Fujii H, Fuyuno Y, Gunji N, Toya Y, Narimatsu K, Manabe N, Nagaike K, Kinjo T, Sumida Y, Funakoshi S, Kawagishi K, Matsuhashi T, Komaki Y, Miki K, Watanabe K, Fukuzawa M, Itoi T, Uemura N, Kawai T, Kaise M. Identifying Bleeding Etiologies by Endoscopy Affected Outcomes in 10,342 Cases With Hematochezia: CODE BLUE-J Study. *Am J Gastroenterol* 2021; **116**: 2222-2234 [PMID: 34388140 DOI: 10.14309/ajg.0000000000001413]

2 **ASGE Standards of Practice Committee**. Pasha SF, Shergill A, Acosta RD, Chandrasekhara V, Chathadi KV, Early D, Evans JA, Fisher D, Fonkalsrud L, Hwang JH, Khashab MA, Lightdale JR, Muthusamy VR, Saltzman JR, Cash BD. The role of endoscopy in the patient with lower GI bleeding. *Gastrointest Endosc* 2014; **79**: 875-885 [PMID: 24703084 DOI: 10.1016/j.gie.2013.10.039]

3 **Wilkins T**, Baird C, Pearson AN, Schade RR. Diverticular bleeding. *Am Fam Physician* 2009; **80**: 977-983 [PMID: 19873964]

4 **Strate LL**, Gralnek IM. ACG Clinical Guideline: Management of Patients With Acute Lower Gastrointestinal Bleeding. *Am J Gastroenterol* 2016; **111**: 459-474 [PMID: 26925883 DOI: 10.1038/ajg.2016.41]

5 **Nagata N**, Ishii N, Manabe N, Tomizawa K, Urita Y, Funabiki T, Fujimori S, Kaise M. Guidelines for Colonic Diverticular Bleeding and Colonic Diverticulitis: Japan Gastroenterological Association. *Digestion* 2019; **99** Suppl 1: 1-26 [PMID: 30625484 DOI: 10.1159/000495282]

6 **van Rongen I**, Thomassen BJW, Perk LE. Early Versus Standard Colonoscopy: A Randomized Controlled Trial in Patients With Acute Lower Gastrointestinal Bleeding: Results of the BLEED Study. *J Clin Gastroenterol* 2019; **53**: 591-598 [PMID: 29734211 DOI: 10.1097/MCG.0000000000001048]

7 **Green BT**, Rockey DC, Portwood G, Tarnasky PR, Guarisco S, Branch MS, Leung J, Jowell P. Urgent colonoscopy for evaluation and management of acute lower gastrointestinal hemorrhage: a randomized controlled trial. *Am J Gastroenterol* 2005; **100**: 2395-2402 [PMID: 16279891 DOI: 10.1111/j.1572-0241.2005.00306.x]

8 **Laine L**, Shah A. Randomized trial of urgent vs. elective colonoscopy in patients hospitalized with lower GI bleeding. *Am J Gastroenterol* 2010; **105**: 2636-41; quiz 2642 [PMID: 20648004 DOI: 10.1038/ajg.2010.277]

9 **Niikura R**, Nagata N, Yamada A, Honda T, Hasatani K, Ishii N, Shiratori Y, Doyama H, Nishida T, Sumiyoshi T, Fujita T, Kiyotoki S, Yada T, Yamamoto K, Shinozaki T, Takata M, Mikami T, Mabe K, Hara K, Fujishiro M, Koike K. Efficacy and Safety of Early *vs* Elective Colonoscopy for Acute Lower Gastrointestinal Bleeding. *Gastroenterology* 2020; **158**: 168-175.e6 [PMID: 31563627 DOI: 10.1053/j.gastro.2019.09.010]

10 **Tanaka Y**, Motomura Y, Akahoshi K, Iwao R, Komori K, Nakama N, Osoegawa T, Itaba S, Kubokawa M, Hisano T, Ihara E, Nakamura K, Takayanagi R. Predictive factors for colonic diverticular rebleeding: a retrospective analysis of the clinical and colonoscopic features of 111 patients. *Gut Liver* 2012; **6**: 334-338 [PMID: 22844561 DOI: 10.5009/gnl.2012.6.3.334]

11 **Aytac E**, Stocchi L, Gorgun E, Ozuner G. Risk of recurrence and long-term outcomes after colonic diverticular bleeding. *Int J Colorectal Dis* 2014; **29**: 373-378 [PMID: 24337782 DOI: 10.1007/s00384-013-1804-8]

12 **Poncet G**, Heluwaert F, Voirin D, Bonaz B, Faucheron JL. Natural history of acute colonic diverticular bleeding: a prospective study in 133 consecutive patients. *Aliment Pharmacol Ther* 2010; **32**: 466-471 [PMID: 20491745 DOI: 10.1111/j.1365-2036.2010.04362.x]

13 **Segev L**, Ozuner G. Natural history of bleeding risk in colonic diverticulosis. *Minerva Gastroenterol Dietol* 2017; **63**: 152-157 [PMID: 28240003 DOI: 10.23736/S1121-421X.17.02384-4]

14 **Jensen DM**, Ohning GV, Kovacs TO, Jutabha R, Ghassemi K, Dulai GS, Machicado GA. Natural history of definitive diverticular hemorrhage based on stigmata of recent hemorrhage and colonoscopic Doppler blood flow monitoring for risk stratification and definitive hemostasis. *Gastrointest Endosc* 2016; **83**: 416-423 [PMID: 26227931 DOI: 10.1016/j.gie.2015.07.033]

15 **Oken MM**, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; **5**: 649-655 [PMID: 7165009 DOI:

10.1097/00000421-198212000-00014]
16 **Koch E**, Lovett S, Nghiem T, Riggs RA, Rech MA. Shock index in the emergency department: utility and limitations. *Open Access Emerg Med* 2019; **11**: 179-199 [PMID: 31616192 DOI: 10.2147/OAEM.S178358]
17 **Rosenbaum PR**, Rubin DB. Constructing a control group using multivariate matched sampling methods that incorporate the propensity score. *Am Stat* 1985; **39**: 33-38 [DOI: 10.2307/2683903]
18 **Kanda Y**. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant* 2013; **48**: 452-458 [PMID: 23208313 DOI: 10.1038/bmt.2012.244]
19 **Nigam N**, Patel P, Sengupta N. Outcomes of Early Versus Delayed Colonoscopy in Lower Gastrointestinal Bleeding Using a Hospital Administrative Database. *J Clin Gastroenterol* 2018; **52**: 721-725 [PMID: 28961575 DOI: 10.1097/MCG.0000000000000937]
20 **Nagata N**, Niikura R, Ishii N, Kaise M, Omata F, Tominaga N, Kitagawa T, Ikeya T, Kobayashi K, Furumoto Y, Narasaka T, Iwata E, Sugimoto M, Itoi T, Uemura N, Kawai T. Cumulative evidence for reducing recurrence of colonic diverticular bleeding using endoscopic clipping *vs* band ligation: Systematic review and meta-analysis. *J Gastroenterol Hepatol* 2021; **36**: 1738-1743 [PMID: 33295071 DOI: 10.1111/jgh.15370]
21 **Ishii N**, Setoyama T, Deshpande GA, Omata F, Matsuda M, Suzuki S, Uemura M, Iizuka Y, Fukuda K, Suzuki K, Fujita Y. Endoscopic band ligation for colonic diverticular hemorrhage. *Gastrointest Endosc* 2012; **75**: 382-387 [PMID: 21944311 DOI: 10.1016/j.gie.2011.07.030]
22 **Okamoto T**, Nakamura K, Yamamoto K, Yoshimoto T, Takasu A, Shiratori Y, Ikeya T, Okuyama S, Takagi K, Fukuda K. Safety and Effectiveness of Endoscopic Band Ligation for Colonic Diverticular Bleeding in Elderly Patients. *Digestion* 2021; **102**: 760-766 [PMID: 33556954 DOI: 10.1159/000513310]
23 **Nagata N**, Ishii N, Kaise M, Shimbo T, Sakurai T, Akiyama J, Uemura N. Long-term recurrent bleeding risk after endoscopic therapy for definitive colonic diverticular bleeding: band ligation versus clipping. *Gastrointest Endosc* 2018; **88**: 841-853.e4 [PMID: 30036505 DOI: 10.1016/j.gie.2018.07.018]
24 **Kobayashi K**, Nagata N, Furumoto Y, Yamauchi A, Yamada A, Omori J, Ikeya T, Aoyama T, Tominaga N, Sato Y, Kishino T, Ishii N, Sawada T, Murata M, Takao A, Mizukami K, Kinjo K, Fujimori S, Uotani T, Fujita M, Sato H, Suzuki S, Narasaka T, Hayasaka J, Kaise M; CODE BLUE-J study collaborators. Effectiveness and adverse events of endoscopic clipping *vs* band ligation for colonic diverticular hemorrhage: a large-scale multicenter cohort study. *Endoscopy* 2022; **54**: 735-744 [PMID: 34820792 DOI: 10.1055/a-1705-0921]
25 **Nagata N**, Niikura R, Aoki T, Shimbo T, Itoh T, Goda Y, Suda R, Yano H, Akiyama J, Yanase M, Mizokami M, Uemura N. Increase in colonic diverticulosis and diverticular hemorrhage in an aging society: lessons from a 9-year colonoscopic study of 28,192 patients in Japan. *Int J Colorectal Dis* 2014; **29**: 379-385 [PMID: 24317937 DOI: 10.1007/s00384-013-1808-4]
26 **Nagata N**, Niikura R, Shimbo T, Kishida Y, Sekine K, Tanaka S, Aoki T, Watanabe K, Akiyama J, Yanase M, Itoh T, Mizokami M, Uemura N. Alcohol and smoking affect risk of uncomplicated colonic diverticulosis in Japan. *PLoS One* 2013; **8**: e81137 [PMID: 24339905 DOI: 10.1371/journal.pone.0081137]
27 **Wheat CL**, Strate LL. Trends in Hospitalization for Diverticulitis and Diverticular Bleeding in the United States From 2000 to 2010. *Clin Gastroenterol Hepatol* 2016; **14**: 96-103.e1 [PMID: 25862988 DOI: 10.1016/j.cgh.2015.03.030]
28 **Peery AF**, Keku TO, Martin CF, Eluri S, Runge T, Galanko JA, Sandler RS. Distribution and Characteristics of Colonic Diverticula in a United States Screening Population. *Clin Gastroenterol Hepatol* 2016; **14**: 980-985.e1 [PMID: 26872402 DOI: 10.1016/j.cgh.2016.01.020]

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Endosc 2022 December 16; 14(12): 769-776

DOI: 10.4253/wjge.v14.i12.769

ISSN 1948-5190 (online)

ORIGINAL ARTICLE

Observational Study

Our initial single port robotic cholecystectomy experience: A feasible and safe option for benign gallbladder diseases

Huseyin Kemal Rasa, Ayhan Erdemir

Specialty type: Surgery

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single-blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Cochior D, Romania; Kumar A, India

Received: September 22, 2022
Peer-review started: September 22, 2022
First decision: October 20, 2022
Revised: November 25, 2022
Accepted: December 1, 2022
Article in press: December 1, 2022
Published online: December 16, 2022

Huseyin Kemal Rasa, Ayhan Erdemir, Department of General Surgery, Anadolu Medical Center Hospital, Kocaeli 41400, Turkey

Corresponding author: Huseyin Kemal Rasa, MD, Attending Doctor, Department of General Surgery, Anadolu Medical Center Hospital, Cumhuriyet Mahallesi 2255 Sokak No 3 Gebze, Kocaeli 41400, Turkey. kemrasa@gmail.com

Abstract

BACKGROUND

Although single-port laparoscopic cholecystectomy has been performed for over 25 years, it is still not popular. The narrow working space used in this surgery limits the movement of instruments and causes ergonomic challenges. Robotic surgery not only resolves the ergonomic challenges of single-port laparoscopic surgery but is also considered a good option with its additional technical advantages, like a three-dimensional display and not being affected by tremors. However, the extent to which these technical and ergonomic advantages positively affect the surgical outcomes and how safe the single-port robotic surgeries need to be assessed for each particular surgery.

AIM

To evaluate the feasibility and safety of single-port robotic cholecystectomy for patients with cholelithiasis.

METHODS

The electronic records of the first 40 consecutive patients with gallbladder lithiasis who underwent single-port robotic cholecystectomy from 2013 to 2021 were analyzed retrospectively. In addition to the demographic characteristics of the patients, we analyzed American Society of Anesthesiologists (ASA) scores and body mass index. The presence of an accompanying umbilical hernia was also noted. The amount of blood loss during the operation, the necessity to place a drain in the subhepatic area, and the need to use grafts during the closure of the fascia of the port site were determined. Hospital stay, readmission rates, perioperative and postoperative complications, the Clavien-Dindo complication scores and postoperative analgesia requirements were also evaluated.

RESULTS

The mean age of the 40 patients included in the study was 49.5 ± 11.6 years, and 26 were female (65.0%). The umbilical hernia was present in 24 (60.0%) patients,

with a body mass index median of 29.3 kg/m^2 and a mean of 29.7 ± 5.2 kg/m^2. Fifteen (37.5%) of the patients were evaluated as ASA I, 18 (45.0%) as ASA II, and 7 (17.5%) as ASA III. The mean bleeding amount during the operation was 58.4 ± 55.8 mL, and drain placement was required in 12 patients (30.0%). After port removal, graft reinforcement during fascia closure was preferred in 14 patients (35.0%). The median operation time was 93.5 min and the mean was 101.2 ± 27.0 min. The mean hospital stay was 1.4 ± 0.6 d, and 1 patient was readmitted to the hospital due to pain (2.5%). Clavien-Dindo I complications were seen in 14 patients (35.0%), and five (12.5%) complications were wound site problems.

CONCLUSION

In addition to the technological and ergonomic advantages robotic surgery provides surgeons, our study strongly supports that single-port robotic cholecystectomy is a feasible and safe option for treating patients with gallstones.

Key Words: Cholecystectomy; Laparoscopic cholecystectomy; Robotic surgery; Single-port surgery; Single-port laparoscopic cholecystectomy; Single-port robotic cholecystectomy

Core Tip: We retrospectively analyzed 40 consecutive patients with cholelithiasis who underwent single-port robotic cholecystectomy from 2013 to 2021. We believe that the learning curve for single-port robotic cholecystectomy surgery is not long, and after a particular experience, the operation times are significantly shortened. Our data suggest that it is a safe surgery with acceptable intraoperative blood loss, no conversion, and no bile duct injury or postoperative bile leak. Our data also support more liberal graft use during the fascia closure. Single-port robotic cholecystectomy is a feasible and safe option that should be considered when treating patients with gallstones.

Citation: Rasa HK, Erdemir A. Our initial single port robotic cholecystectomy experience: A feasible and safe option for benign gallbladder diseases. *World J Gastrointest Endosc* 2022; 14(12): 769-776
URL: https://www.wjgnet.com/1948-5190/full/v14/i12/769.htm
DOI: https://dx.doi.org/10.4253/wjge.v14.i12.769

INTRODUCTION

The first successful laparoscopic cholecystectomy (LC) was performed in 1985 and quickly became the preferred method for all benign gallbladder diseases. The laparoscopic approach was also favored for different surgeries and initiated the evolution of "single-port" and "robotic" surgeries. Single-port laparoscopic cholecystectomy (SPLC) was first introduced in 1995[1] and was shown to be a reasonable option for various surgeries like appendectomy[2] and colectomy[3].

The narrow working space in SPLC limits the movement of instruments and causes ergonomic challenges like crowding and collision between instruments. These technical difficulties have prevented SPLC from becoming the gold standard approach[4]. Robotic surgery gained popularity after 2010 and resolved the ergonomic challenges of single-port surgeries. Its additional technical advantages, like a three-dimensional display and not being affected by tremors, enable robotic surgery to be a good option for surgeries with single-port use. On the other hand, the extent to which these technical and ergonomic advantages positively affect surgical outcomes and how safe robotic surgeries are performed with a single port still need to be assessed.

To evaluate the feasibility and safety of single-port robotic cholecystectomy (SPRC) surgery, we analyzed the results of our first 40 consecutive SPRC operations for cholelithiasis from 2013 to 2021.

MATERIALS AND METHODS

The electronic patient records of the first 40 consecutive patients who underwent SPRC using the "da Vinci SI" platform (Intuitive Surgical, Sunnyvale, CA, United States) in our hospital between 2013 and 2021 were reviewed retrospectively. The indication for surgery in all patients was gallbladder lithiasis. No distinction was made between patients with or without symptoms, and patients with acute cholecystitis or suspected malignancy were not included in the group.

Gel port or SILS port was used in surgeries. The port was placed through an open technique, and a 3 cm incision was made from the umbilicus. After port placement, the patient was placed in a partial reverse Trendelenburg and right tilt position. The port was positioned with the camera trocar at the bottom and the working trocars at the top. After the camera trocar was inserted, the docking was done. Monopolar scissors and bipolar fenestrated forceps were placed in the study arms. A technique similar to LC was used in the surgeries. To reduce the risk of bile duct injuries and to avoid complications due to anatomical alterations, we used the "Critical View of Safety" technique introduced by Strasberg in all our SPRC surgeries[5]. Admittedly, the view achieved by SPRC is usually better than that of laparoscopy.

Similar care with laparoscopic surgeries in the postoperative period was applied. Patients were allowed to take fluids in the 2nd hour, mobilized at the 6th hour, and discharged within 1 d to 3 d post-surgery.

In addition to the demographic characteristics of the patients, we analyzed American Society of Anesthesiologists (ASA) scores and body mass indexes. The presence of an accompanying umbilical hernia was also noted. The amount of blood loss during the operation, the necessity to place a drain in the subhepatic area and the need to use grafts during the closure of the fascia of the port site were determined. Hospital stay, readmission rates, perioperative and postoperative complications, the Clavien-Dindo complication scores, and postoperative analgesia requirements were also evaluated.

Ertan Koç reviewed the calculations and statistical methods of this study.

RESULTS

The mean age of the 40 patients included in the study was 49.5 ± 11.6 years, and 26 patients were female (65.0%). The umbilical hernia was present in 24 (60.0%) patients with a body mass index median of 29.3 kg/m^2 and mean of 29.7 ± 5.2 kg/m^2. Fifteen (37.5%) of the patients were evaluated as ASA I, 18 (45.0%) as ASA II, and 7 (17.5%) as ASA III. The mean blood loss during the operation was 58.4 ± 55.8 mL, and drain placement was required in 12 patients (30.0%). After port removal, graft reinforcement for fascia closure was preferred in 14 patients (35.0%). We used a prolene graft for fascia closure reinforcement. After the fascial defect was primarily closed, a properly sized prolene graft was placed as an on-lay, and the graft was fixed with interrupted non-absorbable sutures.

The median operative time was 93.5 min and the mean time was 101.2 ± 27.0 min. The mean hospital stay was 1.4 ± 0.6 d, and 1 patient was readmitted to the hospital due to pain (2.5%). Clavien-Dindo I complications were seen in 14 patients (35.0%), and five complications (12.5%) were wound site problems (Table 1).

We also evaluated our 40 consecutive multi-port laparoscopic cholecystectomies performed in the last 6 mo to guide us in evaluating the results of our study. The average age of the patient in this group was 45.5. Fifteen of the patients were female and twenty-five were male. The mean BMI was 28.7 kg/m^2. For ASA scores, 14 patients were ASA 1, 23 were ASA 2, and 3 were ASA 3. One patient had an umbilical hernia. Thirteen patients were operated on for acute cholecystitis. Perioperative bleeding was minimal and drains were used in 4 patients; no grafts were used in any of the patients. The mean operative time was 54 min, and the average length of stay in the hospital was 1 d. A single dose of paracetamol was used as an analgesic postoperatively in 23 of the patients. Complications at the level of Clavien-Dindo 1 (2 of diarrhea, 1 of pain) developed in 3 patients postoperatively, but no patient required re-hospitalization (Table 2).

DISCUSSION

A systematic review published in 2021 evaluating the intraoperative and postoperative results of robotic cholecystectomy showed that the operating room time for robotic cholecystectomy is longer than its laparoscopic equivalent[6]. When the studies included in this review were evaluated, it was shown that the most critical factor that extended the operation time was the learning curve. While the time difference between the robotic and laparoscopic surgeries was more distinct in the studies before 2010, it was seen that there was less or no difference in the studies published in the following years. SPRC surgeries in our study lasted 60 to 207 min, with a median time of 93.5 min and an average of 101.2 ± 27 min. When we reviewed our data, we saw a similar trend in our study; the surgeries performed at the beginning of our learning curve took longer, and the operating times shortened over time. The increase in the operating room team's experience in preparing the robotic arrangement and the rapid replacement of hand tools shortened the surgery and operation times.

Perhaps the most significant limitation of our study was that the number of included surgeries was only 40. With this total number, it was impossible to perform subgroup analyses such as early and late periods, in which statistically significant differences could be revealed. On the other hand, our observation was similar to the results of a systematic review published in 2018 by Migliore *et al*[7] that showed the learning curve for SPRC surgery to not be long. After a particular experience, the operation

Table 1 Demographic and perioperative data of the patients

Characteristic	Parameter		
Age, yr	Min-Max: 26-73	Median: 48	mean ± SD: 49.5 ± 11.6
BMI, kg/m^2	Min-Max: 20.2–40.9	Median: 29.3	mean ± SD: 29.7 ± 5.2
Operation time, min	Min-Max: 60-207	Median: 93.5	mean ± SD: 101.2 ± 27.0
Amount of bleeding, mL	Min-Max: 15-250	Median: 50	mean ± SD: 58.4 ± 55.8
Length of hospital stay, d	Min-Max: 1-3	Median: 1	mean ± SD: 1.4 ± 0.6
Sex	Female	26	65
	Male	14	35
ASA score	I	15	37.5
	II	18	45
	III	7	17.5
Umbilical hernia	Present	24	60
	Absent	16	40
Drain	Present	12	30
	Absent	28	70
Graft	Present	14	35
	Absent	26	65
Postoperative complication	Present	14	35
	Absent	26	65
Readmission	Present	1	2.5
	Absent	39	97.5

Parameter data are presented as *n* and %, unless otherwise indicated. ASA: American Society of Anesthesiologists; BMI: Body mass index; SD: Standard deviation.

times were shortened significantly.

The same systematic review analyzed the conversion rates of SPRC surgeries. According to the results of the 13 studies included in the review, it was found that this rate was 4.2%, of which 2.2% were converted to multi-port laparoscopic surgery and 2% to open surgery[7]. We had no conversion among the 40 operations, probably due to our inclusion criteria. We did not prefer SPRC operations for patients with acute cholecystitis and its complications, such as perforation, or patients with malignant pathologies.

As a result of increasing experience and developing technological possibilities, the risk of complications in operations performed for benign gallbladder diseases has decreased significantly. Problems such as bile duct injuries and postoperative bile leaks decreased to 0.1%-0.3%. In our study, there were no patients with intraoperative bile duct injury or postoperative bile leakage. These data were again attributed to our patient selection criteria and our limited number of surgeries. We anticipate that this technique will also become one of our options in non-elective gallbladder surgeries and malignant diseases soon. We plan to evaluate whether SPRC surgeries performed for these more complicated aetiologies will affect our complication rates.

The mean perioperative blood loss in our SPRC surgeries was 58 mL. This loss was similar to the blood loss in other cholecystectomy operations where we use different techniques like LC or SPLC and is also comparable with literature data. Our "learning curve" discussion about the operation time may also be valid for our generous drain preference in this cohort (12 surgeries – 30.0%), and we hypothesize that we will have a decreasing trend in the coming years.

An umbilical hernia was present in 24 patients (60.0%). This rate is higher than expected, likely due to the addition of patients with fascia defects detected by ultrasonography to patients with clinically significant hernia. At the end of the surgery, graft reinforcement was preferred in 14 patients (35.0%) during the closure of the port site. In the follow-up, an incisional hernia was observed in 1 patient (2.5%) in whom we did not use a graft. A meta-analysis by Jensen *et al*[8] showed that the risk of incisional hernia development in patients who underwent robotic cholecystectomy ranged from 0% to 16.7%. We also know that prophylactic graft use in the laparoscopic method reduces the risk of incisional hernia

Table 2 Demographic and perioperative data of our last 40 consecutive laparoscopic cholecystectomy patients

Feature		Value
Average age, yr		45.5
BMI, kg/m^2		28.7
Operation time, min		54
Amount of bleeding, mL		10
Length of hospital stay, d		1
Sex	Female	15
	Male	25
ASA score	I	14
	II	23
	III	3
Umbilical hernia	Absent	39
	Present	1
Drain	Absent	36
	Present	4
Graft	Absent	40
	Present	0
Postoperative complication	Absent	37
	Present	3
Readmission	Absent	40
	Present	0

ASA: American Society of Anesthesiologists; BMI: Body mass index.

development[9]. Our study had only 1 patient with an incisional hernia, and we did not use a graft for that patient. All those facts support more liberal graft use during the fascia closure. Graft reinforcement should be considered more frequently, especially in patients with a body mass index > 30 kg/m^2, over 65 years of age, who are diabetic, and who have a chronic obstructive pulmonary disease with impaired wound healing and a high risk of incisional hernia.

It is known that wound site problems are more significant in laparoscopic and robotic cholecystectomy operations performed *via* a single port when compared with multiple ports[10,11]. While the general wound site problems reported for SPRC surgeries accounted for 5%, it was found that this problem was seen in 5 patients (12.5%) in our study. The difference between the literature and the results of our study may be due to the definition of 'wound problem'. While in most series only patients with surgical site infection and significant seroma were included in this group, we added patients with surgical site dehiscence and incision healing problems to the list.

LC operations performed using a single port have better cosmetic results than LC operations performed using multiple ports and provide higher patient satisfaction[10,11]. However, in robotic surgery, there is no study evaluating the impact of the port number on cosmetic results and patient satisfaction. The general belief is that patients are happier with a single incision, and our observations support this data.

There is no robust data that support that any of the surgical options for cholecystectomy have an impact on postoperative pain. A systematic review published in 2021 analyzed 15 studies for postoperative pain. It was concluded that it is impossible to say whether there is a difference between patients who underwent robotic surgery or LC due to different study methodologies and pain assessment methods[6]. In a recently published study, it was found that the pain scores of patients who underwent SPRC were lower than the scores of patients who underwent LC *via* a single port[12]. It was observed that the pain scores of the patients included in our study were low, and pain control could be achieved effectively using single (paracetamol) or dual (paracetamol and nonsteroidal anti-inflammatory) painkillers. In 1 patient included in the study, post-discharge pain scores remained high, and he was re-hospitalized to maintain pain control.

Sun *et al*[13] published a systematic review and meta-analysis in 2018, which compared SPRC and multi-port laparoscopic cholecystectomy surgeries. They concluded that the risk of incisional hernia and the high cost of the procedure should be considered when performing SPRC. However, their main conclusion was that, so far, the advantages and disadvantages of SPRC still have not been studied extensively and we need more high-quality studies and data to be able to comment on robot-assisted cholecystectomy operations. Indeed, there is also a lack of concrete evidence from comparisons of the advantages and disadvantages of the single-port *vs* multi-port robotic cholecystectomy operations, with the exceptions of features related to ergonomics and technical components. More high-quality studies are also needed for applicability in more complex gallbladder diseases.

Another limitation of our study was the inability to evaluate whether SPRC increased the cost of treating benign gallbladder diseases. The cost of the operations showed a significant difference during the study period (2013-2021) due to a number of reasons. According to current calculations, the mean cost for SPRC is $6659 and for multi-port laparoscopic cholecystectomy is $2439.

CONCLUSION

The findings from this study, which we performed on 40 consecutive patients, strongly support the view that SPRC is a feasible and safe surgery. Considering the technological and ergonomic advantages it provides to the surgeon, SPRC seems to be an excellent option that should be considered for all benign gallbladder pathologies. It would be appropriate to confirm this inference with randomized controlled studies with a large number of patients in the near future.

ARTICLE HIGHLIGHTS

Research background

Single-port laparoscopic cholecystectomy has been performed for over 25 years but is not popular. The narrow working space in this surgery limits the movement of instruments and causes ergonomic challenges. Robotic surgery resolves the ergonomic challenges. However, the extent to which these technical and ergonomic advantages positively affect the surgical outcomes and the safety of the single-port robotic surgeries need to be assessed.

Research motivation

Our first motivation for the study was to determine the feasibility and safety of single-port laparoscopic cholecystectomy. We also evaluated patient outcomes after robotic surgery.

Research objectives

Our main objective was to evaluate the safety of single-port laparoscopic cholecystectomy by determining intraoperative blood loss, conversion rate, and risk of bile duct injury or postoperative bile leak. We also determined the necessity of grafts during fascia closure.

Research methods

Our research methodology was retrospective electronic patient record evaluation.

Research results

We observed that the mean blood loss during the operation was 58.4 mL, and drain placement was required in 12 patients (30.0%). The median operative time was 93.5 min. We hypothesize that experience of the surgeon will have a positive effect on those numbers, and future studies will have better results. After port removal, graft reinforcement for fascia closure was preferred in 14 patients (35.0%). One patient was readmitted to the hospital due to pain (2.5%). Clavien-Dindo I complications were seen in 14 patients (35.0%), and 5 complications (12.5%) were wound site problems. These data support the safety of single-port robotic cholecystectomy.

Research conclusions

The findings of this study, which we performed on 40 consecutive patients, strongly supported the view that single-port robotic cholecystectomy is a feasible and safe surgery. Considering the technological and ergonomic advantages it provides to the surgeon, single-port robotic cholecystectomy seems an excellent option that should be considered for all benign gallbladder pathologies.

Research perspectives

It would be appropriate to confirm our results with randomized controlled studies to be conducted with more patients in the near future. Also, comparing single-port laparoscopic cholecystectomy and single-

port robotic cholecystectomy will be helpful.

FOOTNOTES

Author contributions: Rasa HK contributed to conceptualization of the study, methodology, writing, review and editing of the manuscript, and project administration; Erdemir A contributed to conceptualization of the study, methodology, formal analysis of the data, investigation into the literature and writing of the original draft of the manuscript; both authors read and approved the final manuscript.

Institutional review board statement: The study was conducted following the Declaration of Helsinki (as revised in 2013) and was approved by Anadolu Medical Center Hospital review board and ethics committee (ASM-EK-22/186).

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest.

Data sharing statement: The datasets analyzed during the current study are available in the hospital's "electronic patient records" and from the corresponding author on reasonable request.

STROBE statement: The authors have read the STROBE Statement—a checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—a checklist of items.

Country/Territory of origin: Turkey

ORCID number: Huseyin Kemal Rasa 0000-0002-2872-3249; Ayhan Erdemir 0000-0002-5353-6496.

S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

REFERENCES

1 **Navarra G**, Pozza E, Occhionorelli S, Carcoforo P, Donini I. One-wound laparoscopic cholecystectomy. *Br J Surg* 1997; **84**: 695 [PMID: 9171771 DOI: 10.1046/j.1365-2168.1997.02586.x]
2 **Duza G**, Davrieux CF, Palermo M, Khiangte E, Azfar M, Rizvi SAA, Trelles N, Zorraquin C, Sbai-Idrissi M, Le Brian Alban Z. Conventional Laparoscopic Appendectomy Versus Single-Port Laparoscopic Appendectomy, a Multicenter Randomized Control Trial: A Feasible and Safe Alternative to Standard Laparoscopy. *J Laparoendosc Adv Surg Tech A* 2019; **29**: 1577-1584 [PMID: 31613689 DOI: 10.1089/lap.2019.0460]
3 **Hirano Y**, Hiranuma C, Hattori M, Douden K, Yamaguchi S. Single-incision or Single-incision Plus One-Port Laparoscopic Surgery for Colorectal Cancer. *Surg Technol Int* 2020; **36**: 132-135 [PMID: 32196563]
4 **Lee SH**, Jung MJ, Hwang HK, Kang CM, Lee WJ. The first experiences of robotic single-site cholecystectomy in Asia: a potential way to expand minimally-invasive single-site surgery? *Yonsei Med J* 2015; **56**: 189-195 [PMID: 25510764 DOI: 10.3349/ymj.2015.56.1.189]
5 **Sgaramella LI**, Gurrado A, Pasculli A, de Angelis N, Memeo R, Prete FP, Berti S, Ceccarelli G, Rigamonti M, Badessi FGA, Solari N, Milone M, Catena F, Scabini S, Vittore F, Perrone G, de Werra C, Cafiero F, Testini M; SYoN Italian Collaborative Group. The critical view of safety during laparoscopic cholecystectomy: Strasberg Yes or No? *Surg Endosc* 2021; **35**: 3698-3708 [PMID: 32780231 DOI: 10.1007/s00464-020-07852-6]
6 **Shenoy R**, Mederos MA, Ye L, Mak SS, Begashaw MM, Booth MS, Shekelle PG, Wilson M, Gunnar W, Maggard-Gibbons M, Girgis MD. Intraoperative and postoperative outcomes of robot-assisted cholecystectomy: a systematic review. *Syst Rev* 2021; **10**: 124 [PMID: 33892794 DOI: 10.1186/s13643-021-01673-x]
7 **Migliore M**, Arezzo A, Arolfo S, Passera R, Morino M. Safety of single-incision robotic cholecystectomy for benign gallbladder disease: a systematic review. *Surg Endosc* 2018; **32**: 4716-4727 [PMID: 29943057 DOI: 10.1007/s00464-018-6300-3]
8 **Jensen SAS**, Fonnes S, Gram-Hanssen A, Andresen K, Rosenberg J. Low long-term incidence of incisional hernia after cholecystectomy: A systematic review with meta-analysis. *Surgery* 2021; **169**: 1268-1277 [PMID: 33610340 DOI: 10.1016/j.surg.2020.12.027]
9 **Armañanzas L**, Ruiz-Tovar J, Arroyo A, García-Peche P, Armañanzas E, Diez M, Galindo I, Calpena R. Prophylactic mesh vs suture in the closure of the umbilical trocar site after laparoscopic cholecystectomy in high-risk patients for

incisional hernia. A randomized clinical trial. *J Am Coll Surg* 2014; **218**: 960-968 [PMID: 24680572 DOI: 10.1016/j.jamcollsurg.2014.01.049]

10 **Pisanu A**, Reccia I, Porceddu G, Uccheddu A. Meta-analysis of prospective randomized studies comparing single-incision laparoscopic cholecystectomy (SILC) and conventional multiport laparoscopic cholecystectomy (CMLC). *J Gastrointest Surg* 2012; **16**: 1790-1801 [PMID: 22767084 DOI: 10.1007/s11605-012-1956-9]

11 **Arezzo A**, Passera R, Bullano A, Mintz Y, Kedar A, Boni L, Cassinotti E, Rosati R, Fumagalli Romario U, Sorrentino M, Brizzolari M, Di Lorenzo N, Gaspari AL, Andreone D, De Stefani E, Navarra G, Lazzara S, Degiuli M, Shishin K, Khatkov I, Kazakov I, Schrittwieser R, Carus T, Corradi A, Sitzman G, Lacy A, Uranues S, Szold A, Morino M. Multi-port versus single-port cholecystectomy: results of a multi-centre, randomised controlled trial (MUSIC trial). *Surg Endosc* 2017; **31**: 2872-2880 [PMID: 27778171 DOI: 10.1007/s00464-016-5298-7]

12 **Lee SM**, Lim JH. Comparison of outcomes of single incision robotic cholecystectomy and single incision laparoscopic cholecystectomy. *Ann Hepatobiliary Pancreat Surg* 2021; **25**: 78-83 [PMID: 33649258 DOI: 10.14701/ahbps.2021.25.1.78]

13 **Sun N**, Zhang J, Zhang C, Shi Y. Single-site robotic cholecystectomy versus multi-port laparoscopic cholecystectomy: A systematic review and meta-analysis. *Am J Surg* 2018; **216**: 1205-1211 [PMID: 29866396 DOI: 10.1016/j.amjsurg.2018.04.018]

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Endosc 2022 December 16; 14(12): 777-788

DOI: 10.4253/wjge.v14.i12.777

ISSN 1948-5190 (online)

ORIGINAL ARTICLE

Randomized Clinical Trial

High-flow oxygen *via* oxygenating mouthguard in short upper gastrointestinal endoscopy: A randomised controlled trial

Kim Hay Be, Leonardo Zorron Cheng Tao Pu, Brett Pearce, Matthew Lee, Luke Fletcher, Rebecca Cogan, Philip Peyton, Rhys Vaughan, Marios Efthymiou, Sujievvan Chandran

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Bohara TP; João MPO, Portugal

Received: September 18, 2022
Peer-review started: September 18, 2022
First decision: October 19, 2022
Revised: October 26, 2022
Accepted: November 9, 2022
Article in press: November 9, 2022
Published online: December 16, 2022

Kim Hay Be, Leonardo Zorron Cheng Tao Pu, Rhys Vaughan, Marios Efthymiou, Sujievvan Chandran, Department of Gastroenterology and Hepatology, Austin Health, Heidelberg 3084, Victoria, Australia

Brett Pearce, Matthew Lee, Luke Fletcher, Rebecca Cogan, Philip Peyton, Department of Anaesthesia and Pain Medicine, Austin Health, Heidelberg 3084, Victoria, Australia

Brett Pearce, Matthew Lee, Philip Peyton, Rhys Vaughan, Marios Efthymiou, Sujievvan Chandran, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Parkville 3010, Victoria, Australia

Sujievvan Chandran, Faculty of Medicine, Nursing and Health Sciences, Monash University, Frankston 3199, Victoria, Australia

Corresponding author: Kim Hay Be, MBBS, Doctor, Department of Gastroenterology and Hepatology, Austin Health, 145 Studley Road, Heidelberg 3084, Victoria, Australia.
kim.be@austin.org.au

Abstract

BACKGROUND

Anaesthetic care during upper gastrointestinal (GI) endoscopy has the unique challenge of maintaining ventilation and oxygenation *via* a shared upper airway. Supplemental oxygen is recommended by international society guidelines, however, the optimal route or rate of oxygen delivery is not known. Various oxygen delivery devices have been investigated to improve oxygenation during upper GI endoscopy, however, these are limited by commercial availability, costs and in some cases, the expertise required for insertion. Anecdotally at our centre, higher flows of supplemental oxygen can safely be delivered *via* an oxygenating mouthguard routinely used during upper GI endoscopic procedures.

AIM

To assess the incidence of hypoxaemia (SpO_2 < 90%) in patients undergoing upper GI endoscopy receiving supplemental oxygen using an oxygenating mouthguard at 20 L/min flow compared to standard nasal cannula (SNC) at 2 L/min flow.

METHODS

A single centre, prospective, randomised clinical trial at two sites of an Australian

tertiary hospital between October 2020 and September 2021 was conducted. Patients undergoing elective upper gastrointestinal endoscopy under deep sedation were randomised to receive supplemental oxygen *via* high-flow *via* oxygenating mouthguard (HFMG) at 20 L/min flow or SNC at 2 L/min flow. The primary outcome was the incidence of hypoxaemia of any duration measured by pulse oximetry. Intraprocedural-related, procedural-related, and sedation-related adverse events and patient-reported outcomes were also recorded.

RESULTS

Three hundred patients were randomised. Eight patients were excluded after randomisation. 292 patients were included in the intention-to-treat analysis. The incidence of hypoxaemia was significantly reduced in those allocated HFMG. Six patients (4.4%) allocated to HFMG experienced an episode of hypoxaemia, compared to thirty-four (22.1%) patients allocated to SNC (P value < 0.001). No significant difference was observed in the rates of adverse events or patient-reported outcome measures.

CONCLUSION

The use of HFMG offers a novel approach to reducing the incidence of hypoxaemia during short upper gastrointestinal endoscopic procedures in low-risk patients undergoing deep sedation.

Key Words: Upper gastrointestinal endoscopy; Supplementary oxygen; Hypoxaemia; Oxygenating mouthguard

Core Tip: This randomised controlled trial compared the incidence of hypoxaemia in those receiving supplemental oxygen at 20 L/min *via* an oxygenating mouthguard to those receiving supplemental oxygen at 2 L/min *via* standard nasal cannula during upper gastrointestinal endoscopy performed under deep sedation. A statistically significant difference in the incidence of hypoxaemia was demonstrated. No significant difference was observed in rates of adverse events or patient-reported outcome measures. We conclude that the use of supplemental oxygen at 20 L/min *via* an oxygenating mouthguard offers a novel approach to reducing the incidence of hypoxaemia in patients undergoing upper gastrointestinal endoscopy under deep sedation.

Citation: Be KH, Zorron Cheng Tao Pu L, Pearce B, Lee M, Fletcher L, Cogan R, Peyton P, Vaughan R, Efthymiou M, Chandran S. High-flow oxygen *via* oxygenating mouthguard in short upper gastrointestinal endoscopy: A randomised controlled trial. *World J Gastrointest Endosc* 2022; 14(12): 777-788
URL: https://www.wjgnet.com/1948-5190/full/v14/i12/777.htm
DOI: https://dx.doi.org/10.4253/wjge.v14.i12.777

INTRODUCTION

Upper gastrointestinal (GI) endoscopic procedures are commonly performed under monitored anesthesia to facilitate endoscopic examination. Anaesthetic care during upper GI endoscopy has the unique challenges of balancing adequate patient sedation while maintaining sufficient ventilation and oxygenation *via* a shared upper airway[1]. In addition, anaesthetic agents routinely used during sedation for GI endoscopies, such as propofol, in combination with benzodiazepines and opioids can cause respiratory depression, predisposing patients to upper airway obstruction, hypoventilation, and hypoxaemia[2]. Therefore, supplementary oxygen during upper GI endoscopy under deep sedation is considered the standard practice to reduce the incidence and severity of hypoxaemia[3].

Although supplemental oxygen is a recommendation of various national and international societies, it is unclear what the optimal routes or rates of supplemental oxygen delivery are[4,5]. The incidence of hypoxaemia during upper GI endoscopy with deep sedation is common, and reported to occur in up to 33% of procedures depending on the route and rate of supplemental oxygen used[6,7]. Although transient and mild episodes of hypoxaemia are likely inconsequential, prolonged or severe hypoxaemia is associated with tachycardia and myocardial ischemia[8,9]. Various oxygen delivery devices have been investigated to improve oxygenation during upper GI endoscopy. These include standard nasal cannula (SNC), high-flow nasal cannula (HFNC), modified bite blocks, modified face masks and other more invasive nasopharyngeal (such as Wei Nasal Jet tube) and oropharyngeal devices (such as a gastro-laryngeal tube)[10-12]. The principles underlying these airway devices include the delivery of higher

fractionated oxygen (FiO_2) with or without positive pressure ventilation[1].

Oxygen supplementation *via* SNC is the most common approach to oxygen delivery during upper gastrointestinal endoscopy[11]. However, its use is limited to flow rates of 6 L/min, as higher flow rates cause drying of the nasal passages and nasal mucosa irritation. The advent of HFNC has circumvented these limitations of SNC by passing supplementary oxygen through a humidifier. Flows of up 60 L/min can be achieved, which has added advantages of generating a positive end-expiratory pressure, and reducing physiological dead space, whilst delivering higher FiO_2[7]. The routine use of HFNP is limited by its high costs and the required training and education to set up. Other airway devices described above are limited by the commercial availability, costs and expertise required for insertion[11].

At our centre, an oxygenating mouthguard (Oxyguard™; North Yorkshire, England) is routinely used for all upper GI endoscopy procedures to minimise dental injury and damage to the endoscope, whilst maintaining the mouth in an open position during the procedure. This mouthguard can be used to deliver supplementary oxygen by directing the flow of oxygen *via* a dedicated oxygen port into the oral and nasal cavities simultaneously (Figure 1A-D). It is held in place with a rubber strap wrapped around a patient's head (Figure 1E). This product is commercially available throughout Australia, Europe, and South Africa at the time of writing. Though the benefit of using 3L/min supplementary oxygen *via* this mouthguard in alleviating hypoxaemia during gastroscopy has been demonstrated, compared to a standard plastic mouthguard using room air, there are no publications to date on the use of high flows of supplemental oxygen[13]. Anecdotally, our team found that higher flows of supplemental oxygen can be safely delivered *via* this mouthguard during upper GI endoscopic procedures. An impetus to further investigate the clinical efficacy of delivering higher flows of oxygen *via* this mouthguard was the recent publication by Lin *et al*[7] The use of HFNC at 60 L/min, when compared to a supplemental oxygen flow rate of 2 L/min in a low-risk population for sedation-related adverse events undergoing a short gastroscopy performed under propofol sedation, demonstrated a significant reduction in the incidence of hypoxia (defined as oxygen saturation (SpO_2) < 90% and ≥ 75% for < 60 s) and severe hypoxia (defined as SpO_2 < 75% for any duration, or SpO_2 < 90% and ≥ 75% for ≥ 60 s) from 8.4% to 0% (P value < 0.001) and from 0.6% to 0% (P value = 0.03), respectively[7].

In this article, we report a randomised controlled trial on the novel use of high-flow supplemental oxygen *via* an oxygenating mouthguard in low-risk patients of sedation-related adverse events under propofol sedation.

MATERIALS AND METHODS

This is a single-centre, prospective, randomised clinical trial conducted at two sites of an Australian tertiary health service, between October 2020 and September 2021. Local ethics committee approval (ND 63130/2020) and registration at ANZCTR.org.au (ACTRN12620000930987) were attained before patient recruitment.

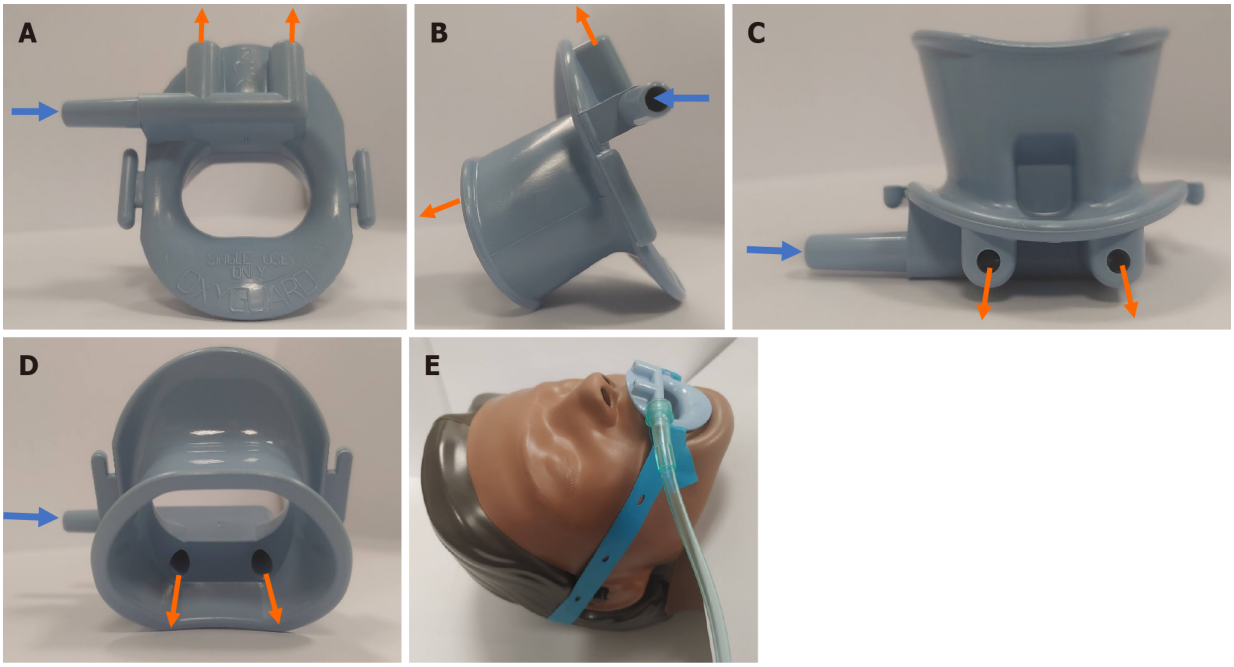
All patients referred for an endoscopy at our centre were considered during the study period. Inpatients scheduled a non-emergent upper GI endoscopy (gastroscopy, endoscopic retrograde cholangiopancreatography (ERCP), upper enteroscopy or upper endoscopic ultrasound (EUS), alone or in combination with another upper GI endoscopy) were offered the patient information and consent form (PICF) at least 12 h before their scheduled procedure. Non-emergent endoscopy was defined as a patient with vital signs within normal limits without evidence of upper GI bleeding or an active infection. Outpatients scheduled for upper GI endoscopies were sent the PICF *via* post or email. Patients scheduled for a combined lower GI tract endoscopy (such as colonoscopy, lower enteroscopy or lower endoscopic ultrasound) or scheduled for endoscopist administered sedation lists were excluded.

Patients scheduled for upper GI endoscopy were assessed for the following inclusion and exclusion criteria by an investigator at the time of their procedure. Inclusion criteria: (1) Age >18 years; (2) Ability to provide informed consent; and (3) An anticipated endoscopic procedure time of fewer than 20 min, as assessed by the accredited gastroenterologist or surgeon responsible for the case. Exclusion criteria: (1) America Society of Anesthesiologist[14] class greater than III; (2) Mallampati score[15] of greater than 3; (3) Body mass index > 35 kg/m^2; (4) Supplementary oxygen dependence; (5) Pregnancy; (6) Deemed high-risk of a sedated-related adverse event by the duty anaesthetist; and (7) Anticipated requirement or plan for general anaesthesia involving airway instrumentation including a laryngeal mask or tracheal intubation.

Intervention

Enrolled participants were randomly assigned to one of two groups: high-flow *via* oxygenating mouthguard (HFMG) at 20 L/min or SNC (Softi Smoothflow®; Victoria, Australia) at 2 L/min flow. Of note, the design of this SNC allows oxygen delivery through one nasal prong and sampling of expired carbon dioxide from the other prong simultaneously.

Supplemental oxygen at 20 L/min was supplied from a high-flow oxygen rotameter and delivered *via* a dedicated oxygen port as depicted in Figure 1A-E. Patients allocated to the SNC received oxygen at a fixed rate of 2 L/min. Initial flow rates were maintained throughout the endoscopic examination unless



DOI: 10.4253/wjge.v14.i12.777

Figure 1 Standard Oxyguard™ and its set-up. A: Front profile; B: Right-sided profile, C: Top profile; D: Rear profile; E: Standard Oxyguard™ with rubber strap demonstrating its set up. The blue arrow describes the direction of oxygen flow into the mouthguard. The orange arrow describes the direction of oxygen flow out of the mouthguard.

a hypoxemic event occurred. At the discretion of the anesthetist, the rate or route of oxygen delivery could be changed.

The endoscopic procedure and anaesthetic care

Proceduralists and anaesthesiologists were instructed to provide usual care except for the assigned initial oxygen delivery method and rate. Standard monitoring, including heart rate, blood pressure and SpO_2 were measured and recorded. The use of capnography was at the discretion of the duty anaesthetist. All physiological measurements were recorded using the GE Datex-Ohmeda Aisys Anaesthesia Machine (General Electric, Boston, United States).

Gastroscopy, EUS and enteroscopy were performed in the left lateral position, unless performed together with an ERCP which were performed in the semi-prone position under intravenous sedation with propofol with or without benzodiazepine and/or opioids.

Data on participants' symptoms post-procedure were collected using a Likert scale questionnaire (Supplementary Appendix III) before the patient's discharge from the endoscopy unit. Incomplete patient-reported symptom forms were excluded.

Outcome measures

The primary outcome was the occurrence of hypoxaemia, defined as $SpO_2 < 90\%$, of any duration measured by pulse oximetry during the procedure[7,16,17].

Secondary outcomes included the lowest SpO_2 measured by pulse oximetry during the procedure, the incidence of hypoxaemia defined as mild (SpO_2 90%-94%), moderate (SpO_2 89%-76%) and severe ($SpO_2 \leq$ 75%) of durations less than 1 minute, between 1 and 5 minutes and more than 5 min, procedure-related adverse events, sedation-related events, and patient-reported symptoms.

A clinically significant episode of hypoxaemia was defined as a need to change the flow or method of oxygen delivery that the patient was randomised to in response to an episode of hypoxaemia.

In addition, a posthoc analysis of the incidence of hypoxaemia defined as $SpO_2 < 85\%$ was performed [18].

Intraprocedural-related adverse events included a need to pause or stop the procedure due to an episode of oxygen desaturation or as directed by the duty anaesthetist. Procedure-related complications including bleeding requiring intervention, perforation, and post-procedure complications including pain, bleeding or sepsis necessitating a hospital admission or delayed discharge from the endoscopy unit were also recorded. Sedation-related adverse events included hypotension, bradycardia, tachycardia, seizure, cardiac arrest, nausea or vomiting, recovery agitation and delayed recovery whilst in the procedure room were noted.

Patient-reported symptoms after the procedure included overall comfort, abdominal pain, abdominal bloating, nose, mouth or throat dryness or pain, and headache.

Endoscopy procedure time was routinely collected and defined as the time the endoscope entered and exited the oral orifice. When more than one upper GI endoscopy was performed, the endoscopy procedure time was defined as the time of the first endoscope entering the oral orifice and the last endoscope exiting. Anaesthetic time was defined as the duration of time during which intravenous propofol was administered.

Randomisation

Allocation was pre-defined through an online research randomiser (https://www.randomizer.org). The allocation was placed into 300 sealed opaque envelopes by an independent person who was not a member of the research team. The envelopes were labelled from 1 to 300 and were consecutively opened. The envelopes were evenly split between the two sites and continued to be evenly distributed until the last patient was recruited.

Blinding

The clinical care team (*e.g.*, anaesthetists, endoscopists, nurses) was advised of the patient's randomisation. Patients were not blinded to their allocation due to the obvious difference in the oxygen delivery devices.

Sample size calculation

Two-tailed 0.05 alpha error and power of 80% were used for the sample size calculation. A 10% loss after randomisation was also accounted for. We aimed to enrol 300 patients, based on an anticipated difference of 8.4% previously observed when comparing HFNC at 40-60 L/min and 2 L/min in upper GI endoscopy[7]. The incidence rates used were 9.4% and 1.0% in the control and interventional group, respectively.

Statistical analyses

SPSS was used for statistical analyses. Collected data were summarised as mean ± standard deviation (SD) or median (25^{th} and 75^{th} percentile) for continuous data, and as frequency and percentages for categorical data. For continuous data, the characteristics, and outcomes for the two groups were compared using Student's *t*-test or Wilcoxon-Mann-Whitney test based on the normality assumption. Categorical data were compared with Chi-square or Fisher's exact test as appropriate. A P value of < 0.05 was considered significant. Statistical analyses were performed with SPSS Version 28.0.1.1.

RESULTS

From October 2020 to September 2021, 300 patients were enrolled and randomised; 8 patients were excluded after randomisation. Five patients were excluded as the accredited anaesthesiologist deemed the patient not appropriate for the study (*e.g.*, change in the anaesthetic plan after review by the accredited anaesthetist for intubation under general anaesthesia), one patient's procedure was cancelled by the proceduralist as anti-coagulation was not ceased as planned, one patient's procedure was abandoned due to the presence of food in the oesophagus and another patient was unable to wear the oxygenating mouthguard as their mouth opening was insufficient.

A total of 292 patients were included in our intention-to-treat analysis. Figure 2 flow chart describes the patient allocation.

In addition, ten patients did not receive their allocated rate and/or route of supplementary oxygen. Three of these patients allocated to HFMG did not receive 20 L/min as per protocol. Instead, two patients received 10 L/min, and one patient received 15 L/min *via* the mouthguard. Furthermore, seven patients were incorrectly allocated to the wrong group. Four patients allocated to HFMG received 2 L/min *via* SNC, and three patients allocated to SNC received 20 L/min *via* mouthguard. A per-protocol analysis was performed to determine the impact of these discrepancies on the primary outcome. The three patients receiving 10 L/min and 15 L/min *via* mouthguard were excluded from the per-protocol analysis. The per-protocol analysis for the primary outcome is described below in the results.

The baseline characteristics of the two groups are described in Table 1.

Details of the anaesthetic care and endoscopy procedure are summarised in Tables 2 and 3, respectively. Of note, the weighted dose of propofol per hour of the two groups and the number of anaesthetic agents used were similar. In addition, the duration of sedation and upper GI endoscopies performed were comparable between the two groups. Most procedures (86.3%) were 20 minutes or shorter. A sub-group analysis of longer procedures for the primary outcome was performed and is described below. More than half (52.7%) of the upper GI endoscopies were diagnostic. The most common procedures were gastroscopies (69.2%) and ERCPs (22.6%).

Table 1 Characteristics of the patient at baseline (*n*, %)

Characteristics	SNC (*n* = 154)	HFMG (*n* = 138)
Age (median, IQR)	64, 56 to 72	59, 48.5 to 69.5
Male	71, 46.1%	67, 48.6%
Weight, kg (mean, SD)	76.4, 13.6	76.1, 14.8
BMI, kg/m^2 (mean, SD)	26.6, 4.1	26.4, 3.9
ASA classification, I/II/III	14/67/73, 9.1%/43.5%/47.4%	16/58/64, 11.6%/42.0%/46.4%
Mallampati class, I/II/III	54/70/30, 35.1%/45.4%/19.5%	48/70/20, 34.8%/50.7%/14.5%
Baseline oximetry, SpO_2 (median, IQR)	97%, 95% to 99%	98%, 97% to 99%
Past medical history		
Current smoking history	14, 9.1%	14, 10.1%
Obstructive sleep apnoea	8, 5.2%	6, 4.3%
Hypertension	69, 44.8%	46, 33.3%
Ischemic heart disease	19, 12.3%	9, 6.5%
Diabetes mellitus	34, 22.1%	33, 23.9%
Dyslipidemia	36, 23.4%	26, 18.8%
Chronic obstructive pulmonary disease	8, 5.2%	11, 8%
Asthma	9, 5.8%	11, 8%
Cirrhosis	25, 16.2%	34, 24.6%
Orthotopic liver transplantation	19, 12.3%	25, 18.1%

ASA: American Society of Anesthesiologists; BMI: Body mass index; HFMG: High-flow *via* oxygenating mouthguard; IQR: Interquartile range; SpO_2: Oxygen saturation; SD: Standard deviation; SNC: Standard nasal cannula.

Table 2 Anaesthetic care parameters (*n*, %)

Anaesthetic care	SNC (*n* = 154)	HFMG (*n* = 138)	*P* value
Duration of sedation, min (median, IQR)	12, 6.9 to 17.1	12, 6.5 to 17.5	0.421
Propofol dose, mg/kg/hr (median, IQR)	13.3, 8.5 to 18.1	14.1, 7.8 to 20.5	0.189
Opioids	89, 57.8%	73, 52.9%	0.631
Fentanyl	52, 33.8%	40, 29.0%	
Alfentanil	37, 24.0%	33, 23.9%	
Midazolam	26, 16.9%	23, 16.7%	0.961

HFMG: High-flow *via* oxygenating mouthguard; IQR: Interquartile range; SNC: Standard nasal cannula.

Outcomes and estimate

We found a statistically significant difference in the primary outcome of hypoxaemia (SpO_2 < 90%) of any duration. Six patients (4.4%) allocated to HFMG experienced at least an episode of hypoxaemia compared to 34 (22.1%) patients allocated to SNC (Table 4). In addition, a statistically significant difference in all secondary outcomes was also observed between the two groups. No episode of severe hypoxaemia (SpO_2 ≤ 75%) was observed in the HFMG group (Figure 3).

A per-protocol analysis performed for the primary outcome of hypoxaemia still demonstrated a statistically significant difference (*P* value < 0.001). A subgroup analysis of longer procedures for the primary outcome was performed. However, the number of patients and event rates were too few to provide a meaningful interpretation. Two patients (8.7%) allocated to HFMG, and four patients (23.5%) allocated to SNC experienced an episode of hypoxaemia in procedures longer than 20 min. The majority (68.3%) of procedures longer than 20 minutes were therapeutic, with ERCPs (48.8%) the most common procedure.

Table 3 Upper gastrointestinal endoscopy parameters (*n*, %)

Endoscopy parameters	SNC, (*n* = 154)	HFMG, (*n* = 138)	*P* value
Duration of procedure, min (median, IQR)	10, 5.5 to 14.5	10, 4.5 to 15.5	0.684
Types of procedure			0.175
Diagnostic Procedure	87, 56.5%	67, 48.6%	
Therapeutic Procedure	67, 43.5%	71, 51.4%	
Types of upper GI endoscopy			0.27
Gastroscopy	106, 68.8%	96, 69.6%	
Duodenoscope	1, 0.6%	1, 0.7%	
ERCP	32, 20.8%	34, 24.6%	
EUS	12, 7.8%	3, 2.2%	
Gastroscopy + EUS	3, 1.9%	4, 2.9%	

EUS: Endoscopic ultrasound; ERCP: Endoscopic retrograde cholangiopancreatography; HFMG: High-flow *via* oxygenating mouthguard; SNC: Standard nasal cannula.

Table 4 Primary and secondary end points for the intention-to-treat analysis end point (*n*, %)

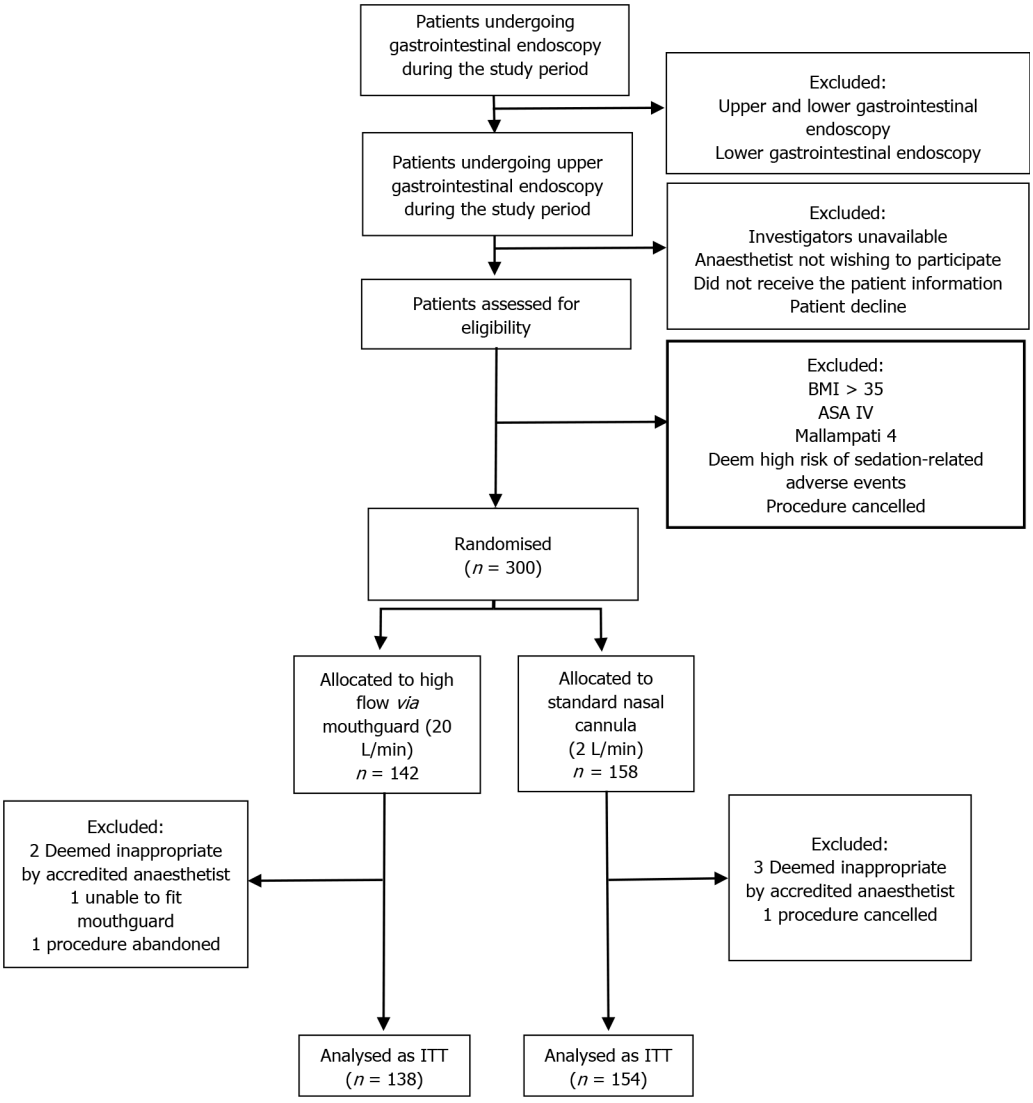
End point	SNC (*n* = 154)	HFMG (*n* = 138)	*P* value
Primary endpoint			
SpO_2 < 90% of any duration	34, 22.1%	6, 4.4%	< 0.001
Secondary endpoint			
Lowest SpO_2 (median, IQR)	95%, 91% to 99%	98%, 96.5% to 99.5%	< 0.001
Any episode of hypoxaemia	74, 48.1%	26, 18.8%	< 0.001
SpO_2 90%-94% of any duration	40, 26.0%	20, 14.5%	0.015
SpO_2 76%-89% of any duration	28, 18.2%	6, 4.3%	< 0.001
SpO_2 ≤ 75% of any duration	6, 3.9%	0, 0%	0.019
Clinically significant episode of hypoxaemia[1]	32, 20.8%	1, 0.7%	< 0.001
SpO_2 < 85% of any duration	19, 12.3%	3, 2.2%	0.001

[1]Clinically significant episode of hypoxemia is defined as a need to change in flow or method of oxygen delivery that the patient was originally randomised to.

HFMG: High-flow *via* oxygenating mouthguard; IQR: Interquartile range; SpO_2: Oxygen saturation; SNC: Standard nasal cannula.

A clinically significant episode of hypoxaemia requiring a need to change the flow or route of oxygen delivery was observed in one patient (0.7%) in the HFMG and 32 patients (20.8%) in the SNC group based on an intention-to-treat analysis. This patient allocated to HFMG incorrectly received SNC and required a higher flow of supplemental oxygen to complete their procedure. Only three patients in the SNC group required a change in the method of oxygen delivery. Two of these patients received a short period of bag-valve-mask ventilation, and a third patient received supplemental oxygen *via* a facemask for a brief period, before completing their upper GI endoscopies on higher flows of supplemental oxygen either *via* SNC or HFNC. No patients required intubation in the study. With regards to airway manoeuvres, a greater proportion of patients in the SNC group (42.9%) required a chin lift and/or jaw thrust manoeuvres compared to those in the HFMG group (17.4%) (*P* value < 0.001).

A total of 7 intraprocedural-related adverse events occurred, the endoscope was either withdrawn and re-inserted or the procedure paused in response to an episode of hypoxaemia or as directed by the duty anaesthetist. Only one of these patients was allocated to HFMG. No procedure-related or post-procedure complications were observed in the study. Sedation-related adverse events were infrequent and observed in ten patients (3.4%). These include hypotension, bradycardia, tachycardia, nausea and vomiting. One patient with hypotension in the HFMG group required two doses of 0.5mg dose of metaraminol. In the SNC group, one patient had bradycardia requiring a dose of atropine for bradycardia and two others received rescue antiemetics.



DOI: 10.4253/wjge.v14.i12.777

Figure 2 Study flow chart. BMI: Body mass index; ASA: American Society of Anesthesiologists; ITT: Intention-to-treat; GI: Gastrointestinal.

No statistically significant difference in patient-reported symptoms was demonstrated. Patient-reported symptoms forms were completed by 74.3% of patients and no statistically significant difference in response rate was found between the two groups (Table 5).

DISCUSSION

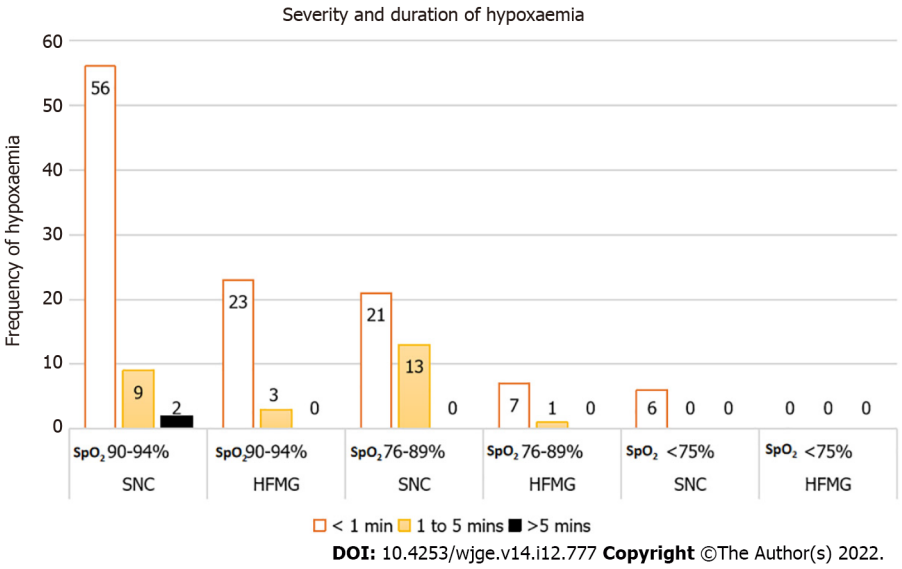
In this single centre, randomised controlled trial, HFMG at 20 L/min of supplemental oxygen significantly reduced the incidence of hypoxaemia, defined as SpO_2 < 90% of any duration, when compared to SNC at 2 L/min of supplemental oxygen in patients undergoing elective upper GI endoscopy under deep sedation. Further, clinically significant hypoxaemia events were significantly reduced in patients assigned to HFMG compared to SNC. No statistically significant difference in patient-rated outcomes was observed between the two groups. To the best of our knowledge, this is the first study comparing the use of supplemental oxygen at 20 L/min *via* a commercially available mouthguard to 2 L/min *via* a standard nasal cannula.

Though further studies are required to elucidate the mechanisms by which HFMG reduces the incidence of hypoxaemia in patients undergoing upper GI endoscopy, we postulate that oxygen delivery into the oral cavity has additional benefits. During upper GI endoscopy, an open-mouth respiratory system, the oropharyngeal cavity serves as a large oxygen reservoir.[19] As such, we hypothesize that higher flows delivered into both the nasal and oral cavities result in higher FiO_2 delivery, greater physiological dead space washout, and positive end-expiratory pressure similar to that seen in HFNC[1].

Table 5 Patient-reported outcomes for the intention-to-treat analysis (*n*, %)

Patient-reported outcomes – Likert scale	SNC (*n* = 154)	HFMG (*n* = 138)	*P* value
(1 = Very uncomfortable or unbearable, 5 = Very comfortable or not at all)			
Response rate	115, 74.7%	102, 73.9%	0.882
Comfort level ≤ 2	4, 3.5%	5, 4.9%	0.6
Abdominal pain ≤ 2	3, 2.6%	0, 0.0%	0.1
Bloating ≤ 2	1, 0.9%	1, 1.0%	0.932
Mouth dryness ≤ 2	2, 1.7%	1, 1.0%	0.633
Mouth pain ≤ 2	2, 1.7%	1, 1.0%	0.633
Headache ≤ 2	1, 0.9%	1, 1.0%	0.932

HFMG: High flow *via* oxygenating mouthguard; SNC: Standard nasal cannula.



DOI: 10.4253/wjge.v14.i12.777

Figure 3 Frequency and distribution of hypoxaemia. HFMG: High-flow *via* oxygenating mouthguard; SpO_2: Oxygen saturation; SNC: Standard nasal cannula.

Most importantly, we acknowledge the criticisms of choosing an oxygen flow rate of 2 L/min[11]. At the conception of the study, this decision was to allow inferences between HFMG and HFNC based on a recent publication by Lin *et al*[7]. In our study, of those allocated to HFMG, five patients (3.6%) experienced hypoxaemia and only one patient (0.7%) experienced an episode of severe hypoxaemia, as defined by Lin *et al*[7], respectively. Compared to HFNC, HFMG offers a relatively inexpensive and simpler method of delivering higher flows of supplemental oxygen. A single-use disposable mouthguard (Oxyguard™) with a rubber strap is approximately 2.33 USD. However, we acknowledge that further comparative studies are required to determine the cost-effectiveness of HFMG in upper GI endoscopy compared to HFNC and other airway devices.

Furthermore, this study has limitations. Firstly, we recognise that this is a single-centre study, and therefore further multicentre trials are required to validate our findings. Secondly, it is unclear whether a lower flow of supplemental oxygen would achieve the same observed benefits, and thus additional studies using different flows through this mouthguard would be warranted. Thirdly, procedures anticipated to be longer than 20 minutes, emergent or combined with a lower GI procedure were excluded. Further studies in these clinical scenarios are required. Finally, an adequate mouth opening is required to accommodate the 60Fr mouthguard. One patient allocated to HFMG did not have sufficient mouth opening which was only evident after randomisation. Although a smaller version of the Oxyguard™ is commercially available, this is not available at our centre. Studies using the miniature version of the mouthguard (Oxyguard™ mini; North Yorkshire, England) would be required to determine its clinical efficacy.

Concerning the use of pulse oximetry as our primary outcome measure, we appreciate its limitations relative to capnography[20]. Pulse oximetry is routinely used in all patients, and offers an objective and practical outcome measure. A strength of our study is the use of clinically significant hypoxemic events, as this encapsulates the anaesthetist's clinical assessment and interpretation of an episode of hypoxaemia and thus is a more clinically relevant outcome.

CONCLUSION

The use of high-flow supplemental oxygen *via* a mouthguard offers a simple and novel approach to reducing the incidence of hypoxaemia during short upper GI endoscopy in low-risk patients undergoing propofol sedation.

ARTICLE HIGHLIGHTS

Research background

Anaesthetic care during upper gastrointestinal (GI) endoscopy has the unique challenges of balancing adequate patient sedation while maintaining sufficient ventilation and oxygenation *via* a shared upper airway. Supplementary oxygen during upper GI endoscopy under deep sedation is considered the standard practice to reduce the incidence and severity of hypoxaemia. However, despite this being a recommendation of international society guidelines, the optimal route or rate of oxygen delivery is not known.

Research motivation

Various oxygen delivery devices have been investigated to improve oxygenation during upper GI endoscopy, however, these are limited by commercial availability, costs and in some cases, the expertise required for insertion. Anecdotally at our centre, higher flows of supplemental oxygen can safely be delivered *via* an oxygenating mouthguard. This oxygenating mouthguard is routinely used during upper GI endoscopic procedures in our practice and as such offers a practical solution to reducing the incidence and severity of hypoxaemia in patients undergoing upper GI endoscopic procedures under deep sedation.

Research objectives

To assess the incidence of hypoxaemia (SpO_2 < 90%) in patients undergoing upper GI endoscopy receiving supplemental oxygen using an oxygenating mouthguard at 20 L/min flow compared to standard nasal cannula (SNC) at 2 L/min flow as a proof-of-concept study.

Research methods

A single centre, prospective, randomised clinical trial at two sites of an Australian tertiary hospital between October 2020 and September 2021 was conducted. Patients undergoing elective upper gastrointestinal endoscopy under deep sedation were randomised to receive supplemental oxygen *via* high-flow *via* oxygenating mouthguard (HFMG) at 20 L/min flow or SNC at 2 L/min flow. The primary outcome was the incidence of hypoxaemia of any duration measured by pulse oximetry. Intraprocedural-related, procedural-related, and sedation-related adverse events and patient-reported outcomes were also recorded.

Research results

Three hundred patients were randomised. Eight patients were excluded after randomisation. 292 patients were included in the intention-to-treat analysis. The incidence of hypoxemia was significantly reduced in those allocated HFMG. Six patients (4.4%) allocated to HFMG experienced an episode of hypoxaemia, compared to thirty-four (22.1%) patients allocated to SNC (P value < 0.001). No significant difference was observed in the rates of adverse events or patient-reported outcome measures.

Research conclusions

The use of HFMG offers a novel approach to reducing the incidence of hypoxaemia during short upper gastrointestinal endoscopic procedures in low-risk patients undergoing deep sedation.

Research perspectives

Additional studies using different flows through the oxygenating mouthguard would be warranted to elucidate the mechanisms by which HFMG reduces the incidence of hypoxaemia in patients undergoing upper GI endoscopy. Further comparative studies are required to determine the cost-effectiveness of HFMG in upper GI endoscopy compared to high-flow nasal cannula and other airway devices.

FOOTNOTES

Author contributions: Be KH, Zorron Cheng Tao Pu L, Peyton P, Efthymiou M, Vaughan R, and Chandran S conceptualized and designed the study; all authors were involved in data collection, analyses, or both; all authors were involved in the interpretation of the results; Be KH, Zorron Cheng Tao Pu L, Lee M, Fletcher L and Chandran S drafted the manuscript; Pearce B, Cogan R, Efthymiou M, and Vaughan R carried the critical revision of the article for important intellectual content; and all authors read and approved the final version of the manuscript.

Institutional review board statement: The study was reviewed and approved by the Austin Health Human Research Ethics Committee (ND 63130/2020).

Clinical trial registration statement: This study is registered at ANZCTR.org.au. The registration identification number is ACTRN12620000930987.

Informed consent statement: All study participants, or their legal guardians, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors disclose no conflicts of interest.

Data sharing statement: No additional data are available.

CONSORT 2010 statement: The authors have read the CONSORT 2010 statement, and the manuscript was prepared and revised according to the CONSORT 2010 statement.

Country/Territory of origin: Australia

ORCID number: Kim Hay Be 0000-0003-0792-3265; Leonardo Zorron Cheng Tao Pu 0000-0002-7921-5631; Brett Pearce 0000-0001-7703-3845; Matthew Lee 0000-0003-4086-1350; Luke Fletcher 0000-0002-1146-763X; Rebecca Cogan 0000-0002-0335-0570; Philip Peyton 0000-0003-1185-2869; Rhys Vaughan 0000-0002-4557-1734; Marios Efthymiou 0000-0003-2569-5163; Sujievvan Chandran 0000-0002-5015-6287.

S-Editor: Ma YJ
L-Editor: A
P-Editor: Ma YJ

REFERENCES

1 **Goudra B**, Singh PM. Airway Management During Upper GI Endoscopic Procedures: State of the Art Review. *Dig Dis Sci* 2017; **62**: 45-53 [PMID: 27838810 DOI: 10.1007/s10620-016-4375-z]
2 **Wadhwa V**, Issa D, Garg S, Lopez R, Sanaka MR, Vargo JJ. Similar Risk of Cardiopulmonary Adverse Events Between Propofol and Traditional Anesthesia for Gastrointestinal Endoscopy: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2017; **15**: 194-206 [PMID: 27451091 DOI: 10.1016/j.cgh.2016.07.013]
3 **Bell GD**, Bown S, Morden A, Coady T, Logan RF. Prevention of hypoxaemia during upper-gastrointestinal endoscopy by means of oxygen *via* nasal cannulae. *Lancet* 1987; **1**: 1022-1024 [PMID: 2883355 DOI: 10.1016/s0140-6736(87)92282-3]
4 **Australian and New Zealand College of Anaesthetists**. Professional Document: Guidelines on sedation and/or analgesia for diagnostic and interventional medical or surgical procedures (PS9). Melbourne: Australian and New Zealand College of Anaesthetists, 2014 [DOI: 10.1136/bmjopen-2018-022625]
5 **Leslie K**, Sgroi J. Sedation for gastrointestinal endoscopy in Australia: what is the same and what is different? *Curr Opin Anaesthesiol* 2018; **31**: 481-485 [PMID: 29846194 DOI: 10.1097/ACO.0000000000000620]
6 **Nay MA**, Fromont L, Eugene A, Marcueyz JL, Mfam WS, Baert O, Remerand F, Ravry C, Auvet A, Boulain T. High-flow nasal oxygenation or standard oxygenation for gastrointestinal endoscopy with sedation in patients at risk of hypoxaemia: a multicentre randomised controlled trial (ODEPHI trial). *Br J Anaesth* 2021; **127**: 133-142 [PMID: 33933271 DOI: 10.1016/j.bja.2021.03.020]
7 **Lin Y**, Zhang X, Li L, Wei M, Zhao B, Wang X, Pan Z, Tian J, Yu W, Su D. High-flow nasal cannula oxygen therapy and hypoxia during gastroscopy with propofol sedation: a randomized multicenter clinical trial. *Gastrointest Endosc* 2019; **90**: 591-601 [PMID: 31278907 DOI: 10.1016/j.gie.2019.06.033]
8 **Vargo JJ 2nd**. Sedation-related complications in gastrointestinal endoscopy. *Gastrointest Endosc Clin N Am* 2015; **25**: 147-158 [PMID: 25442964 DOI: 10.1016/j.giec.2014.09.009]
9 **Jurell KR**, O'Connor KW, Slack J, Fraiz J, Shaar CJ, Kent L, Callon R. Effect of supplemental oxygen on cardiopulmonary changes during gastrointestinal endoscopy. *Gastrointest Endosc* 1994; **40**: 665-670 [PMID: 7859961]

10 **Qin Y**, Li LZ, Zhang XQ, Wei Y, Wang YL, Wei HF, Wang XR, Yu WF, Su DS. Supraglottic jet oxygenation and ventilation enhances oxygenation during upper gastrointestinal endoscopy in patients sedated with propofol: a randomized multicentre clinical trial. *Br J Anaesth* 2017; **119**: 158-166 [PMID: 28974061 DOI: 10.1093/bja/aex091]

11 **Goudra B**, Gouda G, Singh PM. Recent Developments in Devices Used for Gastrointestinal Endoscopy Sedation. *Clin Endosc* 2021; **54**: 182-192 [PMID: 33730777 DOI: 10.5946/ce.2020.057]

12 **Fabbri C**, Luigiano C, Cennamo V, Polifemo AM, Maimone A, Jovine E, D'Imperio N, Zanello M. The Gastro-Laryngeal Tube for interventional endoscopic biliopancreatic procedures in anesthetized patients. *Endoscopy* 2012; **44**: 1051-1054 [PMID: 22983834 DOI: 10.1055/s-0032-1310159]

13 **Brandl S**, Borody TJ, Andrews P, Morgan A, Hyland L, Devine M. Oxygenating mouthguard alleviates hypoxia during gastroscopy. *Gastrointest Endosc* 1992; **38**: 415-417 [PMID: 1511812 DOI: 10.1016/s0016-5107(92)70467-2]

14 Americian Society of Anesthesiologist. ASA Physical Status Classification System. 2022 [DOI: 10.1002/9781119600077.app3]

15 **Mallampati SR**, Gatt SP, Gugino LD, Desai SP, Waraksa B, Freiberger D, Liu PL. A clinical sign to predict difficult tracheal intubation: a prospective study. *Can Anaesth Soc J* 1985; **32**: 429-434 [PMID: 4027773 DOI: 10.1007/BF03011357]

16 **Riccio CA**, Sarmiento S, Minhajuddin A, Nasir D, Fox AA. High-flow *vs* standard nasal cannula in morbidly obese patients during colonoscopy: A prospective, randomized clinical trial. *J Clin Anesth* 2019; **54**: 19-24 [PMID: 30391445 DOI: 10.1016/j.jclinane.2018.10.026]

17 **Doulberis M**, Sampsonas F, Papaefthymiou A, Karamouzos V, Lagadinou M, Karampitsakos T, Stratakos G, Kuntzen T, Tzouvelekis A. High-flow *vs* conventional nasal cannula oxygen supplementation therapy and risk of hypoxia in gastrointestinal endoscopies: a systematic review and meta-analysis. *Expert Rev Respir Med* 2022; **16**: 323-332 [PMID: 35157538 DOI: 10.1080/17476348.2022.2042256]

18 **Cotton PB**, Eisen GM, Aabakken L, Baron TH, Hutter MM, Jacobson BC, Mergener K, Nemcek A Jr, Petersen BT, Petrini JL, Pike IM, Rabeneck L, Romagnuolo J, Vargo JJ. A lexicon for endoscopic adverse events: report of an ASGE workshop. *Gastrointest Endosc* 2010; **71**: 446-454 [PMID: 20189503 DOI: 10.1016/j.gie.2009.10.027]

19 **Yamamoto N**, Miyashita T, Takaki S, Goto T. Effects of Breathing Pattern on Oxygen Delivery Via a Nasal or Pharyngeal Cannula. Respiratory Care 2015; 60(12): 1804-1809 [DOI: 10.4187/respcare.04173]

20 **Chan ED**, Chan MM. Pulse oximetry: understanding its basic principles facilitates appreciation of its limitations. *Respir Med* 2013; **107**: 789-799 [PMID: 23490227 DOI: 10.1016/j.rmed.2013.02.004]

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Endosc 2022 December 16; 14(12): 789-794

DOI: 10.4253/wjge.v14.i12.789

ISSN 1948-5190 (online)

CASE REPORT

Colonic schistosomiasis: A case report

Hajar Koulali, Abdelkrim Zazour, Wafaa Khannoussi, Ghizlane Kharrasse, Zahi Ismaili

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Liu Z, China; Wu C, China

Received: September 20, 2022
Peer-review started: September 20, 2022
First decision: October 13, 2022
Revised: October 20, 2022
Accepted: November 19, 2022
Article in press: November 19, 2022
Published online: December 16, 2022

Hajar Koulali, Abdelkrim Zazour, Wafaa Khannoussi, Ghizlane Kharrasse, Zahi Ismaili, Department of Gastro-enterology, Mohammed VI University Hospital, Oujda 60050, Morocco

Corresponding author: Hajar Koulali, Doctor, Department of Gastro-enterology, Mohammed VI University Hospital, B.P.: 4806 Oujda Université, Oujda 60049, Morocco.
h.koulali@ump.ac.ma

Abstract

BACKGROUND

Schistosomiasis is a chronic parasitic infection endemic in many countries. Colonic schistosomiasis is a rare entity with no specific clinical manifestations or endoscopic aspects, which delays the diagnosis. Diagnosis is primarily dependent on histopathological analysis, and treatment with antihelminthics typically resolves the infection.

CASE SUMMARY

We present the case of a 21-year-old male who suffered from chronic diarrhea and abdominal pain. Physical examination found no abnormalities, blood tests were normal, and stool examination was negative. A colonoscopy revealed a nodular terminal ileal mucosa, two cecal polypoid lesions with no particular surface pattern, and millimetric erosions in the rectum. The presence of *Schistosoma* eggs with thick peripheral capsules and viable embryos inside and numerous eosinophils surrounding the egg capsule were observed on histopathological examination. The patient received praziquantel, and his symptoms were resolved.

CONCLUSION

Colonic schistosomiasis should be considered as a differential diagnosis, especially in endemic countries. Endoscopy and histopathological examination can confirm the diagnosis, and antihelminthics are an effective treatment.

Key Words: *Schistosoma*; Colon; Polyps; Colonoscopy; Histopathology; Ova

Core Tip: Colonic schistosomiasis is a rare disease, often mistaken for other pathologies, such as inflammatory bowel disease, because the clinical and endoscopic manifestations are non-specific and can be misleading. Histopathological examination is key to diagnosis when the stool examination shows no ova. We present a case of colonic schistosomiasis in a 21-year-old male presenting with chronic diarrhea and abdominal pain. The stool examination was negative and colposcopy showed multiple polyps. Histopathological examination confirmed the diagnosis of colonic schistosomiasis. Antiparasitic treatment was effective.

Citation: Koulali H, Zazour A, Khannoussi W, Kharrasse G, Ismaili Z. Colonic schistosomiasis: A case report. *World J Gastrointest Endosc* 2022; 14(12): 789-794
URL: https://www.wjgnet.com/1948-5190/full/v14/i12/789.htm
DOI: https://dx.doi.org/10.4253/wjge.v14.i12.789

INTRODUCTION

Schistosomiasis is a serious chronic parasitic infection caused by trematodes, primarily *Schistosoma mansoni* and *Schistosoma japonicum*. Humans are accidental hosts; infection occurs after ingesting larva-infested water. According to the World Health Organization, 236.6 million people needed preventative treatment in 2019 and the global death rate ranged between 24000 and 200000. *Schistosoma* commonly infects the urinary tract, and intestinal infection is rare. Its clinical manifestations are non-specific, ranging from asymptomatic to intestinal occlusion secondary to larva deposits, diarrhea, abdominal pain, malnutrition, and chronic anemia. Colonoscopy can reveal lesions, among which mucosal edema, ulcerations, and polypoid lesions are frequently observed[1].

Herein, we present a case of a 21-year-old male with colonic schistosomiasis.

CASE PRESENTATION

Chief complaints

A 21-year-old male, originally from Madagascar but living in Morocco for the past 5 years, presented with chronic diarrhea up to 3-4 times a day, diffuse abdominal pain prominent to the right iliac fossa and intermittent subocclusive symptoms for 3 years with no recent aggravation.

History of present illness

The patient suffered from his complaints for 3 years prior to presentation, and they occurred in a flare-up/remission pattern.

Physical examination

The physical examination found no abnormalities. The patient had a normal body mass index. No abdominal tenderness nor mass was noted.

Laboratory examinations

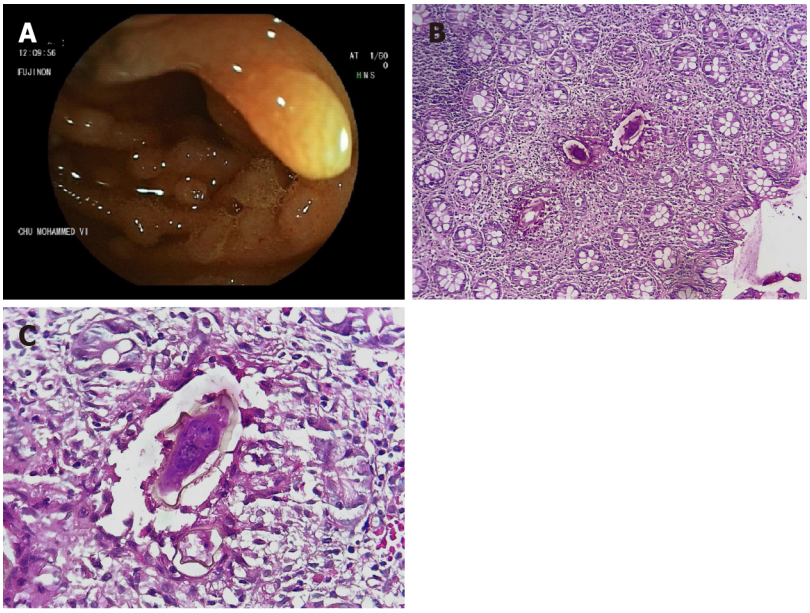
Blood tests gave normal findings, showing negativity for C-reactive protein levels. Stool examination for parasite ova and bacterial culture were negative.

Imaging examinations

A thoracic abdominopelvic computed tomography scan revealed no abnormalities.

ENDOSCOPIC EXAMINATION

Colonoscopy revealed a nodular terminal ileal mucosa, two cecal polypoid lesions with no particular surface pattern, and millimetric erosions in the rectum (Figure 1A). Biopsies were taken with jumbo forceps. Histopathological examination showed the presence of *Schistosoma* eggs with thick peripheral capsules and viable embryos inside (Figure 1B). The egg capsules were surrounded by numerous eosinophils (Figure 1C).



DOI: 10.4253/wjge.v14.i12.789

Figure 1 Colonoscopy and histopathological findings. A: Polyps were observed during colonoscopy; B: Microphotography showed the presence of three *Schistosoma* eggs in the colic mucosa (hematoxylin and eosin, × 40); C: Microphotography of a *Schistosoma* egg showed a thick peripheral capsule and a viable embryo inside. The egg capsule was surrounded by numerous eosinophils (hematoxylin and eosin, × 400).

FINAL DIAGNOSIS

Colonic schistosomiasis.

TREATMENT

The patient received praziquantel (60 mg/kg in two doses over a 1-d period).

OUTCOME AND FOLLOW-UP

The treatment resolved the diarrhea and alleviated the abdominal pain.

DISCUSSION

Schistosomiasis, also known as Bilharzia, is a parasitic infectious disease caused by schistosomes. Its geographical distribution is widespread, with endemic foci in some regions of the world (Africa, South America and Asia). *S. mansoni* and *S. japonicum* are typically involved in digestive schistosomiasis. In Africa, colonic polyposis is generally associated with *S. mansoni* infection[2]. Patients are infected after direct contact with water contaminated with snails carrying the parasite. The urinary system is preferentially affected, while intestinal involvement is rare.

Symptoms can be non-specific, and the evolution of the infection can last for long periods (as reported in our case). Diarrhea is the main symptom, as 3%-55% of a population study presented with diarrhea, with 11%-50% of cases presenting with bloody diarrhea[1]. In a study of 216 patients with intestinal schistomiasis, by Mohamed *et al*[2], abdominal pain and diarrhea were the most frequent symptoms, accounting for 39 % and 27% of cases respectively. In another study by Rocha *et al*[3], diarrhea was also the most common symptom, observed in 56% of cases. Abdominal pain, constipation, weight loss and fatigue are commonly observed, while obstructive symptoms, such as intestinal stenosis, are rare.

Differential diagnosis with inflammatory bowel disease and malignancy can be challenging. Hypereosinophelia is a nonspecific finding of schistomiasis correlating to the stage, intensity, and duration of infection. Stool examination may reveal ova, which is essential in determining larva species [1,2]. However, detecting ova in the stool can be difficult, as the numbers decrease as the infection evolves. Quantitative sampling according to the Kato-Katz technique coupled with concentration

technique improves the sensitivity of egg detection; the diagnosis sensitivity could also be improved by associating Kato-Katz sampling examination with serological testing (*e.g.*, IgG anti-*Schistosoma mansoni*-enzyme-linked immunosorbent assay technique)[4]. Serological diagnosis by detection of serum antibody titer is also available, especially in endemic areas, but it cannot differentiate between active or chronic infection; meanwhile, a negative serological test can rule out infection in endemic areas but cannot be used in post-treatment follow-up due to prolonged positivity post-therapy[5]. Detection of free circulating DNA by polymerase chain reaction can be used for early diagnosis of prepatent schistosomiasis infection[6], with good sensitivity and specificity for urine samples (94.4% and 99.9% respectively)[7]. Serologic tests for the detection of one of the two gut-associated parasite proteins ¾ circulating anodic antigen and circulating cathodic antigen ¾ can also be used for diagnosis[8].

When digestive colonization occurs, superficial submucosal deposits of *Schistosoma* eggs lead to the formation of polypoid lesions corresponding to inflammatory granulation tissue and hypertrophy of the adjacent muscular layer. Colonoscopy can show polypoid lesions, edema, ulcers, and granular patterns [9-13]. In the study mentioned above by Mohamed *et al*[2], polyps were found in only 8 cases (3 were rectal and 5 were colonic), and histopathological examination showed schistosomal ova in all 8 of the polyps. Cao *et al*[10] observed that nodular lesions and polyps are more frequent in the left colon, while mucosal edema, erythema, granular pattern, and ulcers are often seen in the right colon. In this study, 4 patients were misdiagnosed as ulcerative colitis, 1 as Crohn's disease, and 7 as ischemic colitis. While intestinal lesions associated with *S. mansoni* are usually observed in the ileum and the colon, duodenal involvement has been reported as well. Based upon visualization of schistosomal ova, biopsies and histopathological examination are the golden diagnostic standard of colonic schistomiasis. The ova are mainly deposited in the lamina propria and/or submucosa[11], with an observable inflammatory reaction in the tissue surrounding them[10,12]. Other characteristic features are excessive mucus and diffuse or focal infiltration of eosinophilic granulocytes, which may be highly suggestive of colonic schistosomiasis[14], as seen in our patient. In addition, intestinal ultrasound and computed tomography may reveal wall thickening, but they show no abnormalities in most cases. Abdominal X-rays and barium enemas can show images of polyps and structures but are not typically utilized due to their lack of specificity.

Intestinal schistosomiasis is amenable to medical treatment, including praziquantel, with a safe and effective outcome and cure rates ranging between 60% and 90%[15]. It has been shown that antigen tests become negative as early as 5-10 d after successful therapy[16]. A study from Africa that aimed to evaluate the efficacy and safety of praziquantel in preschool-aged children in an area co-endemic for *Schistosoma* concluded the efficacy of crushed praziquantel administered to preschool-aged children at a dose of 40 mg/kg against *S. mansoni* and *Schistosoma haematobium*[17]. Mutapi *et al*[18] had also concluded from their study that praziquantel is safe and efficacious in children aged 1-10 years.

Praziquantel is substantially excreted by the kidney, and elderly patients with decreased renal function may be at greater risk of toxic reactions. In a study conducted by Putri *et al*[19], the group aged 45 to 69 experienced a high proportion of side effects.

A second praziquantel regimen can be prescribed in case of persistence of the infection; oxamniquine alone or combinated with praziquantel and trioxolane can also be used as second-line therapy.

Following treatment, stool analysis or colon biopsy could be considered for assessment of treatment success but should be performed at least 6 wk post-treatment[20]. No data are available in the literature regarding colonic polyps' endoscopic follow-up and monitoring.

Cases of colon cancer associated with *S. japonicum* have been reported. However, the carcinogenic pathways are unclear, and the association is not well established[2,10,21]. A Chinese study including 454 colorectal carcinoma specimens showed that more than half (n = 289) were associated with *S japonicum* infection[22]. Furthermore, a study by Kaw *et al*[23] including 1277 colonic carcinoma patients showed that schistosomiasis was often accompanied by rectal cancer.

Schistosomiasis prevention is key to its elimination; public health awareness campaigns, water sanitation, hygiene programs, and chemotherapy programs are necessary. Preventive chemotherapy in preschool-aged children is deemed appropriate for those aged ≥ 2 years in endemic communities, according to the World Health Organization. While an antischistosomal vaccine will be ideal for long-term protection, clinical trials for its development are still in progress.

CONCLUSION

Colonic schistosomiasis is a rare disease that should be considered a differential diagnosis in endemic regions. Endoscopic appearance is non-specific. Histopathological and stool examinations have a significant role in diagnosis.

FOOTNOTES

Author contributions: Koulali H, Zazour A, Khannoussi W, Kharrasse G, and Ismaili Z participated in collecting and analyzing the patient's data and designing the report.

Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: Morocco

ORCID number: Hajar Koulali 0000-0003-1635-0075.

S-Editor: Liu GL
L-Editor: A
P-Editor: Liu GL

REFERENCES

1 **Akere A**, Oluwasola AO, Fakoya TO, Lawan A. SCHISTOSOMIASIS PRESENTING AS COLONIC POLYPOID MASSES IN A NIGERIAN PATIENT. *Ann Ib Postgrad Med* 2017; **15**: 61-64 [PMID: 28970774]
2 **Mohamed AR**, al Karawi M, Yasawy MI. Schistosomal colonic disease. *Gut* 1990; **31**: 439-442 [PMID: 2110925 DOI: 10.1136/gut.31.4.439]
3 **Rocha MO**, Pedroso ER, Lambertucci JR, Greco DB, Rocha RL, Rezende DF, Neves J. Gastro-intestinal manifestations of the initial phase of schistosomiasis mansoni. *Ann Trop Med Parasitol* 1995; **89**: 271-278 [PMID: 7668918 DOI: 10.1080/00034983.1995.11812952]
4 **Carneiro TR**, Pinheiro MC, de Oliveira SM, Hanemann AL, Queiroz JA, Bezerra FS. Increased detection of schistosomiasis with Kato-Katz and SWAP-IgG-ELISA in a Northeastern Brazil low-intensity transmission area. *Rev Soc Bras Med Trop* 2012; **45**: 510-513 [PMID: 22930048 DOI: 10.1590/s0037-86822012000400019]
5 **Leder K**, Weller PF. Eosinophilia and helminthic infections. *Baillieres Best Pract Res Clin Haematol* 2000; **13**: 301-317 [PMID: 10942627 DOI: 10.1053/beha.1999.0074]
6 **Hussein HM**, El-Tonsy MM, Tawfik RA, Ahmed SA. Experimental study for early diagnosis of prepatent schistosomiasis mansoni by detection of free circulating DNA in serum. *Parasitol Res* 2012; **111**: 475-478 [PMID: 22290447 DOI: 10.1007/s00436-012-2822-0]
7 **Gundersen SG**, Ravn J, Haagensen I. Early detection of circulating anodic antigen (CAA) in a case of acute schistosomiasis mansoni with Katayama fever. *Scand J Infect Dis* 1992; **24**: 549-552 [PMID: 1411323 DOI: 10.3109/00365549209052643]
8 **Sandoval N**, Siles-Lucas M, Pérez-Arellano JL, Carranza C, Puente S, López-Abán J, Muro A. A new PCR-based approach for the specific amplification of DNA from different Schistosoma species applicable to human urine samples. *Parasitology* 2006; **133**: 581-587 [PMID: 16834820 DOI: 10.1017/S0031182006000898]
9 **Ebigbo A**, Kahn M, Zellmer S, Messmann H. Advanced endoscopic imaging of colonic schistosomiasis. *Endoscopy* 2021; **53**: E251-E252 [PMID: 32968976 DOI: 10.1055/a-1252-2637]
10 **Cao J**, Liu WJ, Xu XY, Zou XP. Endoscopic findings and clinicopathologic characteristics of colonic schistosomiasis: a report of 46 cases. *World J Gastroenterol* 2010; **16**: 723-727 [PMID: 20135720 DOI: 10.3748/wjg.v16.i6.723]
11 **Godyn JJ**, Siderits R, Hazra A. Schistosoma mansoni in colon and liver. *Arch Pathol Lab Med* 2005; **129**: 544-545 [PMID: 15794687 DOI: 10.5858/2005-129-544-SMICAL]
12 **Nebel OT**, el-Masry NA, Castell DO, Farid Z, Fornes MF, Sparks HA. Schistosomal colonic polyposis: endoscopic and histologic characteristics. *Gastrointest Endosc* 1974; **20**: 99-101 [PMID: 4815036 DOI: 10.1016/s0016-5107(74)73894-9]
13 **Qin X**, Liu CY, Xiong YL, Bai T, Zhang L, Hou XH, Song J. The clinical features of chronic intestinal schistosomiasis-related intestinal lesions. *BMC Gastroenterol* 2021; **21**: 12 [PMID: 33407185 DOI: 10.1186/s12876-020-01591-7]
14 **Radhakrishnan S**, Al Nakib B, Shaikh H, Menon NK. The value of colonoscopy in schistosomal, tuberculous, and amebic colitis. Two-year experience. *Dis Colon Rectum* 1986; **29**: 891-895 [PMID: 3792173 DOI: 10.1007/BF02555371]
15 **Elbaz T**, Esmat G. Hepatic and intestinal schistosomiasis: review. *J Adv Res* 2013; **4**: 445-452 [PMID: 25685451 DOI: 10.1016/j.jare.2012.12.001]
16 **Van 't Wout AB**, De Jonge N, Tiu WU, Garcia EE, Mitchell GF, Deelder AM. Schistosome circulating anodic antigen in serum of individuals infected with Schistosoma japonicum from the Philippines before and after chemotherapy with

praziquantel. *Trans R Soc Trop Med Hyg* 1992; **86**: 410-413 [PMID: 1440819 DOI: 10.1016/0035-9203(92)90243-6]

17 **Coulibaly JT**, N'gbesso YK, Knopp S, Keiser J, N'Goran EK, Utzinger J. Efficacy and safety of praziquantel in preschool-aged children in an area co-endemic for Schistosoma mansoni and S. haematobium. *PLoS Negl Trop Dis* 2012; **6**: e1917 [PMID: 23236526 DOI: 10.1371/journal.pntd.0001917]

18 **Mutapi F**, Rujeni N, Bourke C, Mitchell K, Appleby L, Nausch N, Midzi N, Mduluza T. Schistosoma haematobium treatment in 1-5 year old children: safety and efficacy of the antihelminthic drug praziquantel. *PLoS Negl Trop Dis* 2011; **5**: e1143 [PMID: 21610855 DOI: 10.1371/journal.pntd.0001143]

19 **Putri ASD**, Vera Diana T, Daris R, Afriana F, Hidayat SH. Does the presence of praziquantel-related adverse events affect the health community's perception toward the mass chemopreventive program in the highest prevalence area of Schistosomiasis in Indonesia? *Gac Sanit* 2021; **35** Suppl 2: S487-S490 [PMID: 34929882 DOI: 10.1016/j.gaceta.2021.10.078]

20 **Issa I**, Osman M, Aftimos G. Schistosomiasis manifesting as a colon polyp: a case report. *J Med Case Rep* 2014; **8**: 331 [PMID: 25296942 DOI: 10.1186/1752-1947-8-331]

21 **Li WC**, Pan ZG, Sun YH. Sigmoid colonic carcinoma associated with deposited ova of Schistosoma japonicum: a case report. *World J Gastroenterol* 2006; **12**: 6077-6079 [PMID: 17009414 DOI: 10.3748/wjg.v12.i37.6077]

22 **Ming-Chai C**, Chi-Yuan C, Pei-Yu C, Jen-Chun H. Evolution of colorectal cancer in schistsosomiasis: transitional mucosal changes adjacent to large intestinal carcinoma in colectomy specimens. *Cancer* 1980; **46**: 1661-1675 [PMID: 7417960 DOI: 10.1002/1097-0142(19801001)46:7<1661::aid-cncr2820460728>3.0.co;2-o]

23 **Kaw LL Jr**, Punzalan CK, Crisostomo AC, Bowyer MW, Wherry DC. Surgical pathology of colorectal cancer in Filipinos: implications for clinical practice. *J Am Coll Surg* 2002; **195**: 188-195 [PMID: 12168965 DOI: 10.1016/s1072-7515(02)01186-9]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com