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Endoscopic *vs.* Medical Therapy for Bleeding Peptic Ulcers with Adherent Clot: A Randomized Comparative Trial

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Abstract

Upper gastrointestinal bleeding is the most common and potentially life threatening emergency. Despite great advances in the field of medicine, the optimal management of bleeding peptic ulcer with adherent clot on endoscopy is still controversial. The aim of this study is to compare the combined endoscopic and medical therapy with medical therapy alone for bleeding peptic ulcer with adherent clot (Forrest type IIB). During two-year study period, around 342 patients presented to our Tertiary care hospital with acute upper gastrointestinal bleeding. Out of these, 81 patients were noted to have adherent clot (Forrest type IIB) during endoscopy and were included in study. 40 patients received combined endoscopic and medical treatment, whereas 41 patients received medical treatment only. The base line characteristics of patients in two groups were comparable and statistically significant. Primary Outcome being recurrence of bleeding within 7 days of treatment was less in combined therapy group compared to medical therapy group (2.5% *vs.* 17.1%) This was statistically significant. Secondary outcome like recurrence of bleed in 30 days and need for repeat endoscopy were less in combined group compared to medical therapy group. These were statistically significant as well. Other secondary outcomes like necessity for surgery and mortality were fewer in combined group, but these were not statistically significant. In conclusion combination endoscopic therapy consisting of epinephrine injection, removal of the adherent clot, and treatment of underlying stigmata is more effective than medical therapy alone.

Keywords: Gastrointestinal bleed; Adherent Clot; Endoscopic therapy; Medical therapy

Introduction

Upper gastrointestinal bleeding (UGIB) is common and potentially life-threatening gastrointestinal emergency. The annual incidence of hospitalization for acute UGIB is 1 per 1000 people in America [1] with a mortality rate of 7% to 10% [2]. Upper gastrointestinal Endoscopy (EGD) is the prime diagnostic and therapeutic tool for UGIB [3]. It precisely delineates the bleeding site and determines the specific cause. EGD is 90% to 95% diagnostic for acute UGIB [4]. Patients after initial resuscitation should undergo early endoscopy (within 24 hours). It helps to identify stigmata of recent hemorrhage (SRH), in patients with underlying peptic ulcer disease. Patient with high risk SRH like active bleed or visible vessel needs endoscopic intervention to reduce morbidity and mortality [5-7]. Ulcers with a clean base or with a flat pigmented spot have a low risk of rebleeding and do not require endoscopic-therapy [7-9]. Ulcers with adherent clot carry 8 to 36 percent risk of rebleeding [7,10]. The optimal management of ulcers with adherent clot is controversial. Endoscopic therapies include injection, ablation, and mechanical therapy. The above three endoscopic therapies are effective as monotherapies, but combined therapies increase the efficacy [11-15].

Proton pump inhibitor (PPI) therapy is recommended for patients with acute UGIB. This therapy reduces the severity of SRH at endoscopy and reduces the need for endoscopic therapy as compared with no treatment or histamine-2 antagonist (H2 Blocker) therapy [16,17]. PPI therapy modestly reduces the risk for rebleeding, need for surgery, and blood transfusions, however so far hasn't shown to reduce mortality [18]. The benefit is greatest in patients who have high risk SRH, such as a visible vessel. Although intravenous infusion is ideal, oral PPI therapy provides much of the benefit [19]. The rationale for PPI therapy is that most common causes of UGIB, including ulcers, gastritis, duodenitis and hemorrhagic reflux esophagitis are medically treated with acid-suppressive therapy. PPI therapy is also useful for hemostasis, by neutralization of intraluminal gastric acid it promotes stabilizing of blood clots [20]. Omeprazole has been the most extensively studied intravenous PPI, others are Pantoprazole and esomeprazole. The suggested dose of intravenous pantoprazole is 80 mg bolus followed by 8 mg/hr infusion. Omeprazole and esomeprazole have also been used as 80 mg boluses followed by 8 mg/hr infusions. The infusion is usually continued for 72 hours. If there is no rebleeding the patient may be switched to oral pantoprazole 40 mg/day or omeprazole 20 mg/day.

Till date, the management of ulcers containing adherent clots has been controversial. Some investigators do not recommend endoscopic therapy for patients with non-bleeding adherent clots because of the potential to induce severe hemorrhage [21,22]. In contrast, others advocate removal of the overlying clot and treatment of underlying stigmata for patients with adherent clot in an ulcer base [1,23]. Two recently published randomized, controlled trials have shown that injection of epinephrine followed by removal of adherent clot and treatment of underlying stigmata significantly reduced the rate of recurrent ulcer bleeding when compared with leaving the clot undisturbed [24,25]. However later on meta-analysis found no clear evidence for need of specific endoscopic interventions in patients with an adherent clot [5].

The purpose of this study is to compare the effectiveness of combined therapy vs. medical therapy alone for the patients with bleeding peptic ulcers with an adherent clot.

Material and Methods

This prospective randomized single center study was conducted in the Division of Gastroenterology, Sheri-I-Kashmir Institute of Medical Science, Srinagar, India over a period of two years from Nov 2011 to Nov 2013. The study was approved by post graduate clinical research and ethics committee of institute. Patients who presented with UGIB, after initial resuscitation, underwent upper GI endoscopy. Patients with adherent clot (which was defined as a lesion that was red, maroon, or black and amorphous in texture and that could not be dislodged by suction or forceful water irrigation) on endoscopy were randomized into two groups. Randomization was done by computer generated random numbers. One group with adherent clot received medical therapy only i.e. intravenous pantoprazole 80 mg boluses followed by 8 mg/hr infusions for 72 hours. The other group received endoscopic therapy in addition to medical therapy. The endoscopic therapy involved injection of 1:10000 solution of epinephrine into and around the clot, followed by removal of clot with polypectomy snare. After the removal of the clot, ulcers with underlying stigmata was treated with multipolar electrocoagulation (generator setting of 15 W) applied for a moderate amount of time (10 sec) with moderate pressure on the bleeding site until formation of white coagulum appears. All patients in the two groups were monitored for 72 hours after endoscopy. Patients who remained stable at 72 hours were discharged on oral omeprazole 20 mg daily and followed weekly for 30 days.

The primary outcome of the study was to assess the rate of rebleeding within 7 days of treatment in two groups. Secondary outcomes included 30-day rate of recurrent bleeding, need for repeat endoscopy or surgery and rate of mortality.

Exclusion Criteria

- Age less than 15 years.
- Pregnant and lactating women.
- Patients not giving written Informed consent.
- Patients with comorbidities like Liver Disease, GI Malignancy, CKD, Systemic infection, Cardiovascular and Pulmonary Disease.
- Patients with previous gastric acid reducing surgeries (vagotomy, gastric resection)
- Patients on anticoagulants.

Statistical Analysis

Data analysis was performed using the SPSS version 20 (IBM). Continuous variables were expressed as mean ± SD. Independent-Sample T Test was performed for continuous variables and chi square test (or Fisher's exact test when appropriate) for discrete variables. A value of $P \leq 0.05$ was considered statistically significant.

Results

During the study period, around 342 patients presented to our hospital with acute upper gastrointestinal bleed. Out of these, 81 patients were noticed to have adherent clot (Forrest type IIB) on endoscopy and were included in study. 40 patients received endoscopic treatment in combination with medical treatment; whereas 41 patients received medical treatment only.

Variables	Endoscopic Therapy group (n=40)	Medical Therapy group (n=41)	P Value
Age	46 ± 15	49 ± 16	0.393
Sex	21/19	21/20	0.908
Prior upper GI bleed	5 (12.5%)	6 (14.6%)	0.779
Prior peptic ulcer disease	7 (17.5%)	5 (12.2%)	0.502
NSAID/Aspirin Use	4 (10.0%)	3 (7.3%)	0.712
PPI Use	6 (15.0%)	7(17.1%)	0.799
Smoker	10 (25.0%)	8 (19.5%)	0.553
Systolic Blood Pressure (<90 mmHg)	15 (37.5%)	13 (31.7%)	0.584
Heart Rate (>100 b/m)	18(45.0%)	17 (41.5%)	0.748
Hemoglobin g/dl	8.6 ± 2.7	8.9 ± 2.4	0.6
Platelets (<100,000/mm^3)	4 (10.0%)	4(9.8%)	>0.999
Prolonged Prothrombin Time (>15 Sec)	3 (7.5%)	2 (4.9%)	0.675
Helicobacter Pylori Positive	22 (55.0%)	24 (58.5%)	0.748
Glasgow Blatchford Score	11.23 ± 4.0	10.78 ± 4.1	0.624
Rockall Score (Post Endoscopic)	5 (2-7)	6 (2-7)	0.257
Mean ± SD, n (%), Median (range), NSAID- Non-Steroidal Anti-inflammatory Drug; PPI - Proton Pump Inhibitor			

Table 1: Baseline characteristics of patients with adherent clots.

The base line characteristics of patients in two groups were comparable (Table 1). During endoscopy, gastric ulcer was found in 38 and duodenal ulcer in 43 patients. Underlying stigmata, after removal of clot, in endoscopic group revealed visible vessel in 16 (40%), flat red spot in 10 (25%), active bleed – ooze/spurt in 6 (15%) and Clean base ulcer in 8 (20%) patients (Table 2).

Visible vessel	Flat red spot	Active bleed (Ooze/ spurt)	Clean base ulcer
16 (40%)	10 (25%)	6 (15%)	8 (20%)

Table 2: Underlying stigmata after removal of clot in endoscopic group.

Primary Outcome

Recurrence of bleed within 1 week of treatment

Recurrence of bleeding within 7 days of treatment occurred in 9 (11.1%) patients. Recurrence was lower in the combined therapy group compared to medical therapy group (2.5% *vs.* 19.5%) This was statistically significant with P value of 0.029 (Table 3).

Secondary Outcome

Recurrence of bleed within 30 days of treatment

Recurrent bleeding within 30 days was less in combination therapy group compared to medical therapy group (5% *vs.* 22%). This was statistically significant with P value of 0.026 (Table 3).

Surgical therapy within 30 days

Surgical therapy for treatment of bleeding ulcer within 30 days was less in combined therapy group compared to medical therapy group (0% *vs.* 2.4%). But this was statistically insignificant with P value of >0.999 (Table 3).

Mortality within 30 days

Mortality within 30 days was less in combined therapy group compared to medical therapy group (0% *vs.* 2.4%) and again statistically insignificant with P value of >0.999 (Table 3).

Variable	Endoscopic Therapy group(n=40)	Medical Therapy group(n=41)	P Value
Rebleed 7 Days	1 (2.5)	8 (19.5)	0.029
Rebleed 30 Days	2 (5.0)	9 (22.0)	0.026
Surgical therapy	0(0.0)	1 (2.4)	>0.999
Mortality	0(0.0)	1 (2.4)	>0.999
Values are presented as n (%)			

Table 3: Comparison of outcomes between endoscopic therapy and medical therapy.

Discussions

The management of non-variceal UGIB has evolved immensely over a period of decade or so, with the availability of PPIs and endoscopic therapy. But the optimal management of bleeding peptic ulcer with adherent clot is still controversial. The purpose of our study was to address the controversies in the management of bleeding peptic ulcer with adherent clot. The present study is the largest randomized prospective study to compare combination endoscopic and medical therapy with medical treatment only of peptic ulcers with adherent clots and to evaluate the effectiveness of combination endoscopic therapy in a clinical setting.

Non-bleeding adherent clots are commonly identified when endoscopy is performed for acute upper GI bleed. The study by Laine et al. [26] consisted of young, low-risk patients and found that the rates of recurrent bleeding for patients with adherent clots treated with medical therapy were as low as 8%. Laine et al. [5] found that Endoscopic therapy was effective for active bleeding and a non-bleeding visible vessel but not for a clot. In a randomized controlled study of 27 patients with adherent clots, Jensen et al. [27] noted recurrent bleeding rates of 33% for patients treated with a heat probe, 37.5% with injection therapy, and 30.0% with medical therapy. Based on these findings, these investigators recommended that adherent clots should not be forcibly removed and be managed with medical therapy. Recent study by Jensen et al. [11] randomized 32 high-risk patients with severe upper GI Bleed due to ulcer and non-bleeding adherent clot resistant to target irrigation to combination endoscopic or medical therapy. Combination endoscopic therapy consisted of epinephrine injection, shaving the clot down with cold guillotining, and multipolar electro coagulation of the underlying stigmata. The frequency of recurrent hemorrhage during hospitalization was significantly lower in patients treated with combination endoscopic therapy than in those treated with medical therapy alone (0% *vs.* 35.3%; p=0.01). Similar findings were reported by Bleau et al. [12] who randomized 56 high-risk patients with severe GI Bleed due to ulcer and non-bleeding adherent clots resistant to target irrigation to receive combination endoscopic treatment or medical therapy. The frequency of recurrent hemorrhage within 1 month was significantly lower in the combination endoscopic treatment study group compared with the medical therapy only group (4.8% *vs.* 34.3%; p<0.02). Edmund et al. [28] during their study found rates of recurrent bleeding within 7 days of endoscopy in high-risk patients treated with combination endoscopic therapy were significantly lower than those treated with medical therapy group (8.7% *vs.* 27.4%; p<0.001). Combination endoscopic therapy was also associated with a significant decrease in the length of hospitalization, less number of packed red blood cell transfusions after endoscopy, the need for repeat endoscopy, and recurrent bleeding within 30 days compared with medical therapy only. Kim et al. [29], in their study on adherent clot found that endoscopic therapy significantly reduced bleeding related mortality (1.2% *vs.* 10%; p=0.018) and all-cause mortality (3.7% vs. 20.0%; p=0.005). However, there was no difference between endoscopic therapy and medical therapy regarding rebleeding (7.1% *vs.* 9.5%; p=0.641).

Our results were similar with most of the recent studies [11,12]. The rates of recurrent bleeding in patients treated within 7 days with combination endoscopic therapy were significantly lower than those treated with medical therapy only (2.5% *vs.* 17.1%: P Value 0.031). In addition, combination endoscopic therapy was associated with a significant decrease in recurrence of bleed within 30 days and the need for repeat endoscopy compared with medical therapy only. The need for surgical intervention for ulcer and the 30-day mortality rates were also lower in the endoscopic therapy group in the study, but these differences were not statistically significant.

Conclusion

Combination endoscopic and medical therapy is more effective than medical therapy alone for bleeding peptic ulcers with adherent clot. Any patient presenting with non-variceal UGIB should be immediately started on PPIs, preferably I.V bolus followed by infusion for 72 hours. After initial resuscitation, patients with bleeding peptic ulcer with adherent clot should be taken for early endoscopic intervention followed by medical therapy.

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