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ORIGINAL ARTICLES

A COMPARATIVE STUDY OF OMEPERAZOLE WITH FAMOTIDINE FOR ULCER HEALING ASSOCIATED WITH NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

H MASUD, SK SAHA, MA KABIR, PK ROY, M HASAN

Abstract

Nonsteroidal antiflammatory drugs (NSAIDS) are commonly used to treat pain & inflammation. NSAIDS are generally well tolerated, adverse gastrointestinal events occur in a small but important percentage of patient, resulting in substantial morbidity and mortality. This prospective study was conducted in the department of Gastroenterology in collabaration with Rhematology clinic of BSMMU to compare the efficacy of omeprazole with famotidine for ulcer healing associated with nonsteroidal anti inflammtory drugs. Sixty patients who are taking regular NSAIDS with different rheumatological disorders were included in the study. The age range of the patient were 25 to 70 years of the mean age of the patients were 42.08 with SD±8.804.

In the omeprazole group, out of 30 patients, 5 patients had gastric ulcer, 11 patients had duodenal ulcer and 14 patients had erosions. After completion of omeprazole therapy (20 mg twice daily for 6 weeks), two patients healed out of 5 patients in gastric ulcer, 7 patients headed out of 11 patients in duodenal ulcer and 11 patients healed out of 14 patients in erosions respectively.

In the famotidine group, out of 30 patients, 6 patients had gastric ulcer, 8 patients had duodenal ulcer and 16 patients had erosion. After completion of therapy with famotidine (20 mg twice daily for 6 weeks), 1 patient healed out of six patients in gastric ulcer, 3 patients headed out of 8 patients in duodenal ulcer and 8 patients healed out of 16 patients in erosions respectively. After completion of therapy endoscopic healing of the individual lesions like gastric ulcer, duodenal ulcer & erosions were statistically significant in subjects receiving omeprazole with that of receiving famotitide (x_2= 4.315, P < 0.05).

In conclusion in patients taking NSAIDS, it has been found in this study that tratment with omeprazole 20 mg twice daily is superior to famotidine 20 mg twice daily in respect to healing of gastro duodenal ulcers and erosions.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat pain and inflammation[1]. Acetyl salicylic acid (Aspirin) is the first non-steroidal anti-inflammatory drug (NSAJD)[2,3]. NSAIDs constitute one of the most widely used classes of drugs, with more than 70 million prescriptions and more than 30 billion over the counter tablets sold annually on the United States[4]. Although NSAIDs are generally well tolerated, adverse gastrointestinal events occur in a small but important percentage of patients resulting in substantial morbidity and mortality.

Unfortunately, other anti-inflammatory agents substituted for aspirin because of continuing use in joint symptoms may also cause gastric mucosal damage. Starting on the early 1970s, numerous new NSAIDs were developed that were initially believed to be devoid of gastrointestinal toxicity, but few of them are not entirely harmless. Their use is frequently limited by gastrointestinal side effects, ranging from dyspeptic symptoms to life threatening bleeding or perforation of gastroduodenal ulcers, especially in the elderly[5,6]. A high prevalence of peptic ulcer disease has been well established in rheumatic disease patients on chronic aspirin therapy[7-10]. A prospective endoscopic study performed on patients attending a rheumatology clinic revealed a prevalence rate of 20% for gastric ulcer and 5% for duodenal ulcer in patients consuming greater than 3 g aspirin daily[11,12]. If peptic ulcer disease develops in this setting, it is generally recommended that salicylates should be stopped[13]. If salicylates are not stopped, these ulcers are considered very difficult to heal. In at least two large series over 50% of patients with salicylate associated ulcers required gastrectomy for persistence of the ulceration or complications such as bleeding or perforation [14,15].

NSAIDs are thought to cause mucosal injury by several mechanisms[16]. Some have a direct toxic action on the gastric mucousa that is exacerbated by acidity, since acidity promotes the absorption of

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NSAIDs in their nonionized form[17]. They also impair prostaglandin dependent mucosal protective mechanisms. When the surface cells have been damaged by either of these mechanisms, a second wave of injury mediated by luminal acid often occurs and generates deeper ulcerative lesions[18]. Former approaches to prevention the side effects of NSAIDs included treatment with histamine H_2-receptor antagonists to inhibit acid secretion and the administration of prostaglandin analogues to replace the depleted endogenous prostaglandins. However, H_2-receptor antagonists are not very effective for healing or preventing NSAID associated gastric ulcers during continued therapy with NSAIDs, although they speed healing and help prevent duodenal ulcers[19,20]. The use of prostaglandin analogues such as misoprostol is limited by gastrointestinal side effects such as diarrhea and abdominal cramps[21].

Omeprazole inhibits the final step in the formation of hydrochloric acid by blocking the enzyme H+K+ ATPase[22]. It is a highly effective inhibitor of acid secretion and has been shown to promote rapid healing of peptic ulcer disease[23,24]. In short-term studies, the proton-pump inhibitor omeprazole prevented NSAID induced gastro-duodenal mucosal damage and lesions[20,25]. Omeprzole heals ulcers effectively and is equally efficacious for gastro-duodenal ulcers in the presence or absence of NSAID treatment.[21-24]

Famotidine (H_2 receptor antagonist) inhibit gastric acid secretion elicited by histamin and with H_2 agonist on a dose dependent competitive manner. H_2 receptor antagonist also inhibit acid secretion elicited by gastrin and to lesser extent by muscarinic agonist. It is important to note that H_2 receptor antagonist inhibit basal and nocturnal acid secretion and this effect contribute in a major way to their clinical efficacy.

There is no data of NSAIDs use in Bangladesh. With increasing awareness of joint and connective tissue disorder, with increasing diagnostic facilities and functioning of specialized clinic such as the rheumatology clinic of Bangabandhu Sheikh Mujib Medical University, the rational use of NSAIDs is growing. The prevalence of NSAIDs associated gastrtointestinal adverse effects have not been investigated in Bangladesh. But anecdotal evidence indicates that this is likely to be significant.

NSAIDs may be a major factor in the etiopathogencsis of duodenal ulcer disease. So that, it is rational to investigate the upper gastrointestinal adverse effect of long term use of NSAIDs. In Bangladesh the point prevalence of peptic ulcer disease is 15% (Duodenal ulcer disease 11.98%, gastric ulcer 3.58%[26]. This study will help to formulate strategies for prevention and management of the gastrointestinal adverse effect of NSAIDs.

Aims and Objectives

The aims and objectives of the present study are to evaluate the efficacy of proton pump inhibitor-omeprazole in comparison with famotidine for ulcers healing associated with non steroidal anti-inflammatory drugs.

Patients and Methods :

The present study was a prospective case controlled study.

The study was carried out at the Department of Gastroenterology with the collaboration of Rheumatology Clinic, Bangabandhu Sheikh Mujib Medical University, Dhaka. A total number of 60 patients were selected for the present study. Basis of inclusion and exclusion groups are as follows:

Inclusion criteria:

(i) Patient willing to provide informed written consent.

(ii) Over the age of 18 years.

(iii) Both sexes

(iv) Ingestion of NSAIDs, for at least 1 month prior to first endoscopy.

(v) Ulcers and erosions on the stomach and duodenum at endoscopy.

Exclusion criteria:

(i) Age <18 years and >80 years

(ii) Women who are pregnant/breast feeding or planning to become pregnant.

(iii) Presence of neck instability that compromises upper GI endoscopy.

(iv) Presence of erosive or ulceration oesophagities, pyloric stenosis or disorder that modify drug absorption.

Study procedure

Patient found eligible for the study will included after eliciting history of:

Presence of connective tissue disease, presence of arthritis with duration of symptoms, drugs with dose and duration of use, presence of GI side effects like abdominal pain, discomfort, nausea, vomiting, heart burn, acid eructation and history of haematemesis and melaena. History of previous use of acid

suppressor agents like antacid, H_2-blockers, proton pump inhibitor and degree of relief of symptoms and duration of remission, history of concomitant drugs like anxiolytic drugs, antispasmodic drugs.

After physical examination, the following laboratory examination- CBC with Hb%, ESR, Platelet count, serum bilirubin, SGPT, urea and creatinine were done. All patients were undergone upper GI endoscopy. Finding like ulcers and erosions in the stomach and duodenum were noted.

Administration of medication

The enrolled patients will be put on random basis on one of the the treatment regimens:

Group-A: Tab. Famotidine, 20 mg twice daily for 6 weeks

Group-B: Cab. Omeprazole, 20 mg twice daily for 6 weeks.

During this period if any side effects (adverse effects) or complication of peptic ulcer disease occur, the patients will be withdrawn from the study. After completion of the medication patients were re-endoscoped and findings (ulcers and erosions) were recorded.

Statistical analysis

All data are expressed in frequencies or mean ±SD as applicable and statistical analysis were done by SPSS methods. Comparison between nonparametrics variables were done by Chi-square test. P values <0.05 is considered significant.

Observations and Results

A total sixty patients were included in this study, the age range of the patients were 25 to 70 years and the mean age of the patients were 42.08 years. The study population were divided into two groups according to the therapy they had received.

Group-A: Omeprazole group comprises of 30 patients. The mode age of omeprazole group were 30 to 35 years and the mean age of the patients were 40.5 years and male to female ratio was 7:3.

Group-B: (Famotidine group) comprises of 30 patients. The mode age of famotidine groups were 30 to 35 years and the mean age of the patients were 43.66 years and the male to female ratio was 19.11

All the patients were included in the study having history of taking NSA IDs for at least one month prior to first endoscopy. The study populations were stratified according to their age and sex group (Table-I).

The study populations were classified according to the nature of connective tissue disorders. The results of the omeprazole group were better than the famotidine group in the form of percentage. The results of omeprazole group, 20 (66.67%) patients improved and in famotidine group, 12 (40%) patients improved (Table -II).

Endoscopy were done in every patients. Gastroduodenal lesions were included, gastric ulcer 11 (18.33%) patients. erosions 30 (50%) patients and duodenal ulcer 19 (33.66%) patients (Table-Ill).

Table-I

Comparison of age and sex between Omeprazole and Famotidine therapy

Age group	Given therapy Omeprazole			Given therapy Famotidine		
	Male (M)	Female (F)	Total	Male (M)	Female (F)	Total
25-30	2	0	2	1	0	1
30-35	6	3	9	4	3	7
35-40	3	2	5	3	1	4
40-45	3	3	6	3	3	6
45-50	3	0	3	3	1	4
50-55	3	0	3	2	2	4
55-60	0	1	1	1	0	1
60-65	0	0	0	1	1	2
65-70	1	0	1	1	0	1
Total	21	9	30	19	11	30

Table-II

Type of connective tissue disorder and condition of patient after therapy.

	Omeprazole				Famotidine			
	No. of Patient	Improve-ment	Not improve-ment	% of improved	No. of Patient	improve-ment	Not improve-ment	% of improved
Serone-gative arthritis	16	9	7	56.25%	12	5	7	41.67%
Anky-losing spondylitis	1	1	0	100%	1	0	1	0%
Polyar-thritis	2	1	1	50%	0	0	0	0%
Rheumatoid arthritis	3	3	0	100%	3	1	2	33.33%
Low bakc ache	3	2	1	66.67%	5	3	2	60%
Osteo-arthritis	0	0	0	0%	3	2	1	66.67%
Multiple joint pain	0	0	0	0%	1	1	0	100%
Cervical spondy-litis	5	4	1	80%	5	0	5	0%
Total	30	20	10	66.67%	30	12	18	40%

Comment

In different type of connective tissue disorder improvement are better in omeprazole group than famotidine group.

Table-III

Type of endoscopic lesion found before therapy

Type of lesion	No. of patient	0% of patient
Gastric ulcer	11	18.33
Duodenal ulcer	19	31.67
Erosions	30	50
Total	60	100

In Omeprazole group out of 30 patients, twenty one patients were male and nine patients were female. Out 21 patients 11 were smoker and 10 were non smoker. Nine patients were female and nonsmoker.

In Famotidine group out of 30 patients, 19 patients were male and 11 patients were female. Of the nineteen patients 4 were smoker and 15 were nonsmoker. 11 patients were female and nonsmoker.

In omeprazole group out of 30 patients, 5 patients had gastric ulcer, 11 patients had duodenal ulcer and 14 patients had erosion. After completion of therapy with omeprazole 20 mg twice daily for 6 weeks, two patients healed out of 5 patients in gastric ulcer and seven patients healed out of 11 patients in duodenal ulcer and 11 patients healed out of 14 patients in erosion respectively.

In famotidine group out of 30 patients 6 patients had gastric ulcer, 8 patients had duodenal ulcer and 16 patients had erosions. After completion of therapy with famotidine 20 mg twice daily for 6 weeks, 1 patient healed out of six patients in gastric ulcer, three patients healed out of 8 patients in duodenal ulcer and 8 patients healed out of 16 patients in erosion respectively.

Endoscopic improvement found in subjects receiving omeprazole were statistically significant when compared with that of famotidine receiving subjects (X^2-3.842 and $P<0.05$) (Chi-square test). It was also found that involvement in the individual lesions like gastric ulcer, duodenal ulcer and erosion were found statistically significant in the omperazole group compared with that of famotidine group (X^2-4.315 & p value <0.05) (Chi-square test with Brant and Snedecor formula).

Table-IV

Lesion condition of patient after therapy

	PPI				Famotidine			
	No. of Patient	Improve-ment	Not improve-ment	% of improved	No. of Patient	improve-ment	Not improve-ment	% of improved
Gastric ulcer	5	2	3	40%	6	1	5	16.67%
Duodenal ulcer	11	7	4	63.64%	8	3	5	37.5%
Erosion	14	11	3	78.57%	16	8	8	50%
Total	30	20	10	66.67%	30	12	18	40

Comment :

According to percentage the improvement effect of omeprazole therapy are better than famotidine on all the lesion

Table-V

Comparison between Omeprazole and Famotidine group

Therapy group	Endoscopic improvement	No improvement	Total	% of improvement
Omeprazole	20	10	30	66.67%
Famotidine	12	18	30	40%
Total	32	28	60	

Discussion

Nonsteroidal anti-inflammatory drus (NSAIDs) are commonly used to treat pain and inflammation[1]. Acetyl salicylic acid (Aspirin) is the first non-steroidal anti-inflammatory drug (NSAID)[2,3]. NSAIDs represent one of the most commonly used medications in the United States'. More than 30 billion over the counter tablets and 70 million prescriptions are sold yearly in the United States alone. Although NSAIDs are generally well tolerated, adverse gastrointestinal events occur in a small but important percentage of patients, resulting in substantial morbidity and mortality. The spectrum of NSAID induced morbidity ranges from nausea and dyspepsia (prevalence reported as high as 50 to 60%) to a serious gastrointestinal complication such as frank peptic ulceration complicated by bleeding or perforation in as many as 3% to 4% of users per year. About 20,000 patients die each year from serious gastrointestinal complications from NSAIDs.

Starting on the early 1970s, numerous new NSAIDs were developed that were initially believed to be devoid of gastrointestinal toxicity, but few of them are not entirely harmless. Their use is frequently limited by gastrointestinal side effects, ranging from dyspeptic symptoms of life threatening bleeding or perforation of gastroduodenal ulcers, especially in the elderly[5,6]. A high prevalence of peptic ulcer disease has been well established in rheumatic disease patients on chronic aspirin therapy[7-10]. A prospective endoscopic study performed on patients attending a rheumatology clinic revealed prevalence rate of 20% for gastric ulcer and 5% for duodenal ulcer in patients consuming greater than 3 g aspirin daily[11,12]. If peptic ulcer disease develops in this setting, it is generally recommended that salicylates should be stopped[13]. If salicylates are not stopped, these ulcers are considered very difficult to heal. In at least two large series, over 50% of patients with salicylate associaled ulcers required gastrectomy for persistence of the ulceration or complications such as bleeding or perforation[14,15].

NSAIDs are thought to cause mucosal injury by several mechanisms[16]. Some have a direct toxic action on the gastric mucosa that is exacerbated by acidity, since acidity promotes the absorption of NSAIDs in their nonionized form[17]. They also impair prostaglandin dependent mucosal protective mechanisms. When the surface cells have been damaged by either of these mechanisms, a second wave of injury mediated by luminal acid often occurs and generates deeper ulcerative lesions[18] Former approaches to preventing the side effects of NSAIDs included treatment with histamine H_2-receptor antagonists to inhibit acid secretion and the administration of prostaglandin analogues to replace the depleted endogenous prostaglandins. However, H_2-receptor antagonists are not very effective for healing or preventing NSAID- -associated gastric ulcers during continued therapy with NSAIDs, although they speed healing and help prevent duodenal ulcers[19,20]. The use of prostaglandin analogues such as misoprostol is limited by gastrointestinal side effects such as diarrhea and abdominal cramps[21].

Omeprazole inhibits the final step in the formation of hydrochloric acid by locking the enzyme H+K+ ATPase[22]. It is a highly effective inhibitor of acid secretion and has been shown to promote rapid healing of peptic ulcer diseasc[23,24]. In short-term studies, the proton-pump inhibitor omeprazole prevented NSAID induced gastro-duodenal mucosal damage and lesions[20,25]. Omeprzole heals ulcers effectively and is equally efficacious for gastro-duodenal ulcers in the presence or absence of NSAID treatment[21,24].

Famotidine (H_2 receptor antagonist) inhibit gastric acid secretion elicited by histamin and with H_2 agonist on a dose dependent competitive manner. H_2 receptor antagonist also inhibit acid secretion elicited by gastrin and to lesser extent by muscarinic agonist. It is important to note that H_2 receptor antagonist inhibit basal and nocturnal acid secretion and this effect contribute in a major way to their clinical efficacy.

Medical intervention for NSAID related mucosal injury includes treatment of an active ulcer and prevention of future injury, recommendations for the treatment and prevention of NSAID related mucosal injury.

Ideally the injurious agent should be stopped as the first step in the therapy of an active NSAID induced ulcer. If that is possible, then treatment with one of the acid inhibitory agents (H_2 blockers, PPIs) is indicated. Cessation of NSAIDs is not always possible because of the patient's severe underlying disease. Only PPIs can heal GUs or DUs, independent of whether NSAIDs are discontinued[27]. Prevention of NSAID induced ulceration can be accomplished by misoprostol. Oral PPI, high dose H_2 blockers have also shown some promise[27].

There is no data of NSAIDs use in Bangladesh. The prevalence of NSAIDs associated gastrtointestinal adverse effects have not been investigated in Bangladesh. But anecdotal evidence indicates that this is likely to he significant. In Bangladesh the point prevalence of peptic ulcer disease is 1 5% (Duodenal ulcer disease 11.98%, gastric ulcer 3.58%[27]. For this reason the study was carried out to see the comparative efficacy of proton pump inhibitor and famotidine in NSAIDs associated gastroduodenal lesions.

There are limited data on the efficacy of H_2 receptor antagonist in healing NSAID- associated ulcers. Current evidence suggest that conventional doses of H_2 receptor angatonists affectedly heal duodenal ulcers but are infective for gastric ulcers. In a multi centre study, the effects of renitidine on ulcer healing wire compared in a group of patients who had stopped NSAID therapy and another group who continued NSAID therapy. Gastric ulcers healed in 63% of those still taking NSAIDs compared with 95% of those who had stopped. At 12 weeks 79% of gastric ulcer and 92% of duodenal ulcers were heal in the group continuing NSAIDs whereas all ulcers healed in those who had stopped taking NSAIDs.[28] The ability of H_2 receptor antagonist given in conventional doses to him NSAID associated ulcer also depends on the size of the ulcers. One early study reported that when NSAIDs were continued, 90% of gastric ulcers smaller than 5mm healed after 8 weeks of cimetidine, whereas only 25% ulcers larger than 5mm healed.[29]

The effect of more potent acid suppression achieved by proton-pump inhibitors on the healing of NSAID-induced gastroduodenal ulcers has been assessed previously in a multicenter trial. Walan et al[30] compared the efficacy of omeprazole (20 mg/d or 40 mg/d) and ranitidine (150 mg twice daily) in the treatment of gastric ulcers in patients who continued taking NSAIDs. Gastric ulcer healing at 4 weeks was 81% in the group receiving 40 mg of omeprazole, 61% treated in the group receiving 20 mg of orneprazole, and 32% in the group receiving ranitidine. The corresponding healing rates after 8 weeks were 95%, 82% and 53% respectively. A more recent study by Yeornans et al[31] in a group of 541 patients showed the superiority of omeprazole to ranitidine in the treatment of NSAID-related gastroduodenal ulcers. In this group of' patients, ulcer healing rates at 8 weeks were 79% in those receiving 40 mg of omeprazole, 80% in those receiving 20 mg of omeprazole, and 63% in those receiving ranitidine. Agrawal et al[32] compared the efficacy of lansoprozole and ranitidine in the healing of gastric ulcers greater than 0.5 cm in diameter in patients continuing NSAID therapy. After 8 weeks, ulcers were healed in 57% of the patients receiving ranitidine, whereas healing rates were 73% and 75% in patients treated with lansoprazole, 15mg and 30 mg respectively. These observations suggest that proton-pump inhibitors heal gastroduodenal ulcers more effectively than H_2-receptor antagonists whether or not NSAIDs are continued.

A total sixty patients were included in the study, the age range of the patients were 25 to 70 years and the mean age of the patients were 42.08 years. The study population were divided into two groups according to the therapy they have received.

In the omeprazole group out of 30 patients, 5 patients had gastric ulcer, 11 patients were duodenal ulcer and 14 patients had gastric erosions. After completion of therapy with omeprazole 20 mg twice daily for 6 weeks, 2 patients healed out of 5 patients in gastric ulcer and seven patients healed out of 11 patients in duodenal ulcer group and 11 patients healed out of 14 patients in erosion group respectively.

In the famotidine group out of 30 patients 6 patients had gastric ulcer. 8 patients had duodenal ulcer and 16 patients had gastric erosion. After completion of therapy with famotidine 20 mg twice daily for 6 weeks, 1 patient healed out of six patients in gastric ulcer, three patients healed out of 8 patients in duodenal ulcer and 8 patients healed out of 16 patients in erosion group respectively.

Endoscopic improvement found in subjects receiving omeprazole were statistically significant when compared with that of famotidine receiving subjects, P value <0.05 by Chi-square test. It was also found that improvement in the individual lesions like gastric ulcer, duodenal ulcer and erosion were found statistically significant in the omeprazole group compared with that of the famotidine group P value <0.05 by Chi-square test of Brant and Snedecor formula.

So in my study rates of healing of all types of gastroduodenal lesions were higher with omeprazole

than with famotidine. There fore it is concluded that patients who use NSAIDs regularly omeprazole healed the lesions more effectively than famotidine. So, this study showed similar results as found in other studies by Walan et al[28].

Yeomans et al also showed the superiority of omeprazole and ranitidine in the treatment of NSAIDs related gastroduodenal ulcer[29].

Agarwal et al[30] compared the efficacy of lansoprazole and ranitidine in the healing of gastric ulcer in patients continuing NSAIDs therapy and proton pump inhibitor was found to be more effective.

In conclusion, in patients taking NSA IDs it has been found in this study that treatment with omeprazole 20 mg twice daily is superior to famotidine with respect to healing of gastroduodenal ulcers and erosion, as well as controlling dyspeptic symptoms.

This is a small scale study based on patients attending a quaternary reference hospital. A large scale study including more patients should be carried out for a conclusive results. As the prevalence of H. pylori infection is more than 90% in our country it was better to do this study after eradication of H. pylori. The analysis of prognostic factor could not be evaluated in this study. Whether COX-2 inhibitor is sufficient enough for analgesia and anti-inflammatory agent. If COX-1 inhibition is to be needed for rheumatic problem then a better drug in preventing gastroduodenal complication should be searched.

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LOW DOSE D -PENICILLAMINE IN THE TREATMENT OF SYSTEMIC SCLEROSIS

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Abstract:

Objective: Systemic sclerosis has no adequately effective and proven treatment. This study was carried out to see the efficacy of low dose d-penicillamine (D-pen) in the treatment of systemic sclerosis in comparison to Methotrexate (MTX).

Method: Nineteen patients of systemic sclerosis were enrolled in this trial. All patients were randomly selected into two groups. Nine patients were treated with D-Pen 250mg every alternate day and ten with MTX 15mg orally weekly for 6 months. Primary outcome measures were total skin score (both modified Rondan and UCLA), physicians and patients global assessment.

Results: At baseline, there were no statistically significant differences between two groups except disease duration. At the end of six months trial, five (55.5%) cases out of nine in D-Pen group and five (50%) cases out of ten in MTX group achieved improvement in their total skin score (both mRss and UCLA). Both patients and physicians global assessment improved in four out of nine cases in D-Pen group (44.5%) and five out of ten cases in MTX group (50%). Treatment responses were significant in both group but intergroup differences were non significant (p>0.05). Forced vital capacity-improved in three cases of D-pen group by >15% but no improvement in MTX group. Digital pitting scars disappeared both in four cases of D-pen and MTX group. Differences in other outcome variable were non significant.

Conclusion: Although the results of this trial suggest that low dose d-penicillamine and MTX are almost equally effective in systemic sclerosis, the number of patients enrolled in this study was small and study duration was short.

Introduction:

Systemic sclerosis (SSc) is a multi system disease of unknown aetiology characterized by excessive deposition of collagen and other extracellular matrix component, endothelial damage of small blood vessels, resulting in intimal hyperplasia and tissue ischaemia and activation of the immune system (1). Systemic sclerosis is distributed world wide. Its prevalence varies from country to country but affects all races. The average annual incidence was found 10 cases per million of population in the United States male vetern, New Zealand 2.3 cases per million, Russia 7 cases per million and England 3.7 cases per million (2). Probably systemic sclerosis is not very rare in Bangladesh. But as there is no epidemiologic study till now, its exact prevalence is not known. The disease is more common in females. During child bearing age, the male female ratio become 1: 15 and in other period's male female ratio varies from 1:3 to 1:8 (3). Systemic sclerosis is the disease of all ages. The peak age of onset is 3rd to 5th decades of life (4). The disease is associated with increasing mortality. Several studies have given estimate of 5 years cumulative survival rate ranging from 34 to 73% (1, 5). But patient with early diffuse cutaneous systemic sclerosis are reported to have a 20 -34% 5 year survival rate (5,6). Mortality depends on renal, cardiac or pulmonary involvement and intercurrent infection.

All of the above facts emphasize the importance of developing an effective management of systemic sclerosis. We lack any therapy that predictably affects any of the three pathogenic aspects of scleroderma: vasculopathy, immune activation and fibrosis. Prevention of fibrosis by interference with collagen metabolism were extensively studied with several drugs but only d–penicillamine and interferon–gamma showed mild to moderate effectiveness by preventing the fibrosis of skin and other viscera. Both high dose penicillamine and low dose penicillamine were given in one study. Eighty percent of the adverse event related withdrawls occurred in high dose d–penicillamine group. The course of skin score, frequency of scleroderma renal crisis and mortality in high dose d–penicillamine group were not different

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from those in low dose d–penicillamine group. This study suggests that there is no advantage of using d–penicillamine in doses higher than 125 mg every other day (7).Some other studies were designed to prevent fibrosis by immuno-suppressive drugs like methotrexate (8), cyclosporin (9), tacrolimus (10)., mycophenolate mofetil(11), Efficacy was not satisfactory in other studies except with methotrexate, tacrolimus, cyclosporin and mycophenolate mofetil. But in most of the studies study periods were short and sample sizes were small. Methotrexate is a anti folate drug and it has already been established as a disease modifying drug in rheumatoid arthritis, dermato and polymyocytis (12,13). In several studies MTX was compared with placebo in the treatment of systemic sclerosis. In the study of Ven Den Hoogen et al in1996 low dose MTX appeared to be more effective than placebo. The authors suggested that randomized trials comparing MTX with for example d-Penicillamine or cyclosporin, will determine the position of MTX therapy in the treatment of scleroderma (1). Few studies with cyclosporin, tacrolimus, and mycophenolate mofetil demonstrated favorable results but these drugs are expensive and not easily available in our country.

In developing countries like Bangladesh, majority of the people are of poor socioeconomic condition. Low dose d-penicillamine is cheap and has minimum adverse effects. MTX is also available, cheap and has acceptable toxicity profile. This study was undertaken to compare the efficacy of low dose d-penicillamine and MTX in our systemic sclerosis patients.

Materials and Methods:

This was a prospective randomized study to see the efficacy of d-penicillamine in comparison to MTX in systemic sclerosis. It was performed in the department of medicine, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, from August 2002 to March 2003**.**

Selection of patients:

All patients of systemic sclerosis attending the out patients department of the Rheumatology wing of department of medicine, BSMMU, were considered for inclusion in the study. After history taking and physical examination with laboratory investigation patients who fulfilled the ACR preliminary criteria for the diagnosis of systemic sclerosis were selected for the study. Verbal informed consent was taken before enrollment.

We applied the following Inclusion criteria: Patients must fulfill the ACR preliminary criteria for the diagnosis of SSc, duration < 3 years, but after 3 years duration if there is evidence of progression, more than 16 years of age.

We also applied the following exclusion criterias: Age<16 years, associated with other rheumatologic diseases, pseudo-scleroderma, pregnancy, significant internal organ damage [such as: a) renal: serum creatinine > 130 mmol/L and renal crisis, b) lungs involvements with FVC < 40% of predicted value, c) cardiomegaly, pericardial effusion, left ventricular ejection fraction <40%, d) hepatic involvement with value exceeding twice the upper limit of normal for a hepatic function test], treatment with steroid > 10mg/day of prednisolone, previous treatment with d-penicillamine, cyclosporine or any other disease modifying anti-rheumatic drugs within past 3 months, haematological disorder (WBC count <3500/cu mm and platelet count < 150,000/cu mm), presence of concurrent neoplastic disease and documented non-compliance.

Baseline clinical and laboratory assessment:

For each patient detail history was taken followed by thorough physical examination with a special emphasis to anaemia, jaundice, oral ulcer, lymphadenopathy, proximal muscle weakness, total skin score (TSS) –mRss and UCLA skin score, lip to lip distance, extension indices, handgrip strength, visual analog scale (VAS) –both patient and physician global assessment, digital ulceration, digital pitting scar and pulmonary basal crepitations. Baseline laboratory investigations included urine analysis, complete blood count with ESR, X-ray chest, ECG, serum bilirubin, ALT, alkaline phosphatase, serum creatinine, ANA, anti Scl-70, skin biopsy and spirometry. When needed, more detailed investigations were done, e.g. blood sugar, serum electrolyte, anti-RNP antibody, creatinine phosphokinase, anti-ds DNA, and ultrasonogram of whole abdomen, echocardiography and Ba-swallow of oesophagus.

Treatment regimens:

A total of 24 patients were included and randomly divided into two groups, 10 patients in D-pen group and 14 patients in MTX group. Patients in D-pen group were treated with oral d-penicillamine 250 mg every alternate day and patients in MTX group were treated with oral methotrexate (starting at 10 mg weekly, increasing 2.5 mg every month to a maximum dose of 15 mg weekly).

Follow up by clinical and laboratory parameters:

Clinical parameters were: total skin score - modified Rodnan skin score (mRss) and University of California and Loss Angeles (UCLA) skin score, pitting scar (digital

and toe), digital ulceration, lip- to-lip distance, extension indices of hand, handgrip strength, physician global assessment on 0-10 cm VAS, patients global assessment on 0-10 cm VAS and HAQ disability index. Laboratory parameters were: Spirometry/FVC (done at entry, after six months and after one year), Hb%, TC, DC, platelet count, ESR, serum creatinine, ALT and urine R/E (at entry, after 2 weeks and then monthly).

Response criteria:

Favorable response was defined when total skin score (TSS) improved by > 30% of the baseline or physicians and patients global assessments (on VAS) improved by > 30% or FVC improved by > 15 % of the baseline value or digital ulceration were healed up and no new ulcer appear, all pitting scar were abolished or reduced in number. Responses were considered unfavourable if no change or deterioration occurred in TSS or persistence or appearance of new digital pitting scar and no change of VAS.

Statistical analysis:

All collected data were analyzed using computer based SPSS programme and expressed as mean (+ SD) or in frequency or percentage unless mentioned otherwise. Comparisons between two groups were done by Mann–Whitney U test and comparison within group was done by sign test. P value < 0.05 was considered as a level of significance.

Results:

Out of 24 patients of systemic sclerosis in this study twenty two (22) were female and two male. Female male ratio 91.7: 8.3. Average age of the patients varied from 16 to 58 years. Mean age was 32.46 ± 12.81 years. Among 24 cases, 2 (two) cases (8.33%) had limited cutaneous systemic sclerosis and 22 cases (91.67%) had diffuse cutaneous systemic sclerosis. Raynaud's phenomenon was present in 19 cases (79.2%). Pitting scar was present in 20 cases (83.3%). ANA was positive in 12 cases (50%) and Anti Scl -70 was positive in 12 cases (50%). Among them ten patients were

Table I

Baseline characteristics at study entry

Character	Groups		p
	D-pen. (n =10)	MTX (n =14)	
Age (years; mean ± SD)	25.20 ± 7.42	37.64 ± 13.52	0.030
Sex (Female /Male)	10 /0	12 / 2	0.493
Disease duration (months)	29 ± 17.64	20.57 ± 18.05	0.108
Skin distribution: (Dif / Limit)	9/1	13/1	1.000
Antinuclear antibody (ANA)	7	5	0.214
Anti –Scl -70	6	6	0.680
Raynaud's phenomenon	9	10	0.358
Pitting scar	9	11	0.615
Sclerodactyly	5	7	1.000
Telangiec tasia	7	6	0.240
Total skin score (mRss)	25.3 ± 10.23	24 ± 9.21	0.666
Total skin score (UCLA)	14.9 ± 5.95	14.71 ± 5.58	0.886
Lip to lip distance (mm)	41.50 ± 5.25	44 ± 4.93	0.192
Physician global assessment	1.24 ± 0.39	0.89 ± 0.23	0.138
Patient global assessment	1.08 ± 0.34	0.91 ± 0.24	0.172
Handgrip strength right hand (mm Hg)	149 ± 31.07	143.93 ± 22.12	0.709
Handgrip strength left hand (mm Hg)	142.50 ± 34.42	140.36 ± 26.13	0.977
Extension index right hand (mm)	90.90 ± 5.00	91.50 ± 4.29	0.666
Extension index left hand (mm)	91.70 ± 4.24	91.14 ± 4.75	0.585
HAQ disability index score	1.49 ± .33	1.41 ± 0.55	0.796
Hb (gm/dl)	10.99 ± 1.27	12.01 ± 1.19	0.096
Total count of WBC (per mm3)	11.94 ± 3.10	9.56 ± 2.33	0.009
Thrombocyte count (per mm3)	279 ± 76.94	297 ± 49.83	0.403
ESR (Westergren mm in 1st hour)	57.10 ± 32.08	44.07 ± 20.70	0.285
Serum creatinine (m mol/L)	74.86 ± 11.53	70.71 ± 15.88	0.371
SGPT (U/L)	22.50 ± 8.15	28.29 ± 10.64	0.253
Forced vital capacity (FVC, %)	61.46 ± 16.16	70.33 ± 12.32	0.192

randomly assigned to the d-penicillamine (D-pen) group and fourteen patients to the methotrexate (MTX) group. But a total of five cases dropped out during study period. Finally, nineteen patients among twenty four cases completed the trial for six months. Among them nine cases belonged to D–pen group and ten cases belonged to MTX group. Data of these subjects were used in all subsequent analysis.

Table I shows the baseline characteristics of all patients in this study. Age in the two groups had significant difference. Disease duration in the two groups had some difference but not significant. Pitting Scars were present in nine patients in D-pen group and eleven patients in MTX group. Total skin score (both modified Rodnan and UCLA skin score), lip to lip distance, HAQ disability index score, patient and physician global assessment and other outcome variable in two groups were similar. Among laboratory data almost all (except total count of WBC) in two groups were similar. The two groups differed significantly only in respect of total count of WBC. History of previous steroid therapy and internal organ involvement in two groups were similar.

Table II

Outcome variables after six months in D–pen group

Character	Entry (n =9)	6 months (n =9)	p*
Total skin score (MRSS)	23.33 ± 8.62	16.33 ± 6.93	0.004
Total skin score (UCLA)	13.78 ± 5.07	9.33 ± 3.81	0.004
Lip to lip distance (mm)	42.0 ± 5.32	42.78 ± 5.07	0.063
Handgrip strength right hand (mm Hg)	151.11 ± 32.19	173.89 ± 19.49	0.008
Handgrip strength left hand (mm Hg)	148.33 ± 20.82	172.78 ± 21.23	0.008
Extension index right. (mm)	91.33 ± 5.10	91.78 ± 4.84	0.375
Extension index left. (mm)	92.22 ± 4.15	92.56 ± 3.91	1.000
HAQ disability index score	1.41 ± 0.22	1.05 ± .22	0.008
Digital pitting scar	8	5	0.250
Forced vital capacity(%, predicted value)	62.06 ± 17.02	67.22 ± 16.47	0.508
Physician global assessment	4.66 ± 1.06	3.55 ± .80	0.004
Patients global assessment	4.77 ± 0.87	3.16 ± 0.66	0.004
ESR	54.44 ± 32.84	40.11 ± 22.68	0.453

* sign test

Table III

Outcome variables after 6 months in MTX group

Character	Entry (n =10)	6 months (n =10)	p*
Total skin score (mRss)	24.00 ± 11.07	18.40 ± 11.37	0.003
Total skin score (UCLA)	14.50 ± 6.67	10.70 ± 6.73	0.003
Lip to lip distance (mm)	42.60 ± 4.55	43.60 ± 4.48	0.031
Handgrip strength right hand (mm Hg)	142.00 ± 22.10	174.00 ± 24.01	0.002
Handgrip strength left hand (mm Hg)	138.00 ± 27.51	174.00 ± 24.01	0.002
Extension indices right. hand (mm)	92. 60 ± 3.81	93.80 ± 3.99	0.180
Extension indices left. hand (mm)	92.20 ± 4.94	93.40 ± 4.25	0.180
HAQ disability index score	1.44 ± 0.59	1.12 ± 0.59	0.002
Digital pitting scar	8	6	0.500
Forced vital capacity(% of predicted value)	68.12 ± 11.56	67.82 ± 12.53	1.000
Physician global assessment	5.60 ± 1.02	4.35 ± 1.29	0.001
Patients global assessment	5.70 ± 0.92	4.05 ± 1.12	0.002
ESR	46.50 ± 17.63	39.20 ± 12.32	0.070

* sign test

Table II shows treatment response in D-pen group. Nine cases completed the trial for six months, four cases responded favourably and the responses were not favourable in five cases. Among laboratory parameters all were nonsignificant except haemoglobin after 6 month of treatment (P=0.016).

Table III shows treatment response in MTX group. After six months five patients responded favourably, and the response was not favourable in five cases. Among laboratory parameters all were non significant.

CharacterGroupsp*D –pen. (n =9)MTX (n =10)Total skin score (mRss)7.00 ± 4.395.60 ± 4.030.464Total skin score (UCLA)4.44 ± 2.923.80 ± 2.700.651Lip to lip distance (mm)0.78 ± 0.831.00 ± 1.050.862Handgrip strength right hand (mm Hg)22.78 ± 15.2332.00 ± 23.940.508Handgrip strength left hand (mm Hg)24.44 ± 16.8536.00 ± 28.160.972Extension indices right. hand (mm)0.44 ± 0.881.20 ± 1.750.345Extension indices left. hand (mm)0.33 ± 1.001.20 ± 2.530.464HAQ disability index score0.36 ± 0.250.31 ± 0.260.345Digital pitting scar561.000Forced vital capacity (%of predicted value)5.15 ± 8.07-0.30 ± 5.770.095Physician global assessment 1.11 ± 0.481.25 ± 0.860.808Patients global assessment 1.61 ± 0.701.65 ± 0.620.651ESR14.33 ± 22.487.30 ± 10.740.422

Table IV

Comparison of differences of outcome after 6 months: D-pen vs MTX

Character	Groups	p*	
	D –pen. (n =9)	MTX (n =10)	
Total skin score (mRss)	7.00 ± 4.39	5.60 ± 4.03	0.464
Total skin score (UCLA)	4.44 ± 2.92	3.80 ± 2.70	0.651
Lip to lip distance (mm)	0.78 ± 0.83	1.00 ± 1.05	0.862
Handgrip strength right hand (mm Hg)	22.78 ± 15.23	32.00 ± 23.94	0.508
Handgrip strength left hand (mm Hg)	24.44 ± 16.85	36.00 ± 28.16	0.972
Extension indices right. hand (mm)	0.44 ± 0.88	1.20 ± 1.75	0.345
Extension indices left. hand (mm)	0.33 ± 1.00	1.20 ± 2.53	0.464
HAQ disability index score	0.36 ± 0.25	0.31 ± 0.26	0.345
Digital pitting scar	5	6	1.000
Forced vital capacity (%of predicted value)	5.15 ± 8.07	-0.30 ± 5.77	0.095
Physician global assessment	1.11 ± 0.48	1.25 ± 0.86	0.808
Patients global assessment	1.61 ± 0.70	1.65 ± 0.62	0.651
ESR	14.33 ± 22.48	7.30 ± 10.74	0.422

* Mann – Whitney U test

Table -V

Response to treatment at six month

Group	Total pt.	Responders	Non responders	P
D-pen	9 (100%)	5 (55.5%)	4 (44.5%)	0.548
MTX	10 (100%)	5 (50%)	5 (50%)	
Total	19 (100%)	10 (52.6%)	9 (47.4%)	

Table-VI

Adverse reactions

Adverse effect	D-pen (n=9)	MTX (n=10)	Adverse effect	D-pen (n=9)	MTX (n=10)
Anorexia	4	4	Pruritus	4	0
Nausea	4	5	Raised ALT	0	2
Vomiting	1	1	Vertigo	0	3
Oral ulcer	0	1	Weakness	0	4
Skin rash	2	0	Cough	0	2
Loss of taste	2	0	Dyspnea	0	2

Table IV shows comparison of differences of outcome variables at 6 months of trial between two groups. TSS of both groups decreased but differences between two groups were non significant. Five (55.5%) cases out of nine in D–pen group and five (50%) cases out of ten in MTX group achieved improvement in their total skin score (both MRSS and UCLA). The inter group differences were statistically non significant (P>0.05). Forced vital capacity decreased in two cases of D–pen group by >10 % and two cases of MTX group >15 %. Forced vital capacity improved in three cases of D–pen group by >15 % but no improvement in MTX group. Pitting scars disappeared or decreased in four cases of D–pen group and five cases in MTX group. Both patients and physicians global assessment improved in four out of nine cases in D–pen group (44.5%) and five out of ten cases in MTX group (50%). These are statistically non significant.

Responders versus nonresponders:

In the D–pen group (total nine patients), five (55.5%) cases responded favourably and four (44.5%) cases had no response to drug. In the MTX group (total ten patients) five cases (50%) responded favourably and five cases (50%) had no response to drug.

Adverse reactions to therapy:

Anorexia, nausea were the most common side effects in both D–pen and MTX therapy. Anorexia was found in three patients (33.33%) of D–pen group and four patients (40%) in MTX group. Nausea was found in four patients (44.44%) in D–pen group and five patients (50%) in MTX group. These minor side effects subsided despite continuation of drug. In the D–pen group four (44.44%) cases out of nine developed pruritus with mild to moderate itching. Pruritus subsided or decreased with use of emollients and antihistamine. Oral ulcer developed only in one patient in MTX group but healed up spontaneously. Serum ALT increased in two patients. In one patient ALT increased more than three times of upper limit of normal value in MTX group and became normal after discontinuation of the drug. After three weeks of withdrawal MTX given to the patient again. ALT also increased in one patient but it was more than two times of upper limit of normal value and became normal after reduction of dose to 10 mg weekly. In MTX group some patients complained of vertigo and weakness, two patients developed new onset of cough with dyspnoea and one of this two developed features of interstitial lung disease.

Discussion:

Systemic sclerosis is a multisystem disease of unknown aetiology. We lack any therapy that predictably affects any of the three major pathogenic aspects of scleroderma: immune activation, vasculopathy and fibrosis. Till today, some randomized placebo-controlled trials have been reported. But in most of the studies, study periods were short and sample sizes were small (1,7,14,15,16).

In the present study, we have our own study design keeping uniformity with the "Guidelines for Clinical Trial in Systemic Sclerosis" by White et al in 1995(17). We employed a combination of TSS, VAS (both patient and physician global assessment on 0-10 cm VAS), FVC and presence or absence of digital pitting scar to differentiate responders from non responders. Though the designed study period in this trial was one year, analysis was carried out at the end of six months to assess any difference of response at short term.

A randomized comparative trial of high dose (750 to1000 mg /day) and low dose (125 mg every other day) d-penicillamine was conducted by Clement et al in 1999. Skin score in both groups improved significantly during the trial. So, possibility was that low dose D-pen may be equally effective as high dose D-pen. They concluded that - 1) The course of skin score, the occurrence of renal crisis and other organ involvements and the occurrence of mortality were notdifferent between the low dose and high dose d-penicillamine; 2) Majority of adverse event related withdrawals occurred in the high dose. D-pen group and were largely because of proteinuria; and 3) If D-pen is to be used to treat SSc, our results suggest that there is no advantage to using dosages higher than 125 mg every other day. A placebo controlled trial of MTX was conducted by Van Den Hoogen et al. in 1996 (1). The study duration was six months followed by uncontrolled trial (observational) for another six months. Improvement occurred in eight (53%) out of fifteen in the MTX group with favorable response after six month and nine (90%) patients in the placebo group did not improve.

In this study trial duration was six month with use of 250 mg D-pen every alternate day in one group and 15 mg oral MTX weekly in divided dose twelve hours apart in another group. Mean disease duration was 30.88 month in D-pen group and 19.80 month in MTX group. In the D-pen group five out of nine cases fulfilled the predefined favourable response criteria (55.5%) and four patients showed unfavorable response. Five cases of the MTX group fulfilled the predefined response criteria (50%) and five of the MTX group showed no favorable response. Inter group differences were nonsignificant (P > 0.05). In terms of internal organ involvement, beneficial effects were observed in both D-pen and MTX groups. But no

significant differences are observed between two groups. In MTX group, two patient developed new onset of cough and dyspnoea and one of the two develop features of interstitial lung disease. In D-pen group at the end of six month, the skin score improved in five out of the nine patients (both mRss and UCLA skin score) by > 30% compared with five out of ten patients in the MTX group. Results were nearly similar in two groups. Patients and physicians global assessment on VAS improved by > 30% in four out of nine patients (44.5%) in the D-pen group compared to five out of the ten (50%) patients in the MTX group. Results in the two groups were nearly identical. Adverse effect with low dose d–penicillamine was very minimum and there is no withdrawal. Adverse effect with MTX was minimum and manageable with continuation of drug. In MTX group there was only one temporary withdrawal. Thus both low dose D-pen and MTX appeared to be safe and reasonably well tolerated.

A definition of favourable response was predetermined. On the basis of these criteria, improvement was found in both D-pen and MTX group but inter group differences were nonsignificant. Despite the smaller size of the sample in this study, it appeared that d-penicillamine and MTX have similar efficacy in the treatment of systemic sclerosis. Recommendation of this study was that a long term study with larger sample has to be carried out with low dose d-penicillamine and MTX in the treatment of systemic sclerosis.

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EFFICACY OF TOPICAL TACROLIMUS ON HAIR REGROWTH IN ALOPECIA AREATA: A RANDOMIZED CONTROLLED TRIAL

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Abstract:

Tacrolimus is a calcineurin inhibitor, a powerful immunomodulator. Alopecia areata is amenable to treatment with topical tacrolimus. To evaluate the efficacy and safety of topical tacrolimus in hair regrowth in alopecia areata. Forty consecutive Patients (case-20, control-20) with alopecia areata were included in this study. Topical tacrolimus was applied twice daily at a dose of 125ìgm/cm^2 / week to the case group and the control group got placebo (vaseline) only. The study was carried out for 8 weeks. At the end of the study regrowth of hair was evaluated on the basis of the grading system proposed by McDonald Hull and Norris. Of 20 patients in case group, 7(35%) showed hair regrowth after use of tacrolimus. Hair regrowth was failed to occur in 13 (65%) patients after same medication. Among 20 respondents of control group, 6(30%) showed hair regrowth after use of placebo (Vaseline) and rest 14(70%) did not show any hair regrowth. Among 7 responders of case group grade-3 regrowth in 3(15%) and grade-4 in 4(20%), in control group grade-3 regrowth in 1(5%) and grade-4 in 5(25%) was observed. 4(20%) patients developed minimal side effects after tacrolimus use. Though safe topical tacrolimus ointment at a dose of 125ìgm/cm^2 /week is an ineffective option for the treatment of alopecia areata.

Introduction:

Alopecia areata is hypothesized to be an organ specific auto-immune disease mediated by T-lymphocytes directed to hair follicles,[1] accounting for1-4/100 patients in dermatology practices.[3] Treatment of alopecia areata poses a great therapeutic challenge. Tacrolimus a hydrophobic macrolide lactone,[2] a powerful immunomodulatory agent is used in transplantation medicine to prevent graft rejection.[3]On topical application after penetrating the cell membrane, tacrolimus binds to block the function of the Ca^{2+}-calmodulin dependent phosphatase calcineurin, which results in suppression of NF-AT dependent cytokine gene transcription [2] It Inhibits transcription of several cytokines including interleukin-2 (IL-2), interferon-g (IFN-g), and tumor necrosis factor-a (TNF-a). In alopecia areata the peribulbar mononuclear cell infiltrate is composed predominantly of activated CD_4+ and CD_8+ T-lymphocytes and type-1 cytokines, including IL-2, IFN-g and TNF-a mediate initiation of immune response.[4]

Initial studies on topical tacrolimus in two animal models of alopecia areata the Dundee experimental bald rat (DEBR).[5] and the C3H/HeJ mouse showed hair regrowth with topical tacrolimus.[3] DEBR rat lesion bears striking similarities to human alopecia areata lesion.[5]. It is opined that topical tacrolimus might also be effective in human with alopecia areata.[3]

Material and Methods

A randomized controlled trial was conducted from April 2004 to April 2005 in the department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University, Dhaka. Forty consequetive patients of alopecia areata (case-20, control-20) attending the department of Dermatology and Venereology, were included in this study. Patients with alopecia areata irrespective of any age, sex and duration, with or without any associated diseases, not responding to any other modalities of treatment and those willing to give consent were included. Pregnant and lactating mother, history of hypersensitivity to tacrolimus, renal impairment, alopecia totalis /alopecia universalis and refusal of the patient to be included in the study were excluded.

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By lottery odd number was given to the case and even number to the control group. Randomization was done by using Random number table. A careful history was taken from each patient concerning general health, duration of illness, age of onset, the presence of autoimmune diseases, history of atopy and family history of alopecia areata. At the initial visit general examination and dermatological examinations including, site of hair loss, number of patches, size of the patches, extent of hair loss, nail involvement, any skin change; was done to each patient. Diagnosis was confirmed by clinical assessment. All patients after giving informed consent topical tacrolimus ointment at a dose of 125igm/cm^2 /week was applied twice daily for 8 weeks to the case group. The control group got placebo (Vaseline) only.

Follow-up was done at 4^{th} week and at 8^{th} week. Clinical assessment at each follow-up visit consists of examination of all treated lesions to see the extent of hair growth and to monitor the adverse effects. Hair regrowth was evaluated by using grading system proposed by McDonald Hull and Norris: grade 1-'regrowth of vellus hair', grade 2-'regrowth of sparse pigmented terminal hair', grade 3-'regrowth of terminal hair with patches of alopecia' and grade 4-'regrowth of terminal hair on the whole scalp.' Statistical analysis was done with the help of SPSS software version 12.0. Differences between case and control group were compared by T-test and differences between treatment results of case and control group were analyzed by Chi square test.

Results:

40 patients with alopecia areata (case-20, control-20) were included in the study. The main demographic and clinical characteristics of enrolled patients of both the groups are given in table-1.Of 20 respondents of case group, hair regrowth was seen in 7 (35%) after application topical tacrolimus at the end of 8 weeks. Of these 7 patients, 4 had grade 4 regrowth and 3 had grade 3 regrowth. Hair regrowth was not observed in 13 (65%) patients in case group after same medication. In the control group, 6(30%) had hair regrowth after use of placebo (Vaseline). Out of these 6, 5(25%) had grade 4 regrowth and 1 had grade 3 regrowth. Rest 14(70%) did not show any hair regrowth (table-2 and table-3). There was no statistical significant difference between the response in two groups ($p > 0.05$).

Of 20 respondents in case group 4 (20%) noticed side effects. Among them erythema and burning developed in 1 and 3 patients respectively (table-1). All were able to continue the treatment with tacrolimus ointment. Rest 16 (80%) respondents were free from any kind of side effects after tacrolimus application.

Table-I

Demographic and clinical characteristics (n=40):

Characteristics	Case; n (%)	Control; n (%)	P value
No. of patient	20	20	
Male/ Female	10/10	12/8	P=0.577
Mean age (y)	22.80± 9.32	24.83 ± 9.6	P =0.499
Duration of illness (m)	12.11±8.25	7.96±9.14	P = 0.193
Age of onset of illness (y)	21.95±9.32	24.65±9.64	P = .372
Family history of AA	5(25%)	7(35%)	
Personal history of atopy	4(20%)	3(15%)	
Family history of atopy	6(30%)	1(5%)	
Side effects after tacrolimus	4(1 erythema)	nilUse	(3 burning)

Table-II

Distribution of hair regrowth after medication. (n-40) Treatment type

	Hair regrowth	
	YesNo (%)	NoNo (%)
Tacrolimus (Case)	7 (35%)	13 (65%)
Placebo (Control)	6 (30%)	14 (70%)
Total	13 (32.5%)	27 (67.5%)

Table-III

Distribution of hair regrowth according to grading system proposed by McDonald Hull and Norris.

Treatment type	Hair regrowth	
	Grade 3	Grade 4
Case =20	3 (15%)	4 (20%)
Control = 20	1 (5%)	5 (25%)

Discussion:

Alopecia areata is an unpredictable usually patchy, non-scaring hair loss condition. It is hypothesized to be an organ specific autoimmune disease mediated by T-lymphocytes directed to hair follicles. Although genetic predisposition and environmental factor may trigger the initiation of the disease, the exact cause is still unknown.[1]

A wide range of treatments has been tried in alopecia areata but none was consistent in its efficacy. Modalities such as corticosteroids (topical, oral, intramuscular, intralesional), topical anthralin, topical minoxidil, contact sensitizers (Squaric acid dibutyl ester-SADBE, Cyclopropinone-DCP), PUVA therapy (topical and systemic), cyclosporine, methotrexate and cryotherapy have been tried with variable success.[6-9]

Tacrolimus is a new immunomodulatory drug. Topical application in Dundee experimental bald rat (DEBR) results in regrowth of hair at the site of application. It stimulates hair growth in a dose dependent manner. DEBR rat lesion bears striking similarities to human alopecia areata lesion.[5,10] There was also regrowth of hair in C3H/HeJ mice with alopecia areata treated with topical tacrolimus.[3]

Present study revealed that 7(35%) patients showed hair regrowth after application of topical tacrolimus in case group and 6(30%) showed hair regrowth after use of Vaseline (placebo) in control group. Among 7 responders of case group 3(15%) patients had grade3 hair regrowth and 4(20%) had grade 4 regrowth. In control group grade 3 hair regrowth in 1(5%) and grade 4 in 5(25%) was observed. There was no statistical significant difference between the response in case and control groups ($p > 0.05$) that there is no correlation between tacrolimus use and regrowth of hair.

Experience with topical tacrolimus therapy in human with alopecia areata is limited. There is a few published studies evaluating its role. Thiers BH has reported that a patient of alopecia areata was treated with 0.3% topical tacrolimus for 6 months. After 6 months of therapy there was no evidence of hair regrowth inspite the patient was progressed to alopecia totalis.[11]

Price VH et al. studied 11 patients of alopecia areata affecting 10-75% of scalp with average duration of 6 years and has reported no terminal hair regrowth in response to tacrolimus ointment 0.1% applied to the affected area twice daily for 24 weeks. They have stated that this treatment failure may be due to insufficient depth of penetration of ointment formulation and less than optimal patient selection.[4] Feldmann KA et al. has reported that five patients with alopecia areata universalis were treated with 0.1% topical tacrolimus on a 6×6 cm area on the scalp once daily for 6 months. None of them showed regrowth of hair.[3]

Park S-W et al. studied 4 patients (2 males, 2 females) of alopecia universalis with topical tacrolimus. Topical tacrolimus was applied as 0.1% solution 0.5 ml twice daily in females and 0.1% ointment 0.5 mg twice daily in males to a approximately 10×10 cm of hair less patch on the scalp for 12 weeks. No evidence of hair growth from all 4 patients was observed during 3 months application period and 6 months follow-up period.[12]

In studies done by Price VH et al.[4], Feldmann KA et al.[3], Park S-W et al.[12] patients selection were unfavorable. Patients were either of long duration or of alopecia areata totalis/ universalis. In our study patient selection was favourable, all patients were of less than 2 years duration and alopecia areata totalis/ universalis were excluded from the study. Despite favorable patients selection topical tacrolimus at a dose of 125ìgm/cm^2 /week failed to show statistical significant hair regrowth.

The present study also documented the safety of topical tacrolimus. Twice-daily application of topical tacrolimus ointment was well tolerated. Erythema and burning were reported only in 20% of patients (table-1) and were transient. Eighty percent (80%) of patients were free from any kind of side effects. None of the patient discontinued the treatment due to adverse events. This result is supported by Grimes et al. Grimes et al. have reported that twice daily application of topical tacrolimus 0.1% was well tolerated.[13]

Conclusion:

This randomized controlled trial has assessed the efficacy and safety of tacrolimus ointment in patients with alopecia areata compared with control. It is proposed that tacrolimus ointment may be an ineffective option for the treatment of alopecia areata. Even the ease of topical self-administration with minimal side effects can not make this novel immunomodulatory agent as a promising addition to the therapeutic armamentarium for alopecia areata.

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REVIEW ARTICLE

INTERMITTENT PREDNISOLONE THERAPY IN DUCHENE MUSCULAR DYSTROPHY-A NEW HOPE

MD.ABUL KALAM AZAD, MD. ABDUR RAHIM, TAIMUR AK MAHMUD, TOFAYEL AHMED, SAIKAT DHAR.

Abstract

Duchene Muscular Dystrophy (DMD) is a common childhood muscular dystrophy without any specific treatment. It is a progressive muscular degenerative disease, which goes unholtered to death, respiratory failure or cardiac failure being the cause of death. The steroid administration on a continuum basis at an intermittent, low-dosage, regime of prednisolone (0.75mg/kg/day for 10 days each month, or alternating 10 days on and 10 days off) in DMD is effective for prolongation of ambulation period and delaying scoliosis and also for prolongation of life.

Introduction

Duchene Muscular Dystrophy (DMD), the most common childhood muscular dystrophy, occurs in approximately one in every 4500 males[1]. Duchene Muscular Dystrophy is an X-linked inherited disorder characterized by progressive muscle weakness, loss of ambulatory ability between 8 and 13 years and necessitates wheelchair use[2,3]. Progression of muscle degeneration and worsening of clinical symptoms lead to death in the late teen's or early twenties as a result of respiratory failure or cardiac failure[4]. In this review, we discuss the role of steroid in the management of DMD.

The Molecular Pathology of DMD

Dystrophin, the product of the human Dystrophin gene (dys*)*, is a 427-kDa protein composed of 3685 amino acids residues, localizes to the sarcolemma[5], where it constitutes 5% of sarcolemmal protein and 0.002% of total striated protein[6]. Dystrophin contains four distinct domains and structural homology with spectrin and alpha-actinin[7]. The sarcolemmal dystrophin-associated protein complex (DPC) provides a crucial structural link between the cytoskeleton and the extracellular matrix [4,8]. The DPC is shown in figure1[4].

Dystrophin is required to maintain the mechanical stability of muscle, and is involved in Ca++ homeostasis[9]. Three important points about the role of the DPC in skeletal muscle has emerged, 1) directly takes part in the pathogenesis of muscular dystrophy, 2) the cellular signaling and 3) the sarcoglycans and a-dystrobrevin might have specific, non-redundant roles in muscle. These findings are directly applicable to any proposal concerning the role of dystrophin in the CNS[8]. Muscles in patients with DMD are deficient in dystrophin[6]. The deficiency causes sarcolemmal instability, which leads to destabilization of the sarcolemmal dystrophin-associated protein complex[10]. Dystrophin deficiency also occurs in patients with Becker muscular dystrophy (BMD), although to a lesser extent[11]. In dystrophic muscle, regeneration gradually fails and the normal cycle of degeneration is tipped in favour of degeneration. Cycles of necrosis and repair in dystrophic muscle continue throughout postnatal development until the endogenous satellite-cell pool can no longer compensate for ongoing muscle-fiber destruction[12].

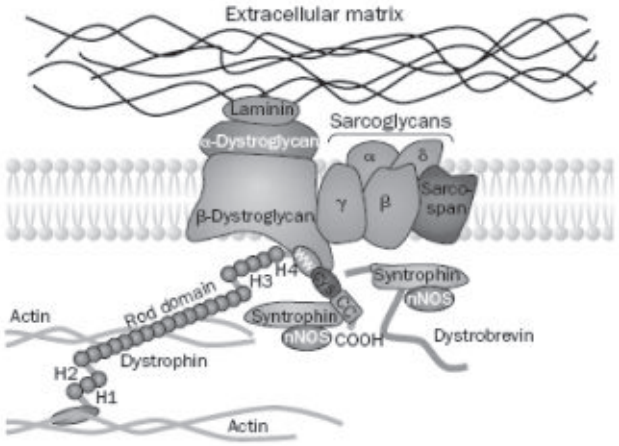

Figure1. *The sarcolemmal dystrophin-associated protein complex (DPC). Dystrophin has a critical role in the maintenance of stability by creating a link between the contractile machinery in the cell and the extra cellular matrix via the dystroglycan complex.*

The Molecular Genetics of DMD

The DMD gene was one of the first human genes to be cloned by positional cloning and is notable not only for its medical importance, but also for its size. To date, the DMD is the largest gene in the human genome and occupies approximately 2.5 Mb of the human X chromosome[8]. Both DMD and Becker muscular dystrophy (BMD) are caused by mutations in the same gene (i.e. *dys* gene). Most *dys* mutations (roughly 99%) in patients with DMD are large deletions or insertions that result in downstream codon reading frame shifts (58%) or small frame shift rearrangements or point mutations (41%), with the reminder being duplication mutations[13]. All of these mutations affect the correct expression of the cysteine-rich domain. By contrast, the cysteine-rich domain is preserved in patients with BMD mutations, which results in the expression of a partially functional dystrophin protein, and consequently milder symptoms[4].

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Treatment

Specific treatment of DMD is yet to be established. Physiotherapy, rehabilitation and use of steroids may prolong the ambulatory period and therefore improve the quality of life[14]. Some options are currently being explored in the search for an effective therapy. Gentamicin[15], up regulation of utrophin[16] or á7â1 integrin[17], and targeted corrective gene conversion are likely to induce changes at non-target loci needs to be considered[4]. The targeting capacities of various therapies are also important: strategies that target existing muscle fibers will eventually lead to replacement by dystrophic satellite cells[4]. Strategies involving muscle derived precursor cells will probably require ablation of existing muscle before they can exert any therapeutic influence [18,19]. but all are yet to be established. Steroids have been demonstrated to be efficacious in slowing the progression of the disease and in delaying the loss of independent ambulation[20]. Multiple randomized trials have found improved function and strength in children treated with prednisolone[21-24].

Steroid in DMD

In DMD, a combination of necrosis and progressive insufficiency of muscle fiber regeneration is thought to be responsible for the replacement of muscle with connective tissue and fat in later stages of the disease[25]. Steroids have been demonstrated to be efficacious in slowing the progression of DMD and in delaying the loss of independent ambulation by improving muscle strength[7]. Corticosteroids may enhance myoblast proliferation and promote muscle regeneration. Steroids may inhibit muscle degeneration by stabilizing lysosomal-bound proteases or muscle cell membrane. Finally, prednisolone could reduce muscle damage and necrosis through its immunosuppressive and anti-inflammatory effects [26,27].

Exact mechanism is not known, but steroid may act on the immune system. Although muscular dystrophy is not considered as an immunological disorder, there is evidence that both humoral and cellular immune responses contribute to the pathological process[28]. The necrotic fibers of muscular dystrophy are invaded by macrophages, Arthata and Engel showed with selective monoclonal antibodies that many of these mononuclear cells were in fact cytotoxic T- cells[29]. In addition, complement activation with deposition of membrane attack complex was observed on necrotic fibres[30]. HLA class I antigens (MHCI) are expressed in Duchene muscular dystrophy fibers, as in polymyositis, but not in normal muscle. This would render the dystrophic muscle susceptible to T-cell-mediated attack [31,32]. Mast cell degranulation may also play a role in dystrophin-deficient muscle[32]. The dystrophin-deficient muscle is more susceptible to myofibre necrosis when exposed to intramuscular injections of purified mast call granules[33]. An increased pathology was documented in mdx mice with exaggerated mast cell activity[34]. So, steroids might influence different aspects of the immunological reaction in dystrophic muscle. Recent studies of genetic profiling have generated a vast amount of new data on up regulation or down regulation of a variety of genes in Duchene muscular dystrophy[35].

The mainstay of problem in the steroid treatment in DMD is to determine the functional outcome and dosage schedule to combat side effects. Michelle Eagle (UK) and Birgit Steffensen (Denmark) suggested the ideal functional outcome measures to reflect real issues relevant to the disease. The outcome measures[36] were summarized in table 1.

Unfortunately, once the drug is stopped, the muscle weakness rapidly returns to baseline. Since the steroid effect disappears when the drug is stopped, and the medication is associated with potential side effects, many different regimes have been suggested to reduce the risks with the long-term use of daily steroids. The dose of 0.75mg/kg /day was shown to be the most effective dose in the early randomized

Table-1: *Suggested procedures for monitoring for efficacy of steroid treatment[36].*

Effect	Measure	Frequency	Adaptation for long term follow up
Function (1)	Milestones of disease progression…. can do (hop, jump, get up from floor, stand on one leg, step up, step down, walk, stand)	0,3,6,12 months, etc….	Needs no adaptation. Can be gathered by history and observation at long-term foll ow up and has high clinical relevance
Function (2)	Timed testing (time to get up from floor, to run defined distance)	0,3,6,12 months, etc….	Timed tests will become impossible as milestones of disease progression are reached
Function (3)	Hammersmith motor ability score	0,3,6,12 months, etc….	Scale may be less sensitive as children become less ambulant, May need adaptation or additional scale to accommodate changes in upper limb function
Muscle strength (1)	MRC score 34 muscle groups	0,3,6,12 months, etc….	Applicability may be limited in the log term
Muscle strength (2)	Quantitative muscle testing six muscle groups	0,3,6,12 months, etc….	Grip strength may remain useful measure in the long-term follow up
Respiratory capacity	Forced vital capacity	0,3,6,12 months, etc….	Will need additional respiratory investigation as FVC drops
Cardiac status	Ecchocardiography, electrocardiology	0,3,6,12 months, etc….	Will need to be continued in the long term as part of best practice monitoring [20]
Quality of life	CHQ-PF50, CHQ-CF87	0,3,6,12 months, etc….	Annual administration in the long term

controlled trials, where dose of 0.35 mg/kg/day was not as effective as 0.75mg/kg/day, while 1.2mg/kg/day gave no additional benefit[23,24]. Deflazacort 0.9mg/kg/day is said to be the equivalent dose to 0.75 mg/kg/day of prednisolone, and appears to be equally as effective[37.38]. The recurrent observations showed that the effect of steroids usually became apparent within the first few weeks of treatment, and at times as early as 10 days, reached a peak in the first few months, and then plateaued[39,40]. But prolong steroid use may cause weight gain, behavioral changes, adrenal suppression, susceptibility to infection, hypertension, impaired glucose tolerance, gastrointestinal irritation, skin fragility and vertebral fracture. The most commonly reported side effects in the published series have been weight gain and behavioral changes[36]. So, adverse events should be monitored carefully and these monitoring may be according to Table 2. Deflazacort appears to cause less weight gain, but is more likely to be associated with the development of asymptomatic cataracts and vertebral fractures[41,42].

Table 2: *Adverse event monitoring and responses*[36]

Adverse event group	Measure	Prophyl actic measur es	Event to be recorded/ treated without dose alteration	Events as criterion for dose reduction	Events as criterion for drug withdrawal	Long-term monitoring
Behavior changes	CHQ-PF50, CHQ-CF87	Behavior modificati on	Change in behavior from baseline Psychology input as necessary	Behavior changes disrupting family/ school life	Severe behavior changes disrupting family/ school life	As for QOL issues
Weight (Wt)	Wt for age/ Ht/ BMI 0,3,6, 12 months,	Dietary advice	Change in weight centile from baseline Reinforced dietic input as necessary	25% or 3 centile increase from baseline	Weight gain unacceptable to child/ family despite dietic input/ dose reduction	Continue annually in long term
Height (Ht)	Standing Ht for arm span in non ambulatory children 0,3,6,12 m		Change in height compared to predicted centiles	Failure to gain height that is unacceptable to child/ family	Failure to gain height that is unacceptable to child/ family despite dose reduction	Arm span necessary for assessment of respiratory function in non ambulant pts
BD	0,3,6,12 months, etc….	Vit D, calcium dietary advice, sunshine , exercise	Fracture (#) , site, trauma. Limb # to be treated with early mobilization. Vertebral # to be treated with iv bisphosphonates			Long term risk of vertebral # s needs to be addressed by history Careful checking of Xrays obtained for other reasons for vertebral #
Glucose tolerance	Blood, urine glucose 0,3,6,12 months, etc….	Dietary advice		FBS >110 <126 mg/dl after dietary modification or 2hrs ABFI>140 <200mg/dl	Diabetes mellitus as defined as FBS >126mg/dl or blood glucose 2 hrs after a meal <200mg/dl	Urinalysis
Blood pressure	BP compared to age norms, measured 0,3,6,12 months, etc….	Advice about dietary sodium intake		Consistent ? in SBP 15mmHg over the 97th centile or DBP of 10mmHg over the 97th centile for age after sodium restriction	Confirmed HTN as defined as an ? SBP of 15-30 mm Hg over the 97th centile or DBP increased 10 30 mmHg over the 97$_{th}$ centile for height	
Immune/ adrenal suppression	Weight for age/ height/ BMI 0,3,6,12 months, etc	Dietary advice	Infectious disease. Abnormal response to stress	Unusually high frequency of infection/ unusual organisms		
Gastroint estinal symptoms	History of 0,3,6,12 months, etc….	Advise to avoid NSAIDs	Abdominal pain/ peptic ulceration	Persistent GIT symptoms despite treatment		H/O other GI symptoms in long term, e.g. constipation
Cataract	Opthalmologic al exam yearly for cataracts & IOP		Cataracts -,surgery. Increased IOP - opthalmological advice			Visual acuity assessment
Skin changes	H/O & exam at 0,3,6,12 m for atropy, easy bruising, fragility, striae, infections		Skin changes, type and extent. Treat infections as indicated			

Intermittent dosing allows the body to recover from the effects of steroids by allowing a period off the drug (alternate day regimes, regimes using 10 days on steroids and 10 or 20 days off, or vice versa) with or without reduction in the overall dose given[43-45]. Other regimes (daily low dosing) aim regimes (daily low dosing) aim to reduce the cumulative steroid dose, but good enough[46]. Children should have had chicken pox or chicken pox immunization prior to starting steroids. It is safe to use live vaccines in children treated with less than 2mg/kg/day of prednisolone[36].

Conclusion:

Long-term steroid use improves pulmonary function, delays boys becoming full-time wheelchair users, and at least delays the development of scoliosis. Current evidence raises the possibility that long-term use of steroids will result in improvement in quality and length of life in Duchene Muscular Dystrophy patients. So, all boys with this disorder should be treated with steroids early in their disease course, well before they reach the stage of full-time wheelchair use.

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CASE REPORTS

CASTLEMAN'S DISEASE: A CASE REPORT

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Abstract:

A 45 years old diabetic male was admitted under Department of Internal Medicine BIRDEM on June 2006 with the complaints of fever, multiple nodular swellings in neck and axilla for 6 months. On examination he had anemia, generalized lymphadenopathy involving all groups of cervical, axillary and inguinal nodes. He also had moderate hepato-splenomegaly. The patient was provisionally diagnosed as a case of Lymphoma. The differentials were – Chronic Lymphocytic Leukemia and Disseminated Tuberculosis. The hematological and radiological tests were inconclusive. The lymph node biopsy was diagnostic that revealed – Castle man's Disease. Castle man's Disease is a lymphoproliferative disorder, related to lymphoma. Although benign, it has malignant potential as it turns into Non-Hodgkin's Lymphoma. It is more in HIV infected people. It is clinically indistinguishable from lymphoma and the treatment is almost similar to that of Lymphoma

Introduction:

Castleman's disease is a benign disorder first described by Dr. Benjamin Castleman in 1956. Castleman's disease is also referred to as angiofollicular hyperplasia1, and is non-clonal disease of the lymph nodes. As the name angiofollicular hyperplasia (1) implies there is a follicular hyperplasia of lymph nodes with abnormally increased interfollicular vascularity. Castleman's disease is a rare disorder characterized by non-cancerous (benign) growths (tumors) that may develop in the lymph node tissue throughout the body (i.e., systemic disease [plasma cell type]). Most often, they occur in the chest, stomach, and/or neck (i.e., localized disease [hyaline-vascular type]). Less common sites include the armpit (axilla), pelvis, and pancreas. Usually the growths represent abnormal enlargement of the lymph nodes normally found in these areas (lymphoid hamartoma). There are two main types of Castleman's disease: hyaline-vascular type [2] and plasma cell type. The hyaline vascular type accounts for approximately 90 percent of the cases. Most individuals exhibit no symptoms of this form of the disorder (asymptomatic) or they may develop non-cancerous growths in the lymph nodes. The plasma cell type of Castleman's disease may be associated with fever, weight loss, skin rash, early destruction of red blood cells, leading to unusually low levels of circulating red blood cells (hemolytic anemia), and/or abnormally increased amounts of certain immune factors in the blood (hypergammaglobulinemia).

Case Summary:

The patient was a 45 year old diabetic, normotensive, smoker male with lower socio-economic background. He presented with 6 months history of gradual onset of low grade, irregular fever that was associated with rise of temperature mostly at evening or night. Fever persisted for about 1-2 hours and subsided with sweating. Fever was not associated with any chill, rigor, headache or myalgia. Patient also had severe anorexia, nausea along with generalized weakness and progressive weight loss for same duration. For the last 5 months, he noticed development of multiple nodular swellings at the neck, both axilla and groin. The swellings were gradually enlarging in size with a feeling of discomfort and heaviness, but there was no history of any local pain, temperature or discharge from the swellings. There was no history of any cough, sputum, breathlessness or vomiting. His bowel and bladder habits were normal. He was a known diabetic for last 6 years.

On examination, the patient had poor nutrition with BMI 20.2 and was anemic. He had generalized Lymphadenopathy involving cervical, axillary, inguinal regions. The lymph nodes were 2-5 in number in each group, Size varied from 2-5 cm, firm to rubbery in consistency, non-tender, discrete, mobile without any discharging sinus. Temperature and color of overlying skin was normal. There was hepato-splenomegaly. Liver was palpable, 4 cm, firm, smooth, non- tender. Spleen was also 4 cm, firm, and smooth, non-tender. There was no bony tenderness or any other organomegaly.

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Based on those findings and considering the socio-economic status, a provisional diagnosis was made as - Lymphoma (? Non – Hodgkin's)

Differential diagnosis was –
1. Chronic Lymphocytic Leukemia (CLL)
2. Disseminated TB
3. Sarcoidosis

Investigations revealed: Normochromic normocytic anemia (Hb- 10.2 gm/dl), normal count of WBC (8200/cmm), Platelet – 3, 55,000/cmm

ESR – 80 mm in 1st hr, C-reactive protein- positive (24 U/L)

PBF –non specific finding, STP- 72.4 gm/dl, Alb – 26.0 gm/dl. Other

biochemical parameters were normal. Chest X-ray was normal. USG of W/A showed - hepato-splenomegaly. Mantoux test was negative.

To confirm the diagnosis a lymph node biopsy was done from the axillary (Lt) nodes. Histopathology report of the biopsy revealed:

The normal nodal architecture is lost. The follicles show deposition of amorphous acidophilic material at the centre. The interfollicular area reveals diffuse infiltration by lymphocytes, plasma cells, polymorphs and histiocytes. A number of Russell bodies are found. Vascular proliferation is also noted. No granuloma or malignancy seen.

Comment:

Features are suggestive of Castleman's disease, plasma cell type. The histopathology slide was reviewed by the department of pathology BSMMU and re-confirmed the diagnosis. So the final Diagnosis was -Multicentric Castleman's Disease (Plasma cell type).

Subsequent investigations were done to exclude associated POEMS syndrome [3]. Clinically there was no evidence of any polyneuropathy or skin changes. He had no laboratory evidence of paraproteinaemia and his HIV status was negative.

For treatment, combination chemotherapy was planned and patient was referred to Oncology centre.

Discussion:

Castleman's disease can be classified as a) unicentric vs. multicentric, based on clinical and radiological findings, b) hyaline vascular vs. plasmacytic vs. mixed cellularity variety based on histopathology and c) as HIV negative versus HIV positive based on the HIV status of the patient. All three factors need to be taken into account in the assessment of patients.

Unicentric Castleman's Disease is usually a slow growing solitary mass typically located in the mediastinium or mesenteries. There are no constitutional symptoms and no elevation of acute phase reactants (Interleukin 6, ESR and CRP). Symptoms if present are due to a mass effect of bulky lymphadenopathy. In a few cases abnormal clonal, cytogenetic findings have been described arising from a dysplastic follicular dendritic cell network, but these findings are probably secondary and not causative to unicentric Castleman's Disease. In 90-95% cases surgical resection is curative and usually there is no progression to lymphoma or association with other tumors. The prognosis is excellent with a 5 yr survival of close to 100%.

In multicentric Castleman's Disease there is usually widespread lymphadenopathy with in some instances hepato-splenomegaly. "B" symptoms including severe fatigue (65%), night sweats, fever (69%), wt-loss (67%), anorexia are typically present. These symptoms are typically driven by overproduction of interleukin 6. Overproduction of interleukin 6 also results in an acute phase reactions with elevated ESR (77%), CRP, fibrinogen, thrombocytosis, and hypergammaglobinemia (73%). Patients typically have peripheral edema poorly responsive to loop-diuretics and suffer from anemia (61%) and hypoalbumenia. Approximately 20% of patients have peripheral neuropathy. The disease is non-clonal with no IgM or TCR gene rearrangements. Other conditions associated with multicentric Castleman's Disease include autoimmune hemolytic anemia, multiple myeloma, amyloidoisis, Pemphigus, and overlap syndromes with POEMS. Multicentric Castleman's Disease runs a more aggressive course and can progress to non-Hodgkin's lymphoma. Multicentric Castleman's Disease often requires systemic therapy. Our patient's presentations were like that of multicentric Castleman's disease.

The histopathology of hyaline vascular Castleman's disease shows that the lymph node germinal centers are poorly formed with dysplastic/ atrophic $CD21^+$ follicular dendritic cell networks surrounded by an expanded mantle zone consisting of rims of small $CD20^+$ lymphocytes arranged in an onion skin manner. There is increased interfollicular vascularity with capillary proliferation and endothelial hyperplasia. Plasmacytic variety of Castleman's Disease is characterized by both more numerous and larger hyperplastic follicles, which have more expanded mantle zones compared to hyaline vascular Castleman's disease. Sheets of plasma cells of plasma cells are present in the interfollicular areas.

The mixed cellularity form of Castleman's Disease has features of both hyaline vascular and plasmacytic types Castleman's Disease.

Classically it is thought that Unicentric Castleman's disease is usually of the hyaline vascular variety and multicentric disease of the plasmacytic type or mixed cellularity variety. These relationships are based on the analysis of the small numbers of patients since Castleman's disease is rare. Review of 37 patients with Castleman's disease treated at UAMS, which is the largest single institution experience in the world with Castleman's Disease. We found that patients with Unicentric Castleman's disease indeed have as pathology the hyaline vascular variety. However, the histopathology of multicentric disease can be evenly divided between hyaline vascular variety on one hand and plasmacytic type and mixed cellularity variety on the other hand. Mixed cellularity clinically behaves more like plasmacytic type rather than hyaline vascular disease.

HIV status is important as HIV+ patients with Multicentric Castleman's Disease have much frequent plasmacytic disease and the clinical course is less favorable than in HIV negative patients. Further, a good case can be made for HHV8 being the causative agent in HIV+ Castleman's Disease patient. HIV+ patients have more often Kaposi's sarcoma and more frequently progress to (plasmablastic non-Hodgkin's lymphoma)[4].

The etiology of Castleman's disease is still poorly understood. No genetic or toxic factor has been identified. The hypothesis of a viral infection has been raised. The authors of several studies have suggested the role of human herpes virus 8 (HHV 8), already implicated in Kaposi's sarcoma and which could be sexually transmitted [5]. In multicentric forms of CD, HHV-8 sequences have detected in 60% to 100% 0f the patients infected with HIV and in 20% to 40% of those who were not. These suggest two possibilities concerning the genesis of Castleman's disease: 1) the opportunistic presence of HHV-8, favored by immune perturbations; 2) the direct pathogenic role of HHV-8, in association with a dysregulation of cytokines. Recent studies seem to support the latter hypothesis because it was demonstrated that HHV-8 was able to produce an IL-6 homologue, vIL-6.

IL6 has been implicated in the pathophysiology of CD. It causes B-cell proliferation resulting in hyperplastic follicles and hence the enlarged lymph nodes (LNS). IL6 also increases secretion of vascular endothelial growth factor (VEGF), causing angiogenesis and capillary proliferation with endothelial hyperplasia. IL6 is also responsible for polarization of T lymphocytes to a Type 2 cytokine profile leading to autoimmune phenomena including AIHA, ANA positivity and elevation of IgE. IL6 induces an acute phase reaction comprising increases in ESR, CRP, IgGs, serum fibrinogen, and serum Amyloid A Protein (SAA). Increased SAA levels may result in AA Amyloidoisis, whilst hyperfibrinogenemia may play a role in venous thrombosis and thrombotic Finally, B-type symptomatology is virtually always associated with increased IL6 levels.

The diagnosis of CD is based upon a thorough clinical evaluation that includes a detailed patient history, laboratory studies, including IL6 and ESR, CRP, histopathology of affected lymph node(s) and a variety of imaging techniques (e.g. CT scan, MRI and more recently PET-scanning)[6]. Especially PET-scanning can complement CT-scanning by giving information regarding the metabolic status of lymph nodes. Usually the specific uptake values (SUV) of FDG-avid lymph nodes are less than those observed with active lymphoma. However, after therapy with for instance IL6-receptor antibody disappearance of all increased metabolic activity can be observed in responding patients. PET scanning therefore is not only useful in diagnosis, but also in assessment of response to therapy.

Surgical excision is the preferred treatment in most cases of unicentric Castleman's Disease and adjuvant therapy e.g. steroids and/or rituxan before surgery is very useful to shrink bulky or inoperable disease. In some cases, radiotherapy has proven effective, although this is currently usually avoided.

A number of therapies have been used for multicentric disease: intravenous immunoglobulin, anti-herpes drugs e.g. acyclovir, (Val) ganciclovir in HIV+ and HHV8+ disease, combination chemotherapy [7] e.g. CHOP and in intractable cases even autologous stem cell transplantation. Other therapies include the anti-angiogenesis factor thalidomide and anti-IL6 therapy. Surgery may also be useful in debulking disease.

Anti-IL6 therapies include suramin, anti-IL6- or anti-IL6 receptor antibody. Suramin is polysulfonated urea compound originally used for trypanosomiasis.. Suramin inhibits viral reverse transcriptase and it has a number of biological effects, which include inhibition growth factor and cytokine binding to their respective receptors e.g. IL6, L2, IL6, PDGF, and FGF. Suramin also modulates cytokine secretion. Anti-IL6 antibody is particularly effective in controlling IL6 related symptoms, but can also induce disease regression with durable remissions. More recently, a clinical trial with anti-IL6 receptor antibody has

been used started at MIRT with equal if not better responses than observed with IL6 antibody.

Overall, the diverse therapies induce a partial remission in 65% of the patients and a cure in 21%. But the prognosis of multicentric form remains poor, with a 5 year mortality rate of 18%.

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KALA-AZAR IN A PATIENT WITH HEMOGLOBIN E DISEASE: A DIAGNOSTIC PITFALL—A CASE REPORT

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Introduction

A Young lady from an endemic area for kala-azar presented with the history of irregular fever and splenomegaly of three years duration. Within this period, she had received four full courses of Inj. Sodium stibogluconate as treatment for Kala-azar on the basis of positive Aldehyde Test (AT) and Direct Agglutination Test (DAT) without any demonstration of Leishman - Donovan (LD) bodies in various tissues. Subsequently, the patient was admitted in Bangabandhu Sheikh Mujib Medical University (BSMMU) and investigated further. Though AT, DAT and ICT for Kala-azar with rK 39 antigens were positive, repeated splenic aspirates and a bone marrow study for LD bodies yielded no parasite. Splenic aspirate culture in NNN media was also negative. Investigation for her anaemia revealed Hemoglobin E disease.

Case report

A 26-year-old woman, mother of 5-year-old healthy daughter hailing from Tangail was admitted with the history of irregular fever and splenomegaly of 3 years. Initially, the fever was of high grade and intermittent in nature. Then, she was diagnosed as a case of Kala-azar on the basis of DAT and treated with adequate dose and duration of Inj. Sodium stibogluconate. Following the treatment, her fever had subsided but splenomegaly failed to regress and progressively increased in size. Later she developed occasional bouts of low-grade intermitent fever, which were never documented. AT and DAT were positive throughout this period and on this basis she was treated with further three full courses of inj. Sodium stibogluconate as a relapse case of Kala-azar. There was increased tiredness but no history of weight loss or any bleeding manifestations. There was no history of blood transfusion in the past. Other past and family histories were unremarkable. However, a number of her other family members had received treatment for Kala-azar in the recent past.

Examination revealed that the patient was of frail build and average nutrition with moderate anemia and mild icterus. She also had mild facial dysmorphism. She remained afebrile during her 2 weeks of hospital stay. The patient had no clubbing, oedema or lymphadenopathy. There was moderate, firm hepatosplenomegaly. Ascites was absent.

Blood examination revealed haemoglobin-7.4 gm/dl, ESR-135 mm in first hour, WBC- $11X10^9$/L. In peripheral blood film, RBCs showed severe anisopoikilocytosis with microcytosis and hypochromia. Plenty of target cells and few pencil and teardrop cells were also seen. Platelets were adequate. MP was not found. Reticulocyte count was 1%. Routine urine examination and chest skiagram were unremarkable. USG revealed hepato-splenomegaly with normal echotecture and also had cholelithiasis. Aldehyde test, DAT and ICT for Kala-azar with rK 39 antigen were strongly positive. Kala-azar antigen detection in urine (Latex agglutination) was negative. Liver function tests revealed serum bilirubin-29 μmol/L, SGPT 57U/L, SGOT 40 U/L, albumin 30 gm/L and PT 15 secs. Oesophago-gastroduodenoscopy revealed normal oesophagus stomach and duodenum. Repeated splenic aspirates and a bone marrow study for LD bodies yielded no parasite, neither macroscopically nor by culture. Hemoglobin electrophoresis revealed Hemoglobin E disease (Hb-E- 91.8%) and shown in figure 1.

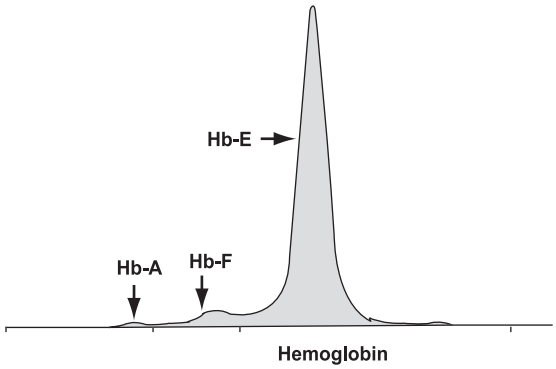

Fig.-1. *Hemoglobin electrophoresis report (Hb-E disease i.e. Hb-A 1.4%, Hb-F 6.8% & Hb-E 91.8%).*

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Discussion

Kala-azar or Visceral leishmaniasis is endemic in many regions of Bangladesh. Until 2005, cases were reported from 34 of Bangladesh's 64 districts[1]. Of all cases, more than 90 percent were reported from just 10 districts[1] of which Tangail is one of them. This patient hailed from there. The disease is characterized beside other features by fever and hepatosplenomegaly. This patient initially had one bout of high-grade intermittent fever 3 years back, which probably was due to Kala-azar because she resided in an endemic area. It is also evidenced by positive DAT and ICT. After receiving the first course of Inj. Sodium stibogluconate she was probably cured. Her subsequent bouts of fever were never documented. They could have been due to any other common self-limiting febrile illnesses. The patient was repeatedly treated with Sodium stibogluconate considering her to be a relapse case of Kala-azar because of hepatosplenomegaly and positive DAT tests. However, DAT does not differentiate between past kala-azar, sub-clinical infection and active disease[2]. It remains positive in patients for several years after cure of the disease[3].

At present, she had no evidence of current infection with Leishmania as her repeated splenic aspirates and a bone marrow study were negative for LD bodies. Even, splenic aspirate in NNN media yielded no growth. However, her hepatosplenomegaly probably persisted because she had coexisting Hemoglobin E (Hb E) disease. Though Hb E disease is asymptomatic, this patient had anemia, jaundice and hepatosplenomegaly. So, we are not sure whether the past morbidity aggravated the condition. It could also be because of the ongoing hemolysis as the patient has moderate degree of anemia, mild icterus, raised bilirubin level and cholelithiasis in USG.

This report also shows that in a patient with kala-azar whose liver and spleen fail to regress in time following treatment, the treating physicians should bear in mind the possibility of other causes. The disease may coexist with other diseases having similar features. In our set up, hemoglobin disorders should specifically be considered as Hemoglobin E (Hb E) is the most prevalent hemoglobinopathy in South-East Asia[4]. It is found in the eastern half of the Indian sub-continent and throughout South-East Asia, where in some areas, carrier rates may exceed 60% of the population[5].

The diagnosis of kala-azar is classically made by demonstration of *Leishmania* parasites in various tissues like lymph node, bone marrow and spleen. Of the procedures, splenic aspiration is more sensitive than bone marrow aspiration. In a study carried out in Bangladesh, LD bodies were found in 90 percent and 72 percent of the spleen and bone marrow aspirates of Kala-azar patient's respectively[6]. However, these procedures for demonstration of parasites are not available in rural health set up of Bangladesh and the diagnosis is very often based on DAT. However, this test cannot differentiate among past kala-azar infection and active disease as demonstrated in our case. Besides, DAT may be positive in endemic healthy individuals. This may be explained by constant exposure of individuals to sand fly bite resulting in latent or subclinical infection[7]. Therefore, clearly, there is a need for the provision of other simple, sensitive and affordable serological tests that can be performed in the peripheral health set ups which can differentiate these conditions.

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