Effects of aspirin and anticoagulants on morbidity and mortality in patients with non-variceal upper gastrointestinal bleeding

thesis

Submitted for the Partial Fulfillment of
Master Degree in Internal medicine

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2016

بسم الله الرحمن الرحيم

قالوا

سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم الحكيم

صدق الله العظيم

سورة البقرة الآية: ٣٢

Acknowledgements

*First of all, thanks to **ALLAH** for helping and guiding me accomplishing this work and for everything else I have.*

*I would like to express my deep gratitude and sincere appreciation to **Prof.Dr. Kadry Mohammed Elsaeed,** Professor of internal medicine ,Faculty of Medicine, Ain Shams University, for his Sustained support, continued encouragement and for his precious time and effort that made this thesis possible. It was great honor to me to do this thesis under his supervision.*

*My deep appreciation to **Prof.Dr.Sherif Sadek Shabana,** Assistant Professor of internal medicine ,Faculty of Medicine,Ain Shams University, for his valuable instructions, unlimited help and great deal of support, his endless patience with me and for his experienced guidance and helpful suggestions that make the completion of this work possible.*

*I owe special feeling of gratitude to **Dr.Hany Aly Hussein**, Lecturer of internal medicine ,Faculty of Medicine, Ain Shams University for his great help, close supervision, wise opinions, guidance and his continuous encouragement and for his precious effort.*

Finally, but most important, I can't thank enough my family, for their sacrifice, moral support, continuous encouragement and help that made this work possible.

Mahamoud Galal Eldeeb

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List of abbreviations

ACE	Angiontensin – converting enzyme
ACS	Acute coronary syndrome
ADP	Adenosine diphosphate
AF	Atrial fibrillation
AMI	Acute myocardial infarction
APTT	Activated partial thrombo plastin time
ASGE	American society for gastrointestinal endoscopy
ASS	Acetyl salicylic Acid (Aspirin)
AT	Antithrombin
ATT	Anti thrombotic trialist
CABG	Coronary artery by pass graft
COX	Cyclooxy genase
COX2	Cyclo oxygenase II
DES	Drug eluting stent
DVT	Deep venous thrombosis
ECMO	Extra corporeal membrane oxygenation
FDA	Food and Drug Administration
FEIBA	Factor eight inhibitor by passing avtivity
FFP	Fresh frozen plasma
HDV	high dependency unit
HIT	Heparin induced thrombo cytopenia
HP	Helicobacter pylori
HPR	High platelet reactivity
INR	International normalization ratio
IV	Intravenous
LFTs	Liver function tests
LMWH	Low molecular weight heparin
MW	Mole cular weight
NICE	National institute for Health and care excellence
NOACS	Novel oral anticoagulants
NSAIDS	Non steroidal anti-inflammatory drugs
NSTEMI	Non elevated st segment Myocardial infarction
NVUGIB	Non variceal upper gastro intestinal bleeding
PAF	Platelet activating Factor

PCC	Prothrombin complex concentration
PCI	Percutaneous cororary intervention
PE	Pulmonary embolism
PF4	Platelet Factor 4
PPI	Proton pump inhibitor
RBCs	Red blood cells
RFTs	Renal function tests
SC	Subcutaneous
SEE	Second endoscopic examination
SRH	Stigmata of recent Haemorrhage
TIA	Transient ischemic attack
TXA	Thromboxane A
UFH	Un fractionated heparin
UGIB	upper gastrointestinal bleeding
VKA	Vitamin k antagonist
VTE	Venous thromboembolism
WBCs	White blood cells

Introduction

Upper gastrointestinal bleeding (UGIB) is a common, potentially life threatening condition responsible for more than 300,000 hospital admissions and about 30,000 deaths per annum in America. Acute upper gastrointestinal bleeding remains a common medical emergency and is a major source of morbidity and mortality; and despite the progress in endoscopic and intensive care therapies, the mortality remains unchanged; it results from increasing number of high-risk patients mainly the older ones with significant comorbidity **(Palmer, 2007)**.

The incidence of UGIB is 2-fold greater in males than in females, in all age groups; however, the death rate is similar in both sexes. The population with UGIB has become progressively older, with a concurrent increase in significant comorbidities that increase mortality. Mortality increases with older age (> 60 years) in males and females **(**Marmo R **et al., 201**0**)**.

Non-variceal upper gastrointestinal bleeding (UGIB) is a critical clinical condition that requires an urgent management. It remains a clinically important issue due to the increase in the proportion of elderly population, use of non-steroidal anti-inflammatory drugs (NSAIDs) and in-hospital UGIB **(Laine and Jensen, 2012)**.

Anticoagulant therapy has historically consisted of heparins for the treatment of acute thrombosis and Vitamin K Antagonists (VKA) for long-term or chronic treatment. Though effective if appropriately dosed and monitored, these traditional agents have shortcomings that stem mainly from their nonspecific mechanisms of action and variable pharmacodynamics. This has left a persisting need for novel

anticoagulants that have more specific and targeted action and are easier to administer and manage **(Nutescu et al., 2006)**.

The platelet is integral to the initiation of thrombosis. The indications for the use of antiplatelet drugs in the management of thrombotic diseases include stroke, acute myocardial infarction (AMI), acute coronary syndrome (ACS), angina, percutaneous coronary intervention (PCI), cardiac surgery, primary and secondary cardiovascular disease prevention, peripheral vascular disease, and thrombotic disorders such as atrial fibrillation. There are several antiplatelet drugs available for use in clinical practice and several under investigation **(Jennings, 2009)**.

Management of patients who are receiving antiplatelet drugs during the perioperative period requires an understanding of the underlying pathology and rationale for their administration, pharmacology and pharmacokinetics, and drug interactions **(Newsome et al., 2008)**.

Many patients receive chronic antithrombotic therapy for various cardiac diseases. Antiplatelet drugs are widely used in patients with coronary artery disease. Dual antiplatelet therapy, with a combination of aspirin plus a P2Y12 receptor inhibitor (such as clopidogrel, prasugrel or ticagrelor), is often necessary for a period of 12 months after an acute coronary event or after the implantation of a coronary stent **(Hamm et al., 2011)**.

Vitamin-K antagonists (VKA) are indicated in patients with atrial fibrillation, thromboembolic venous disease or a mechanical heart valve, while recently the novel oral anticoagulants (NOAC), such as dabigatran, rivaroxaban and apixaban, have been used increasingly in nonvalvular atrial fibrillation and venous thromboembolism **(Camm et al., 2012)**.

Aim of the work

In this study, we aime to determine the impact of aspirin and anticoagulants on the clinical outcomes of patients who were admitted to hospital due to PUD-related UGIB, and to investigate the etiology of death in patients who had a fatal outcome

Non-variceal upper gastrointestinal bleeding

Upper gastrointestinal bleeding (UGIB) is a common,potentially life threatening condition responsible for more than 300,000 hospital admissions and about 30,000 deaths per annum in America**.** Treating and preventing UGIB costs many billions of dollars per annum**.** UGIB is defined as bleeding proximal to the ligament of Treitz, to differentiate it from lower gastrointestinal bleeding involving the colon, and middle gastrointestinal bleeding (GI B) involving the small intestine distal to the ligament of Treitz**.** Acute upper gastrointestinal bleeding remains a common medical emergency and is a major source of morbidity and mortality; and despite the progress in endoscopic and intensive care therapies, the mortality remains unchanged; it results from increasing number of high-risk patients mainly the older ones with significant comorbidity **(Palmer, 2007)**.

The incidence of UGIB is 2-fold greater in males than in females, in all age groups; however, the death rate is similar in both sexes. The population with UGIB has become progressively older, with a concurrent increase in significant comorbidities that increase mortality. Mortality increases with older age (> 60 years) in males and females **(Marmo R et al., 2010)**.

Non-variceal upper gastrointestinal bleeding (UGIB) is a critical clinical condition that requires an urgent management. Although there was a significant reduction in the incidence of bleeding peptic ulcers

with the introduction of proton pump inhibitor (PPI) and eradication of *Helicobacter pylori*, UGIB still remains a clinically important issue due to the increase in the proportion of elderly population, use of non-steroidal anti-inflammatory drugs (NSAIDs) and in-hospital UGIB **(Laine and Jensen, 2012)**.

Epidemiology:

UGIB has a mortality of 7% to 10%. The mortality has decreased only minimally during the last 30 years, despite the introduction of endoscopic therapy that reduces the rebleeding rate. This phenomenon is attributed to the increasing percentage of UGIB occurring in the elderly, a group with a worse prognosis than other patients because of their increased use of antiplatelet medications or anticoagulants, and their frequent comorbid conditions. Endoscopic therapy has, however, been shown to reduce the rate of rebleeding, the need for blood transfusions, and the need for surgery **(Boonpongmanee et al., 2004)**.

Causes:

A cause for upper gastrointestinal bleeding is found in approximately 80% of cases **(Rockall et al., 1995)**.

Table (1): Causes of acute upper gastrointestinal haemorrhage **(Rockall et al., 1995)**

Diagnosis	Approx %
Peptic ulcer	35–50
Gastroduodenal erosions	8–15
Oesophagitis	5–15
Mallory Weiss tear	15
Upper gastrointestinal malignancy	1
Vascular malformations	5
Rare	5

Initial assessment and risk stratification:

The first step in the management of patients presenting with overt UGIB is the assessment of hemodynamic status and initiation of resuscitative measures as needed. Intravenous (IV) fluids and transfusion of red blood cells targeting hemoglobin level of ≥7 g/dL may be required in euvolemic patients. Higher hemoglobin levels may need to be targeted in patients with clinical evidence of intravascular volume depletion or comorbidities such as coronary artery disease.

Risk assessment of patients is clinically useful to determine which patients are at higher risk of further bleeding and may aid in making management decisions such as timing of endoscopy, time of discharge and level of care. The widely studied methods used to assess risk and to predict risk of rebleeding and mortality include the Rockall score **(Rockall et al., 1996)** and Blatchford score **(Blatchford et al., 2000)**.

Rockall et al defined independent risk factors (table 2) which were subsequently shown to accurately predict death. These comprise:

(i) **Increasing age.** There is a close relationship between mortality and age. Deaths in patients under the age of 40 years are rare while the risk of death is 30% in patients aged more than 60 years.

(ii) **Comorbidity.** Deaths are almost entirely restricted to patients who have significant general medical diseases. These diseases are decompensated by bleeding, and postoperative complications are more likely to occur in patients who have significant comorbid illness. The number and severity of comorbid illnesses are closely related to mortality in patients hospitalised for gastrointestinal bleeding. Patients who have advanced renal or