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PPI before versus after Endoscopy in Treatment of Non-Variceal Upper Gastrointestinal Bleeding and their Impact on 30-days Clinical Outcome.

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ABSTRACT:

Background: Acute upper gastrointestinal bleeding is a widespread medical emergency that represents a challenge to healthcare workers. Despite the notable improvement in management choices, there is no difference in mortality rate. Attentive assessment and examination before determining a treatment plan is associated with fewer complications. Deficient management of patients with upper gastrointestinal bleeding may escalate the risk of re-bleeding and other complications. Moreover, the timing of pharmacological and/or endoscopic intervention may influence the patient's outcome and should be precisely assigned to lower the risk of mortality and morbidity.

Aim: To compare the management of upper gastrointestinal bleeding with pharmachological treatment before and after endoscopic intervention on 30 days' incidence of re-bleeding.

Method: Fifty patients presenting with non-variceal upper gastrointestinal bleeding were either treated with proton pump inhibitors as the first line of management or went directly for upper Esophagogastroduodenoscopy to control the bleeding. The impact of either way of treatment on 30 days' clinical outcome was evaluated.

Results: no difference in 30 days' outcome between the patients who received proton pump inhibitors first before upper Esophagogastroduodenoscopy and the patients who had their endoscopy done first.

Conclusion: Giving proton pump inhibitors before or after doing upper Esophagogastroduodenoscopy in patients with non-variceal upper gastrointestinal bleeding doesn't change the incidence of re-bleeding, but early endoscopy is associated with better outcomes.

Keywords: Non-variceal, gastrointestinal bleeding, proton pump inhibitors, endoscopy, re-bleeding

INTRODUCTION

Acute upper gastrointestinal bleeding (UGIB) is a common health problem that is thought to be a life-threatening medical emergency and can be seen daily by health care workers. Despite the observed improvement in diagnosis and treatment options, mortality has remained the same for many years. [1]

UGIB is defined as bleeding originating before the ligament of Trietz. Patients may present with hematemesis, hematochezia, and/or melena. There are many causes of UGIB, including stomach ulcers, peptic ulcers, bleeding esophageal varices, gastritis, and bleeding tumor. The patient may present with melena, occult blood in stools, up to profound haemetemesis and even shock, that's why an early intervention is mandatory for life saving and for better outcome. [2]

The initial management of patients presenting with acute UGIB involve adequate assessment of their haemodynamics. Once steady, endoscopy should commence in order to identify the source of bleeding and intervene accordingly. [3] Endoscopic intervention should only be applied to lesions with active bleeding, non-bleeding visible vessels, and if the ulcers have an adherent clot. Other minor stigmata of recent bleeding such as red or black spots have minimal risk of re-bleeding and usually don't need endoscopic intervention, and medical treatment is enough. [4] One or more endoscopic techniques can be applied to stop bleeding like injection of adrenalin or sclerosants, heat probe, diathermy, haemoclips, or laser photocoagulation. [5]

The endoscopist should have a second look within 24 hours if there was obscured visualization, poor access, or difficult technique in initial endoscopy, or if the risk of re-bleeding is life threatening. The predictors of endoscopic failure to control UGIB are multiple co-morbidities, haemodynamic derangement, the need for > 4–6 units of blood transfusion within 24 hours, and an ulcer with visible vessel, actively bleeding vessel,

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adherent clot or size >2cm in diameter; all of which are the indicators for surgery [6]

Proton pump inhibitors (PPIs) should be initiated once the patient presents with UGIB and should not be postponed or delayed before endoscopy. European Society of Gastrointestinal Endoscopy Guidelines advocates starting high-dose PPIs (80mg/day) administrated intravenously or orally within the first 72 hours post-endoscopy, because this period shows the highest incidence of re-bleeding. After 72 hours, the patients with major endoscopic stigmata of re-bleeding should have PPIs twice daily for 2 weeks, but patients with minor risk lesions need PPIs only once daily for 4-8 weeks. [7] Whether to start these medications before or after the endoscopy and the potential effect on clinical outcome of the patient need further study.

Aim: To compare the management of upper gastrointestinal bleeding with pharmachological treatment prior to and after endoscopic intervention on 30 days' incidence of re-bleeding.

Methods

Study design

A prospective randomized clinical trial was conducted on 50 patients with UGIB attending the Gastroenterology Outpatient Clinic or admitted to the Medical Research Institute inpatient ward during the period from January 2024 to April 2024. The timing of administration of pharmacological treatment and endoscopic intervention was monitored and its effect on their 30-days clinical outcome regarding re-bleeding has been evaluated. The study was started after an informed consent has been taken from all patients and after getting accepted by the local Ethics Committee which adopts the Helsinki Declaration rules (E/C.S/N.R7/2024).

Inclusion criteria

Patients aged 18 years old or more who presented with acute non-variceal upper gastrointestinal bleeding during the study period were included. They were randomly allocated into two groups; I and II. Group I received medical treatment first and group II had their endoscopy done first.

Exclusion criteria

Patients who had any of the following were excluded from the study: diabetes mellitus, chronic liver disease, chronic renal failure, congestive heart failure, bleeding diathesis, or malignancy.

All patients were subjected to the following:

- Complete clinical assessment including vital signs (blood pressure, pulse rate, respiratory rate).
- Routine laboratory investigations including liver function tests, renal function tests, electrolytes, coagulation profile, and complete blood count. [8]
- Ultrasound abdomen to exclude any liver disease and/or renal disease. [9]
- Esophagogastroduodenoscopy (EGD) using Olympus GIF 240 [10] to diagnose and treat any gastroduodenal pathology. Hemoclip was used for visible vessels, closure of mucosal defects, and perforation holes, [11] Argon plasma coagulation (APC) was used for vascular ectasia, and oozing from superficial lesions, [12] Epinephrine injection was used in combination with other methods to achieve hemostasis. [13]
- Omeprazole 80 mg bolus followed by 8 mg/hr infusion [7] was given to group I (n=35) on first presentation with UGIB after stabilization of hemodynamics and before EGD, and the same dose was given to group II (n=15), after they had their endoscopy done first as their hemodynamics were more stable.
- Follow up of patients for 30 days to monitor the incidence of re-bleeding in all patients.

Statistical analysis

The utilized system to analyze data was the IBM SPSS package version 20.0. Software (Armonk, NY: IBM Corp). Qualitative data were described using numbers and percentage and were compared using the Chi-square test and Fisher Exact test. Mean and standard deviation were employed to examine quantitative data. Student t-test was used for comparison of quantitative variables (normally distributed). The significance was considered at the 5% level.

Results

A total of 50 cases with non-variceal upper gastrointestinal bleeding were recorded, group I, n=35 they were given PPI first before endoscopy and needed hemodynamic stabilization, the bleeding was in the form of hematemesis in 60% of cases, melena in 30% of cases, and both hematemesis and melena in 10 % of cases.

Hemoglobin level ranged from 7 g⁄dl in most severe cases, up to 11 g⁄dl in less severe cases at the time of admission, 7 patients in group I needed blood transfusion before endoscopy, 14 patients needed IV fluids before endoscopy in group I and 2 patients in group II. Blood pressure ranged from 80-100 mmHg (systolic), and from 50-70 mmHg (diastolic) in group I, and ranged from 90-125 mmHg (systolic), and from 60-90 mmHg (diastolic) in group II. Pulse rate ranged from 100-120 BPM in group I, and ranged from 80-100 BPM in group II. Respiratory rate ranged from 20-24 cycles/min in group I, and ranged from 16-20 cycles/min in group II. The mean age of the patient was 61.7 ± 23.8 years, 52% of patients were > 60 years and 48% of patients were < 60 years. p= 0.41 (Table 1). The majority of cases were males (56%), while female patients were (44%) of the cases, but no statistical significance was established (p=0.32, Table 1)

Table (1): Demographic data of the studied patients

	No. (%)	P
Age (mean± SD)	61.7 ± 23.8	
<60 years	24(48%)	0.41
≥60 years	26(52%)	
Gender		
Male	28(56%)	0.32
Female	22(44%)	

*SD: standard deviation

Endoscopic findings regarding the causes of the bleeding were peptic ulcer disease in 74% of cases, divided into ulcer >2 cm (14%), visible vessel (10%), red/black spots (24%), adherent clot (18%), active bleeding vessel (8%). Non- peptic ulcer bleeding occurred in 26% of cases divided into esophagitis (10%), Mallory Weiss tear (8%), gastroduodenal erosions (8%). (Table 2)

Table (2): Baseline endoscopic pathology of the studied patients

Peptic ulcer bleeding	Number of patients	Percentage
Ulcer>2 cm	**7**	**14%**
Visible vessel	**5**	**10%**
Red/black spots	**12**	**24%**
Adherent clot	**9**	**18%**
Active bleeding vessel	**4**	**8%**
Non-Peptic ulcer bleeding		
esophagitis	**5**	**10%**
Mallory weiss tear	**4**	**8%**
Gastroduodenal erosions	**4**	**8%**

Re-bleeding after 30 days occurred in 14% (n=7) of cases, the most significant cause of recurrent bleeding was large ulcers >2cm (42.9%) p=0.048, and the most predicting factors for re-bleeding were low hemoglobin level at the time of presentation (7-9.1 g/dl) p<0.001, and the need for blood transfusion p=0.048 (Table 3). In patients in whom re-bleeding occurred (7/50), 57.1% had their PPI treatment given before endoscopy, while 42.9% had their PPI treatment given after endoscopy. In the patients without re-bleeding (43/50), 72.1% received PPI before endoscopy versus 27.9% received PPI after endoscopy; there was no statistically significant difference between the two groups. (p=0.41, Table 4). The clinical outcome after 30 days according to the timing of the endoscopy showed better outcomes in those who had their endoscopy done within 24 hours after bleeding as only (2/7), 28.6% of cases had re-bleeding, and (33/43), 76.7% of cases had no re-bleeding, while in patients who had endoscopy after 24 hours of bleeding they had re-bleeding in (5/7), 71.4% of cases and no re-bleeding in (10/43), 23.3% of cases. (p=0.02,Table 4)

Table (3): Relation between 30 days clinical outcome and different risk factors

	Total (n = 50)	No re-bleeding (n = 43)	Re-bleeding (n = 7)	Test of Sig.	p
Gender					
Male	**25 (50.0%)**	**20 (46.5%)**	**5 (71.4%)**	χ^2=	^{FE}p=
Female	**25 (50.0%)**	**23 (53.5%)**	**2 (28.6%)**	**1.495**	**0.417**
Age					
Min – Max	**30 – 71**	**30 – 71**	**41 – 69**		
Mean ± SD	**55.4 ± 11.9**	**54.6 ± 12.1**	**60.1 ± 10.3**	t=	**0.256**
Median (IQR)	**59 (47 – 65)**	**56 (46 – 64.5)**	**65 (56.5 – 66.5)**	**1.150**	
Hypotension	**20 (40.0%)**	**15 (34.9%)**	**5 (71.4%)**	χ^2=3.350	^{FE}p=0.100
Tachycardia	**20 (40.0%)**	**15 (34.9%)**	**5 (71.4%)**	χ^2=3.350	^{FE}p=0.100
Hb (g/dl)					
Min – Max	**7 – 13.20**	**7 – 13.20**	**7 – 9.10**		
Mean ± SD	**9.90 ± 1.97**	**10.26 ± 1.87**	**7.71 ± 0.82**	t=	**<0.001***
Median (IQR)	**10.1 (8 – 11.5)**	**10.5 (8.8 –11.6)**	**7.5 (7 – 8.2)**	**6.032***	
Need for IV fluid	**16 (32.0%)**	**12 (27.9%)**	**4 (57.1%)**	χ^2=2.365	^{FE}p=0.190
Need for blood transfusion	**7 (14.0%)**	**4 (9.3%)**	**3 (42.9%)**	χ^2=5.630*	^{FE}p=0.048*
Ulcer>2 cm	**7 (14.0%)**	**4 (9.3%)**	**3 (42.9%)**	χ^2=5.630*	^{FE}p=0.048*
Visible vessel	**5 (10.0%)**	**3 (7.0%)**	**2 (28.6%)**	χ^2=3.119	^{FE}p=0.138
Red/black spot	**12 (24.0%)**	**12 (27.9%)**	**0 (0.0%)**	χ^2=2.570	^{FE}p=0.174
Adherent clot	**9 (18.0%)**	**9 (20.9%)**	**0 (0.0%)**	χ^2= 1.787	^{FE}p=0.325
Active bleeding vessel	**4 (8.0%)**	**2 (4.7%)**	**2 (28.6%)**	χ^2= 4.680	^{FE}p=0.089
Esophagitis	**5 (10.0%)**	**5 (11.6%)**	**0 (0.0%)**	χ^2= 0.904	^{FE}p=1.000
Mallory weiss tear	**4 (8.0%)**	**4 (9.3%)**	**0 (0.0%)**	χ^2= 0.708	^{FE}p=1.000
Gastroduodenal erosions	**4 (8.0%)**	**4 (9.3%)**	**0 (0.0%)**	χ^2= 0.708	^{FE}p=1.000

IQR: Inter quartile range **SD: Standard deviation** **t: Student t-test**
χ^2: Chi square test **FET: Fisher Exact test**
p: p value for comparing between the two studied groups
***: Statistically significant at p ≤ 0.05**

Table (4):Relation between re-bleeding after 30 days and timing of pharmacologic and endoscopic intervention

	Clinical outcome after 30 days		
	Re-bleeding (n= 7)	No Re-bleeding (n= 43)	p
Endoscopy			
Done after 24 hours	**5(71.4%)**	**10(23.3%)**	**0.020***
Done within 24 hours	**2(28.6%)**	**33(76.7%)**	
PPI			
Given before endoscopy	**4(57.1%)**	**31(72.1%)**	**0.415**
Given after endoscopy	**3(42.9%)**	**12(27.9%)**	

Discussion

Proper management of patients with UGIB decreases the risk of complications and re-bleeding. In this study, evaluation of the type and timing of management was the goal.

Most of the patients in this study were in the age group > 60 years (52%) with a mean age of 61.7 ± 23.8 years, but with no statistically significant value. In contrast other studies showed that age was a major risk factor for UGIB, along with repetitive use of Non-steroidal anti-inflammatory drugs (NSAIDs) and low socio-economic class. It has been proven that people over 60 years old have a higher risk of getting UGIB than younger age groups. [14]

Also, it was noticed in this study that men have a higher incidence of UGIB than women but with no significant

difference. Likewise, a study by Kim et al found that persons aged over 40 years are more prone to UGIB with a non-significant relation to gender. [15] However, in a recent study they found that age and male gender are among the independent risk factors of UGIB. [16]

It is known that a low pH of the stomach ≤ 6 converts pepsinogen to pepsin, which decreases platelet aggregation and weakens the stabilization of the clot that has already formed at the site of bleeding. That's why trying to neutralize stomach acidity is vital in the start of the management of UGIB. [17] Previous reviews reported that re-bleeding is much lowered by the use of PPIs, which subsequently decreases the need for re-endoscopy and the necessity for surgery. Despite this, the use of PPIs has not been proven to increase the survival of the patients. [18] This may be due to the fact that PPIs have a prime role in the continuation of hemostasis not in starting the cascade. [19]

There is also some proof that PPI therapy started before EGD can improve stigmata of high-risk bleeding during endoscopy and may eliminate the need for further endoscopic therapy. [20] Meanwhile, British and Scottish Gastroenterology societies do not advocate the administration of PPIs before endoscopy, and emphasize that their use should not cause any hold to the endoscopy. [21] In the present study, the clinical outcome after 30 days of bleeding was better in those who had their PPIs given before endoscopy than in those who initiated PPIs after endoscopy but the difference was not statistically significant.

EGD is the principal tool for the diagnosis and management of patients with acute UGIB. A retrospective study on patients with non-variceal UGIB involving 81 patients showed no outstanding difference in clinical outcomes or period of admission between patients who had endoscopy done within 3 hours and patients who had endoscopy done after 48 hours. [22] In contrast, a study by Khamaysi et al reported that early endoscopy (within 24 hours) lowers the requirement for blood transfusion, re-bleeding, and the necessity for surgical intervention, but they also found that early endoscopy does not decrease the mortality rate considerably. [23]

The ordinary causes of re-bleeding after 30 days are linked to large ulcers, epinephrine mono-therapy, persistent use of NSAID, low hemoglobin level (≤ 9 g⁄dl) at the time of presentation, and relatively untrained intervening endoscopist. [24] In the present study, there was increased incidence of re-bleeding in patients who had large ulcers > 2cm and in patients presented with hemoglobin between 7-9.1g/dl and those needed blood transfusion.

However, the most significant factor that affects the rate of re-bleeding was the time of initiation of endoscopy; the earlier the endoscopic intervention the less is the rate of re-bleeding. So not only does early endoscopy help in the identification of the source of bleeding, risk stratification, and therapeutic intervention but also it decreases the re-bleeding rate and the need for subsequent endoscopy.

Some limitations in this study should be avoided in the future studies include small number of the patients, lack of comparison between the different types of PPI, and lack of follow up data of the patients after re-bleeding like severity of bleeding, the need for hospital admissions or the need for endoscopic or surgical intervention.

Conclusion

Giving PPIs before or after doing EGD in patients with non-variceal UGIB doesn't change the clinical outcome, but early endoscopy within 24 hours has been associated with significantly better outcomes.

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