Prospective comparison of the diagnostic yield of the Mirocam® and Pilcam SB2® videocapsules in patients with obscure digestive bleeding.

Pioche M, Gaudin JL, Filoche B, Jacob P, Lamouliatte H, Duburque C, Chaput U, Ben Soussan E, Daudet , Tournan, Gaudric M, Edery J, Cellier C, D'Halluin PN, Saurin JC[1], and the French Society of Digestive Endoscopy (SFED)

[1] Service d'hépatogastroentérologie, Hôpital E. Herriot, Lyon.

Jean-Christophe SAURIN

Gastroenterology

Hôpital E. Herriot

5 Place d'Arsonval

69437 Lyon Cedex 03

Tel : 04 78 86 16 89 fax : 04 78 86 10 63

saurin@lyon.inserm.fr

Introduction:

Obscure digestive bleeding, defined as overt bleeding and/or anemia with a negative endoscopic workup including complete colonoscopy and gastroscopy, represents 5 % of digestive bleedings and 10000 cases each year in the United States. Bleeding lesions located in the small bowel explain the majority of these clinical situations (1,2), and the major aetiologies are telangiectasias, tumors and ulcerations. Capsule endoscopy, a highly efficient and non invasive test, is now recommended as the first line exploration in this situation of obscure digestive bleedings. Other modalities of small bowel examination (including double balloon enteroscopy) compared negatively to capsule endoscopy in prospective studies and metaanalyses, with a 55 to 75% diagnostic yield of capsule endoscopy (3,4).

Different capsule endoscopy systems exist, 3 of them being commercialized respectively by Given Imaging (Pilcam SB2®), Olympus and Intromedics (Mirocam®). Most small-bowel capsule studies have been performed with the Pilcam SB2® capsule and its efficiency has been widely reported. Few studies used the Olympus® capsule, and only one comparative study including 40 patients suggested a comparable diagnostic yield of the two capsules in patients with obscure digestive bleeding (5,6). The major difference between these two sytems is the image capture system : CCD type for Olympus®, CMOS for Pilcam SB2®. The Mirocam® capsule is more recent, with one important difference compared with the 2 previous systems : the image transmission

system of the Mirocam capsule uses electric field propagation instead of Radio Frequency (RF). This system is based on the natural electrical impulses of the human body as the transport medium, leading to a lower energy requirement and thus a longer recording time (ref). A first study, in 41 volunteers has shown the safety of the Mirocam capsule and it's ability to produce high quality images of the small bowel in all patients (7). The aim of the present study was to compare the diagnostic yield of the Pillcam SB2® and Mirocam® capsules in a prospective, randomized study, including patients with obscure digestive bleeding. The major end-point of the study was to evaluate the concordance between the two capsule examinations, and the secondary objectives were the diagnostic yield and the quality of images obtained by both systems.

Materials and Methods :

Patients :

We included 83 consecutive patients (39 men, 44 women, mean age 65, range 22-86 yr), between July 2008 and August 2009, in 7 french referal centers from the french society of digestive endoscopy (SFED). Patients were refered for small-bowel capsule exploration of unexplained (obscure or occult) digestive bleeding. Previous endoscopic work-up included negative gastroscopy and colonoscopy within 6 months before the capsule examination in all patients. Patients below 18 years of age, or with occlusive symptoms, or with a pace maker, were excluded.

Capsule procedure :

Given imaging SB2® and Mirocam® capsules were used. The Given imaging capsule has been described before.(Ref) The Mirocam® capsule measures 24 x 11 mm, has a view angle of 150 °, takes 3 images per second, and has an 11 hours recording time potential. A small-bowel preparation (mostly PEG) was performed in most centers before capsule ingestion, but there was no recommendation, and in 1 of the centers patients didn’t take any preparation. Each patient ingested the two capsules at 1 hour interval, in a randomized order. For each patient, the two capsule films were red in randomized order by 2 experimented readers in each center. The two readings were performed blindly, the reading frame was free to each operator, but the Given Imaging quick-view

algorithm was not used. The quality of the preparation was evaluated by each reader in a 5 value scale from 1 (insufficient preparation) to 5 (excellent). For each dedicated lesion identified, the image quality, depth and lightening were estimated by each reader on a scale from 1 (bad quality) to 3 (excellent). Technical issues, the time of gastric and small bowel transit, and the reading time of the small bowel examination were recorded. For each lesion identified by the reader, the transit time, the small-bowel site, the image quality, and the possible diagnosis were recorded. Images were classified according to their relevance, using a previously validated scale : P2 with high bleeding potential, P1 with intermediate bleeding potential and P0 with no bleeding potential [1]. The major endpoint of the study was the concordance between the two capsule examinations with a k value > 0.6. An image per image review of discordant cases by three experimented readers was performed.

Interpretation of the results :

Non significant (P0) lesions and images located outside the small intestine were not considered. As for *per patient* analysis, we considered the final diagnosis corresponding to a P1 or P2 lesion, according to the description of the most important or the most relevant lesion or group of lesions. The sensitivity of each capsule examination was calculated using as true-positive cases the sum of positive cases obtained at Mirocam® and Given imaging® readings, after expert review of discordant cases. In a *per lesion* analysis, each lesion (up to three main lesions found at capsule reading) or group of lesions was analysed independently. In patients with multiple (> 10) repetitive lesions (ulceration in Crohn's, telangiectasia in Weber-Rendu disease), only one diagnosis was considered and

no image-per-image analysis was made. Review : After a first interpretation of the results was performed by each independent reader, cases were classified into concordant positive, concordant negative, and discordant cases. All discordant cases, and only discordant cases, were reviewed during one session by 5 experienced readers. An image per image comparison was done and the complete film was red a second time when necessary.

Statistical analysis : We calculated the k inter-observer agreement coefficient between paired (Given Imaging and Mirocam) capsule readings. For statistical analysis, we used the SPSS 12.0 version software (SPSS Inc, Chicago, Il) in a Windows XP (Microscoft, Seattle, WA) environment. A p value < 0.05 was considered significant.

Results:

A total of 83 patients were included. No side effect was reported by any patient during the procedures. Capsule excretion was observed by 64 patients during an 8 day period after ingestion. Because of 10 technical issues, only 73 patients had comparative data analyzed. The technical issues were due to 6 premature stops of the Mirocam® capsule recording and two premature stops of the Pillcam SB2® capsule recording, 1 failure of Mirocam® film extraction and one destruction of a Mirocam® capsule by the patient. Technical failures thus concerned the Mirocam® capsule in 8 patients (9,7%) and the Pillcam SB2® capsule in 2 patient (2,4 %). All Mirocam® technical issues occurred in the first six months of the study.

Crude results of capsule readings and expert review :

Initial reading : Initial capsule reading was considered as positive in 50,7 % of the 73 patients (n= 37, 21 P2 lesions, 16 P1 lesions) with Pillcam SB2® capsule and in 54,8% (n= 40, 28 P2 lesions, 12 P1 lesions) with Mirocam® capsule. In 27 cases (37,0 %) both readings were negative in a concordant way (with no lesions or P0 lesion). In 21 patients (28,8 %, figure 3) both readings were positive in a concordant way : 18 (24,6%) with concordant P2 images, 3 (4,1 %) with concordant P1 images. There was a total of 48 concordant results (65,8%). In 25 cases (34,3 %) the conclusion after both readings was different, and these films were reviewed (Table 3).

Discordant cases : Expert review of the 25 discordant cases showed that the same images were classified differently in 13 cases : 4 false positive cases in

one procedure, 1 false negative at Given SB2 reading (P2 telangiectasia) and positive at Mirocam, 8 lesions classified differently by the two readers but identical for experts (4 P1 and 4 P2 lesions). Regarding the 12 remaning discordant cases, 9 patients (12,3 %) had positive findings at Mirocam® but no image detected at Pillcam SB2®, even after a second reading (4 P2 telangiectasias, 3 P1 telangiectasias, 2 P1 duodenitis) ; in 2 patients (2,7%) the Pillcam SB2® reading identified a lesion (1 P1 ulceration and 1 P1 telangiectasia) that was absent from the Mirocam° film. One patient had a different lesion identified by each capsule reading (one P2 telangiectasia at Mirocam° and one P1 ulceration at Pilcam SB2® reading).

Final results : After review, a positive diagnosis was obtained in 46,6 % of patients (n= 34, 24 P2, 10 P1) with Pillcam SB2® and 56,2% (n= 41, 30 P2, 11 P1) with Mirocam®. There were 31 (42,4 %) concordant negative cases, 30 (41,1 %) concordant positive cases, and 12 discordant cases (16,4 %) (figure 3).

Per patient analysis :

After review of discordant cases, the value or the kappa concordance coefficient was of 0,66 corresponding to the main objective of the study. We then considered, as a gold standard, all significant lesions detected in the 73 analyzable cases and confirmed after expert review. In this setting, the Mirocam® procedure identified 95.2 % of positive patients as compared to 78,6 % for Pillcam SB2®. In an intention to treat analysis, thus considering the first reading before review and including technical failures (83 patients), the Mirocam® procedure led to a positive diagnostic in 49,4 % (n=41, 29 P2, 12 P1) as compared to 49,4 % (n=41, 23 P2, 18 P1) for the Pillcam SB2® procedure (one

positive diagnosis in the two patients with Pillcam SB2® failure, 4 positive diagnosis in 8 cases with Mirocam® failures.

Per lesion analysis (Table 1) :

Table 1 shows the number and different types of lesions identified at both capsule readings. Considering the results after expert review, 53 lesions or groups of lesions were observed at Mirocam® reading (11 P1, 42 P2) and 43 at Pillcam SB2° reading (8 P1, 34 P2). There were 9 P2 lesions (8 telangiectasias, 1 tumor) and 5 P1 lesions (4 telangiectasias, 1 jejunal ulcer) described only at Mirocam® reading. Inversly, 2 P1 telangiectasias and 2 P2 telangiectasias were observed only at Pilcam SB2® reading. Thus, the Mirocam® capsule detected 93.0 % of significant lesions detected by combined procedures, as compared to 75.4 % for Pilcam SB2® capsule.

Transit time, reading time and image quality (Figure 3) :

The mean gastric and small bowel transit time were of 37,8 min (range 1-203 min) and 234,5 min (range 51-502 min) with the Pilcam SB2® capsule versus 47,9 min (range 3-232) and 268,1 min (range 58-538) with the Mirocam® capsule. The mean reading time was of 25,4 min with Pilcam SB2® capsule and 40,3 min with Mirocam® capsule ($p < 0.05$). The reading time of the Mirocam films decreased comparing the first 6 months to the last 6 months of the study from a mean of 42,6 min (range 22-130 min) to a mean 34,4 min (range 22-80 min). On a scale from one to three (see methods), the mean quality score of image quality, field depth and lightening, were of 2.7, 2.5 and 2.5 for and of 2.6, 2.5 and 2.5 for the Pilcam SB2® and the Mirocam® capsules respectively (NS for all criteria).

The mean preparation quality score was comparable as evaluated with the Pilcam SB2® (3.9) and Mirocam® (3.8) capsules.

Discussion :

The Given Pilcam SB2® capsule endoscopy system is largely used worldwide, and this methodology of small bowel examination has been progressively accepted as the first intention exam in patients with obscure digestive bleedings. The Mirocam® capsule endoscopy system is much more recent with only one descriptive study published in an abstract form and concerning 41 volunteers. This study showed the absence of side effects of this system and its ability to produce high quality images of the small bowel in all patients (7). The present prospective randomized study was necessary to demonstrate the clinical efficiency of this new system. The observed concordance rate between the two capsule examinations performed in the same patients shows that the Mirocam° system can be used efficiently in clinical practice. In 73 patients having both examinations completed, the diagnostic yield of the Mirocam° and Given SB2° systems were of 56.2 % and 46.6 % respectively. In these 73 patients, 18 lesions were diagnosed by only one procedure (14 Mirocam®, 4 Pillcam®). According to the limited number of patients, this difference was not significant. Increasing the study power by including a high number of patients would have been necessary to seek for a significant difference regarding the diagnostic yield, but this was not the aim of the present work. There is a possibility, yet to be demonstrated, that increasing the image number (3 versus 2 images per second) and increasing the transit time, wich was the case with the Mirocam° capsule for an unknown reason, increases the diagnostic yield of a small bowel capsule examination. The mean calculated number of images obtained with the Pilcam SB2® capsule was of 28140 as compared to 48258

images for the Mirocam® capsule. Regarding transit time, the mean small bowel transit time was clearly different with the two sytems (Mirocam® small-bowel transit time : a mean of 268,1 min versus 234,5 min with Pilcam SB2®). This difference can possibly be explained by the higher weight of the Mirocam® capsule.

We observed frequent technical issues in the first 6 months of the study, mostly with the Mirocam° capsule. However, unusual technical failures were also observed in few cases with the Pilcam SB2° capsule, so that a technical interference between the two capsules ingested in the same patients cannot be excluded. Including these technical issues resulted, in an intention to treat analysis, into an identical diagnostic yield of both capsule systems. One important issue regarding the use of capsule endoscopy is the reading time. According to a higher number of recorded images, the reading time was significantly longer using the Mirocam® system (a mean of 40,3 min versus 25,4 min). Interestingly, the reading time of the Mirocam® capsule films dropped in the second part of the study with from a mean of 42.6 to 34.4 min. Anyway, reading time is a major point in clinical practice and reducing it is an important aim of future developments. Given Imaging® developed a “Quick view” informatic algorithm with two potentials including shortening of reading time and improving the detection of significant lesions. The French capsule commission reported the evaluation of the Quick view system® [26] with a clear reading time reduction (a mean of 11,6 min) and a 93.5 % detection rate of significant lesions, comparable to standard reading. Comparable systems will probably be available in the near future with other capsule systems, including the Mirocam° system.

Limitations of the present work included the number of patients, the lack of blind capsule reading, and interferences between the two capsules. The study was designed to evaluate the diagnostic concordance of the two capsule systems. Accordingly, only 80 patients were included compared to 300 if the major objective had been to compare the percentage of patients with a significant diagnosis, estimating a 10 % difference between the two systems. Secondly, there was no obvious feasibility of performing unblinded reading of the two capsules films : we did perform a randomization of the two readers in each center, but the very different appearance of the softwares used did not allow a bling reading of the films. Finally, capsules came in contact to each other in several patients, maybe partly because of a shorter transit time of the Pillcam SB2® capsule. As the screen was partially obstructed by the other capsule, there was a reduction of the mucosal surface visualized in this situation. Moreover, this interference could possibly explain some of the technical issues encountered during the study. An important point, in order to limit interpretation bias, was the review of discordant cases. In fact, 25 initially discordant cases were reviewed, and among them only 12 were finally considered as really different : 13 (17,8%) were considered as concordant after review. There is also a possibility, yet unevaluated, that new discordant cases would have been observed by reviewing also concordant cases.

In conclusion, this study shows a comparable efficiency of the Mirocam® capsule as compared to Pilcam SB2° capsule system regarding the diagnostic yield and image quality. In patients with both capsule films available, the Mirocam® system gave a 56,2 % positive diagnostic rate versus 46,6 % for the

Pilcam SB2° system. This non significant difference may be explained in part by the longer transit time and the higher number of images produced. On the other hand, this higher number of images was associated with a longer reading time (40.3 min versus 25.4), that can probably be reduced after a short learning curve.

References

1. Gong F, Swain P, Mills T. Wireless endoscopy. Gastrointest Endosc 2000;51:725-729.

2. Zuckerman GR, Prakash C, Askin MP, Lewis BS.® AGA technical review on the evaluation and management of occult and obscure gastrointestinal bleeding. Gastroenterology 2000;118:201-221.

3. Bandorski D, Irnich W, Bruck M, Beyer N, Kramer W, Jakobs R. Capsule endoscopy and cardiac pacemakers: investigation for possible interference. Endoscopy 2008;40:36-39.

4. Appleyard M, Glukhovsky A, Swain P. Wireless-capsule diagnostic endoscopy for recurrent small-bowel bleeding. N Engl J Med 2001;344:232-233.

5. Ogata H, Kumai K, Imaeda H, Aiura K, Hisamatsu T, Okamoto S, et al. Clinical impact of a newly developed capsule endoscope: usefulness of a real-time image viewer for gastric transit abnormality. J Gastroenterol 2008;43:186-192.

6. Hartmann D, Eickhoff A, Damian U, Riemann JF. Diagnosis of small-bowel pathology using paired capsule endoscopy with two different devices: a randomized study. Endoscopy 2007;39:1041-1045.

7. Bang S, Park J, Park S, Chung J, Chung S, Cho W, et al. Clinical trial of "Miro" capsule endoscope using novel transmission technology "E-field propagation" for the evaluation of safety and diagnostic feasibility. Gastroenterology 2007;132, 4 suppll:S1084.

8. Saurin JC et al. Diagnostic value of endoscopic capsule in patients with obscure digestive bleeding: blinded comparison with video push-enteroscopy. Endoscopy 2003 Jul;35(7):576-84.

9. Van Gossum A, Hittelet A, Schmit A, Francois E, Devière J. A prospective comparative study of push and wireless-capsule enteroscopy in patients with obscure digestive bleeding. Acta Gastroenterol Belg 2003;66(3):199-205.

10. Agence française de sécurité sanitaire des produits de santé. Video capsule M2A®, système d'exploration diagnostique de l'intestin grêle. Avis de la Commission d'évaluation des produits et prestations du 05 juin 2002. Saint Denis: AFSSAPS; 2002.

11. Comité d'évaluation et de diffusion desinnovations technologiques, Dowidar S, Perrin JP, Baffert S, Charpentier E, Kluvie V, *et al.* Vidéocapsule endoscopique digestive (mise à jour). Paris: CEDIT [cedit.aphp.fr]; 2005.

12. Saurin JC, Delvaux M, Vahedi K, Gaudin JL, Villarejo J, Florent C, *et al.* Clinical impact of capsule endoscopy compared to push enteroscopy: 1-year follow-up study. Endoscopy 2005;37(4):318-23.

13. Buchman AL, Wallin A. Videocapsule endoscopy renders obscure gastrointestinal bleeding no longer obscure. J Clin Gastroenterol 2003;37(4):303-6.

14. Adler DG, Knipschield M, Gostout C. A prospective comparison of capsule endoscopy and push enteroscopy in patients with GI bleeding of obscure origin. Gastrointest Endosc 2004;59(4):492-8.

15. Kinzel F, Eickhoff A, *et al.* A prospective twocenter study comparing wireless capsule endoscopy with intraoperative enteroscopy in patients with obscure GI bleeding. Gastrointest Endosc 2005;61(7):826-32.

16. Mata A, Bordas JM, Feu F, Ginés A, Pellisé M, Fernández-Esparrach G, *et al.* Wireless capsule endoscopy in patients with obscure gastrointestinal bleeding: a comparative study with push enteroscopy. Aliment Pharmacol Ther 2004;20(2):189-94.

17. Fineberg HV, Bauman R, Sosman M. Computerized cranial tomography. Effect on diagnostic and therapeutic plans. JAMA 1977;238(3):224-7.

18. Triester SL, Leighton JA, Leontiadis GI, Fleischer DE, Hara AK, Heigh RI, *et al.* A metaanalysis of the yield of capsule endoscopycompared to other diagnostic modalities in patients with obscure gastrointestinal bleeding. Am J Gastroenterol 2005;100(11):2407-18.

19. Pennazio M, Santucci R, Rondonotti E, Abbiati C, Beccari G, Rossini FP, *et al.* Outcome of patients with obscure gastrointestinal bleeding after capsule endoscopy: report of 100 consecutive cases. Gastroenterology 2004;126(3):643-53.

20. Moreno C, Arvanitakis M, Devière J, Van Gossum A. Capsule endoscopy examination of patients with obscure gastrointestinal bleeding : evaluation of clinical impact. Acta Gastroenterol Belg 2005;68(1):10-4.

21. Selby W. Can clinical features predict the likelihood of finding abnormalities when using capsule endoscopy in patients with GI bleeding of obscure origin ? Gastrointest Endosc 2004;59(7):782-7.

22. Ben Soussan E, Antonietti M, Hervé S, Savoye G, Ramirez S, Lecleire S, *et al.* Diagnostic yield and therapeutic implications of capsule endoscopy in obscure gastrointestinal bleeding. Gastroenterol Clin Biol 2004;28(11):1068-73.

23. Chong AK, Taylor A, Miller A, Hennessy O,Connell W, Desmond P. Capsule endoscopy vs.push enteroscopy and enteroclysis in suspectedsmall-bowel Crohn's disease. Gastrointest Endosc 2005;61(2):255-61.

24. Triester S, Leighton J, Leontiadis G; Fleisher D, Hara A et al. A meta-analysis of the yield of capsule endoscopy compared to other diagnostic

modalities in patients with obscure gastrointestinal bleeding. Am J Gastroenterol 2005;100: 2407-18.

25. Saurin JC, Delvaux M, Gaudin JL, Fassler I, Villarejo J et al. Diagnostic value of Endoscopic capsule in patients with obscure digestive bleeding : blinded comparison with push enteroscopy.Endoscopy 2003;35: 576-84.

26. Saurin JC, Ben Soussan E, Gaudric M, Lapalus MG, Cholet F et al. Can we shorten the small-bowel capsule reading time ? Validation of the « Quick View » Image Detection System. Gastrointest Endosc 2009;69:abstract s1509.