

Predictors of double balloon endoscopy outcomes in the evaluation of gastrointestinal bleeding

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2010 and April 2012. The mean age of the sample was 67 with 32 males (58.2%). Twenty-four DBE had no diagnostic yield and 30 DBE did not require therapy. Non-diagnostic yield was associated with performing two or more DBE studies in one day [odds ratio (OR): 13.72, $P = 0.008$], absence of blood transfusions within a year of the DBE (OR: 7.16, $P = 0.03$) and absence of ulcers or arteriovenous malformations (AVMs) on prior esophagogastroduodenoscopy (EGD) or colonoscopy (OR: 19.30, $P = 0.033$). Non-therapeutic DBE was associated with performing two or more DBE per day (OR: 18.579, $P = 0.007$), gastrointestinal bleeding episode within a week of the DBE (OR: 11.48, $P = 0.003$), fewer blood transfusion requirements prior to DBE (OR: 4.55, $P = 0.036$) and absence of ulcers or AVMs on prior EGD or colonoscopy (OR: 8.47, $P = 0.027$).

CONCLUSION: Predictors of DBE yield and therapeutic intervention on DBE include blood transfusion requirements, previous endoscopic findings and possibly endoscopist fatigue.

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Key words: Double balloon endoscopy; Enteroscopy; Obscure gastrointestinal bleeding; Small bowel; Anemia; Arteriovenous malformations; Arteriovenous malformations

Core tip: Double balloon endoscopy (DBE) is an excellent tool to visualize the small bowel and provide treatment. However, it may be unable to identify a source for bleeding in 20% to 40% of obscure gastrointestinal bleeding (OGIB) cases. This small retrospective case-control study showed that factors such as fewer blood transfusion requirements, absence of arteriovenous malformations or ulcers on prior endoscopies and possibly endoscopist fatigue may predict a negative diagnostic and therapeutic yield of DBE. This may help manage patients with OGIB and multiple comorbidities and potentially reduce health care costs by classifying patients who are most likely to

Abstract

AIM: To identify patients' characteristics associated with double balloon endoscopy (DBE) outcomes in investigation of obscure gastrointestinal bleeding (OGIB).

METHODS: Retrospective study performed at an academic tertiary referral center. Evaluated endpoints were clinical factors associated with no diagnostic yield or non-therapeutic intervention of DBE performed for OGIB evaluation.

RESULTS: We included fifty-five DBE between August

benefit from this time intensive procedure.

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INTRODUCTION

Obscure gastrointestinal bleeding (OGIB) is defined as persistent or recurrent gastrointestinal hemorrhage for which no definite source has been identified by esophagogastroduodenoscopy (EGD) or ileocolonoscopy. It accounts for approximately 5% of all cases of gastrointestinal bleeding^[1]. It can present as overt bleeding, or without visible blood but signs of iron deficiency anemia suggestive of a gastrointestinal source.

OGIB is a dilemma for gastroenterologists. It often requires multiple endoscopies^[2]. Push enteroscopy, small bowel follow-through, radionuclide scanning, and angiography have had variable success in this setting^[3,4]. Traditionally, intraoperative enteroscopy has been the only method available for complete small bowel evaluation. However, because of its increased morbidity and mortality compared to wireless capsule endoscopy and device assisted small bowel enteroscopy, it has decreased in popularity^[5].

Video capsule endoscopy (VCE) is safe, simple and has a high sensitivity in evaluation of small bowel lesions. It is however limited in its ability to obtain tissue for histology and to provide endoscopic therapy^[5]. Double-balloon endoscopy (DBE) was first introduced by Yamamoto *et al*^[6] in 2001. In contrast to push enteroscopy and wireless capsule endoscopy, DBE can potentially visualize the entire small bowel and offers therapeutic potential^[7-9]. Wireless capsule endoscopy and double balloon endoscopy provide similar diagnostic yield and have satisfactory concordance rate in the evaluation of OGIB^[10,11].

DBE is associated with a relatively low complication rate profile of 1.2%^[12]. Suspected small bowel bleeding is the main indication for DBE^[7]. However, DBE may be unable to identify a source for bleeding in 20% to 40% of OGIB cases^[13-16]. DBE is also time-consuming and labor-intensive, with an average examination time of approximately 60 to 90 min^[8,13]. Identifying patients with a higher probability of successful detection and therapy of bleeding sources with DBE is important for resource utilization. Our study investigates factors that may predict negative findings on double balloon endoscopy based on clinical, laboratory and endoscopic findings.

MATERIALS AND METHODS

Study patients

We retrospectively reviewed patients referred to Saint Louis University Hospital for double balloon endoscopy

between August 1, 2010 and April 6, 2012. Inclusion criteria included 18-80 years old patients who underwent double balloon endoscopy for OGIB.

Review of medical records

The medical records of all patients who met inclusion criteria were reviewed. Data collected included demographics, clinical, laboratory and endoscopic data. This study was approved by the institutional review board at Saint Louis University.

Endoscopists

Two experienced endoscopists performed all the DBE procedures. The endoscopists received dedicated training in balloon endoscopy through an ASGE course and initial case monitoring by an expert in the field.

DBE procedure

Informed consent was obtained prior to all DBE procedures. The DBE system (Fujinon, Inc., Saitama, Japan) was utilized. Initial approach with antegrade double balloon endoscopy was performed if capsule findings were within the proximal two third of small bowel, rectal approach if findings were more distal in the small intestine. We used the standard DBE method for insertion, withdrawal and observation, as described previously^[17]. For antegrade DBE, patients were kept nothing by mouth (NPO) at least 8 h prior to procedure and no particular bowel preparation was given. For retrograde DBE, bowel preparation with 4 L polyethylene glycol was used. Monitored anesthesia care with intravenous propofol, administered by staff anesthesiologists was used for most cases. Midazolam and narcotics were added occasionally to optimize sedation at the discretion of the anesthesiologist. Spot ink tattoo was placed to mark the maximum insertion depth reached. The small bowel segment suspected to have pathology on VCE was carefully inspected. The opposite route was used if pathology was not reached with the initial insertion route as deemed clinically appropriate.

Classification

Active gastrointestinal (GI) bleeding at the time of DBE was defined as overt bleeding within one week from DBE while non-active GI bleeding was defined as overt bleeding beyond one week from DBE. Acute GI bleeding was defined as GI bleeding within one month from VCE or DBE. Positive diagnostic yield on DBE was defined as cases with significant endoscopic findings [ulcers, arteriovenous malformations (AVMs), ulcerated masses or polyps] consistent with patients' clinical presentation and/or VCE findings. Therapeutic yield on DBE was defined as cases in which endoscopic intervention was performed. Positive findings on capsule endoscopy were defined as either the visualization of a lesion (AVMs, ulcerated polyps, mass, ulceration, multiple erosions) or the presence of blood and/or blood clots in the lumen of the small bowel. Negative or nonspecific capsule findings were assigned when an investigation showed no ab-

Table 1 Double balloon endoscopy findings

Findings	n (%)
AVM	20 (36.4)
Ulcer	3 (5.5)
Ulcerated polyp	3 (5.5)
Ulcerated mass	1 (1.8)
Multiple erosions	2 (3.6)
Portal HTN enteropathy	1 (1.8)
Vascular polyp	1 (1.8)
Negative findings	24 (43.6)

AVM: Arteriovenous malformation.

Table 2 Bivariate analysis of negative diagnostic double balloon endoscopy

Variables	Negative diagnostic yield	No therapeutic intervention
Pre-DBE ASA score ≤ 2	0.611	0.044
GI bleed within 1 wk prior to DBE	0.179	0.010
Blood transfusions ≤ 4 units 10 yr prior to DBE	0.149	0.027
> 1 DBE in one day by single endoscopist	0.016	0.024
Hgb > 9 mg/dL in the week prior to DBE	0.010	0.035
No blood transfusions in the year prior to DBE	0.019	0.044
Prior EGD with no ulcers or AVMs	0.031	0.004
Prior EGD or colonoscopy with no ulcers or AVMs	0.001	0.001
Prior enteroscopy with no AVMs	0.013	0.009

DBE: Double balloon endoscopy; GI: Gastrointestinal; EGD: Esophagogastroduodenoscopy; AVM: Arteriovenous malformation.

normalities or showed nonspecific findings (isolated red spots or single erosion). Endoscopic hemostasis by argon plasma coagulation, electrocoagulation, or clipping was used for vascular lesions. Ulcers were treated if they were actively bleeding or had visible bleeding vessels. Small polyps were removed and tumors were generally tattooed and biopsied for histopathology.

Statistical analysis

SPSS software (Version 20 SPSS Inc., Chicago) was used to collect and analyze the data. Descriptive statistics, chi square, Fisher's exact test and logistic regression were conducted to analyze and identify variables associated with negative findings or no therapy during DBE. A *P* value < 0.05 was considered to be statistically significant.

RESULTS

A total of 55 DBE cases were reviewed. The mean age of the sample was 67.4 ± 11.2 years old with 32 men (58.2%). The majority of patients with overt GI bleeding presented with melena (30 cases, 54.5%), whereas 9 (16.4%) presented with hematochezia. An additional 5 cases presented with both (9%). The majority of patients had chronic GI bleeding of more than 1 mo duration (75.5%). The mean lowest hemoglobin was 7.42 ± 2.16 mg/dL in the 5 years prior to DBE.

A total of 13 cases were missing prior EGD or colonoscopy official reports. Push enteroscopy was performed on 23 cases prior to DBE and most procedures had preceding VCE (96.4%). 83.6% of cases had positive findings on VCE. However only 54.3% of positive VCE led to significant DBE findings. Presence of AVMs or active bleeding on VCE were noted on DBE in 65% of cases. Ulcers on VCE were only found in half of the follow up DBE cases. Polyps on VCE led to the lowest DBE yield (22%). Also, 5 cases had positive DBE findings that were not seen on VCE. The missed lesions were AVMs, ulcers, an ulcerated hamartoma and carcinoid tumor that led to surgery.

The mean duration of the DBE procedures was 109.8 ± 26.4 min. Fifty DBE cases (90.9%) were performed via the antegrade route. All of the antegrade DBE procedures reached the mid-distal jejunum and 35 (70%) reached the ileum. One patient had a total enteroscopy through the antegrade approach and one patient had a total enteroscopy using both oral and rectal approach.

AVMs accounted for most of our DBE findings (36.4%), as shown in Table 1. In total, 24 DBEs (43.6%) had negative diagnostic findings and 30 DBEs (54.5%) did not require endoscopic therapy. Based on our classification: 20 cases (36.4%) had active bleeding at the time of DBE, 23 (41.8%) were not active and 11 (20%) had occult GI bleeding. Positive diagnostic yield was seen in 10 (50%) active GI bleeding cases, 16 (69.5%) non-active and 4 (36.3%) occult GI bleeding cases. Five of 11 cases (45.5%) with acute GI bleeding at the time of DBE had positive diagnostic yield on DBE as opposed to 12 out 13 cases (92.3%) with acute GI bleed at the time of VCE. 4 patients required repeat DBE during our study period due to recurrent GI bleeding. Lower ASA score, negative findings on previous push enteroscopy and hgb of more than 9 prior to DBE were associated with negative diagnostic and therapeutic yield on bivariate analysis (Table 2). DBE diagnostic or therapeutic yield was not associated with age, gender, use of antiplatelets or anticoagulation medications, occult or overt bleeding, DBE procedure time, platelets, INR or albumin on bivariate analysis. Table 3 illustrates the relationship between diagnostic and therapeutic outcomes and time between GI bleed, VCE and DBE. In multivariate analysis, smaller blood transfusion requirements, absence of findings on EGD and colonoscopy and performance of more than one DBE per day per endoscopist were associated with negative diagnostic and negative therapeutic yield (Tables 4 and 5).

DISCUSSION

DBE was first described by Yamamoto *et al*^[6] in 2001. Due to its potential insertion depth and total enteroscopy success, it has been an effective tool in obscure GI bleeding evaluation and management^[18,19]. Previous reports indicate a 60%-80% diagnostic yield of DBE^[13-16]. However, past studies have not focused on factors that may

Table 3 Time between gastrointestinal bleed, video capsule endoscopy and double balloon endoscopy in relation to outcomes *n* (%)

Variables		Less than 1 wk	1 wk to 1 mo	1 mo to 1 yr	More than 1 yr
Time from onset of GI bleed to VCE	VCE with positive findings/total No. of VCE	10/10 (100)	2/3 (66.7)	11/14 (78.6)	15/18 (83.3)
Time from onset of GI bleed to DBE	DBE with positive findings/total No. of DBE	2/8 (25)	3/3 (100)	9/14 (64.3)	17/27 (63)
	DBE leading to therapy/total No. of DBE	1/8 (12.5)	3/3 (100)	7/14 (50)	14/27 (51.9)
Time from VCE to the DBE procedure	DBEs with positive diagnostic yield/total No. of DBEs	8/15 (53.3)	3/6 (50)	15/25 (60)	3/6 (50)
	DBEs that led to therapy/total No. of DBEs	7/15 (46.7)	2/6 (33.3)	13/25 (52.0)	2/6 (33.3)

VCE: Video capsule endoscopy; DBE: Double balloon endoscopy; GI: Gastrointestinal.

Table 4 Multivariate logistic regression of factors associated with negative diagnostic yield of double balloon endoscopy

Variables	OR (95%CI)	P value
> 1 DBE in one day by single endoscopist	16.63 (2.04-135.45)	0.009
No blood transfusions within year prior to DBE	13.04 (1.53-111.04)	0.019
Prior EGD or colonoscopy with no ulcers or AVMs	19.30 (1.26-295.18)	0.033

DBE: Double balloon endoscopy; EGD: Esophagogastroduodenoscopy; AVM: Arteriovenous malformation.

Table 5 Multivariate logistic regression of factors associated with non-therapeutic double balloon endoscopy

	OR (95%CI)	P value
> 1 DBE in one day by single endoscopist	18.28 (2.24 -148.86)	0.007
GI bleed within 1 wk prior to DBE	10.77 (2.18-53.14)	0.004
Blood transfusions ≤ 4 units in the year prior to DBE	4.27 (1.03-17.71)	0.045
Prior EGD or colonoscopy with no ulcers or AVMs	8.47 (1.28-55.87)	0.027

DBE: Double balloon endoscopy; GI: Gastrointestinal; EGD: Esophagogastroduodenoscopy; AVM: Arteriovenous malformation.

help to predict outcomes of DBE.

To our knowledge, this is the first study to look at factors associated with both negative diagnostic and therapeutic yield of DBE. In the management of OGIB, patients often undergo multiple endoscopic procedures prior to DBE. The absence of findings on prior endoscopies may predict a negative diagnostic and therapeutic yield of DBE. In addition, patients with lower blood transfusion requirements were more likely to have a negative diagnostic and therapeutic yield. This is in line with what one would expect clinically and may have implications for risk stratification, utility, and timing of the procedure. Active GI bleeding in the week prior to DBE was not associated with positive DBE findings and led to less therapeutic interventions. This may be due to missed pathology on upper or lower endoscopy or due to poor visualization within the small bowel with active GI bleeding. However, most of the DBE reports did not indicate active bleeding suggesting that perhaps it is not an issue with missed pathology but a source that is no longer bleeding. This may be related to medications that are stopped while awaiting definitive therapeutic management such as anticoagulants or antithrombotics. One previous study demonstrated increased detection rates of bleeding sources on DBE for patients with two or more recurrent bleeding episodes. This was not looked at in our study^[20].

Our study involved an older population undergoing DBE for obscure GI bleeding, mainly presenting with overt and chronic GI bleeding. Most of our DBE procedures were through the oral route. Small bowel AVMs

were the most common findings in our study. This is consistent with previous studies where vascular lesions accounted for nearly two-thirds (65.9%) of positive findings in the western population^[21]. VCE preceded DBE in 96.4% of cases. This helped guide the route and insertion depth of DBE. There was a high rate of positive VCE findings that led to non-diagnostic DBE in our study. These lesions could be classified as falsely positive VCE findings and were mainly polyps (88%), followed by ulcers (50%) and AVMs (35%). This is consistent with a previous multicenter prospective study showing acceptable concordance between DBE and VCE for AVMs and inflammatory lesions, but not for polyps or masses^[11]. Protruding or bulging lesions would be falsely seen as polyps or masses on capsule endoscopy but then flattened by air insufflation when endoscopically visualized. This can explain the high rate of false positive findings for polyps. We still recommend further evaluation of polyps seen on VCE with imaging studies or endoscopy.

There are several possible reasons for negative findings on DBE. First, inability to perform complete enteroscopy in most DBE cases may limit findings. Several studies have reported widely variable rates of complete enteroscopy with DBE, ranging from 0% to 86%^[7,9,13,14]. Similar to previous study designs, we relied on VCE findings to guide insertion depth and DBE insertion route. The absence of bleeding source beyond our insertion depth could not be confirmed; however our DBE cases evaluated the majority of the small intestine and reached suspected areas where positive lesions were seen on

VCE. An interesting study by Bollinger *et al*^[22] using VCE to map the distribution of AVM in the western population identified the jejunum as the most common location for AVMs (80%). The ileum had the lowest distribution of AVM (5.7%)^[22]. Thus, it is reasonable that the distance reached in our DBE would capture most AVMs.

Another reason for negative findings may be that lesions found on VCE may heal with time. The same number of cases had acute GI bleed at the time of VCE and DBE based on our classification of acute GI bleed, however more findings were seen with acute GI bleed at the time of VCE. This could be due to increased detection rate on VCE related to shortened time interval to onset of GI bleed. No association was found between DBE outcomes and time between VCE and DBE or time between onset of GI bleed and DBE; this could be due to a limited sample size. Third, lesions may have been missed on prior endoscopies. Fry *et al*^[23] reported that a definite source of bleeding was detected in 24.3% of patients outside the small bowel and suggested that repeat upper and lower endoscopy should be considered prior to DBE. Our study only included 7 cases with repeat EGD and colonoscopy prior to DBE. Repeating endoscopy in our study did not alter findings or the need for DBE. Furthermore, an evaluation of the upper GI tract at the time of oral route DBE did not reveal any additional findings.

It is possible that negative diagnostic yield is related to missed lesions on DBE. It was hard to evaluate re-bleeding rates post DBE in our study since most patients were seen at the time of DBE for the first time. However as this institution is only one of 2 referral centers in the state to perform DBE (located approximately 250 miles apart). One would assume that repeat DBE requests would again come to our institution for continued bleeding to attempt total enteroscopy through a combined approach. Thus, the low repeat DBE rate may indicate that patients did not have significant recurrent bleeding. Byeon *et al*^[24] studied the diagnostic value of repeat DBE. Of 32 patients who underwent repeat DBE, all patients with negative initial DBE had a negative repeat DBE suggesting the reproducibility of the findings. On the other hand, seventeen of 21 patients with positive initial DBE again showed a probable bleeding source on repeat DBE^[24]. Additionally, among the patients with normal findings at the first DBE procedure, 62.5% had no recurrent bleeding during the follow-up period of 40.4 ± 16.2 mo^[25]. Negative DBE may portend a different clinical picture and a low likelihood of a small bowel source of bleeding.

DBE procedures are labor intensive, and can be tiring. The average examination time is approximately 60 to 90 min^[9]. Our cases took longer than average to perform; however length of the procedure was not associated with diagnostic yield. It is known that colonoscopies have lower completion rates and adenoma detection rates in procedures performed in the afternoon compared with the morning, thought to be related to endoscopist fatigue. However, a study by Sanaka *et al*^[26] evaluating DBE

performance did not show a difference between morning or afternoon procedures. In our study we compared the cumulative effect of doing 2 or more procedures as opposed to one DBE a day. We found that there is an association with negative findings with more procedures in a day, which may indicate fatigue related factors affecting diagnostic and therapeutic yield. Thus, it may not be the timing of the procedure that matters but in fact the number of procedures one does given the long duration of DBE procedures.

There were several limitations to our study. First the small sample size and the retrospective design resulted in a wide confidence interval and less precise findings. Second of all, we were unable to accurately determine insertion depth and could not completely exclude the absence of findings in the unexamined small intestine as very few patients had complete enteroscopy.

In conclusion, this study may help stratify patients into high likelihood or low likelihood of negative diagnostic yield or therapy in DBE for gastrointestinal bleeding. This may help manage patients with multiple comorbidities and reduce health care costs by identifying those who are most likely to benefit from this time intensive procedure.

COMMENTS

Background

Double balloon endoscopy (DBE) is valuable in the setting of obscure gastrointestinal bleeding (OGIB). However, it is invasive, time-consuming and may be unable to identify a source for bleeding in 20% to 40% of OGIB cases.

Research frontiers

To identify patients' characteristics associated with DBE outcomes in investigation of OGIB.

Innovations and breakthroughs

To our knowledge, this is the first study to look at factors associated with both negative diagnostic and therapeutic yield of DBE. Fewer blood transfusion requirements, absence of arteriovenous malformations or ulcers on prior endoscopies and possibly endoscopist fatigue may predict a negative diagnostic and therapeutic yield of DBE.

Applications

This study may help stratify patients into high likelihood or low likelihood of negative diagnostic yield or therapy in DBE for gastrointestinal bleeding. This may help manage patients with multiple comorbidities and reduce health care costs by identifying those who are most likely to benefit from this time intensive procedure.

Peer review

This is a descriptive retrospective study into DBE. The results are therefore to be viewed with some caution and this in mind. Otherwise this study is worthy of publication.

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