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Research Article

Association of Upper GI Bleed in Patients with Budesonide and SSRI Therapy in Chrons Disease: A Comparative Clinical Study

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Abstract
Aim: *To compare the association of Upper g.i bleed in patients with chron's disease on Budesonide and SSRI therapy.*
Methods: *Total 30 patients of chrons disease were included for the study. Patients of both sexes with age group between 18-40 yrs were included. Patients were divided into two groups. Group I received Budesonide 9mg OD. Group II received SSRI in the dose of 40 mg/day. All patients were cases of chron's disease. Budesonide 9mg OD were given to patients for remission of chron's disease and SSRIs are given to patients of chron's disease associated with depression. Both the drugs were given on daily basis for 6 months.*
Result: *All 30 patients included in the study were assessed for the presence of upper g.i bleed by G.I endoscopic and non-endoscopic parameters. The no of patients showing presence of upper g.i bleed is more in Group A in comparision to Group B.*
Conclusion: *Acute upper gastrointenstinal haemorrhage is a common medical emergency and mortality rate remains high as 6-8%.From this study it is concluded that patients of chron's disease taking budesonide have high incidence of upper g.i bleed in comparision to patients with SSRIs.*
Keyword: *Upper G.I bleed, Chrons disease, SSRIs, Budesonide.*

Introduction

Acute upper gastrointenstinal haemorrhage (bleeding proximal to the duodenojejunal flexure) is a common medical emergency (170 per 100 000 adults annually). Although its incidence may be declining, the mortality rate of upper gastrointenstinal haemorrhage remains high, approximately 6-8 %.(1) Depending on the site and rate of bleeding a patient may present with melaena (black, tarry stool), haematemesis (vomiting "coffee-ground "or fresh blood), haematochezia (red blood per rectum). The bleeding from GIT can present in different ways. Haematemesis is defined as vomiting of blood, Which is indicative of bleeding from the oesophagus, stomach or duodenum.

Haematemesis includes vomiting of bright red blood, which suggests recent and ongoing bleeding, and dark material (coffee ground emesis), which suggests bleeding that stopped some time ago. Maelena is defined as black tarry stool and results from degradation of blood to

haematin or other hemochromes by intenstinal intenstinal bacteria. Melaena signifies bleeding that originates from UGI tract, small bowel or proximal colonic source. Maelena generally occurs when 50-100ml or more blood is delivered into GI tract (usually the upper tract), with passage of characteristic stool occurring several hours after the bleeding event.[2,3] Upper gastrointenstinal bleeding has an annual incidence of 48 to 160 cases per 100,000 adults,[4,5,6] with a mortality rate of 10%-14%.[7] SSRIs (Selective serotonin reuptake inhibitors) seem to be associated with an increased risk of upper gastrointenstinal bleeding (UGIB).[8,9,10,11]

Serotonin (5-HT) is produced by enterochromaffin cells in the gastrointenstinal tract, released into the plasma and quickly taken up by platelets via the plasma membrane serotonin transporter (SERT). Following uptake, 5-HT is stored in dense granules by the actions of the vesicular monoamine transporter (SERT). Following uptake,5-HT is stored in dense granules by the actions of the vesicular monoamine transporter 2.[12,13,14,15] Chronic inhibition of SERT through selective serotonin reuptake inhibitors (SSRIs) leads to dramatically reduced platelet 5-HT granule content.[16,17], altering peripheral 5-HT homeostasis and potentially modifying multiple physiological processes including hemostasis.[18,19] In conjuction with depleting platelet granule 5-HT levels, one would expect that chronic SERT inhibition would increase plasma concentrations of 5-HT as suggested by the effects of SSRIs in the CNS.[20,21] However because 5-HT2AR stimulation by 5-HT alone does not lead platelet activation, loss of SERT function likely leads to local increase in plasma 5-HT levels within the portal vein and indirectly triggers internalization of the 5-HT2AR.It has been demonstrated that 5-HT induces internalization of 5-HT2AR in a β-arrestin-dependent manner within 30 min of initial exposure.[22,23] It has been previously established that 5-HT plays a synergistic role with ADP activation during platelet aggregation.[24,25,26,27] In relation to binding affinity, SSRIs can be divided into three groups: SSRIs can be divided into three groups: a. SSRIs with high affinity (fluoxetine, sertraline, paroxetine) b. SSRIs with intermediate affinity (venlafaxine, fluvoxamine) c. SSRIs with low affinity (mirtazapine,bupropion). Drugs with the highest degree of serotonin reuptake inhibition (fluoxetine, paroxetine and sertaline) are commonly associated with abnormal bleeding and modification of haemostatic marker. The most common abnormalities are reduction in platelet aggregability and activity, and prolongation of bleeding time. Patients with a history of coagulation disorders need monitoring in the case of prescribing any SSRIs.[28] Inflammatory bowel diseases (IBDs), including ulcerative colitis (UC) and Chron's disease (CD), are multifactorial disorders comprised of both environmental and genetic factors. Even though they are different disease entities, UC and CD are grouped under the generic term of IBDs given their similar activity/ remission stages, chronicity, immunological pathophysiology and uncertain etiology.[29,30,31] Various genetic and environmental factors have been associated with development of IBDs. Polymorphisms in a vast number of genes which impair function such as lymphocyte activation, autophagy, pathogen sensing, stress response, antigen presentation and chemotaxis among others have been described.[32] Environmental factors such as diet, smoking, vitamine D deficiency and infection play key roles in inflammatory manifestations and have been described as risk factors for IBDs.[33,34] Diagnosis of Chron's disease should be considered in any patient who presents with chronic or nocturnal diarrhea, abdominal pain, bowel obstruction, weight loss, fever or night sweats.[35] Current treatment options to diminish inflammation in order to control symptoms and keep the patient in a state of remission or symptom improvement. Glucocorticoids (GCs) are used to achieve but not to maintain, remission in patients with moderate to severe activity.[36] Remission was assessed using the CDAI, which is recommended by the

Japanese CD treatment guidelines for the objective evaluation of disease activity and severity.[37] Glucocorticoids suppress the protective functions of prostaglandins via inhibition of phospholipase A2 in the arachidonic acid pathway by a similar mechanism to that of nonsteroidal anti-inflammatory drugs (NSAIDs). Glucocorticoid induced ulcers are typically gastric, Multiple, have little scar tissue and present without induration at the ulcer site. They are usually asymptomatic and might not be discovered until major complications such as hemorrhage or perforation occur. The budesonide 9mg dose was selected based on results from the dose-finding study.[38] Budesonide is a potent corticosteroid with poor systemic absorption because of a 90 percent first-pass metabolism, apparently resulting in fewer side effects and less adrenal suppression than prednisone[39,40]. Budesonide is superior to mesalamine and placebo in patients with active Chron's disease The prevalence of depression and anxiety is higher in patients with chronic diseases compared to the general population.[41] and having a long term medical illness is a risk factor for depression.[42] There is evidence that inflammatory bowel disease (IBD),which includes Chron's disease (CD) and ulcerative colitis (UC), is associated with higher rates of anxiety and depression compared to general population[43] and that depression is associated with decreased quality of life in IBD patients.[44]

Basing on the above concept the present study has been designed to compare the incidence of upper g.i bleed in patients of IBD treated with corticosteroid and SSRIs. The upper g.i bleed was diagnosed by upper g.i endoscopy. For an acute upper GI bleeding, risk scores such as the Rockall Score and Glasgow Blatchford Score (GBS) have been developed and validated.[45,46]

Materials and Methods

30 patients with chron's disease were included in the study. The patients were divided into two groups.

Group A includes 15 patients of chron's disease &were treated with Budesonide 9mg OD. Group B includes 15 patients of chrons disease with depression & were treated with SSRI 40 mg OD. All the patients were observed for 6 months. Budesonide and SSRI were given to both group of patients in the dose of 9mg and 40mg OD respectively for 6 months. Study was conducted in the Dept of Gastroenterology Apollo Hospital Bhubaneswar. All the patients were initially examined clinically, evaluated and were included for the study. All the patients were evaluated on 0,3 & 6 months.

Exclusion Criteria: Presence of an ileostomy pouch or colostomy, presence of total gastrectomy, active CD of rectum or anus, systemic infection, history of gastrointenstinal malignancy and uncontrolled diabetes mellitus.

Study Design

This is a prospective study conducted for 6 months. Patients were diagnosed as chron's disease according to clinical presentation and colonoscopy findings. Again the onset of upper g.i bleed in patients of chron's disease were diagnosed by upper GI endoscopy. Severity of upper g.i bleed was assessed with Rockall Score. All the patients were assessed for upper g.i bleed at 0, 3 & 6 months.

Statistical Analysis: Statistical Analysis were done by using unpaired t-test with degree of freedom 28.P value less than 0.001 is highly significant.

Result

Total 30 patients were included in the stdy.15 patients were in each group. All the patients were assessed for the presence of upper G.I bleed by G.I endoscopic and Non-endoscopic parameters. Group A received Budesonide 9 mg OD for 6 months and Group B received SSRIs 40 mg OD for 6 months.

Table-1 Comparison of Upper G.I endoscopic finding in Group A & Group B

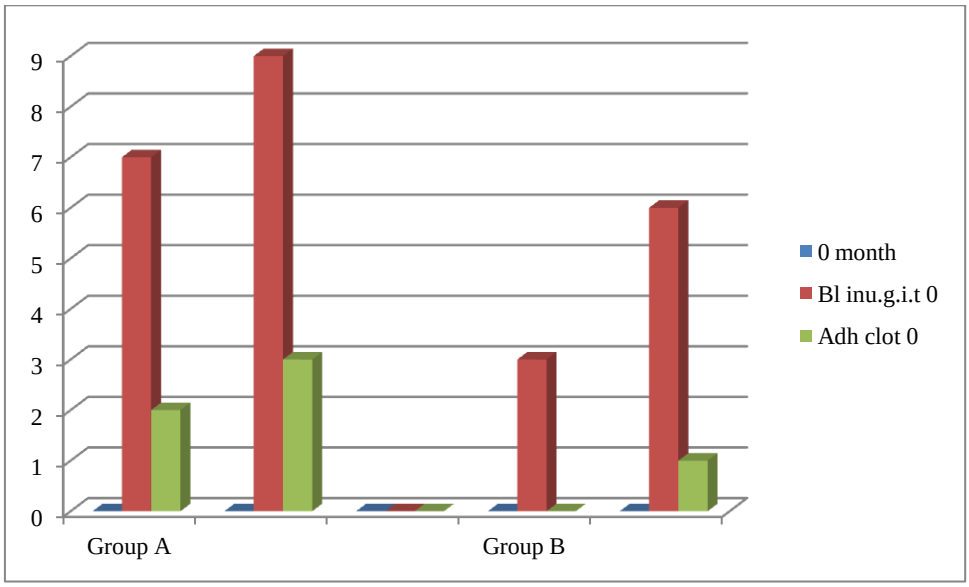
Group-A: n=15 Group-B: n=15

	Group-A (no of pts)			Group-B (no of pts)		
	0 month	3 month	6 month	0 month	3 month	6 month
Blood in upp .g.i tract	0	7	9	0	3	6
Adherent clot	0	2	3	0	0	1

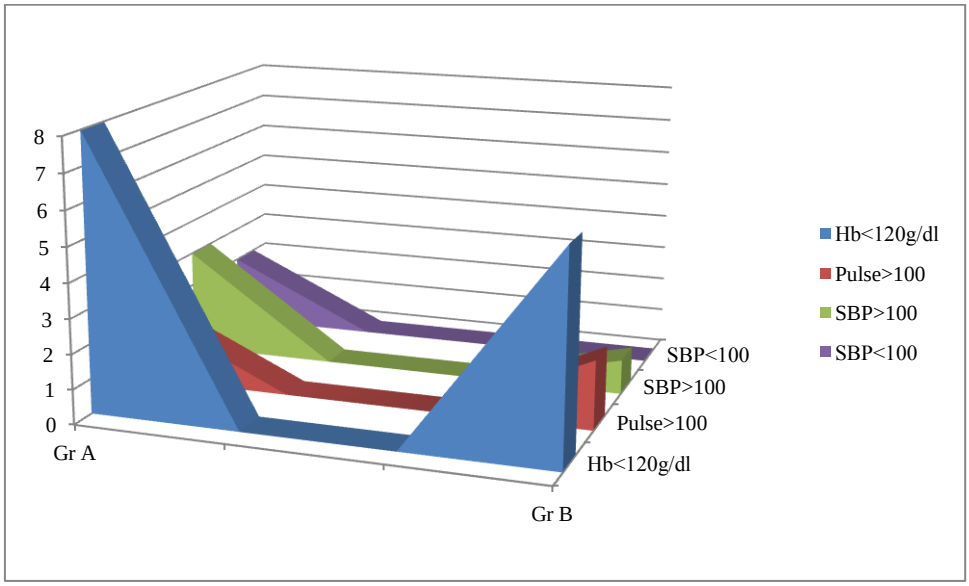
Table-2 Comparison of Non-endoscopic parameters between Group-A & Group-B

Group-A: n=15 Group-B: n=15

	Group-A (no of pts)	Group-B (no of pts)
Hb<120 g/dl	8	6
Pulse >100	2	2
Systolic B.P>100	3	1
Systolic B.P<100	2	0



Graph-1 Shows comparision of endoscopic finding between Gr A & Gr B



Graph-2 Shows comparision of non-endoscopic parameters of upper g.i. bleed between Gr-A & Gr-B

It is observed from Table-1 that patients showing evidence of upper g.i bleed is more in group A in comparision to group B. The no of patients showing presence of blood in upper g.i.t & adherent clot in Group A is more in comarision to Group B. Graph 1 represents the graphical representation of table 1.The presence of upper g.i. bleed is assessed by using non endoscopic parameters like Hb, Pulse rate, Systolic blood pressure. The finding of non endoscopic parameters also showed that the incidence of upper g.i bleed is more in patients of Group A in comparision to Group B. (Table 2). Graph 2 is the graphical representation of Table 2 showing the same result as Table 2.

Discussion

Upper gastrointenstinal bleeding (UGIB) is important and potentially serious worldwide problem[47] Despite development in diagnosis and treatment, mortality and morbidity have continued more or less constant. Bleeding from the upper gastrointenstinal tract (GIT) is about 4 times as common as bleeding from the lower GIT[47,48] In patients with acute upper GI bleeding, upper g.i endoscopy is considered the investigation of choice.[49] The first study that demonstrated the usefulness of Glucocorticoids in controlling severe UC attacks was published in 1955.[50] Sincethe 70s, the first generation of GCs (prednisolone, methylprednisolone, hydrocortisone) has been used to induce clinical remission in IBDs patients. However, significant adverse effects have led to the development of second generation GCs (budesonide, Beclomethasone dipropionate.[51,52,53] Selective serotonin reuptake inhibitors (SSRIs) are widely prescribed to treat depression and again depression requires months or even years of continuous pharmacotherapy.

Conclusion

In patients of IBD Budesonide is given for remission. Again the patients of IBD often associated with depression for which SSRIs are given. Both glucocorticoid (Budesonide) & SSRIs can cause upper g.i bleed. From this study it is concluded that the incidence of upper G.I bleed is more in patients with Budesonide therapy in comparision to patients on SSRIs.

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