OUTCOMES OF ENDOSCOPIC THERAPY FOR BLEEDING PEPTIC ULCERS; A RETROSPECTIVE STUDY IN HOSPITAL SERDANG

By

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Dissertation Submitted In Partial Fulfilment of the Requirements for the

Degree of Master of Medicine (General Surgery)

2020

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ACKNOWLEDGEMENTS

Before we start, I would like to take a moment to arrange my hands in thanks to God almighty who has given me the will and strength to complete this thesis. Without Him, none of this would have been possible.

Not forgetting my utmost respect and gratitude to my supervisors, Prof Madya Dr Zaidi bin Zakaria, Department of Surgery, USM and Prof Madya Dr Mohd Faisal Jabar, Department of Surgery, UPM. Withtheir wisdom, guidance and encouragement, I have managed to successfully complete this thesis.

And finally, much love and endearment to my lovely wife, Dr NorbijaseriZakaria, my 2 children and both my parents and in-laws. Without their support, both mentally and physically, I definitely wouldn't have been able to cross the finish line.

ABSTRAK

Latarbelakangdanobjektif:

Terapiendoskopimerupakankaedahutamadalamrawatanpenyakit “upper gastrointestinal bleeding” (UGIB). Walaupunterdapatkemajuandalambidangterapiendoskopi, kadarkematianpesakit UGIB tetapdalamlinkungan 10% untukbeberapadekad yang lalu. Kajianinibermatlamatmengenalpasti “prevalence” hasilselepasterapiendoskopiuntuklukaperutberdarah.

KaedahKajian: Iniadalahkajianrekodsecararetrospektifbagipesakit yang menjalani “emergency upper endoscopy for UGIB” dari Mac 2014 ke Mac 2019 di Hospital Serdang, Selangor. Data diperolehidarirekodsuite endoskopidanprevalen“permanent haemostasis”, endoskopiulangan, angio-embolization, pembedahandankematiandihitung-kirakan.

Keputusan: Seramai204 pesakit yang telahmenjalani “emergency upper endoscopic therapy for UGIB” dimasukkankedalamkajian kami. Lebihdariseparuhpesakit 113 (55.4%) berjayamencapai “permanent haemostasis” selepasrawatan “endoscopic therapy” pertamamanakala 84 (41.2%) terpaksamenjalaniendoskopiulangandisebabkanpendarahansemulaluka. Sebahagiankecilterpaksamenjalanipembedahan 10 (4.9%) sementaracuma 3 (1.5%) menjalaniangio-embolization. Daripada 204 pesakit yang dimasukkan, terdapat 34 (16.7%) mortalitidanjangkamasaadmisi di wad adalah 5 hari.

Kesimpulan: Dari kajian kami, kami dapatmenyimpulkanbahawa “permanent haemostasis” hasildenganprevalen paling tinggiselepasterapiendoskopi di hospital kami.

Walaubagaimanapun, kitaperlumengurangkankadarendoskopiulangan kami keranamasihlebihtinggidaripada data negaramembangun yang lain.

ABSTRACT

Background and objectives: Endoscopic therapy remains the mainstay in treatment of upper gastrointestinal bleeding (UGIB). Despite the advancement in endoscopic therapy, the mortality rate for UGIB has remained constant at about 10% for the past few decades. This study aims to determine the prevalence of outcomes post endoscopic therapy in bleeding peptic ulcers.

Methods: This is a retrospective record review of patients who underwent emergency upper endoscopy for UGIB from March 2014 to March 2019 in Hospital Serdang, Selangor. Data was collected from endoscopic suite records and the prevalence of permanent haemostasis, re-endoscopy, angio-embolization, surgery and 30-day mortality was calculated.

Results: A total of 204 patients who underwent emergency upper endoscopic therapy for UGIB were included in our study. More than half of the patients 113 (55.4%) achieved permanent haemostasis after initial endoscopic therapy whilst 84 (41.2%) had to undergo re-endoscopy due to re-bleeding ulcer. A small percentage had to undergo surgery 10 (4.9%) while only 3 (1.5%) underwent angio-embolization. Out of 204 patients included, there was 34 (16.7%) mortalities and the median length of stay was 5 days.

Conclusion: From our study, we can conclude that permanent haemostasis is the outcome with highest prevalence after endoscopic therapy for UGIB in our centre.

However, we should strive to reduce our rate of re-endoscopy as it is not up to par with data from other developing countries.

CHAPTER ONE:INTRODUCTION

1.1 LITERATURE REVIEW

Acute Upper Gastrointestinal Bleeding (UGIB) remains a common cause of hospitalization in Malaysia. The incidence is approximately 72 per 100000 in Malaysia (Cheng JLS *et.al*, 2001). Despite important advances made in the management of non-variceal UGIB, the overall mortality has remained constant at 10% for the past few decades (Ruigómez *et.al*, 2000, Rockall *et.al*, 1995, Allan and Dykes, 1976, Fleischer, 1983). This may in part be due to the fact that older patients, who have advanced cardiovascular, respiratory, or cerebrovascular disease that puts them at increased risk of death, now comprise a much higher proportion of cases.

UGIB refers to bleeding from any point proximal to the duodeno-jejunal flexure (Ligament of Treitz). UGIB can be divided into variceal and non-variceal bleeding. Variceal bleeding can be caused by either oesophageal varices or fundal varices. Non-variceal bleeding can be further subdivided into haemorrhagic gastritis, peptic ulcer bleeding, tumour/polyp bleeding or arterio-venous malformation bleeding.

Patients come to the hospital complaining of frank haematemesis, coffee ground vomiting and/or melaena. Fresh bleeding per rectum is usually indicative of lower GI bleeding, however massive UGIB can present with passing of red blood clots per-rectally. Haemodynamic instability may also feature, with patients presenting with dizziness, syncope or in hypovolaemic shock.

Upper endoscopy is crucial in the diagnosis, stratification, and management of patients with bleeding ulcers, and endoscopic haemostatic therapy is the mainstay of treatment in patients with endoscopic findings that predict an increased risk of further bleeding (Laine and McQuaid, 2009).

Once source of bleeding is identified, the ulcer is stratified using the Forrest Classification which differentiates high risk of re-bleeding ulcers from low risk of re-bleeding ulcers (Hadzibulic andGovedarica, 2007).

<table>
<tr><th>I : Active bleeding</th><th>II : Stigmata of recent haemorrhage</th><th rowspan="3">III: Lesions without active bleeding
(No signs of recent haemorrhage)</th></tr>
<tr><td>I a: Arterial, Spurting haemorrhage</td><td>II a: Visible vessel</td></tr>
<tr><td rowspan="2">I b: Oozing haemorrhage</td><td>II b: Adherent clot</td></tr>
<tr><td></td><td>II c: Dark base (haematin covered lesion)</td></tr>
</table>

SRH = stigmata of recent hemorrhage
Major SRH = Forrest Ia, 1b, 2a and 2b
Mild SRH = Forrest 2c and 3

In addition to endoscopic therapy, acid suppressors are administered to patients, particularly proton pump inhibitors. Several studies have examined the role of acid suppression given before or after endoscopy (with or without therapeutic intervention) (Dorward*et.al*, 2006).

The currently available endoscopic haemostatic methods include injection therapy, thermal coagulation, and mechanical therapy. Among these approaches, injection of epinephrine is the most popular endoscopic method used to stop bleeding because of its safety, low cost, and easy application. Studies have shown that adding a second endoscopic therapy to epinephrine injection might improve haemostatic efficacy and patient outcomes (Park *et.al*, 2004, Chung *et.al*, 1997, Pescatore*et.al*, 2002).

The most favourable outcome post endoscopic therapy is of course the control of bleeding. However in some instances the bleeding does not stop after the initial endoscopic therapy thus requiring further intervention in the forms of either repeat endoscopic therapy, angio-embolization or surgery. Ultimately, if the bleeding cannot be arrested, it can cause mortality.

1.2 RATIONALE OF STUDY

Peptic ulcers remain the most common cause of UGIB, accounting for 30-60% of UGIB hospitalizations. Endoscopic therapy remains the mainstay for treatment as it reduces re-bleeding rate, need for surgery, morbidity and mortality of bleeding peptic ulcers.

The overall mortality rate of 10% is a cause for concern.

With the advancement in management of bleeding peptic ulcers, the outcome of patients may differ from centre to centre depending on the availability of treatment and surgeon's expertise.

Apart from that, currently there is no data that shows the outcomes of endoscopic therapy for bleeding peptic ulcers in Malaysia.

CHAPTER TWO: STUDY PROTOCOL

2.1 DOCUMENTS SUBMITTED FOR ETHICAL APPROVAL

OUTCOMES OF ENDOSCOPIC THERAPY FOR BLEEDING PEPTIC ULCERS; A RETROSPECTIVE STUDY IN HOSPITAL SERDANG

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Introduction

Acute Upper Gastrointestinal Bleeding (UGIB) remains a common cause of hospitalization in Malaysia. The incidence is approximately 72 per 100000 in Malaysia [1]. Despite important advances made in the management of non-variceal UGIB, the overall mortality has remained constant at 10% for the past few decades [2-5]. This may in part be due to the fact that older patients, who have advanced cardiovascular, respiratory, or cerebrovascular disease that puts them at increased risk of death, now comprise a much higher proportion of cases.

UGIB refers to bleeding from any point proximal to the duodeno-jejunal flexure (Ligament of Treitz). UGIB can be divided into variceal and non-variceal bleeding. Variceal bleeding can be caused by either oesophageal varices or fundal varices. Non-variceal bleeding can be further subdivided into haemorrhagic gastritis, peptic ulcer bleeding, tumour/polyp bleeding or arterio-venous malformation bleeding.

Patients come to the hospital complaining of frank haematemesis, coffee ground vomiting and/or melaena. Fresh bleeding per rectum is usually indicative of lower GI bleeding, however massive UGIB can present with passing of red blood clots per-rectally. Haemodynamic instability may also feature, with patients presenting with dizziness, syncope or in hypovolaemic shock.

Upper endoscopy is crucial in the diagnosis, stratification, and management of patients with bleeding ulcers, and endoscopic haemostatic therapy is the mainstay of treatment in patients with endoscopic findings that predict an increased risk of further bleeding [6].

Once source of bleeding is identified, the ulcer is stratified using the Forrest Classification which differentiates high risk of re-bleeding ulcers from low risk of re-bleeding ulcers [7].

<table>
<tr><th>I : Active bleeding</th><th>II : Stigmata of recent haemorrhage</th><th rowspan="3">III: Lesions without active bleeding
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SRH = stigmata of recent hemorrhage
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In addition to endoscopic therapy, acid suppressors are administered to patients, particularly proton pump inhibitors. Several studies have examined the role of acid suppression given before or after endoscopy (with or without therapeutic intervention) [8].

The currently available endoscopic haemostatic methods include injection therapy, thermal coagulation, and mechanical therapy. Among these approaches, injection of epinephrine is the most popular endoscopic method used to stop bleeding because of its safety, low cost, and easy application. Studies have shown that adding a second endoscopic therapy to epinephrine injection might improve haemostatic efficacy and patient outcomes [9-11].

The most favourable outcome post endoscopic therapy is of course the control of bleeding. However in some instances the bleeding does not stop after the initial endoscopic therapy thus requiring further intervention in the forms of either repeat endoscopic therapy, angioembolization or surgery. Ultimately, if the bleeding cannot be arrested, it can cause mortality.

Justification of Study

Peptic ulcers remain the most common cause of UGIB, accounting for 30-60% of UGIB hospitalizations. Endoscopic therapy remains the mainstay for treatment as it reduces re-bleeding rate, need for surgery, morbidity and mortality of bleeding peptic ulcers.

The overall mortality rate of 10% is a cause for concern.

With the advancement in management of bleeding peptic ulcers, the outcome of patients may differ from centre to centre depending on the availability of treatment and surgeon's expertise.

Apart from that, currently there is no data that shows the outcomes of endoscopic therapy for bleeding peptic ulcers in Malaysia.

Study Objective

Primary (Specific) objective

To determine the prevalence of permanent haemostasis and rate of re-endoscopy after initial endoscopic therapy for bleeding peptic ulcers in Hospital Serdang.

Secondary objectives

1. To determine the prevalence of angio-embolization and surgery after initial endoscopic therapy for bleeding peptic ulcers in Hospital Serdang.
2. To describe the demographics in patients with bleeding peptic ulcers in Hospital Serdang.
3. To describe the length of stay of patients with bleeding peptic ulcers in Hospital Serdang.
4. To describe the 30-day mortality rate [12] of patients with bleeding peptic ulcers in Hospital Serdang.

Research Questions

What is the proportions of outcomes after receiving endoscopic therapy for bleeding peptic ulcers in Hospital Serdang?

What is the average length of hospital stay for patients that receive endoscopic therapy for bleeding peptic ulcers?

What is the mortality rate of patients that receive endoscopic therapy for bleeding peptic ulcers in Hospital Serdang?

Methodology

Study Design

This is a retrospective record review of patients who underwent emergency upper endoscopy from March 2014 to March 2019 in Hospital Serdang, Selangor.

Study Variables

- Outcome i.e.; permanent haemostasis, re-endoscopy, angio-embolization, surgery, mortality
- Type of endoscopic therapy i.e.; single or dual
- Demographics e.g.: age, race, gender, co-morbidities
- Length of hospital stay in days

Place of Study

This study will be conducted in Hospital Serdang, Selangor.

Study population

Patients who underwent upper endoscopy from March 2014 to March 2019 in Hospital Serdang. Only patients that meet the inclusion criteria will be included in the study.

Inclusion criteria

- Higher risk of re-bleeding ulcers based on the Forrest Classification (Forrest 1A, 1B, 2A, 2B). If there are multiple ulcers present, the ulcer with the highest risk of re-bleed will be taken into account.
- Underwent emergency upper endoscopy
- Age above 18 years old (underaged)

Exclusion criteria

- Presence of another bleeding site e.g.: variceal bleeding, tumor bleeding, AVM, hemangioma bleeding, hemorrhagic gastritis etc.

Sampling method

Universal sampling. Patients who had upper endoscopy done for high risk of re-bleeding ulcers are selected from the scope suite records from March 2014 to March 2019.

Sample Size

Using a single proportion formula, the sample sizes based on the objectives were calculated. Out of the available data, the largest and most feasible sample size required was 185. It was based on the objective in which permanent haemostasis was achieved after initial endoscopic therapy, whereby the proportion was 9.1% based on a previous study by Zaltman et al. 2002[14]. As such, the proportions for angio-embolization and surgery were not calculated as there is no previous data to base our calculation on. The precision was set at 0.05 (5%). After considering 10% no response rate, the required sample size is 204.

$$n = \frac{Z^2 P(1-P)}{d^2}$$

where n = Sample size,
Z = Z statistic for a level of confidence,
P = Expected prevalence or proportion
(If the expected prevalence is 20%, then $P = 0.2$), and
d = Precision (If the precision is 5%, then $d = 0.05$).

Outcome	Reference	P	n	n + 10%
Permanent haemostasis	Zaltman et al. 2002	0.86	185	204
Re-endoscopy	Zaltman et al. 2002	0.09	126	139

Conduct of study

1. After ethics committee approval, a list of patients who underwent emergency upper endoscopy from March 2014 to March 2019 will be collected from the endoscopic suite records, Hospital Serdang.
2. Patients who fulfil the inclusion and exclusion criteria will be recruited into the study. Patient's data will be obtained by retrospective study of patients electronic medical records and entered into a data collection form. (appendix A)
3. Patient's final outcome will then be recorded. I.e.: if patient underwent endoscopic therapy, then surgery and ultimately succumbed to death, his final outcome will be under mortality.
4. Patients who did not turn up for follow up, would be contacted to ascertain whether patients had passed away during the 30-day mortality period. If patients are unable to be contacted, they will be dropped out from the study.

Statistical Analysis Plan

The analyses will be performed using the IBM SPSS Statistics Version 19.0 (IBM Corp, Armonk, NY). The data will be manually entered into the software before the cleaning process takes place. The cleaning process is crucial to prevent any errors that may skew the results. After that, the actual analysis process will be carried out.

Numerical data were presented with mean and standard deviation if normality assumption were found fulfilled, otherwise median and interquartile range. Categorical variables were presented as frequency and percentage.

Pearson Chi Square and Fisher Exact test were used to test the association between mortality and underlying medical illness (Hypertension, Diabetes Mellitus, Cardiovascular Disease, Ischemic Heart Disease and Chronic Kidney Disease). All the tests were two sided and p value less than 0.05 were considered statistically significant.

Ethical Considerations

Ethical approval will be applied from MREC KKM. This study will be registered with the NMRR and JEPEM USM, in compliance with current NIH guideline.

Status of application with NMRR and JEPEM USM – approved.

The study will be conducted in compliance with ethical principles outlined in the Declaration of Helsinki, Malaysian GCP Guideline and CRC's standard operating procedures.

Privacy and Confidentiality

All data collected will be confidential. The author will ensure that the subject's anonymity is maintained. Patient's records and documents that could identify subject will be kept protected, respecting the privacy and confidentiality of individuals in accordance with local data protection regulations.

All electronic data will be identified by unique study numbers only, thereby ensuring that the subject's identity remains confidential. The subject identification list with complete identification information (participant's name, contact number) will be kept protected and will be destroyed at the end of the study.

The data for publication will be the responsibility of the author and duration of data storage will be 2 years after publication as per GCP requirements.

Conflict Of Interest

The author declares no conflict of interest with any parties.

Flow Chart

List of patients underwent emergency upper endoscopy obtained from endoscope suite

↓

Recruitment of patients who fulfilled the inclusion and exclusion criteria

↓

Review of medical records of patients recruited in the study

↓

Data from medical records entered in the data collection form

↓

Data collection and statistical analysis

↓

Report and manuscript write up

Gantt chart of Research Activities

PROJECT ACTIVITIES	2019										
Research Activities	**J**	**F**	**M**	**A**	**M**	**J**	**J**	**A**	**S**	**O**	N
Dissertation TopicDiscussion at Department and Ethics Approval	→	→	→	→	→						
Patient / Subjects Recruitment and Data Collection					→	→	→				
Data Analysis / Interpretation							→	→			
Dissertation Papers Write Up								→	→	→	
Submission of Dissertation Papers										→	→

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Data Collection Form Appendix A

Anonymous Study ID :

Sex : M / F

Race : Malay / Chinese / Indian / Others

Age :

Co-morbidities :

Diabetes	
Hypertension	
Ischaemic heart disease	
Chronic kidney disease	
Cerebrovascular accident	

Forrest Classification :

Forrest IA	
Forrest IB	
Forrest IIA	
Forrest IIB	

Permanent Haemostasis :

YES	
NO	

Repeated Endoscopy :

YES	
NO	

Angio-Embolization:

YES	
NO	

Requiring Surgery:

YES	

NO	

Mortality :

YES	
NO	

Length of Hospital Stay :