

## **Title**

### **Is endoscopic therapy effective for small bowel angiectasia? A prospective multicentre cohort study**

**(Qual a eficácia da terapêutica endoscópica das angiectasias do intestino delgado- Estudo de coorte prospetivo multicêntrico)**

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# **1. INTRODUCTION**

## **1.1 Background**

Obscure gastrointestinal bleeding (OGIB), defined as persistent or recurrent bleeding with negative findings on upper and lower gastrointestinal endoscopic evaluations accounts for 5% of all cases of gastrointestinal bleeding (1).

Angioectasia is the most commonly occurring vascular malformation of the gastrointestinal tract and small bowel angioectasia (SBAE) have been described in ~40% of patients with OGIB (1).

Gastrointestinal angioectasia are pathologically dilated communications between veins and capillaries. Histologically they consist of an accumulation of ectatic, thin-walled veins, venules and capillaries lined by the endothelium in the mucosa and submucosa (2). Endoscopically they are defined, according to the Yano-Yamamoto classification (3) as punctulate erythema with less than 1 mm with or without oozing (type 1 a) or patchy erythema with a few mm with or without oozing (type 1b).

The prevalence of angioectasia is increased in patients older than 60 years of age and in patients with predisposing conditions including aortic stenosis, chronic renal or liver failure, von Willebrand's disease and in those presenting with angioectasias in the upper GI tract (4).

The clinical presentation of SBAE ranges from iron-deficiency anemia to life-threatening gastrointestinal haemorrhage. Approximately 45-50% of SBAE will stop bleeding without any medical or endoscopic treatment and despite endoscopic treatment re-bleeding, anemia and/or need from transfusion has been described in 16-64% of patients (4).

## **1.2 Research hypothesis**

In patients with small bowel angioectasia, endoscopic treatment results in a 50% decrease in red blood cells transfusions requirement;

## **1.3 Rationale for conducting this study**

Endoscopic treatment is considered the standard of care for SBAE. However, the natural history of SBAE and the recurrence rates after endoscopic treatment is not completely understood. A recent systematic review analysed 24 articles (n=490 patients) with data on endoscopic therapy for angioectasia and 6 natural history cohorts (n=130) receiving no

therapy for angioectasia and concluded that re-bleeding rate after endoscopic therapy may be comparable to that expected without therapy and that endoscopic therapy may be ineffective. The number needed to treat is estimated at 15 to 16 (5). Jackson and col (4) in another systematic review concluded that 45% of patients with SBAE experience re-bleeding after endoscopic treatment. In most studies included in these systematic reviews, the authors were unable to extract data on mean haemoglobin level and transfusion requirements before and after endoscopic therapy.

Gastrointestinal angioectasia is a recurrent disease with well-known risk factors that increase the likelihood of the appearance of new lesions. Therefore, re-bleeding rate may not be the best endpoint to evaluate the efficacy of endoscopic therapy. In fact some patients may require some blood cell transfusions but still present with fewer transfusion requirements and higher haemoglobin levels than prior to endoscopic therapy.

#### **1.4 Benefit/risk and ethical assessment**

As an observational study, no risk for individual subjects is expected. The information gathered from this study will bring further information on potential benefit of endoscopic treatment of SBAE.

## **2. STUDY OBJECTIVES**

### **2.1 Primary objectives**

Compare transfusion requirement prior to and after endoscopic therapy

### **2.2 Secondary objectives**

- To prospectively determine, after endoscopic therapy for SBAE:
  - The re-bleeding rate;
  - The transfusional requirement;
  - The mean haemoglobin level;
- Determine risk factors for re-bleeding after endoscopic therapy;
- Evaluate the need for further endoscopic, surgical or medical treatment for SBAE

### **3. STUDY PLAN AND PROCEDURES**

#### **3.1 Overall study design**

This is a multicentre prospective cohort study. Subjects will be recruited from Portuguese and Spanish institutions performing DAE at the day of DAE endoscopic treatment of SBAE, after written informed consent to participate in this study. Patients will be followed for a period of 2 years. All data will be recorded on an electronic data form. Data prior to inclusion will be retrospectively collected from the patients' files. Data after the DAE procedure will be prospectively collected. The physicians performing the DAE will be responsible for data collection and recording.

### **4. PATIENT SELECTION CRITERIA**

#### **4.1 Inclusion criteria**

Patients will be entered into the study if **all** inclusion criteria are fulfilled:

- Age 18 year or above;
- Able to provide informed consent;
- Complete small bowel evaluation by capsule endoscopy prior to DAE;
- Transfusion requirement in the 6 months prior to DAE;
- DAE performed in the setting of OGIB;
- Endoscopic treatment performed for SBAE.

Small bowel vascular lesions should be characterised according to the Yano-Yamamoto classification (3). Angioectasias are defined as punctulate erythema with less than 1 mm with or without oozing (type 1 a) or patchy erythema with a few mm with or without oozing (type 1b).

#### **4.2 Exclusion criteria**

Patients should not enter the study if **any** of the following exclusion criteria are identified:

- Refusal of informed consent for collection and analysis of data;
- A finding during DAE other than a SBAE (ex. tumours, submucosal lesions, other vascular lesions) that the DAE performing physician considers that may cause the OGIB;
- Previous DAE performed for the treatment of angioectasias.

## **5. COLLECTION OF STUDY VARIABLES**

### **5.1 Data recording**

All study data will be collected on electronic data collection forms created and maintained by the CEREGA – Centro Nacional de Registo de Dados em Gastreenterologia from the Sociedade Portuguesa de Gastreenterologia.

### **5.2 Data collection**

Abstracted data will include:

Patient characteristics

Demographic information (age, sex);

Prior medical history (including history of renal insufficiency, cardiac disease, liver disease, von Willebrand disease);

Current medication.

OGIB Characterization prior to DAE:

Time from the diagnosis of OGIB to DAE

Minimum haemoglobin level in the previous 6 months;

Red blood cells transfusion requirement;

Iron intake (intravenous and oral).

Gastrointestinal evaluation prior to DAE

Upper endoscopy results;

Colonoscopy results;

Capsule endoscopy results (Report vascular lesions of the small bowel according to the Saurin Classification (6); whenever possible capsule endoscopies will be reviewed in the centre performing the DAE.

Other exams performed (CT, arteriography, etc);

Prior endoscopic treatment for SBAE.

DAE

Type of DAE

Route of insertion

Depth of insertion in cm according to the method described by May et al. (7,8)

Type of sedation

Findings

Characterization of vascular lesions - should be recorded according to the Yano-Yamamoto classification (3);

Location

Number

Size

Endoscopic therapy

Argon plasma coagulation; Submucosal injection+argon plasma coagulation; other.

Complications

Outcomes

Time to re-bleeding in days.

Haemoglobin level (if there is no evidence of re-bleeding, schedule evaluation to 1, 3, 6 12 and 24 months after the procedure);

Red blood cells transfusion requirement

Iron intake (intravenous and oral)

Further endoscopic treatment

Surgical treatment

Medical treatment

### **5.3 Outcome Variable**

Red blood cell transfusion requirement (per year) will be compared with the requirements in the year prior to endoscopic therapy. Reduction in red blood cell transfusion is defined as a decrease of 50% in transfusion requirement after the endoscopic procedure.

Re-bleeding is defined as an evidence of recurrent visible gastrointestinal bleeding (haematochezia or melena) and/or the need for blood transfusions and/or a recurrent drop in the haemoglobin level by more than 2g/dL from the baseline after the exclusion of other causes (desirably with recent negative upper and lower GI examination). (Sakai) Time to re-bleeding will be defined as the time in months between DAE therapy for SBAE and the first re-bleeding episode.

Haemoglobin levels will be compared with the haemoglobin levels prior to DAE therapy. To perform the comparison the lowest haemoglobin level in the 6 months prior to the

endoscopic procedure will be compared with the lowest haemoglobin level observed 6, 12 and 24 months after the procedure

## **6. ETHICAL AND REGULATORY REQUIREMENTS**

### **6.1 Ethical conduct of the study**

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements for subject data protection. Furthermore, all collect data will be analysed and stored according to the legal requirements of Portuguese and Spanish Law, thereby ensuring the privacy of individual subject's data.

### **6.2 Informed consent**

Informed consent will be required for inclusion in the study.

## **7. STUDY MANAGEMENT**

### **7.1 Training of study site personnel**

Individual site investigators will have formal training on the study protocol during the study start up meeting and will be responsible for the individual training of each site's personnel. Paper copies of each electronic data collection forms will be provided to each centre together with paper logs to record individual subject identification to allow reconciliation of data and handling of queries.

### **7.2 Monitoring of the study**

Electronic standardized data collection forms will be implemented for data abstraction which be centrally maintained. Monitoring of accrual and completeness of data entry will be performed remotely on a monthly schedule until all clinical data is complete and queries resolved.

### **7.3 Study timetable**

Recruitment will be performed until the sample size is reached. Patients will be followed for a period of 2 years after inclusion.

## **8. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION**

### **8.1 Description of analysis sets**

All included subjects will be considered for primary endpoint analysis.

### **8.2 Methods of statistical analyses**

Summary statistics for demographic and baseline clinical will be implemented to describe the included population. As this is a before/after study the paired t-test will be used for numerical variables with approximately normal distributions, the paired samples Wilcoxon signed-rank test will be used for numerical variables with skewed distributions and McNemar's test will be used for categorical variables. Follow up data related to time to rebleeding will be analysed by the Kaplan-Meier method and log-rank test. Univariate and multivariate analysis using Cox regression models will be used to identify predictors of rebleeding.

During data collection all efforts will be made to avoid missing values and to obtain or recover all missing information. The remaining missing values will be handled using standard methods of last observation carried forward and/or regression based multiple imputation.

All the analyses will be performed using SPSS (SPSS Inc., Chicago IL, USA).

### **8.3 Determination of sample size**

The reduction in transfusion requirement after DAE therapy for SBAE is unknown and there are currently not enough data for an accurate determination of the sample size.

One year after the start of this study an interim analysis will be performed and sample size will be estimated based on the preliminary results.

## **9. Limitations**

This is a non-randomized trial with no control group.

## 10. LIST OF REFERENCES

- 1) Raju GS, Gerson L, Das A, Lewis B: American Gastroenterological Association. American Gastroenterological Association (AGA) Institute technical review on obscure gastrointestinal bleeding. *Gastroenterology* 2007, 133:1697–1717.
- 2) Junquera F, Saperas E, deTorres I et al. Increased expression of angiogenic factors in human colonic angiodysplasia. *Am J Gastroenterol* 1999;94:1070-6.
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- 4) Jackson CS, Gerson LB. Management of gastrointestinal angiodysplastic lesions (GIADs): a systematic review and meta-analysis. *Am J Gastroenterol.* 2014;109(4):474-83
- 5) Romagnuolo J, Brock AS, Ranney N. Is Endoscopic Therapy Effective for Angioectasia in Obscure Gastrointestinal Bleeding?: A Systematic Review of the Literature. - *J. Clin. Gastroenterol* 2015; 49 (10); 823-30
- 6) Saurin JC, Delvaux M, Gaudin JL, Fassler I, Villarejo J, Vahedi K, et al. Diagnostic value of endoscopic capsule in patients with obscure digestive bleeding: blinded comparison with video push-enteroscopy. *Endoscopy.* 2003;35:576-84.
- 7) May A, Nachbar L, Schneider M et al. Push-and-pull enteroscopy using the double-balloon technique: method of assessing depth of insertion and training of the enteroscopy technique using the Erlangen Endo-Trainer. *Endoscopy* 2005; 37: 66–70
- 8) López Albors O, Soria F, Pérez- Cuadrado E et al. Validity of insertion depth measurement in double-balloon endoscopy. *Endoscopy* 2012; 44: 1045–50.

Estudo:

**“Is endoscopic therapy effective for small bowel angiectasia? A prospective multicentre cohort study”**

**“Qual a eficácia da terapêutica endoscópica das angiectasias do intestino delgado- Estudo de coorte prospetivo multicêntrico”**

1. Li o presente consentimento informado, relativo ao “Qual a eficácia da terapêutica endoscópica das angiectasias do intestino delgado- Estudo de coorte prospetivo multicêntrico”.

Foi-me devidamente explicado o objetivo, a duração e possíveis riscos e benefícios do estudo, bem como aquilo que é suposto eu fazer. Todas as minhas dúvidas foram satisfatoriamente esclarecidas.

2. Concordo em participar no presente estudo.

3. O meu seguimento e tratamento não serão afetados pelo facto de participar ou não no estudo.

4. Compreendo que a minha participação no estudo é voluntária e que, em qualquer altura, posso retirar o meu consentimento sem que isso afete os meus cuidados médicos ou os meus direitos legais.

5. Dou autorização para que os meus dados pessoais sejam utilizados, guardados e retidos para os fins do estudo descrito no presente documento.

**Participante no estudo:**

Nome \_\_\_\_\_

Assinatura: \_\_\_\_\_

Data: \_\_\_\_\_

**Médico que conduziu a discussão do Consentimento Informado**

Confirmo que expliquei, pessoalmente ao indivíduo acima identificado, a natureza, o objectivo e a duração do estudo, assim como o procedimento médico proposto, benefícios e eventuais riscos e complicações.

Nome do médico: \_\_\_\_\_

Cédula profissional n.º \_\_\_\_\_

Assinatura: \_\_\_\_\_

Data: \_\_\_\_\_

Para qualquer esclarecimento adicional pode contactar a Unidade de Técnicas de Gastrenterologia pelo telefone **217200422** entre as 8 e as 17h (dias úteis).

## CONSENTIMENTO INFORMADO

### FOLHA DE INFORMAÇÃO DO DOENTE

Estudo: “Is endoscopic therapy effective for small bowel angiectasia? A prospective multicentre cohort study”

**“Qual a eficácia da terapêutica endoscópica das angiectasias do intestino delgado- Estudo de coorte prospetivo multicêntrico”**

Pelo fato de lhe ter sido diagnosticada uma angiectasia do intestino delgado que foi submetida a terapêutica endoscópica está-lhe a ser sugerido participar neste estudo. Antes de decidir se participa no estudo, é importante que saiba qual o motivo da sua realização e quais as implicações que este tem para si. Leia atentamente toda a informação presente neste documento e não hesite em colocar questões ao seu Médico ou a um elemento da Equipa de Investigação. Se decidir participar deve assinar um formulário de consentimento, do qual receberá uma cópia, para guardar conjuntamente com o presente documento.

**A sua participação no estudo é inteiramente voluntária. Se decidir não participar neste estudo isso não influenciará os seus cuidados médicos ou a sua relação com o(s) seu(s) Médico(s) Assistente(s).**

#### **Objetivo do Estudo:**

**A terapêutica endoscópica tem sido considerada como a mais indicada para o tratamento de angiectasias do intestino delgado, Contudo, a história natural das angiectasias e a eficácia deste tratamento ainda não são totalmente conhecidas.**

Pretende-se, com o presente estudo, avaliar a eficácia da terapêutica endoscópica através da monitorização clínica após o procedimento dos valores de hemoglobina, necessidade de transfusões de sangue ou de outros procedimentos terapêuticos.

#### **Como vai funcionar o processo de vigilância endoscópica?**

Se aceitar participar no estudo serão recolhidos retrospectivamente dados do seu processo clínico referentes aos exames que efetuou antes da terapêutica das angiectasias

do intestino delgado, valores de hemoglobina e necessidade de suporte transfusional. Será feito o registo prospetivo desde a data do exame e por um período de 2 anos de algumas variáveis clínicas que incluem a evidência de nova hemorragia, necessidade de suporte transfusional, necessidade de novos tratamentos e valores de hemoglobina.

Todos estes dados fazem parte da sua avaliação clínica habitual, não estando programados quaisquer consultas ou exames adicionais decorrentes da sua participação neste estudo.

### **Quais os riscos/complicações deste estudo?**

Este é um estudo observacional pelos que não existem riscos ou complicações.

### **Qual é a vantagem de participar no estudo?**

Com a participação neste estudo irá ajudar a compreender quais os benefícios esperados do tratamento das angiectasias do intestino delgado e poderá permitir a aquisição de conhecimentos que ajudarão futuramente outros doentes.

### **Compensações e Pagamentos**

Não haverá qualquer compensação financeira por participar neste estudo.

### **Confidencialidade dos registos**

Como parte do estudo, a informação médica sobre o seu estado clínico será recolhida, analisada e reportada de forma anónima. Os dados pessoais recolhidos (idade, sexo, dados de saúde) são os estritamente necessários para cumprir com os objetivos do estudo e serão processados pelos elementos da equipa de investigação, exclusivamente para a finalidade descrita. Os resultados deste estudo poderão ser apresentados em reuniões ou publicações; no entanto, a sua identidade não será revelada.