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"Treatment Modalities of Pemphigus Vulgaris: A Study in A Tertiary Care Hospital, Cumilla, Bangladesh"

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Abstract: *We carried out a clinical study in the Dept. of Dermatology and Venereology, Cumilla Medical College Hospital, Cumilla, Bangladesh during the period from January 2017 to December 2017. Our aim was to evaluate the efficacy and safety of three currently used treatment modalities for pemphigus. Sixty (60) patients of pemphigus (pemphigus vulgaris and severe cases of pemphigus vegetans, pemphigus foliaceous and pemphigus erythematosus) were divided into three groups. Thirty (30) patients were treated with Prednisolone, Fifteen (15) with a combination of Prednisolone plus azathioprine and 15 patients with betamethasone-cyclophosphamide pulse (BC) therapy. All patients were followed from 10 to 20 months (mean 15 months), There was no statistical difference between steroid and azathioprine-corticosteroid therapy groups in terms of time taken to achieve initial control of the disease but the frequency of relapses and the incidence of complications were higher in patients treated with corticosteroids alone (p<0.05). A marginally increased susceptibility to infections was seen in patients treated with BC therapy as compared with azathioprine-corticosteroid group (p=O.07). Sixty (60) percent patients treated with BC therapy required additional steroids in between the monthly pulses, indicating failure of BC? as sole therapy. It was concluded that azathioprine-corticosteroid treatment of pemphigus was more effective and comparatively safer than steroid alone or BC therapy.*

Key words: *Effectiveness, Prednisolone, Pemphigus vulgaris*

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I. Introduction

Pemphigus is a disease that causes blisters and sores on the skin or mucous membranes, such as in the mouth or on the genitals. Pemphigus can occur at any age, but it's most often seen in people who are middle-aged or older. It tends to be a long-lasting (chronic) condition, and some types can be life-threatening without treatment. Treatment with medication usually controls it. The risk of pemphigus increases if you're middle-aged or older. Antigen-antibody interaction is responsible for detachment of epithelial cell from each other[1]. Survival of these patients has improved since 1950 when systemic corticosteroids were introduced[2]. Oral piednisolone was administered initially in three divided daily doses to obtain a rapid control of the disease. Daily single-dose and alternate-day corticosteroid treatment schedules do reduce the incidence of side effects8 but the response may be delayed[3,4]. Once the disease process was controlled, a shift to single morning dose and then to alternate day therapy was made in order to reduce the long-term complications of corticosteroid administration. A maximum daily dose of 120 mg of Prednisolone was effective in controlling skin blistering. The much higher dosage recommended by Lever[9] was not used because of the adverse effects observed by others[4,5,6]. Reported deaths with generalized skin lesions became rare but side effects of steroid therapy became the major cause of mortality4. Because of the problem of steroid-related side effects, adjuvants like cytotoxic drugs, gold, dapsone and cyclosporin have been added to the treatment of pemphigus to attain a steroid-sparing effect. These agents, however, are not without side effects. Opinion in the literature is divided the optimum dosage of steroids and efficacy immunosuppressive agents in pemphigus5. The present study was done to evaluate the efficacy and safety of three currently used treatment modalities in pemphigus. Clinical trial of this sort, simultaneously comparing three different treatment regimens, has not been reported locally.

II. Objectives

General Objectives:

- To evaluate thetreatment modalities of Pemphigus vulgaris in Bangladesh

Specific Objectives:

- To find out Type of Pemphigus in Bangladesh

III. Method and Materials

This was a clinical study in the Dept. of Dermatology and Venereology, Cumilla Medical College Hospital, Cumilla, Bangladesh during the period from January 2017 to December 2017. Our aim was to evaluate the efficacy and safety of three currently used treatment modalities for pemphigus. Sixty (60) patients of pemphigus (pemphigus vulgaris and severe cases of pemphigus vegetans, pemphigus foliaceous and pemphigus erythematosus) were divided into three groups. Thirty (30) patients were treated with Prednisolone, Fifteen (15) with a combination of Prednisolone plus azathioprine and 15 patients with betamethasone-cyclophosphamide pulse (BC) therapy. All patients were followed from 10 to 20 months (mean 15 months), Group I had more patients than groups II and III because cytotoxic drugs were avoided in pregnant and lactating women and non-affording patients were also allocated to Group I.Diagnosis of pemphigus was established on the basis of clinical features and skin biopsies with DIF(Direct immunofluorescence). Clinical parameters were recorded in a specially designed proforma and the severity of pemphigus graded according to the percentage of body surface area involved as recommended by Piainphogsant and Ophaswongse[6]. Laboratory evaluation included full platelet count, ESR, fasting blood sugar, blood urea, serum creatinine, LFTs, serum electrolytes, urinalysis, complete stool examination and chest X-ray. Group I was given glucocorticosteroids as the specific therapy. The starting dose varied from 60-120 mg/day of Prednisolone, given in two divided doses, depending upon the seventy and type of pemphigus (Table II). First reduction of 20-25% in the initial dose of steroid and conversion to single daily morning dose were made when 80-90% of the initial lesions had healed. Subsequent reductions of smaller volume were made monthly. Once a daily dose of 40 mg of Prednisolone was achieved without loss of control over disease activity, an attempt was made to shift the patients on alternate-day steroid therapy. They were then, maintained on 40 mg of Prednisolone on alternate days for 4-6 months. If they remained in clinical remission, further gradual reductions of 2.5 mg Prednisolone every 2-3 weeks were made. In case of any relapse, the dose of Prednisolone was escalated by 25 to 50% every one to two weeks, depending upon the rate of progression, until control was attained. Patient's clinical condition was the main parameter used to adjust the dosage of steroids.Group II was given azathioprine (100-150 mg/day) in addition to the usual Prednisolone dosages as mentioned for Group I. With the control of the disease, steroids were tapered first followed by reduction in azathioprine. Group III was placed on betamethasone cyclophosphamide pulse (BCP) therapy. Each monthly pulse consisted of 100 mg of betamethasone, dissolved in 5% dextrose, given in a drip over a period of 2-3 hours on three consecutive days. In addition, 500 mg of cyclophosphamide was added in the same drip on the first day. In between the pulses, patients were given 50 mgofcyclophosphamide orally each day. Each cyclophosphamide infusion was accompanied by vigoms oral hydration to promote frequent urination for 24 hours to protect the bladder from toxic effects. The BCP therapy was divided into four phases. During phase I, patients continued to have pemphigus lesions. The lesions would, however, tend to heal after each monthly pulse but after a few days new lesions would appear. After avariable number of betamethasone-cyclophosphamide pulses, the relapses would start becoming milder and ultimately the patients would go into the next phase (i.e., phase II), the phase of remission while on the therapy. After the patients had remained in clinical remission for a minimum of 6 months, monthly courses of BCPs were stopped, but 50 mg cyclophosphamide was continued (phase III). After one year of phase III, oral cyclophosphamide was also withdrawn and the patients were followed for a minimum of two years (phase IV), to confirm the possibility of a complete cure. The three treatment groups were compared with regards to the time taken for healing of lesions, frequency of relapses and incidence of treatment related complications. Patients were seen every week or two while being treated with divided daily doses of Prednisolone and until the disease was clinically active. Thereafter, regular follow-ups were done once a month. The chi-squared test was used for statistical analysis. Significance was defined as $p<0.05$.

Table 1: Starting dose of Prednisolone (mg/day)

Pemphigus vulgaris and vegetans	
Mild(15% body area)	60
Moderate(15-40% body area)	60-90
Severe(>40 body area)	90-120
Pemphigus foliaceus and erythematosus	
Mild and Moderate(35% body area)	30-40
Severe	40-50

IV. Results

Thirty (30) patients of pemphigus (pemphigus vulgaris 25 and pemphigus foliaceus5) were treated with glucocorticosteroids as the specific therapy (Group I). Of these, Four (4) patients were lost to follow up and ten (10) were non-compliant to the treatment schedules prescribed so that their status could not be evaluated for comparison. Six (6) patients died after a variable period of treatment, three(3) because of uncontrolled infections, two(2) due to adrenal insufficiency and one (1) because of unknown cause (Table III).Initial control of the disease was achieved in 5-50 days (mean 21.9).At the end of the study period, ten (10) patients in this group were in clinical remission and were taking 15-40 mg of Prednisolone on alternate days (Table IV).Group II consisted of 15 patients, thirteen of pemphigus vulgaris and one each of pemphgigusvegetans and pemphigus foliaceus (Table V). One patient was lost to follow up and one died due to bronchopneurnoma. Two patients were non- compliant with the therapy, rest of eleven patients were symptom free at their last follow up and were taking 10-30mg of Prednisolone on alternate days in addition to 100-150 mg/day azathioprine (Table IV).The duration of treatment before the initial control of disease was achieved varied from 7 to 48 days (mean 21.2). Seventeen patients of pemphigus (pemphigus vulgaris 12, pemphigus foliaceus 4 and pemphigus erytheinatosus 1) were treated with betamethasone-cyclophosphamdie pulse (pemphigus vulgaris 10, pemphigus foliaceus 2) were given additional 20-30 mg of Prednisolone per day for first 2-3 months as BCP therapy alone failed to control skin blistering. In this group, three patients were lost to follow up after an average period of 2.7 months. One patient died of bronchopneumonia, one due to septicemia and another because of ischaemic heart disease. One patient died at home of unknown cause. Because of poor response to BCP therapy, two patients of pemphigus foliaceus were shifted to conventional steroid therapy after 4-5 months. Eight patients were in clinical remission at their last follow up; three were receiving BCPs, while in five patients monthly pulses had been stopped and they were taking only 50 mg cyclophosphamide daily. The duration of phase I varied from 3 to 1 month (mean 6.6 months). Once the patients went into clinical remission (phase II), they remained in remission. Table V and VI list the treatment related complications observed in the patients who are now in clinical remission. Some patients developed more than one form of complications and/or repeated episodes of a single side-effect.

Table 1I: Distribution of Type of Pemphigus in the study participants (n=60)

Type of Pemphigus	Group I	Group II	GroupIII
P. vulgaris	25	12	11
P. vegetans		2	
P. foliaceus	5	1	3
P. erythematosus			1
Total	30	15	15

Table III: Status of the patients at the end of the study (n=60)

	Group I	Group II	Group III
Remission	10	9	8
Death	6	1	3
Lost to follow up	4	1	4
Non-complaint	10	4	0
Total	30	15	15

Table IV: Systematic complications of the therapy (n=27)

	Group I(n=10)	Group II(n=9)	Group III(n=8)
Respiratory infection	7	3	5
Dyspepsia	4	2	1
Nausea	1	1	1
Obesity	8	2	1
Myopathy	2	1	1
Hyperglycemia	0	0	0
Psychosis	2	0	0
Amenorrhea	2	1	2
Electrolyte imbalance	2	2	1
Osteoporosis	1	0	0
Cataract	1	0	0

Table V: Cutaneous complications of the theraphy(n=27)

	Group I(n=10)	Group II(n=9)	Group III(n=8)
Pyoderma	8	6	7
Eczema herpeticum	0	1	2
Candidiasis	1	1	1
Moon face	7	6	2

Acne	6	2	1
Striae	8	2	1
Hirsutism	2	0	0
Alopecia	2	3	3
Phlebitis	1	0	0

Table VI: Mode of death among the study participants (n=12)

	Group I	Group II	Group III
Infections	3	1	3
Unknown	1	1	0
Ischaemic heart disease	0	0	1
Adrenal insufficiency	2	0	0
Total	6	2	4

V. Discussion

Oral ulcerations were particularly difficult to treat and were very painful. Indeed, mucosal lesions of pemphigus respond to therapy more slowly than the skin lesions1[7].There was statistically no significant difference between Groups and B in terms of time taken to achieve initial control of the disease (p=0.9), but the frequency of relapses and incidence of treatment complications were higher in patients treated with steroids alone ($p<0.05$). Though at the end of the study period the maintenance doses of steroids in Groups A and B (15-40 and 10-30 mg on alternate days, respectively) were not much different, azathioprine allowed early reductions in Prednisolone dosages in Group II. This resulted in lower cumulative Prednisolone dose and hence reduced incidence of side effects in this treatment group. Group III was treated with an arbitrarily designed regimen pioneered by Pasricha[8]. We, however, used betamethasone instead of dexamethasone for monthly pulses.Prednisolone is the usual brand recommended for glucocorticosteroid pulse therapy[10], but betamethasone was chosen because of its easy availability and cost factor.Our results of betamethasone-cyclophosphamide pulse therapy were not as dramatic as are reported in the literature[9,11,12]. Twelve patients (70%) required additional Prednisolone in between the monthlypulses for first 2-3 months to lessen the seventy of the disease. Although the dosage of additional steroids used was smaller (20-30 mg of predmsolone per day) it does indicate the failure of BCP as sole therapy in initial stages of treatment. The other and more important drawback of BCP therapy was an increase in susceptibility to infections (p=0.07). Nine patients developed 14 episodes of respiratory tract infections, two developed eczema herpeticum and 9 patients suffered repeated attacks of moderate to severe pyogenic cutaneous infections. But metabolic complications of steroids and cyclophosphamide induced bone marrow suppression were not observed.

Though BCP therapy is not suitable for routine management of the patients with pemphigus, it may be used in patients with the severe disease refractory to less toxic form of treatment or for those who have coexisting medical illness (e.g. hypertension, diabetes mellitus) that could be exacerbated by long-term continuous use of corticosteroids.Multiple treatment schedules of glucocorticoids have been proposed for the management of patients with pemphigus. Lever recommended a high initial dose of 180-360 mg/day of prednisone to control the disease rapidly[9]. On the other hand, Hietaman and Salo[9] and Smorle and Arazt1[10] have treated pemphigus patients with Prednisolone in doses as low as 61.4 and 87 mg/day, respectively. Latter workers observed that patients receiving Prednisolone in a dosage of 120 mg/day had lower mortality rates than those who received higher doses of steroids[12]. Ratnam and associates reported that high dose Prednisolone therapy did not have any long termbenefit over the low dose regimenwith respect to the frequency of relapse or the incidence of complications[11].Though corticosteroids remain the mainstay of treatment for control of acute episodes[12], several adjuvants have become available for overall management of patients with pemphigus. Bystryn suggested that the remission rate of patients treated with adjuvants was only slightly better than those treated with corticosteroids alone[5]. But Pianiphongsant and Ophaswongse recommend the use of cyclophosphamide or other immunosuppressant agents like azathioprine as a standard therapy for all types of moderate or severe pemphigus[6]. Peiying and associates also believe that combination therapy in pemphigus is more effective than steroids alone[13]. Our results suggest that azathioprine-- corticosteroid treatment is highly effective and safe. Azathioprine exerted an impressive steroid-saving effect and this resulted in reduction of incidence of side effects (Table IV and V) and rate of relapses ($p<0.05$). Modality is also useful to control superficial variety of mild pemphigus manifested by only a few lesions. Some patients with limited disease can be controlled entirely by it without resorting to systemic therapy.

Limitations of the study

This was a single centre study with small sample size, which may not reflect the scenarios of the whole country.

VI. Conclusion and Recommendations

The treatment of pemphigus is equally an art and a science. Despite the growing catalog of statistics, pemphigus remains a disease that will not yield to a "cook-book" approach. Instead of a rigid treatment schedule, pemphigus patients require an individualized treatment regimen tailored to the needs of each patient, but of course, administered witha standardized approach. The results of our therapeutic trial suggest that azathioprine- corticosteroids combination treatment of pemphigiis is more effective and safe than corticosteroids alone or betamethasone- cyclophosphamide pulse therapy.

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