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RESEARCH ARTICLE

OUTCOME OF ORAL VS. INTRAVENOUS ESOMEPRAZOLE IN BLEEDING PEPTIC ULCER (SRH+) AFTER ENDOSCOPIC TREATMENT.

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Manuscript Info	Abstract

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Context: Peptic ulcer disease is the most common cause of upper gastrointestinal bleed and a common problem in the emergency department. Approximately a third of the patients with significant ulcer bleeding will develop recurrent bleeding on long-term follow-up, in the absence of active intervention . Although endoscopic hemostasis reduces mortality, acid suppression not only helps in achieving hemostasis but also reduces rebleeding .

Aims: To study the outcome of Oral vs. Intravenous esomeprazole in bleeding peptic ulcer (SRH+) after endoscopic treatment in terms of rebleeding and in increasing the intraluminal pH .

Materials and Methods: About 200 patients with upper gastrointestinal bleeding presenting with malena or hemetemesis or both were enrolled for the study. After endoscopic hemostasis , patients were randomized into two groups; one receiving oral esmoprazole and the other receiving intravenous (IV) esmoprazole. The primary end points were rate of rebleeding and secondary end points were surgery; number of deaths, duration of hospital stay, number of blood transfusions and number of rescue therapies required. The intragastric pH study was done in 20 patients; 10 patients on oral esomeprazole and 10 on IV esomeprazole.

Results: The baseline characterstitics of patients including age, sex, previous peptic ulcer disease, concurrent illness, the severity of bleeding at presentation, sight and size of ulcer, use of NSAIDS and endoscopic findings were comparable in the two groups. Rebleeding occured in 25 patients (12.5%); 14 patients (13.86%) in oral group and 11 patients (11.11%) in IV group. Emergency surgery was required in 7 (6%) patients in oral esomeprazole group as compared to 5(5%) patients in esomeprazole group. The mean number of patients who received blood transfusion were 9 (8.9%) in oral esomeprazole group and 11 (11.11%) in IV esomeprazole group. The total duration of hospital stay in oral group was 3.60+1.72 vs. 3.47+1.30 in IV group. The mean 72 hrs. intragastric pH in oral esomeprazole group was 7.06+0.44 and 6.78+0.27 in IV esomeprazole group.

Conclusions: Both oral and intravenous esomeprazole given to patients of bleeding peptic ulcers with SRH after endoscopic

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hemostasis had a similar effect on both the primary and secondary end points.

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Introduction:-

Bleeding from the upper gastrointestinal tract (referred to as UGI bleed) is a common serious problems faced in the emergency department of every hospital. The annual incidence of hospital admission for upper-gastrointestinal bleeding in United States and Europe is approximately 0.1% with a mortality rate of 5 to 10%.(1, Laine L, 1994) Peptic ulcer disease (i.e. ulceration of stomach, duodenum or both defined as mucosal breach , extending through muscularis mucosa into submucosa or deeper layers) accounts for 50%cases of UGI bleed. Bleeding can also occur from erosions, tears, tumors and vascular malformations. (Laine L et al, 1994, Kurata JH et al, 1984, Peterson, WL et al,1981).

Fortunately, ulcer bleeding stops spontaneously in 75-**80% of patients, with a relatively benign outcome. However**, despite the numerous advances in endoscopic and medical therapy, intensive care and surgery, the mortality rate can be high as 8-**10%. Mortality Occurs in patients with massive and** recurrent bleeding, especially in elderly patients with major comorbidities. Bleeding which commences in hospitalized patients is especially serious. Approximately a third of the patients with significant ulcer bleeding will develop recurrent bleeding on long-term follow-up, in the absence of active intervention (Sacks, HS et al, 1990).

Much progress has been made in methods for endoscopic diagnosis and treatment of patients with acute bleeding over recent years. This contribution reviews methods for hemostasis, the care of patients after treatment, and the prediction and prevention of rebleeding (Lee, JG et al, 1999). Further, meta-analyses have shown that endoscopic hemostasis reduces mortality (Jensen DM, 1999). Finally over-emphasis on mortality tends to ignore other important outcomes such as rebleeding, transfusion, hospital stay, cost, and need for surgery, all of which are significantly improved by endoscopic therapy. In 50-60% of patients with peptic ulcer bleeding who don't need hemostasis, early endoscopy is helpful as it can precisely predict the clinical outcome. This information can then be used to triage patients and institute treatment accordingly. The characteristics of an ulcer at endoscopy provide important diagnostic information in the patients with acute hemorrhage. When a platelet plug is seen protruding from vessel wall in the base of ulcer (sentinel clot of visible vessel), risk of major rebleed from ulcer is 40%. A clear based ulcer is associated with low 3-5% risk of rebleed. A flat red or purple spot in the ulcer base having 10% risk and large adherent clot covering ulcer base have 20% risk of rebleeding. Occasionaly active spruting from ulcer is seen with 90% risk of ongoing bleeding (Kurata JH et al, 1984, Jensen DM, 1999, Cook, DJ, et al 1992). Patient with visible vessel or active bleeding are usually treated endoscopically, thereby decreasing rebleeding rate to about half.

Many endoscopic methods for treatment have been developed and evaluated. Injection, 10 Fr heat probe, 10 Fr multipolar electrocoagulation (MPEC), and laser have been shown in randomized controlled studies to be effective at stopping active bleeding and preventing rebleeding in patients with stigmata of recent hemorrhage, significantly reducing transfusion, hospital stay, cost of care, and urgent surgery. Although no single study has been or will be likely to have the power needed to demonstrate significant reduction in mortality, meta- analysis has shown mortality reduction in the range of 45% (Sacks, HS et al, 1990). The results of endoscopic hemostasis appear comparable regardless of the method used for patients with non-bleeding stigmata of recent hemorrhage and oozing ulcers, but combination therapy using epinephrine injection and thermocoagulation is significantly more effective compared to injection alone for spurting ulcer bleeding (hemostasis of 93% vs. 70%) (Lau, JY et al, 1997). On the basis of these data, a large-channel therapeutic endoscope should be used in every patient with upper gastrointestinal bleeding, since it cannot be determined in advance which patient will have spurting hemorrhage and require combination therapy using a 10Fr thermal probe. Finally, clipping appears to be as effective if not better than thermocoagulation (rebleeding rate of 2% vs. 21%) for ulcer bleeding, and can be deployed using a diagnostic endoscope (Laine, L et al, 1994).

However ,endoscopy therapy is associated with its own limitations like it is invasive, cumbersome, requires expertise, and is not available uniformly and complications like perforation (0.5%) and induction of uncontrolled bleeding (0.3%) after initial endoscopic hemostasis bleeding still occurs in upto 20% of patients, and surgery is still necessary in some of these patients. Therefore much of the recent work has emphasized that limitation of gastric acidity, whether by full neutralization with antacid (7) or use of H_2- receptor blockers may bear importantly upon

the cessation of acute mucosal bleeding. Studies have demonstrated and advocated role of intravenous proton pump inhibitors during active UGI bleed and oral proton pump inhibitors after the acute episode to reduce rebleed.(Leontiadis GI et al, 2004, Schaffahtzky et al, 1997, Zed PJ et al, 2001)

As there has been no head to head trial with ORAL vs. IV Esomeprazole in bleeding peptic ulcer with stigmata of recent Haemorrhage (SRH+) so we intended to took the study.

Aims And Objectives:-
"Outcome of Oral vs. Intravenous Esomeprazole in Bleeding Peptic Ulcer (SRH+) after Endoscopic Treatment, a prospective randomized study" in terms.
   1. Rate of Re-Bleeding.
   2. Effect on increase in pH

Materials And Methods:-
The prospective, randomized, double blind study was conducted in the department of Gastroenterology, Sher-i-Kashmir Institute of Medical Sciences. All patients admitted to the hospital with a history of hematemesis and/or malena, or who bleed while in hospital were taken Emergency endoscopy as soon as possible, always within 12 hrs. of bleeding or immediately after resuscitation of patients with massive bleeding or shock..Endoscopy therapy were given and if endoscopy showed peptic ulcer in the stomach or duodenum with active bleeding (spurting hemorrhage, oozing hemorrhage) or stigmata of recent hemorrhage (a non-bleeding visible vessel). Assessment of the presence of those stigmata was made after adherent clots and debris of the ulcer base had been vigorously washed away. Patients who achieved hemostasis with endoscopic therapy were eligible for entry into the study.

Exclusion Criteria
1. Patients who were under 18 years of age.
2. Those who were unable or unwilling to give written informed consent.
3. Pregnant or lactating women.
4. Those who were on anticoagulants.
5. Those who had more than one possible source of bleeding
6. Those who had severe coagulopathy (prothrombin time 30% or less than normal) or platelet count less than 50,000/mm.
7. Those who had previous acid reducing surgeries (vagotomy, gastric resection)
8. Those who were moribund because of terminal cancer or severe comorbid illness: or had bleeding gastric cancer.
9. Those who required treatment with NSAIDS including aspirin or clopidrogel, during IST seven days of study.
10. Those who received more than 40 gm. of PPIs within 24 hours before enrollment.
11. Those who received drugs known to interact with PPIs (phenytoin, clarithromycin, itraconazole, warfarin and other vitamin k antagonists' cisapride, atazanavir or ritonavir).

Method Of Endoscopic Treatment And Intragastric Ph Monitering
Endoscopic hemostasis was achieved by using injection adrenaline (1:10,000 dilution in NS.), heat probe thermocoagulation (Olympus heat probe – 25J) are combination of both (adrenaline + heat probe) and by using endoscopic clips.
INTRAGASTRIC pH MONITORING of eligible patients for 72 hrs. after successful endoscopic hemostasis was done by using proxima light pH monitor. Which is a portable self programmed data logger for regarding of biological varibles, completely based on microprocessing technology.Proxima light enables gathering of data relevant to gastric pH by means of frequency and duration.
After informed consent instrument was placed in stomach via nasal cavity and positioned under fluoroscope in the gastric corps 5cm distal to cardia. pH electrode was calibrated before and after each recording using standard buffer solution pH4&pH7.

Randomization And Pharmacological Treatment
Immediately after Endoscopic control of bleeding, patients 18 years or older presenting to hospital emergency departments, or already hospitalized for another reason, with overt signs of upper gastrointestinal bleeding (hematemesis, malena, or both) in the past 24 hours were eligible for randomization. We recruited patients with

bleeding ulcers that showed 1 of the following endoscopic stigmata of recent hemorrhage: arterial bleeding (Forrest class Ia), oozing (Forrest class Ib), nonbleeding visible vessel (Forrest class IIa), or adherent clot (Forrest class IIb). In the case of Forrest class IIb ulcers, after attempts to remove the clot by using water irrigation or a cold snare, ulcers were either reclassified for inclusion as Forrest class Ia, Ib, or IIa or, if unsuccessful, included as Forrest class IIb Eligible patients were randomly assigned to receive Esomeprazole given as Intravenous bolus of 80 gm. followed by a continuous infusion of 8 mg. per hour for 72 hour oral Esomeprazole in the dosage of 80 mg **bid** for a period of 3 days by a Pharmacist in a double blind manner.

Randomizations were carried out in the endoscopy laboratory itself by random numbers derived from a table of random numbers in block of four by using CENTRAL COMPUTER GENERATED BLOCK RANDOMISATION.

Clinical Monitoring
Patients were observed for rebleeding in a high care facility of the Gastroenterology ward. All patients were given standard medical treatment (PPI's) for peptic ulcer bleeding. Patient's vital signs were checked every hour during the first 12 hours every 2 hours for the second 12 hrs and 4 hours thereafter until patients were discharged. The Hemoglobin (Hb) level and Hematocrit were checked at least once daily, and blood transfusions were given if Hb level fell to 9gm/dl or less, or vital signs deteriorated. Adverse effects were monitored throughout the study in both groups and after 3 days the patients were given esomeprazole 40gm orally once daily for 6 weeks and those +ve for H. pylori were also treated with Triple therapy. Patients were clinically examined on weeks 1, 2, 4 & 6 and repeat endoscopy were done at 6 weeks.the primary end point was the rate of rebleeding.the secondary end points were 1.Surgery, 2. Death , 3. Duration of hospital stay, 4. Number of blood transfusions and 5. Number of rescue therapies required.

Stastical Analysis
The statistical Analysis of the Nominal data was done by using Test Statistics, Chi- Square test (X2) and Fischers exact test (cell frequency <5%). The Quantative data was analyzed by using t-test for differences of Mean. These tests were two sided and were referenced for p-values for there significance. Any value less than 0.05 (p<0.05) was taken to be significant otherwise non-significant. The TYPE I, error among groups and was 0.05. The analysis of the data was done by using stastical package for social sciences (SPSS version 14.0) Chicago-USA for windows.

Observation And Results:-
During the study, 280 patients presenting to emergency department with active bleeding in the form of malena, hematemesis or both were subjected to emergency endoscopy. Endoscopic treatment was unsuccessful in 13 patients due to torrential bleeding that obscured the bleeding area and prevented adequate endoscopic treatment. These patients were treated by emergency surgery and were excluded from the study. 30 patients with no evidence of recent hemorrhage, 9 with malignancy ,3 with severe coagulopathy, 2 with severe comorbid illness and 4 patients who were < 18 years of age were excluded from the study. The remaining 220 patients underwent randomization. 109 received oral Esomeprazole(Group 1) & 111 received IV Esomeprazole (Group2).The dropout rate was 10% (20 patients ;9 patients among oral Esomeprazole group & 11 among IV Esomeprazole group). Eventually 200 patients were enrolled into the study- 101 received oral Esomeprazole and 99 received IV Esomeprazole. Table 1. *The age of the patients in the study group ranged from minimum 19 years to maximum 81 years. The mean age (yrs.) of patients in group 1(oral) was 42.80 +15.10 and in group 2 was (IV) 44.50+16.10. The difference in age in two groups was statistically insignificant.*

The baseline characteristic of patients including age, sex, previous peptic ulcer disease, concurrent illness, the severity of bleeding at presentation, sight and size of ulcer, use of NSAIDS and endoscopic findings were comparable in the two groups with no significant statistical relation.2,3,4&5.

Among the studied patients, rebleeding occurred in 25 patients (12.5%) ; of which 14 patients (13.86%) belonged to Group 1 and 11 patients (11.11%) to Group 2. The results when compared among the two groups were statistically insignificant with odds ratio – 1.03and CI (0.64-1.35).Table 6

Emergency surgical intervention was required in 7 (6%) patients in oral esomeprazole group as compared to 5patients (5%) on IV esmoprazole group with statistically no significanct difference (p=0.57) Table 6.

The mean patients in shock were 13 (13%) in oral esomeprazole group and 15(15%) in IV esomeprazole group p=0.64 .The mean patients who received blood transfusion were 9(8.9%) in oral esomeprazole group and 11 (11.11%) in IV esomeprazole group (p=0.64) Table 7.The total duration of hospital stay in oral group was Mean (3.60 + 1.72) vs. Mean (3.47+1.30) in the IV group. The duration of hospital stay difference in two groups was statistically insignificant (p=0.54). Table 7

Seven patients died, 3 among the IVgroup (3.3%) and 4 (3.99%) from oral group (p=0.72) Table 8.

Intragastric Ph Study Group
Intragastric pH Study was done in 20 patients taken from above 200 patients and after randomization 10 patients received oral esomeprazole and 10patients in IV esomeprazole. The mean pH of 10 patients in oral esomeprazole group was 7.06+0.44 and mean pH of 10 patients in IV esomeprazole was 6.78+0.27. There was statistically no difference in intragastric pH for 72 hrs. with esomeprazole given either orally or IV (p=0.1). The pH remained above 6. We therefore concluded that all the side effects were minor irrespective of route of administration of esmoprazole and their frequencies were similar. None of these patients required termination of drug infusion.

There was statically no significant difference among primary and secondary end points in the two groups.

Discussion:-
Bleeding peptic ulcer is a common and life threatening condition. Although endoscopy therapy has become the mainstay of controlling bleeding, recurrent bleeding after endoscopic control occurs in about 20% of patients with a high associated mortality . Acid suppression has been advoc ated in many studies as a mainstay in the prevention of rebleed.This is based on the hypothesis that pepsin activity is pH dependent. In the treatment of peptic ulcer bleeding (PUB), acid inhibition is based on the hypothesis that clot formation and clot lysis depend on intraluminal pH. Medications used in the prophylaxis of stress ulcer bleeding comprise antacids, H_2RA and PPIs. Two trials showed that patients who receive omeprazole run a significantly lower risk of bleeding than patients receiving ranitidine(Labenz J et al, 1997, Barnert J et al, 1994, Kiilerich S et al, 1995). The optimal initial treatment for bleeding peptic ulcers with active bleeding or non bleeding visible vessel is endoscopic therapy. Among patients with non bleeding visible vessels or adherent clots who do not undergo endoscopic therapy, acid inhibition with PPIs may significantly reduce rebleeding rate and need for surgery. After endoscopic therapy, acid inhibition with PPI may have a beneficial effect on hemostasis (Balanzo J et al, 1988). This hypothesis was also confirmed in our study which demonstrated that the adjuvant use of high dose esomeprazole in patients with bleeding peptic ulcer with SRH reduces the risk of recurrent bleeding (13.86% in Oral group vs. 11.11% in IV group) and thereby improves patient's outcome. Church N I, Palmer K R showed that acid suppression is effective in preventing bleeding from peptic ulcer. Standard dose of i/v Omeprazole may be as effective as high dose regimens. Oral Omeprazole also reduces rebleeding following endoscopic therapy for peptic ulcer.(Church N and Palmer KR, 2003) Another study by A Andriulli et al showed that monotherapy with oral or bolus PPI was superior to placebo and H2RAs in reducing rebleeding in both bleeders and non bleeders at index endoscopy; the need for surgery was reduced only when compared to H2RAs. In non bleeders, PPI monotherapy was as effective as a combination of endotherapy with H2RAs. A combination of endotherapy with PPI was superior to monotherapy in reducing bleeding and surgery, and superior to endotherapy alone in minimizing rebleeding, but not surgery; the benefit was lost when confronted to endotherapy plus H2RAs, whether PPIs were given as infusion or bolus (Andriulli A and Annese V, 2005).

PPI are drugs of choice for patients with PUB because these drugs are more effective than H2RAs or maintaining the target intragastric pH (6 or higher) and preventing the recurrence of PUB. High dose PPI therapy should be used for patients at high risk of rebleeding. Oral PPI therapy may be used for low risk patients (Zuckerman G et al, 1984). Khoshbaten et al did a trial comparing oral Omeprazole with i/v cimetidine. The study demonstrated that oral Omeprazole significantly excels i/v cimetidine in reducing need for blood transfusion and lowering rebleeding rate in patients with upper GI bleeding. Though not statistically significant (p=0.074),shorter periods of hospitalization were found for) Omeprazole group. Need for blood transfusion was much lower in Omeprazole group than in cimetidine group (mean 1.68 vs. 3.58 units; respectively (p<0.003). Moreover rebleeding rate was significantly lower in Omeprazole group (15%) than in cimetidine group (50%) (p<0.001) (Khoshbaten M et al, 2006)

In our study,we compared a newer PPI, esomeprazole which is an S-isomer of Omeprazole and has been found to be very effective compared to other PPI's in a number of randomized trials. We found that esomeprazole when

given orally achieves a similar gastric pH control as when given IV. (pH=7.06 + 0.14 in oral group vs. 6.78 +0.27 in IV group; (p=0.10). The study also showed that there was statistically no significant difference in the rate of rebleeding (patients who received esomeprazole Orally vs. IV), hospital stay (3.60 + 1.72 days in oral group vs. 3.47 + 1.30 in IV group; p=0.54 and transfusion requirement (p=0.64).Thus our study concludes that high dose oral regimen can be used in place of high dose IV formulation.

A number of randomized trials have evaluated the role of high dose PPI's (Omeprazole & Pantaprazole) administered orally and IV in patients with bleeding peptic ulcer and the result of our study are consistent with these studies.(11,12) Our study, infact is the first of its kind in which esomeprazole was compared via oral and IV routes in patients with bleeding peptic ulcer.

Table 1:- Distribution of Cases in oral Vs IV Esomeprazole Group.

STUDY	NO. OF CASES
Patients on Oral Esmoprazole (1)	101.
Patients on Intravenous IV Esmoprazole(2)	99
Total	200

Table 2:- Distribution of age (yrs.) in Group 1 and Group 2.

Age (yrs.)	Mean + S.D.	T value	P value
Group 1	42.00 + 15.10	1.11	0.27
Group 2	44.50 + 16.10		

Table 3: Distribution of sex in group I and group II.

SEX	MALE.	FEMALE	χ^2	P VALUE
I	66	35		
II	68	31	0.362	0.547

Table 4: Distribution of Clinical presentation in group I and group II.

Clinical presentation	I (Oral)	II (iv)	χ^2	P- value
Hematemesis	19	21		
Malena	52	45	1.048	0.592
Both	30	33		

Table 5:- Distribution of endoscopic findings in group I and group II

ENDOSCOPIC FINDINGS	I (ORAL)	II (IV)	X2	P-VALUE	

1. Site of ulcer
   a. Previous ulcer.
   b. Gastric ulcer.
	72
	
	29
		75
		
		24
			0.513	0.494	

2. High risk sites
   a. Posterior duodenal wall
   b. High lesser curvature.
   c. Incisura.
	14
	
	8
	3
		17
		
		5
		7
			2.299	0.317	

3. Stigmata of Hemorrhage (Forrest class)
   a. Ia.
   b. Ib.
   c. IIa.
	22
	41
	38
		20
		44
		35
			0.304	0.859	

4. Ulcer size Mean	1.10+0.37	1.14+0.35	T=0.68	0.49	

Table 6:- Distribution of Results of Treatment in group I and group II.

RISK FACTOR	I (ORAL GROUP)	II (IV GROUP)	P-Value
Rebleeding At 3 days. At 7 days. Mean=6.45 S.D.= 2.75 Odds Ratio = 1.03 CI. = (0.64-1.35)	14 (13.86%) 09 05	11 (11.11%) 07 04	0.973
Number of patients requiring urgent surgical intervention	07 (6%).	05 (5%).	0.576

Table 7:- Distribution of Blood Transfusion and Hospital Stay in group I and group II.

	I (ORAL)	II (IV)	P-Value	T-Value
Shock at presentation	13	15	0.642	0.922
Number of patients requiring Blood Transfusion	09	11	0.64	0.90
Duration of Hospital Stay. Mean	3.60+1.72	3.47+1.30	0.59	0.54

Table 8:- Distribution of overall Mortality in group I and group II.

I (Oral) (n=101)	II (IV) (n=99)	P value
04 (3.9%)	03 (3.0%)	0.720

Table 9:- Comparison of effect on intragastric pH of Patients on Esomeprazole in group I and group II.

pH	I (ORAL)	II (IV)	t-Value	P-Value
Mean	7.06	6.78	1.71	0.1
Median	7.10	6.90		
S.D	0.44	0.27		
S.E	0.14	0.84		

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