**Research Protocol**

FULL STUDY TITLE

A prospective randomised control trial of Early Capsule Endoscopy in patients with Acute Upper Gastrointestinal Bleeding.

SHORT TITLE

Early Capsule Endoscopy in Acute Upper Gastrointestinal Bleeding.

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1. INTRODUCTION

All patients with upper gastrointestinal bleeding (UGIB) undergo a gastroscopy urgently as part of standard care. However, in a significant proportion of these patients a source is not identified. Small bowel bleeding is highly likely to be the source in a large number of these patients. This may be identified by capsule endoscopy. As per current standard practice, patients will undergo a colonoscopy frequently or a capsule endoscopy (CE) less often, in an attempt to find the cause of bleeding. Capsule endoscopy is non-invasive, better tolerated and preferred by patients as bowel prep is generally not required.

It is uncertain however who will benefit most by having a capsule endoscopy as the second test.

The focus of our study is to look at the subgroup of patients who will benefit most by having early Capsule Endoscopy in this context. The study aims to compare two groups of patients, one having capsule endoscopy vs the other having colonoscopy as the second test following a negative gastroscopy to determine differences in ability to detect bleeding source and therefore change patient outcome.

All patients with UGIB with a negative gastroscopy will be considered for the study. This is a prospective randomised control trial. Primary endpoint measured will be identification of the source of bleeding. Secondary endpoints measured will be reduced blood transfusions, reduced length of stay, reduced number of investigations and reduced hospital admissions.

2. Background

Acute upper gastrointestinal bleeding (UGIB) is a commonly encountered condition with significant morbidity and mortality (up to 12%). UGIB presents with either haematemesis or melena, or both. Current guidelines for investigation of acute UGIB recommend urgent gastroscopy within 24 hours of presentation. This recommendation is based on the high likelihood of bleeding from the upper gastro-intestinal tract and the excellent diagnostic sensitivity and therapeutic capability of gastroscopy. However, there is debate on how to further investigate patients who have a negative initial gastroscopy. Typically, the approach is to perform a colonoscopy next to exclude bleeding from the proximal colon. This approach was based on the lack of availability of other modalities such as capsule endoscopy and interventional radiology several decades ago. As our understanding of the causes of GI bleeding have improved, we have identified the small bowel as a significant source for bleeding. However, these patients are often diagnosed late and continue to bleed resulting in longer hospital stays and more blood transfusions. These patients also experience higher morbidity and mortality rates due to chronic re-bleeding.

There is emerging evidence consolidating capsule endoscopy (CE) as the most effective tool in assessing these patients. CE has been available since 2001 and can safely and effectively visualise the entire small bowel and detect bleeding with high sensitivity. Sensitivity rates for investigation of acute gastrointestinal bleeding range from 92-95% but drop to 13-42% when the investigation is delayed. This highlights the importance of prompt investigation. Patients prefer CE over colonoscopy in view of its non-invasive nature, safety and lack of need for anaesthesia and bowel preparation. Early diagnosis of source of bleeding will also lead to better outcomes due to earlier treatment of culprit lesions. This in turn is expected to decrease length of stay, blood transfusions, need for other investigations and surgery.

Our aim was to show that proceeding directly to CE after non-diagnostic gastroscopy would lead to better outcomes due to earlier identification of culprit lesions and earlier administration of appropriate therapy.

3. AIMS OF STUDY

3.1 Key Research Question:

In patients presenting with acute upper gastrointestinal bleeding, who have a negative gastroscopy, is early capsule endoscopy a superior test to colonoscopy in further determining the bleeding source?

3.2 Hypothesis:

In patients with acute upper gastrointestinal bleeding and a negative gastroscopy, CE is a superior secondary investigation compared to colonoscopy, due to its ability to detect both small and large bowel lesions. Early detection of source of bleeding will significantly improve patient care and outcomes with reduced blood transfusions, earlier treatment and reduced hospital stay.

3.3 Aims

1. To determine whether CE has a higher diagnostic sensitivity than Colonoscopy in acute upper GI bleeding with negative Gastroscopy.

2. To determine whether patients who have early CE post Gastroscopy have reduced blood transfusion requirements.

3. To determine whether patients who have early CE have reduced hospital length of stay.

4. To determine whether patients who have early CE have reduced incidence of recurrent GI bleeding.

4. STUDY DESIGN

4.1 Design:

Prospective randomised control trial.

4.2 Methodology

Participants will always undergo gastroscopy as the initial investigation. If the bleeding source is identified on gastroscopy, the lesion will be treated and the patient shouldn’t require further investigation. These patients will be discharged to the ward for observation and ongoing medical management as required. Patients in whom urgent gastroscopy fails to reveal a bleeding source will then proceed to a secondary investigation. Participants will be randomized to either colonoscopy or capsule endoscopy after a negative gastroscopy

These patients will be required to wear a recorder, which receives information from the CE as it travels through the bowels. Recording of information continues until the battery in the unit fails, which is typically after it has entered the large bowel and in the order of 8-12 hours. Patients will be monitored on the ward during this time. After the completion of recording, the images will be transferred to a computer and reviewed by a gastroenterologist with experience in the field. Patients with culprit lesion(s) in the small bowel will undergo therapeutic small bowel enteroscopy, whilst patients without small bowel lesions and/or with colonic lesions, will undergo therapeutic colonoscopy. Patient’s undergoing colonoscopy will require a course of bowel preparation prior to undergoing the procedure to ensure adequate visualization of the bowel wall.

For patients who undergo a colonscopy first, if bleeding is found, this will be treated and the patient will be discharged back to the medical ward for ongoing medical management and observation. Patients who have a non-diagnostic colonoscopy will then undergo CE in order to locate the culprit lesion. If a culprit lesion is identified in the small bowel, the patient will undergo therapeutic small bowel enteroscopy.

All patient’s will receive standard medical treatment for acute upper gastrointestinal bleeding, including admission to the gastroenterology unit, daily medical reviews, daily blood tests for haemoglobin and renal function and intravenous fluid hydration. Some patients may require replacement of blood products, correction of caogulopathies and treatment with intravenous proton pump inhibitors.

There will be no difference in the medical management of control and intervention group participants. Patients will be discharged when they are clinically stable and no longer showing evidence of GI blood loss.

5. Study Setting / Location

This is a single centre study at the Gold Coast University Hospital.

6. Study duration:

Anticipated start date: 15/06/2016

Anticipated finish date: 14/06/2018

Duration: 24 months

6.1 Estimated Timeline of Activities

|  |  |
| --- | --- |
| Date | Activity |
| July 2016 | Patient recruitment / data collection |
| August 2016 | Patient recruitment / data collection |
| September 2016 | Patient recruitment / data collection |
| October 2016  | Patient recruitment / data collection Three month follow up for patients seen in July 2016 |
| November 2016 | Patient recruitment / data collectionThree month follow up for patients seen in August 2016 |
| December 2016  | Patient recruitment / data collectionThree month follow up for patients seen in September 2016 |
| January 2017 | Patient recruitment / data collectionThree month follow up for patients seen in October 2016Six month follow up for patients seen in July 2016 |
| February 2017 | Patient recruitment / data collectionThree month follow up for patients seen in November 2016Six month follow up for patient seen in in August 2016 |
| March 2017 | Patient recruitment / data collectionThree months follow up for patients seen in December 2016Six month follow up for patients seen in September 2016 |
| April 2017 | Patient recruitment / data collectionCommence data analysisThree month follow up for patients seen in January 2017Six month follow up for patients seen in October 2016 |
| May 2017 | Data analysisThree month follow up for patients seen in February 2017Six month follow up for patients seen in November 2016 |
| June 2017 | Data analysisThree month follow up for patients seen in march 2017Six month follow up for patients seen in December 2016 |
| July 2017 | Formulation of scientific reportSix month follow up for patients seen in January 201712 month follow up for patients seen in July 2016 |
| August 2017 | Formulation of scientific report Six month follow up for patients seen in February 201712 month follow up for patients seen in August 2017 |
| September 2017 | Submission for publicationSix month follow up for patients seen in march 201712 month follow up for patients seen in September 2016 |
| October 2017 | Submission for publication12 month follow up for patients seen in October 2016 |
| November 2017 | 12 month follow up for patients seen in November 2016 |
| December 2017 | 12 month follow up for patients seen in December 2016 |
| January 2018 | 12 month follow up for patients seen in January 2017 |
| February 2018 | 12 month follow up for patients seen in February 2017 |
| March 2018 | 12 month follow up for patients seen in March 2017 |
| April 2018 | Analysis of 6 and 12 month follow up data |
| May 2018 | Formulation of scientific report |
| June 2018 | Submission for publication |

7. STUDY POPULATION

7.1 Recruitment Process

All patients presenting to the Gold Coast University Hospital with acute upper gastrointestinal bleeding who meet the inclusion and exclusion criteria will be invited to participate in the study by the treating doctor.

7.2 Inclusion Criteria

Participants will be males or females who present with acute melena and/or haematemesis and have a negative gastroscopy.

7.3 Exclusion Criteria

Patients less than 18 years of age and pregnant females will be excluded form this study.

The pediatric population is excluded, as such patients require investigation from a paediatric gastroenterologist and dedicated paediatric facility. The researches involved in this study are adult-population gastroenterologists and the facility is not equipped to treat such patients.

Pregnant women represent a population requiring a highly specialised approach compared to non-pregnant patients. Endoscopy in pregnant females is inherently risky due to foetal sensitivity to maternal hypoxia and hypotension, both of which can lead to foetal demise. Other risks include teratogenesis and premature birth. These patient require input from a specialist obstetrician, altered medication / sedative regimes and altered positioning and endoscopy technique. Gastroscopy is often deferred to the second trimester if possible in these patients.

8. STUDY OUTCOMES

8.1 Primary Outcomes:

The primary outcomes to be measured in this study are identification and treatment of the bleeding lesion.

8.2 Secondary Outcomes

The secondary outcomes to be measured in this study include number of blood transfusions, length of hospital stay and incidence of recurrent GI bleed at three, six and twelve months.

9. STUDY PROCEDURES

9.1 Participant Recruitment and Consent

After being assessed and stabilized in the emergency department, patients will be invited to participate in the study by the treating doctor. During business hours, the treating doctor will be the gastroenterology registrar covering endoscopy whilst after hours it will be the on-call medical registrar. The research project will be explained to the patient in layperson terms, including all risks. An information sheet will also be provided. Patients will have the opportunity to discuss any aspects of the study at this point. Patients willing to participate in the study will then be asked to sign a pre-made consent form. Participation will be completely voluntary and this will be emphasised. For patients who lack capacity to consent for themselves, the appropriate substitute decision maker will be consulted. Participants will at that point be randomised to either control arm or experimental arm by computer software.

9.2 Withdrawal of Participants

Patients will be free to withdrawal from the study at any point and withdrawal will in no way affect the patients care.

9.3 Randomisation

Randomisation will be done using a statistical program such as SPSS.

9.4 Study involvement by participants

Participants will not be required to complete any tasks as part of this study. Participants will initially undergo gastroscopy. If the gastroscopy is non-diagnostic, they will either go onto have a capsule endoscopy, or colonoscopy according to the group to which they were randomised. Subsequent management of each patient will depend on what is identified in these investigations. Patient will likely remain in hospital for approximately 3-5 days depending on their clinical progress. They will also be subject to routine hospital cares such as regular monitoring of vital signs and daily review by medical staff. After discharge, patients will be followed up at three, six, and twelve months post discharge.

9.5 Data Management

Data will be collected by participating researchers. Endoscopy data will be obtained from the endoscopy database. Duration of hospital stay will be obtained from the Queensland Health Electronic Medical Records program. The number of blood transfusions will be obtained from the patient’s blood transfusion record. Initial data storage will be on Microsoft Excel spread sheet. The data will be de-identified and stored on a password protected Queensland Health computer within our department. Data will be stored for 5 years and then destroyed. Paper based data will be destroyed by means of shredding and disposed of in confidential information bins. Electronic data will be deleted using appropriate software.

9.6 Safety Considerations

This study consists of altering the order of current standard investigations, which are used in the management of acute upper gastrointestinal bleeding. Therefore, participants are not being exposed to any greater risks than non-participants. This study has the potential to alter the protocol for management of patients with acute GI bleeding with a safer, non-invasive approach earlier while improving earlier detection and treatment.

10. Sample Size And Data Analysis

10.1 Sample Size And Statistical Power

Empirical calculations suggest that a sample size of 30 patients in each arm of the study would be required to achieve statistically significant outcomes.

11. Dissemination Of Results And Publications

The results pertaining to this study are intended to be disseminated by publication at a local, national, and international level. Participants will be able to access the results of the study upon completion of the study.

13. Glossary Of Terms

Capsule Endoscopy (CE) – A pill sized camera equipped with it’s own light source. The capsule is swallowed and provides images of the gastrointestinal tract, which are sent to a receiver worn by the patient. It is a single use instrument that is passed in a bowel motion.

Colonoscopy – A procedure whereby a fiber-optic camera is used to visualise the large bowel and last segment of the small bowel. Biopsies and other interventions can be performed during the procedure.

Eneteroscopy – A procedure whereby a long fiber-optic camera is used to visualise the small bowel. Biopsies and other intervention can be performed during the procedure.

Gastroscopy – A procedure whereby a fiber-optic camera is used to visualise the upper gastrointestinal tract (oesophagus, stomach and first section of small bowel). Biopsies and other interventions can be performed during the procedure.

Gastrointestinal bleed (GI bleed, GIB) – Bleeding from anywhere in the gastrointestinal tract.

Haemtemsis – The vomiting of blood

Melena – The passage of dark-coloured, tarry stools, due to the presence of blood altered by gastrointestinal juices.

Upper gastrointestinal bleed (UGIB) – Bleeding from either the oesophagus, stomach or small bowel to the level of the Ampulla of Vater.

14. References

1. Tramèr MR, Moore RA, Reynolds DJ, McQuay HJ: Quantitative estimation of rare adverse events which follow a biological progression: a new model applied to chronic NSAID use. Pain 2000, 85:169-182.
2. Okazaki H, Fujiwara Y, Sugimori S, Nagami Y, Kameda N, Machida H, Yamagami H, Tanigawa T, Masatsuga S, Watanabe K, Tominaga K, Watanabe T, Nobuhide O, Arakawa T. Prevalence of mid-gastrointestinal bleeding in patients with acute overt gastrointestinal bleeding: multicentre experience with 1044 consecutive patients. Journal of Gastroenterology 2009;44:550-555
3. Hearnshaw SA, Logan RF, Lowe D, Travis S, Murphy M, Palmer K. Use of endoscopy for management to acute upper gastrointestinal bleeding the UK: results of a nationalwide audit. Gut 2010;59:1022-109
4. Ell C, May A. Mid-gastrointestinal bleeding: capsule endoscopy and push-and-pull enteroscopy give rise to a new medical term. Endoscopy 2006;38:73-5
5. Hwang J, Fisher D, Ben-Mencachem T, Chandrasekhara V,Chathadi K, Decker G, Early D, Evans J, Fanelli R, Foley K, Fukami N, Jain R, Jue T, Kjan K, Lightdale J, Malpas P, Maple J, Pasha S, Saltzman J, Sharaf R, Shergill A, Dominitz J, Cash B. The role of endoscopy in the management of acute non-variceal upper GI bleeding. Gastrointestinal Endoscopy 2012;75:1132-8
6. Barkun A, Bardou M, Kuipers E, Sung J, Hunt R, Martel M, Sinclair P. International consensus recommendations on the management of patients with non-variceal upper gastrointestinal bleeding. Ann Intern Med 2010;152:101-3.
7. Laine L, Jensen D. Management of patients with ulcer bleeding. Am J Gastroenterology 2012;107:345-60
8. Schlag C, Menzel C, Nennstiel S, Neur B, Phillip V, Schuster T, Schmid R, Delius S. Emergency video capsule endoscopy in patients with acute severe GI bleeding and negative upper endoscopy results. Clinical Endoscopy 2015;81:889-95.
9. Hogan R, Pareek N, Phillips P, Haick A, Hogan R. Video capsule endoscopy in life-threatening GI haemorrhage after negative primary endoscopy. Gastrointestinal Endoscopy 2009;69;2
10. Tew K, Davies R, Jadun C, Kew J. MDCT of acute lower gastrointestinal bleeding. American Journal of Roentgenology 2004;184:427-430
11. Yoon W, Jeong Y, Shin S, Lim J, Song S, Jang N, Kim J, Kang H. Acute massive gastrointestinal bleeding: detection and localisation with arterial phase multidetector row helical CT. Radiology 2006;239:160-7
12. Pennazio M. Capsule endoscopy: where are we after 6 years of clinical use? Digestive and Liver disease 2006;38:867-78
13. Lewis B, Wenger J, Wayne J. Small bowel endoscopy and intraoperative enteroscopy for obscure GI bleeding. American Journal of Gastroenterology 1991;86:171
14. ASGE standards of practice committee. The role of endoscopy in the management of obscure GI bleeding. Gastrointestinal Endoscopy 2010;72
15. Pennazio M, Eisen G, Goldfarb N; ICCE. ICCE consensus for obscure gastrointestinal bleeding . Endoscopy 2005;37:1045-50
16. Raju G, Gerson L ,Das A, Lewis B; American Gastroenterological Association. American Gastroenterological Association (AGA) institute technical review on obscure gastrointestinal bleeding. Gastroenterology 2007;133:1697-717
17. Muhica V, Barkin J. Occult gastrointestinal bleeding. General overview and approach. Gastrointestinal Endoscopy Clinics of North America 1996;6;833-45
18. Apostolopoulos R, Liastos C, Gralnek I, Kalantzis C, Giannokoulopoulou E, Alexandrakis G, Tsibouris P, Kalafatis E, Kalantzis N. Evaluation of capsule endoscopy in active, mild-to-moderate, overt, obscure GI bleeding. Gastrointestinal Endoscopy 2007;66:1174-1181.
19. Pennazio M, Santucci R, Rondonotti E, Abbiati C, Beccari G, Rossini F, De Franchis R. Outcome of patients with obscure gastrointestinal bleeding after capsule endoscopy: Report of 100 consecutive cases. Gastroenterology 2004;126:643-53.
20. Delvaux M, Fassler I, Gay C. Clinical usefulness of the endoscopic video capsule as the initial intestinal investigation in patients with obscure digestive bleeding: validation of a diagnostic strategy based on the patient outcome after 12 months. Endoscopy 2004;36 1067-73.
21. Leung W, Ho S, Suen, B, Lai L, Yu S, Ng E, Ng S, Chiu P, Sung J, Chan F, Lau J. Capsule endoscopy or angiography in patients with acute overt obscure gastrointestinal bleeding: a prospective randomized study with long-term follow-up. The American Journal of Gastroenterology 2012;107
22. Bresci G, Parisi G, Bertoni M, Tumino E, Alfonso C. The role of video capsule endoscopy for evaluating obscure gastrointestinal bleeding: usefulness of early use. Journal of Gastroenterology 2005;40:256-259