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Gastrointestinal Bleeding Diagnosed by Capsule Endoscopy – A Change towards More Patients with Bleeding-related Drugs

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Authors' contributions

This work was carried out in collaboration among all authors. Authors AH and EZ designed the Conception. Authors AH and TS managed provision of study materials. Authors AH, LG and EZ managed the analysis and interpretation of the data. Authors AH and EZ were drafting of the article. All the authors managed the critical revision of the article for important intellectual content. All authors read and approved the final manuscript.

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ABSTRACT

Background: Video capsule endoscopy (VCE) is the standard procedure for a work-up of a suspected bleeding source after negative gastroscopy and colonoscopy. Popularity of this procedure increased in the last decade. In this work we aimed to identify the changes in patient characteristics and how those changes influence bleeding related findings. In particular the assumed higher risk of gastrointestinal bleeding of the new oral anticoagulants (nOAC) compared to phenprocoumon was of interest.
Methods: Consecutive VCE examinations performed at our center from January 2004 to March 2018 were identified retrospectively. Baseline characteristics of the patients, VCE results and treatment that was initiated were analyzed.
Results: 560 VCE were included in the analysis. The rate of VCE per month increased from 2.3/month in the period of January 2004 – December 2012 up to 5.0/month in January 2013 – March 2018. Accompanied by this increase the examined patients suffered from significantly more

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comorbidities (72 vs. 82%, p 0.001) and used a higher number of bleeding-related drugs (47 vs. 66%, p <0.001), especially nOACs. Age above 65 and bleeding-related drugs were significantly associated with angiodysplasias found on VCE examinations. NOACs and phenprocoumon showed no difference in their correlation to angiodysplasias.

Conclusion: This single center retrospective analysis revealed a steep increase in VCE examinations over the last years with an increase in the prevalence of comorbidities and the use of bleeding-related drugs. Interestingly, use of both nOACs and phenprocoumon did not result in a significant higher rate of angiodysplasias in the VCE.

Keywords: Video capsule endoscopy; small bowel bleeding; nOAC; VCE.

1. INTRODUCTION

Video capsule endoscopy (VCE) examination is the standard-of-care procedure to identify a bleeding source in the small bowel after negative findings on high-quality gastroscopy and colonoscopy [1,2]. New capsule devices present improved image quality [3], greater battery capacity and improved field of view of up to 360 degree [4]. Additionally new algorithms that preselect images containing new information or suspicious findings decrease the time required for image analysis [5–7]. Taken together these developments increase acceptance of the technique. Still many factors influence the yield of a VCE examination. Careful selection of the patients including regarding the age, sex and minimum hemoglobin level can improve diagnostic yield [8,9].

The number of factors leading to a gastrointestinal bleeding has expanded through the last years: i.e. percutaneous coronary interventions with the implantation of drug eluting stents [10] often result in a dual anti-platelet therapy. These drugs can increase the risk of gastrointestinal bleeding consecutively [11]. Anticoagulants like vitamin K antagonists have an additional effect on the bleeding risk [12,13]. Since 2009 the new oral anticoagulants (nOAC) presented a lower risk for overall major bleeding incidence compared with vitamin K antagonists. Still, in different analysis some of those drugs presented an increased risk for bleeding particular in the gastrointestinal tract [14,15].

In the year 2013 our department experienced a rise in VCE examinations performed for the indication of gastrointestinal bleeding. The annual number of VCE examinations remained high in the following years. Evaluating this phenomenon we performed a retrospective study of all VCE examinations scheduled in our department from January 2004 to December 2012 and from January 2013 to March 2018, respectively. The investigations in these both periods of time were analyzed for different factors, e.g. indication, patients characteristics etc. This analysis should help to reveal the factors leading to the increased number of VCE investigations. Especially we were interested in the question if there is an effect of the new anticoagulation therapy on the number of VCE-procedures and consecutively on the incidence of bleeding in small bowel section.

2. MATERIALS AND METHODS

2.1 Patients

We performed a retrospective analysis on all the consecutive VCE examinations performed from January 2004 to March 2018 at the University Hospital Ulm, Germany. Examinations with another indication but not a gastrointestinal bleeding were excluded. Examinations were excluded if the record was not complete due to technical problems, there was insufficient preparation of the small bowel, the capsule could not pass to the small bowel due to pylorus-stenosis or the documentation in patient records was insufficient, respectively. Patients with repetitive examinations were considered only once with their first complete examination.

2.2 Video Capsule Endoscopy Procedure

Video capsule endoscopy examinations were performed using the PillCam SB (Medronic, Dublin, Ireland) of the second generation from 2004 on, followed by the usage of the third generation from September 2013 to April 2017. In the period of time after Mai 2017 VCE examinations were performed using the Endocapsule EC-10 system from Olympus (Olympus Deutschland GmbH, Hamburg, Germany). After fasting period and bowel preparation patients received 10 mL Simethicone orally 30 minutes before capsule administration. The recorded data were subsequently

downloaded and first reviewed by an trained technician as the pre-reader with a revision by an experienced physician according to recommendation of the European Society of Gastrointestinal Endoscopy [2]. The final diagnosis was established by the attending physician. The lesions were classified as highly relevant with bleeding stigmata (P2), less relevant (P1), and no lesion (P0) as previously described [16].

2.3 Statistical Analyses

All analyses were performed using IBM SPSS Statistics 24 (SPSS Inc. Chicago Illinois, USA). Continuous variables were presented as mean and standard deviation and were compared using Student's *t*-test. Categorical variables were expressed by percentage and were compared using the χ^2-test. P less than 0.05 was considered statistically significant.

3. RESULTS

3.1 Patient Characteristics

914 VCE examinations were performed in our department between January 2004 and March 2018. We excluded 260 VCE recordings performed for another indication but a suspected gastrointestinal bleeding. Further 94 examinations were subsequently excluded due to insufficient documentation, incomplete recording due to technical problems, poor bowel preparation, obstructive pylorus and duplicate examination (Fig. 1). 560 VCE were included in the final analysis.

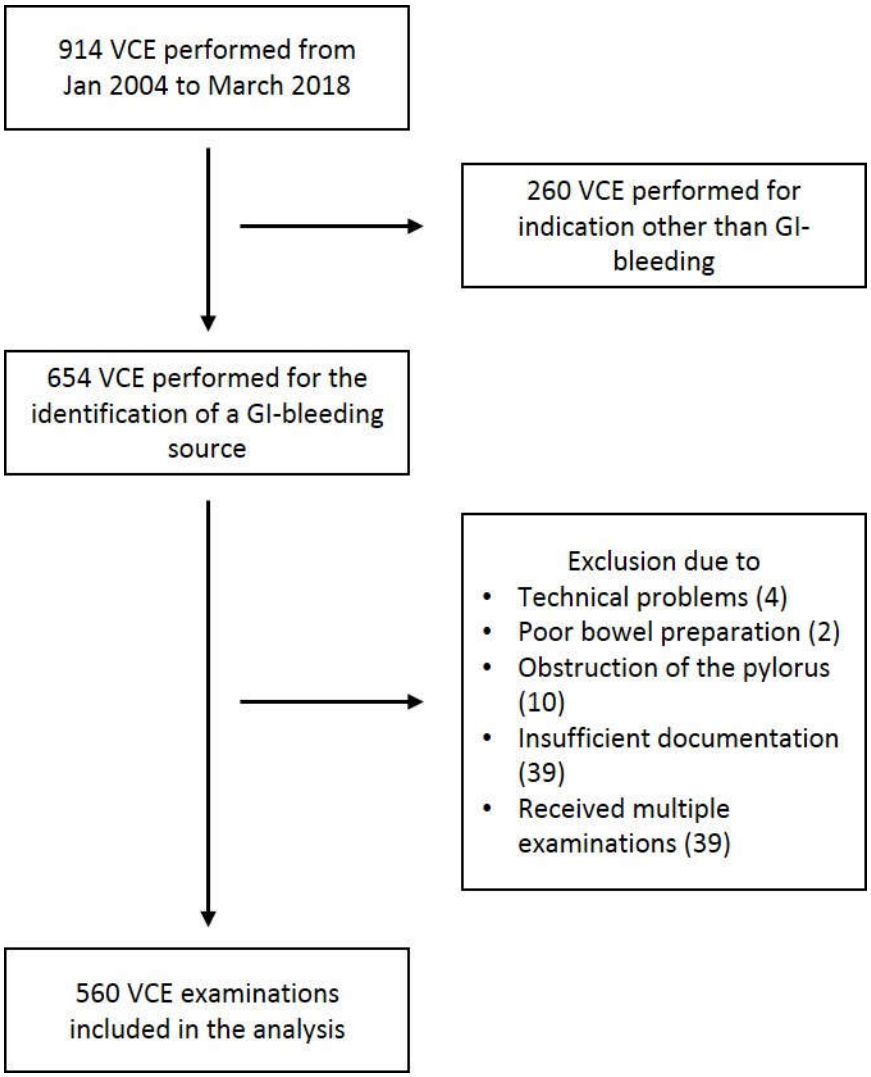

Fig. 1. Selection process for the video capsule endoscopy (VCE) examinations that were included for the final analysis

Patients´ characteristics in the final group are listed in Table 1. The mean age was 66.3 (±17) years. 57.7% of the patients were male. Most of the examinations were performed to evaluate patients with an overt bleeding. Laboratory examinations presented the lowest hemoglobin level with 7.7 g/dL (mean value). 77.9% of the patients had one comorbidity at least (arterial hypertension most prevalent). 57.7% of all the patients were on bleeding-related drugs, 12.1% with phenprocoumon and 13.9% with nOAC-medication.

3.2 Changes in VCE-Statistics from 2004 to 2018

Our recordings revealed an increase in the number of VCE examinations performed per year and per month beginning in the year 2013: 2004 to 2012 2.3 VCE-examination were scheduled per month vs. 5.0 per month in the years 2013 to 2018.

Characteristics of the patients examined in these two periods revealed no significant difference regarding age, sex or bleeding type (Table 2). The patients with the VCE investigation in the latter period of time showed more comorbidities and a significantly higher percentage of bleeding-related drugs in their medication. After the first record of nOACs in a medication list in November 2012 percentage of patients treated with phenprocoumon continuously dropped and were significantly lower in the latter period of time (2013-2018). Likewise in the second period of our recordings the hemoglobin level significantly dropped from 8 g/dL (2004-2012) to 7.4 g/dL (2013-2018).

3.3 Findings in VCE Examinations

2013-2018 significantly more positive lesions (P2) were identified in VCE-recordings, mostly due to the increase angiodysplasias that were diagnosed (Table 3). The number of equivocal lesions like non-bleeding diverticula or small erosions without active bleeding increased in the same period of time, as well. The number of VCE examinations with P0 significantly decreased in 2013-2018, respectively.

Table 1. Baseline characteristics of the patients that received a VCE examination. CE, capsule endoscopy, NSAIDs, nonsteroidal anti-inflammatory drugs

	[n=560] (%) / (mean ±SD)
Age (years)	66.3/ (±17)
Male gender (%)	323 (57.7)
Age > 65 years (%)	365 (65.2)
Lowest Hb value /available data (g/dl)	7.7/558 (±2.2)
Overt bleeding/available data (%)	381/558 (68.3)
Occult bleeding/available data (%)	173/558 (31)
Comorbidities/available data (%)	430/552 (77.9)
• Heart disease	293 (53.1)
• Chronic renal failure	129 (23.4)
• Diabetes	161 (29.2)
• Hypertension	334 (60.5)
Bleeding-related drugs (%)	323 (57.7)
• Anticoagulants (%)	164 (29.3)
○ Phenprocoumon	68 (12.1)
○ nOAC	78 (13.9)
○ LMWH	18 (3.2)
○ with single antiplatelet	51 (9.1)
○ with dual antiplatelet	17 (3.0)
• Single antiplatelet drug (%)	162 (28.9)
• Dual antiplatelet drug (%)	65 (11.6)
• NSAIDs (%)	35 (6.3)
Patients with transfusion of red blood units	362 (64.6)
Mean number of red blood units/ available data	3.74/338 (±3.8)
1-2 PRBCs (%)	154 (27.5)
3-9 PRBCs (%)	133 (23.8)
≥ 10 PRBCs (%)	26 (4.6)

Table 2. Baseline characteristics of the patients that received a VCE examination divided by years 2004 to 2012 and 2013 to March 2018. CE, capsule endoscopy, NSAIDs, nonsteroidal anti-inflammatory drugs

Characteristics	Years 2004 to 2012 (n=248)	Years 2013 to 3.2018 (n=312)	P-value
Age (mean ±SD) (years)	65.2±16.5	67.1±17.3	NS
Sex			
• male (%)	134 (54)	189 (61)	NS
• female (%)	114 (46)	123 (39)	NS
Bleeding type			
• Overt cases/available data(%)	166/247(67)	215/307 (70)	NS
• Occult cases/available data(%)	81/247(33)	92/307 (30)	NS
Bleeding-related drugs total (%)	117 (47)	206 (66)	<0.001
• Anticoagulants [n]	57(23)	107(34)	0.002
○ Phenprocoumon [n]	45(18)	23(7)	<0.001
○ nOAC [n]	1(0.4)	77(25)	<0.001
○ LMWH [n]	11(4)	7(2)	NS
○ with single antiplatelet	16(7)	35(11)	0.035
○ with dual antiplatelet	7(3)	10(3)	NS
• Single antiplatelet drug [n]	60(24)	102(33)	0.017
• Dual antiplatelet drug [n]	23(9)	42(14)	NS
• NSAIDs [n]	14(6)	21(7)	NS
Comorbidity total/available data (%)	175/242(72)	255/310(82)	0.001
• Hypertension [n]	133(55)	201(65)	0.012
• Diabetes [n]	68(28)	93(30)	NS
• Chronic renal failure [n]	46(19)	83(27)	0.02
• Heart disease [n]	115(48)	178(57)	0.013
Minimal hemoglobin level before CE (mean ±SD) (g/dL)	8±2.2	7.4±2.2	0.004
Patients with transfusion of red blood units before CE [n (%)]	159/248(64)	203/312(65)	NS
Number of Red blood units necessary before CE (mean ±SD)	3.45±3.6	3.98±4	NS
Number of transfused red blood units/documented cases	524/152	741/186	NS
• 1-2 PRBCs (%)	60(24)	94(30)	
• 3-9 PRBCs (%)	57(23)	76(24)	
• ≥10 PRBCs (%)	11(4)	15(5)	

3.4 Factors Associated with Incidence of Angiodysplasias in VCE

We performed a single variate analysis to identify parameters associated with finding of angiodysplasias (Supplementary Table 1). A significant link was identified with the age > 65 years (p <0.001), comorbidity in general (p <0.001), incidence of hypertension (p <0.001) or cardiac disease (p <0.001), usage of bleeding-related drugs in general (<0.001), the medication with a single antiplatelet drug (p <0.001) or with a combination of anticoagulation drugs with a single antiplatelet drug (p 0.028), respectively. Interestingly, there was no difference between patients treated with phenprocoumon and those treated with NOACs in the incidence of angiodysplasias.

In order to identify if any factors have been more or less significant for incidence of angiodysplasias in the groups before and after the year 2012 we performed a single variate analysis for both patient groups separately: in

patients with a VCE-investigation after 2012 the age > 65 years, medication with a single antiplatelet drug and comorbidities like cardiac disease and hypertension were still significantly associated with the incidence of angiodysplasias as a bleeding source. In contrast, in the group before 2012 the medication with more than one antiplatelet drug was significantly associated with incidence of angiodysplasias.

3.5 Single Variate Analysis for Factors Associated with Elderly Who Received a VCE

Since there are reports about a correlation between elderly patients and the etiology of small bowel bleeding due to angiodysplasia more likely than Crohn-lesions [17], we paid special interest in our analysis for evaluation of other factors associated with small-bowel bleeding in elderly patients (Supplementary Table 2). A significant link between the age > 65 years and the following variables was identified in both the population group before and after 2012: comorbidities ($p < 0.001$), usage of anticoagulating drugs ($p < 0.001$) and use of single and dual antiplatelet drugs (p 0.002).

3.6 Treatment Strategies after VCE

The most common treatment strategy after VCE was endoscopic treatment using single or double balloon enteroscopy, followed by discontinuation of drugs (Table 4). The latter significantly increased in the newer cohort from 16 to 23%. This is presumably due to the higher prevalence of bleeding related drugs in this cohort. Nonspecific treatment mostly represented by supplementation of iron was significantly higher in the latter cohort.

Table 3. Findings on capsule endoscopy comparing 2004 to 2012 and 2013 to 03/2018. CE, capsule endoscopy, NSAIDs, nonsteroidal anti-inflammatory drugs

Characteristics	Years 2004 to 2012 (n= 248)	Years 2013 to 03/2018 (n=312)	P-value
Positive lesions, P2 (%)	128 (52)	186 (60)	0.035
Vascular lesions (%)	60 (24)	120 (39)	<0.001
• Angiodysplasia	60 (24)	119 (38)	<0.001
• Portal enteropathy	0 (0)	2 (1)	NS
Ulcerated or erosive lesions (%)	47 (19)	66 (21)	NS
• Crohn´s disease	3 (1)	3 (1)	NS
• NSAIDs induced ulcer	8 (3)	9 (3)	NS
• Ulcerations or erosions of unknown origin	36 (15)	54 (17)	NS
Tumors (%)	7 (3)	11 (4)	NS
• Polyps [n]	4 (2)	8 (3)	NS
• Tumors of unknown origin [n]	3 (1)	3 (1)	NS
Bleeding diverticulum (%)	2 (1)	2 (1)	NS
Active bleeding in the small bowel including red blood or hematin (%)	59 (24)	76 (24)	NS
• Active bleeding with no identifiable cause (%)	28 (11)	31 (10)	NS
Intussusception (%)	0 (0)	1 (0.3)	NS
Equivocal lesions, P1 (%)	22 (9)	65 (21)	<0.001
Hemorrhagic spot [n (%)]	7 (3)	11 (4)	NS
Mucosal erosions [n (%)]	9 (4)	25 (8)	0.022
Small nonbleeding polyps [n (%)]	4 (2)	12 (4)	NS
Small nonbleeding diverticulum [n (%)]	3 (1)	27 (9)	<0.001
Negative examination, P0 (%)	95 (38)	88 (28)	0.007

Table 4. Treatment strategies after positive CE comparing 2004 to 2012 and 2013 to 03/2018. SBE, single balloon enteroscopy, DBE, double balloon enteroscopy

Characteristics	Years 2004 to 2012 (n= 248)	Years 2013 to 03/2018 (n=312)	P-value
Specific treatment (%)	88 (36)	146 (47)	0.004
SBE/DBE	44 (18)	64 (21)	NS
Surgery	7 (3)	5 (2)	NS
Angiography	4 (2)	7 (2)	NS
Discontinuation of drugs	40 (16)	73 (23)	0.021
Redosing of drugs	1 (0.4)	9 (3)	0.025
Thalidomid	0 (0)	2 (1)	NS
Somatostatin	0 (0)	0 (0)	NS
Anti-inflammatory drugs	2 (1)	8 (3)	NS
non-specific treatment (%)	32 (13)	58 (19)	0.043
iron supplement	31 (13)	57 (18)	0.04

4. DISCUSSION

VCE is the standard procedure of care for the evaluation of a small bowel bleeding after gastroscopy and colonoscopy did not reveal the bleeding source. In the year 2013 we experienced a significant increase in the number of VCE-examinations per year at our institution. The increased number of examinations has constantly remained at a high level for the following years. This study should display changes in characteristics of patients that received VCE examination in the two different periods of time. In the years since 2008 nOACs were introduced into clinical practice and were successively approved for a broad number of indications [18,19]. The first patient in our institution being anticoagulated by a nOAC-drug with a suspected small intestine bleeding received a VCE examination in November of 2012. The total number of patients with anticoagulation drugs significantly increased from 23 to 34% in the period after 2012. In total 66% of the patients in the group 2013-2018 used bleeding-related drugs. On the one hand this statistic mirrors the high rate of cardiac comorbidities in our population. On the other hand the steady increase of percutaneous coronary interventions in Germany [20] induces an increased use of antiplatelet drugs as shown in the characteristics of the population in our study. Interestingly this relation did not show an increased number of active bleeding or mucosal erosions in our population. But the finding of vascular lesions in small intestine significantly increased – in combination with antiplatelet and anticoagulation drugs a possible potent source of bleeding. Our study presents data that are in line with other single center reports. Nennstiel et al. published 2017 a study that analyzed 512 VCE examinations performed from 2001 to 2011 with positive findings in 68% [21]. This rate is slightly higher than 56% in our population. The report of Nennstiel et al. showed with 24% a similar rate of patients taking oral anticoagulants like our patients investigated before 2013 (23% in our statistics). In our study this group rose to 34% of patients taking anticoagulants after 2012. In both studies age of > 65 years showed a significant relationship with presence of angiodysplasia in VCE-examination. But unlike Nennstiel et al. we were able to identify more factors associated with angiodysplasia, e.g. comorbidities in general and usage of bleeding related drugs, respectively.

Another study that analyzed 853 VCE from 2004 until 2015 in an Chinese center was published 2016 by Li et al. [22]. Although the study included years after nOACs-approval they reported with 3 to 7% a fewer proportion of patients receiving bleeding related drugs compared with 58% in our study. One reason might be the geographic location and the higher comorbidity rate in the same age cohort (92% in our population >65 years vs. 75% in the report by Li et al.).

One other big report including a meta-analysis of 17 trials with results of 1722 VCE presented a lightly higher incidence of angiodysplasias as a typical VCE-finding [23] in patients with small bowel bleeding: 40.9% published before vs. 32% in all of our patients and 38% in our patients with VCE after 2013, respectively. The results of this metaanalysis [23] underline the importance of VCE as the step-in diagnostics before an invasive DBE-procedure should be performed. The patients we characterized in our study take a big advantage of these results in consideration of the increasing multimorbidity and co-medication profile we described.

The obvious limitation of our study is the retrospective assessment of data. The other limitation is the single center experience. Thus, many factors might have influenced the way why patients received a VCE examination and how those patients were treated, e.g. guidelines changed and new scientific evidence was collected that influenced the treatment strategy in the years before and after 2012. One example is that patients with an age above 65 were significantly more likely to receive blood transfusions in the patient cohort before 2013 in contrast to after 2013. A possible explanation is the increased scientific evidence with favor for a more restrictive transfusion strategy [24,25].

5. CONCLUSION

In conclusion, our data demonstrates a relationship between the increased number of VCE-investigations and the increased comorbidities, the use of antiplatelet and anticoagulation drugs, respectively. We found out that neither NOACs nor phenprocoumon separately are significant associated with angiodysplasias. The increasing comorbidity profile of patients with small bowel bleeding underlines the importance of the VCE vs. DBE as a less invasive method for detection of bleeding source.

Due to the limitations of our study this result needs to be further analyzed in a multi-center setting. Especially a prospective study might help to minimize bias in detecting clinical predictors for angiodysplasias [26].

KEY SUMMARY

Summarize the established knowledge on this subject?

- Video capsule endoscopy (VCE) is the standard examination procedure for a work-up of a suspected bleeding source after negative gastroscopy and colonoscopy
- Popularity of this procedure increased in the last decade.

What are the significant and/or new findings of this study?

- The rate of VCE per month increased from 2.3 in the period January 2004 to December 2012 to 5.0 in the period January 2013 to March 2018
- Patients with a VCE examination for a suspected bleeding source presented with a higher rate of different comorbidities and increased usage of bleeding-related drugs in the latter cohort.
- Both patients treated with vitamin K antagonist and those treated with nOAC didn´t show a significant correlation to angiodysplasias.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

The study has been approved by the local ethics committee of the University of Ulm (approval number 146/17). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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