76455_Auto_Edited-check.docx

Effect of small bowel transit time on accuracy of video capsule endoscopy in evaluating suspected small bowel bleeding

Mohan N *et al*. SBTT effect on VCE for SBB

Nandakumar Mohan, Simone Jarrett, Alexander Pop, Daniel Rodriguez, Robert Dudnick

Abstract

BACKGROUND

Obscure small bowel bleeding is defined as gastrointestinal bleeding (GIB) that is unidentifiable with esophagogastroduodenoscopy (EGD) and a colonoscopy with video capsule endoscopy (VCE) being the next gold standard step for evaluation. Small bowel transit time (SBTT) is a metric of a VCE study that is defined as the time the capsule takes to travel through the small intestine.

AIM

To determine if SBTT within the VCE study, correlates to overall detection of obscure small bowel bleeds. Furthermore, we attempted to identify any existing correlation between SBTT and re-bleeding after a negative VCE study.

METHODS

This is a single center retrospective analysis of VCE studies performed for overt and occult GIB at Einstein Medical Center, Philadelphia, between 2015 and 2019. Inclusion criteria primarily consisted of patients 18 years or older who had a VCE study done as part of the workup for a GIB. Patients with incomplete VCEs, poor preparation, or with less than 6 mo of follow up were excluded. A re-bleeding event was defined either as overt or occult within a 6-mo timeframe. Overt re-bleeding was defined as Visible melena or hematochezia with > 2 gm/dL drop in hemoglobin defined an overt re-

bleeding event; whereas an unexplained > 2 gm/dL drop in hemoglobin with no visible bleeding defined an occult re-bleed.

RESULTS

Results indicated that there was a significant and positive point biserial correlation between SBTT of 220 min and detection of a bleeding focus with a statistically significant p value of 0.008. However, the area under the curve was negligible when trying to identify a threshold time for SBTT to discriminate between risk of re-bleeding events after a negative VCE.

CONCLUSION

In terms of SBTT and association with accuracy of VCE finding a bleeding focus, 220 min was found to be adequate transit time to accurately find a bleeding focus, when present. It was found that no threshold SBTT could be identified to help predict re-bleeding after a negative VCE.

Key Words: Small bowel transit time; Endoscopy; Video capsule endoscopy; Obscure bleed; Small bowel; Anemia

Mohan N, Jarrett S, Pop A, Rodriguez D, Dudnick R. Effect of small bowel transit time on accuracy of video capsule endoscopy in evaluating suspected small bowel bleeding. *World J Gastrointest Pharmacol Ther* 2022; In press

Core Tip: Understanding the utility of Small bowel transit time (SBTT) in Video Capsule Endoscopies can help with assessing accuracy and yield of video capsule endoscopy studies as well as whether a certain SBTT exists to achieve appropriate accuracy in detecting small bowel bleeding acutely or if a threshold exists in order to predict future small bowel bleeding.

INTRODUCTION

Video capsule endoscopy (VCE) has become the standard of investigation for obscure gastrointestinal (GI) bleeding[1]. Suspected small bowel bleeding is defined as recurrent and/or persistent GI bleeding from a source that remains unidentified after bidirectional GI endoscopy, both esophagogastroduodenoscopy (EGD) and a colonoscopy. This bleeding may be further subcategorized as occult or overt. *Obscure-overt* GI bleeding requires persistent or recurrent visible evidence of bleeding, hematochezia, or melena, whereas *obscure-occult* GI bleeding is defined as persistently positive fecal occult blood testing, iron deficiency anemia, or both without evidence of gross GI hemorrhage[2].

VCE is a method of colonic investigation that has been available to gastroenterologists since 2001, with multiple capsule endoscopy systems evolving over the years. While capsule endoscopy has been successfully used to investigate colonic pathologies ranging from inflammatory bowel disease, small intestinal tumors and polyposis syndromes, and celiac disease, the main indication for its use is to identify an obscure GI bleeding source[3]. While colonoscopy and EGD remain the gold standards to identify lower gastrointestinal and upper GI bleeding (GIB) sources, respectively, these methods are not physically capable of reaching the small bowel, without the help of the push enteroscopy method, but even then, as many as 21% of patients end up with an undetected bleeding site[4,5]. This is where the value of VCE studies predominate with studies showing that VCE has been found to be superior to other methods such as push enteroscopy and small bowel barium enema for the diagnosis of obscure GI bleeding[6].

Studies have found that small bowel bleeding is the most common indication for VCE, which accounts for approximately 5%-10% of all GI bleeding[7]. The most common small bowel cause of obscure GI bleeding has been found to be arteriovenous malformations or angioectasias, dominating over 20%-55% of cases[8].

The diagnostic yield is approximately 60% for overt small bowel bleeding and 30% for obscure small bowel bleeding. The negative predictive value of a normal VCE is

high[1]. This has been shown in studies where there are higher re-bleeding rates in patients with occult obscure GI bleeding who had a positive VCE as compared with those with a negative VCE[9]. A recent meta-analysis demonstrated that the overall odds ratio for re-bleeding was lower after a negative VCE for obscure GI bleeding as compared with a positive VCE, especially with a short follow-up duration of 2 years. Approximately 80% of patients will not re-bleed during long term follow-up after a negative VCE[10]. This meta-analysis also did not find a statistically significant difference in re-bleeding between patients with overt *vs* occult GI bleeding on presentation.

VCE studies generate a small bowel transit time (SBTT), which is defined as the time that the video capsule takes to travel from the first duodenal image to the first cecal image[11]. The goal of VCE studies is to find obscure GI bleeding sources that other methods are unable to identify, but without anywhere close to a 100% detection rate, follow up for patients with negative VCE studies become critical to monitor for rebleeding events. Many studies have investigated rebleeding rates after a negative VCE study where patients will rebleed at rates between 4% and 27%[12,13]. While these studies investigated rebleeding events, they failed to investigate any tangible data points within the VCE studies to associate with rebleeding rates. With SBTT being one of the primary metrics used in VCE studies, we aimed to determine whether SBTT influences VCE yield and whether any correlation between SBTT and rebleeding after a negative VCE might exist.

MATERIALS AND METHODS

Patients and methods

Study design, participants, and data collection: This study was a single center retrospective analysis of all negative VCE studies for GIB, including both obscure-overt GI bleeding and obscure-occult GI bleeding between 2015 and 2019. Pill Cam SB2/3 capsule systems were used in all studies. Inclusion criteria included adult patients aged 18 years above whom underwent VCE for indication of suspected small bowel GI

bleeding which included occult GI bleeding, overt/obscure GI bleeding, heme positive stools, melena, rectal bleeding, hematochezia, blood loss anemia and were found to have a negative VCE study. Patients were excluded from the study if they were found to have an incomplete VCE (the capsule did not reach the cecum, prohibiting a full visualization and calculation of the SBTT), poor bowel preparation resulting in an inadequate study, and if they were lost to follow up (Table 1).

VCE Rapid Reader was utilized to identify studies performed for obscure GI bleeding. Study indication was determined using diagnosis/indication listed for the VCE in the system. Key phrases used include GI bleeding, rectal bleeding, hematochezia, melena, heme positive stools, occult GI bleeding, obscure GI bleeding and blood loss anemia of unknown etiology. After identification of studies for the above stated indications, the negative VCE reports from this database were identified. VCE reports were deemed negative once the results were reported as normal and/or absent pathology identified to explain blood loss. All studies were read by gastroenterologists with at least 10 years of experience in capsule study interpretation.

The hospital electronic medical records were reviewed for patients with a negative VCE for GI bleeding to determine all re-bleeding rates. Re-bleeding events were defined either as overt re-bleeding or occult re-bleeding. Overt re-bleeding was defined as melena or hematochezia with > 2 gm/dL drop in hemoglobin. Occult re-bleeding was defined as unexplained > 2 gm/dL drop in hemoglobin after the initial VCE or the failure of initial hemoglobin to improve throughout the hospital stay.

Statistical analysis
We used means and standard deviations for continuous variables, and frequencies and proportions for discrete variables. We computed a point biserial correlation (PBC) to assess the strength of association between SBTT (continuous variable) and VCE yield or post VCE re-bleeding rates (binary variable)[14]. We used PBC instead of Pearson or Spearman correlations because one of our variables compared is a binary discrete variable. To identify the optimal threshold time, we used a receiver operator

characteristic (ROC) curve. The ROC curve plots the sensitivity (true positive rate; probability of testing positive given one is positive) against 1-Specifiity (False positive rate; probability of testing positive given one is negative), with sensitivity on the vertical axis and False Positive on the horizontal axis[15,16]. A diagonal line is drawn to indicate equal sensitivity and specificity across all possible values. An empirical curve is drawn plotting sensitivity by specificity at different values (potential cut points) of the measure in question (transit time). Ideally, this empirical curve will be higher than the diagonal line, as the diagonal line indicates random assignment of a patient to having an abnormal result. The higher the empirical curve, the greater the likelihood of a true versus false positive result. Assessment is conducted by calculating the area under the curve (AUC). In the ROC analysis, the AUC represents the probability of being a true versus a false positive. AUC's close to 1.0 are better, as they indicate a greater sensitivity to false positive ratio, with AUC's around 0.5[17] being equivocal. A statistical test is employed to compare the calculated AUC to an AUC of 0.5.

RESULTS

A total of 316 VCE studies were reviewed by experienced gastroenterologists (Table 2). Of note, two patients were lost to follow up following VCE or did not get 6-mo re-bleeding data in the form of overt bleeding or occult bleeding, and therefore could not be included in the final analysis to assess for re-bleeding rates after a negative VCE study, giving a total cohort consisting of 314 patients. Our final resulting cohort used for analysis was 99.4% of the initial evaluated studies. Further analysis of the data revealed that 99 out of the 314 patients (31.5%) underwent initial VCE in order to evaluate overt or occult bleeding; whereas the other 215 patients (68.5%) underwent initial VCE to evaluate for unclear causes of iron deficiency anemia.

The mean (SD) SBTT for capsule studies in which re-bleeding was not identified was 199.56 min (95.818) with 95% confidence interval (CI) = 188.458 to 210.668. In those in whom re-bleeding was seen, the mean (SD) for SBTT was 218.14 (110.260 with 95%CI = 177.302, 258.984).

AUC was not significantly different from 0.5 (AUC = 0.545, P = 0.429), suggesting no relationship between SBTT and the risk of re-bleeding after a negative VCE (Figure 1).

There was a significant and positive point biserial correlation between SBTT of 220 min and detection of a bleeding focus (r_{pbc} = 0.149, P = 0.008).

DISCUSSION

VCE is the gold standard for identifying obscure GIB[18]. Our study aimed to assess whether SBTT in VCE studies correlated with VCE yield in detecting obscure GIB as well as whether SBTT had any correlation with re-bleeding rates after a negative VCE.

The literature reports that the average SBTT is approximately 245 min with ranges anywhere between 18 min and 522 min[19]. Our study demonstrated that there was a significant correlation between SBTT and VCE yield in identifying an obscure GIB. We found that an average SBTT of 220 min correlated with identification of a small bowel source of bleeding on VCE. A study conducted by Girelli *et al*[20] in 2017 investigated the correlation between SBTT and the detection of significant small bowel lesions using capsule endoscopy. They found that the longer the SBTT (283 min and above), the higher the detection rate using capsule endoscopy. The initial part of our study also investigated this correlation to detect the rates within our institution and we found that a shorter SBTT than the average was able to yield significant results in terms of detecting an obscure GIB. This variation may speak to differences in capsule endoscopy type and technique, proficiency of detecting bleeding by the physician reviewing the endoscopy, or cause and severity of the bleed[20]. While many studies such as Girelli *et al*[20] show that SBTT has a significant impact on diagnostic yield of capsule endoscopy studies, there is virtually no literature that investigates those same SBTT timings and its specific correlations to re-bleeding rates in a patient with an unidentified obscure GIB which could suggest that further research into this area is needed.

VCE studies with significant findings tend to lead to specific treatments applications such as device-assisted enteroscopy which aims to treat identified lesions. The main goal at investigating an obscure GIB and identifying a treatable lesion is to assure

prevention of future re-bleeding events[21]. A study by Carey *et al*[22] which included a trial of 260 patients demonstrated that re-bleeding events and overall outcomes improved in the subsequent months after VCE was able to identify a lesion that was then successfully treated. Viazis *et al*[23] also reported that VCE affects long-term outcome (*i.e.*, resolution of bleeding) in patients with positive VCE (65.2% *vs* 35.4% of negative VCE group), since these patients are prone to undergo aggressive interventions. Angiodysplasia was the most common finding among patients with positive VCE (70%) and most of them received a mode of treatment that lead to resolution of bleeding (69%)[23].

Long term outcomes and re-bleeding events after a positive VCE study has been extensively studied, however few reports in the literature report the long-term outcomes as well as rebleeding rates of a negative VCE study. This may be due to the fact that when a bleed is identifiable, VCE has quite a good diagnostic yield and therefore the numbers do not favor looking into long term effects of negative VCE studies. Khamplod *et al*[24] found that out of 142 overt GIB patients, only 9 patients had small bowel lesions missed by VCE and they found that almost all those patients re-bled months after their negative VCE study. This is where the importance of our study comes in. VCE studies are reliable in finding an obscure GIB, but in those with negative VCE studies, with them being at high risk for re-bleeding events, finding a measure to predict the rate of re-bleeding would allow for closer monitoring and likely prevention of a re-bleeding event. With SBTT being such a good and well-studied measure, in terms of correlating with diagnostic yield of VCE studies, it only makes sense to try and use SBTT as the measure to help predict re-bleeding events after a negative VCE, which is exactly what our study set out to accomplish.

Our study was unable identify any correlation between SBTT and re-bleeding rates after a negative VCE. Considering this we were unable to identify a threshold SBTT that could be used as a predictive index for re-bleeding after a negative VCE. This is likely due to the limitation of the sample size of the study. With capsule endoscopy being such a refined and reliable technique, gathering enough negative VCE studies under an

already small overall patient population could have resulted in the numbers being far from statistically significant. To find a correlation between SBTT and re-bleeding after a negative VCE, a larger study population (possibly *via* a multicenter study) that consists of more negative VCE studies would be necessary to find a statistically significant SBTT threshold number. Having a predictive threshold SBTT would be extremely beneficial to the general clinician. If a threshold SBTT could be found during the study, the general clinician could then know how at risk a patient will be for re-bleeding and possibly hasten follow up in higher risk individuals and therefore prevent re-hospitalization.

One of the biggest limitations to our study is the statistical power due to sample size. Our study only looked at a total of 315 VCE studies across a single institution and therefore future studies should include a much larger cohort. Another limitation of this study was the number of patients lost to follow up, as 28 of 343 patients did not follow up after the initial evaluation to then be able to assess for re-bleeding rates. One way to remedy this in future studies is to expand patient population by conducting a multi-institutional study, which would not only allow for a much larger sample size, but also compensate for patients lost to follow up, and allow for greater generalizability as the patient population would be more representative of the general population. Future studies looking into more correlational data for SBTT is recommended as being able to correlate SBTT with newer parameters such as types and severity of lesions in initially positive VCE as well as in negative VCE with later re-rebleeding events, would allow for clinicians to have more tools at hand in order to predict clinical severity for their patients with obscure GIB.

CONCLUSION

In this single center retrospective study, we were unable to determine a relationship between SBTT and the risk of re-bleeding following a negative VCE. However, we were able to identify an average SBTT of 220 min as correlational to VCE studies being able to identify a small bowel source of bleeding. We also identified a re-bleeding rate of 8.9%

at 6 mo within our institution, which demonstrates the low likelihood of re-bleeding after a negative video capsule study.

ARTICLE HIGHLIGHTS

Research background

Identified and evaluated the various use case scenarios and benefits of video capsule endoscopy (VCE) and used prior existing data to identify a metric within the existing technology to be used for improved and more accurate medical care.

Research motivation

To find a metric within already existing VCE studies to help predict re-bleeding episodes when the study comes back negative. Finding an appropriate metric to use to be able to predict such a clinical outcome would allow for improved and early clinical intervention.

Research objectives

To assess whether small bowel transit time (SBTT) influences VCE yield in detecting a small bowel bleed and if there was any correlation between SBTT and re-bleeding rates when VCE study was negative. If a correlation to re-bleeding rates could be found, it could allow for earlier follow-up with the patients and possible earlier interventions prior to re-bleeding events.

Research methods

Single center retrospective electronic health record-based analysis of VCE studies performed for overt and occult GIB at Einstein Medical Center, Philadelphia. To identify the optimal threshold time, receiver operator characteristic (ROC) curve was used. area under the curve (AUC) was also used to assess the measure's ability to discriminate between variables.

Research results

Our study found that there was no valuable threshold time for SBTT that could be linked to re-bleeding rates in negative VCE studies. While our study may have been too small in scale to truly see a correlational link in the predictive value of SBTT, we were able to show that SBTT is a good metric to follow in detection of the initial bleed, therefore highlighting the importance of the metric itself as a clinical tool that can aid in improvement of overall clinical care. The major problem that remains to be solved is that, with a larger amount of statistical power and the backing of multi-institutional data, will a correlational threshold for SBTT be found? If so, what is that threshold and how can it be implemented directly to benefit patient care?

Research conclusions

While we were unable to find a correlation between SBTT and re-bleeding rates in negative VCE studies, our study was able to identify a threshold value of 220 min for SBTT in order to accurately identify a small bowel source of bleeding. This study proposes that SBTT, a tangible metric within VCE studies, due to its ability to correlate to identification of obscure gastrointestinal bleeds, should be a major metric used to predict valuable clinical outcomes.

Research perspectives

Future studies are needed to further look into correlational data for SBTT along with newer parameters such as types and severity of lesions in initially positive VCE as well as in negative VCE with later re-rebleeding events. This would allow for clinicians to have more tools at hand in order to predict clinical severity for their patients with obscure GIB.

Figure Legends

Figure 1 Correlation between small bowel transit time and the yield of video capsule endoscopy detection of bleeding focus. ROC: Receiver operator characteristic.

Table 1 Descriptive statistics

Discrete variables			
Variable	**Level**	**_n_**	**%**
Sex	Male	124	39
	Female	191	61
Race/ethnicity	African American	177	58
	White	71	23
	Other	67	19
Positive VCE	Yes	115	37
	No	200	63
Continuous variables			
		Mean	SD
Age		65.19	12.673
Small bowel transit time		201.35	97.016

Table 2 Case processing summary

	Cases					
	Included		Excluded		Total	
	n	Percent	*n*	Percent	*n*	Percent
Small bowel transit time (min); rebleeding in 6 mo from VCE (Y = 0/N = 1)	314	99.4%	2	0.6%	316	100.0%

VCE: Video capsule endoscopy.

76455_Auto_Edited-check.docx

7   Georgios Tziatzios, Paraskevas Gkolfakis, George D. Dimitriadis, Konstantinos Triantafyllou. "Long-term effects of video capsule endoscopy in the management of obscure gastrointestinal bleeding", Annals of Translational Medicine, 2017
Crossref
21 words — 1%

8   e-sciencecentral.org
Internet
21 words — 1%

9   www.cureus.com
Internet
20 words — 1%

10   ecommons.aku.edu
Internet
18 words — < 1%

11   "Endoscopy in Small Bowel Disorders", Springer Science + Business Media, 2015
Crossref
15 words — < 1%

12   escholarship.umassmed.edu
Internet
15 words — < 1%

13   students.kennesaw.edu
Internet
15 words — < 1%

14   "OUTCOMES RESEARCH", The American Journal of Gastroenterology, 09/2008
Crossref
14 words — < 1%

15   Esteve Saperas. "Capsule Endoscopy Versus Computed Tomographic or Standard Angiography for the Diagnosis of Obscure Gastrointestinal Bleeding", The American Journal of Gastroenterology, 4/2007
Crossref
13 words — < 1%

16 Gerson, Lauren B, Jeff L Fidler, David R Cave, and Jonathan A Leighton. "ACG Clinical Guideline: Diagnosis and Management of Small Bowel Bleeding", The American Journal of Gastroenterology, 2015.
Crossref

12 words — < 1%

17 "Diagnostic and Therapeutic Procedures in Gastroenterology", Springer Science and Business Media LLC, 2018
Crossref

11 words — < 1%

18 Handbook of Capsule Endoscopy, 2014.
Crossref

11 words — < 1%

19 link.springer.com
Internet

11 words — < 1%

20 Ehrhard, Florent, Pierre Nazeyrollas, Hedia Brixi, Alexandra Heurgue-Berlot, and Gérard Thiéfin. "Proximal predominance of small bowel injury associated with uncoated low-dose aspirin therapy : a video capsule study in chronic users", European Journal of Gastroenterology & Hepatology, 2013.
Crossref

10 words — < 1%

21 Veronica Baptista. "Continuing challenges in the diagnosis and management of obscure gastrointestinal bleeding", World Journal of Gastrointestinal Pathophysiology, 2014
Crossref

10 words — < 1%

22 www.mdpi.com
Internet

10 words — < 1%

23 "SMALL INTESTINE/UNCLASSIFIED", The American Journal of Gastroenterology, 9/2005
Crossref

9 words — < 1%

24 jitc.biomedcentral.com
Internet   9 words — < 1%

25 www.coursehero.com
Internet   9 words — < 1%

26 "Abstracts Submitted for the 69th Annual Scientific
Meeting of the American College of
Gastroenterology", The American Journal of Gastroenterology,
10/2004
Crossref   8 words — < 1%

27 C. Engelhart, N. Eisenstein, J. Meininger.
"Psychometric properties of the neurobehavioral
cognitive status exam", Clinical Neuropsychologist, 1994
Crossref   8 words — < 1%

28 Jun Kawachi, Hidemitsu Ogino, Rai Shimoyama,
Chikamasa Ichita et al. "Intraoperative
angiography with indocyanine green injection for precise
localization and resection of small bowel bleeding", Acute
Medicine & Surgery, 2020
Crossref   8 words — < 1%

29 K. Mergener. "Literature review and
recommendations for clinical application of small-
bowel capsule endoscopy, based on a panel discussion by
international experts", Endoscopy, 10/2007
Crossref   8 words — < 1%

30 Marcia Irene F. Canto, Amitabh Chak, Thomas
Stellato, Michael V. Sivak. "Endoscopic
ultrasonography versus cholangiography for the diagnosis of
choledocholithiasis", Gastrointestinal Endoscopy, 1998
Crossref   8 words — < 1%

31 epdf.pub

Internet

8 words — < 1%

32   new.salvemlarieradepineda.pangea.org
Internet

8 words — < 1%

33   www.tandfonline.com
Internet

8 words — < 1%

34   Chryssostomos Kalantzis, Konstantinos Triantafyllou, Angelos A. Papadopoulos, George Alexandrakis et al. "Effect of three bowel preparations on video-capsule endoscopy gastric and small-bowel transit time and completeness of the examination", Scandinavian Journal of Gastroenterology, 2009
Crossref

7 words — < 1%

35   Georgios Tziatzios, Paraskevas Gkolfakis, Cesare Hassan, Ervin Toth et al. "Meta-analysis shows similar re-bleeding rates among Western and Eastern populations after index video capsule endoscopy", Digestive and Liver Disease, 2018
Crossref

7 words — < 1%

36   Henrique Mendes Castilho, Cairo Lucio Nascimento, Wlamir Olivares Loesch Vianna. "Aircraft bleed valve fault classification using support vector machines and classification trees", 2018 Annual IEEE International Systems Conference (SysCon), 2018
Crossref

7 words — < 1%

EXCLUDE QUOTES	OFF	EXCLUDE SOURCES	OFF
EXCLUDE BIBLIOGRAPHY	OFF	EXCLUDE MATCHES	OFF