ORIGINAL RESEARCH

Comprehensive Analysis of Dexamethasone Methotrexate Pulse Therapy in Autoimmune Bullous Diseases: A Prospective Study on Clinical Types, Treatment Responses, and Complications

[1]Vithya R, [2]Mani Priya S, [1]Ammasaigoundan V, [*3]Selvaraju G

[1]Senior Assistant Professor, Department of Dermatology, Venereology, and Leprosy, Government Medical College and ESI Hospital, Coimbatore, Tamil Nadu, India.
[2]Senior Resident, Department of Dermatology, Venereology, and Leprosy, Velammal Medical College and Research Institute, Madurai, Tamil Nadu, India.
[*3]Senior Assistant Professor, Department of Anaesthesiology, Government Medical College and ESI Hospital, Coimbatore, Tamil Nadu, India.

Corresponding Author
Dr.Selvaraju G
Senior Assistant Professor, Department of Anaesthesiology, Government Medical College and ESI Hospital, Coimbatore, Tamil Nadu, India

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ABSTRACT

Background: This prospective study aimed to evaluate the efficacy and safety of Dexamethasone Methotrexate Pulse therapy in treating autoimmune bullous diseases, specifically Pemphigus Foliaceus, Pemphigus Vulgaris, and Bullous Pemphigoid.**Methods:**Eighteen patients were enrolled and treated at the Dermatology Department, Coimbatore Medical College and Hospital, undergoing monthly assessments, individualized medication, and close monitoring. Sociodemographic factors, clinical types, treatment responses, and complications were systematically analyzed.**Result:**Pemphigus Vulgaris emerged as the predominant clinical type (55%), with 67% of participants exhibiting severe disease. Remission rates varied; Pemphigus Foliaceus achieved 100% remission within 6 months, while Pemphigus Vulgaris showed rates of 30% within 6 months and 80% within 9 months. Bullous Pemphigoid demonstrated robust responses, with 100% achieving remission within 9 months. Immediate complications affected 11% of participants, including palpitations and diarrhea, while delayed complications were observed in 53%, encompassing weakness, infections, and weight gain.**Conclusion:**Dexamethasone Methotrexate Pulse therapy demonstrated varying efficacy across autoimmune bullous diseases. Notably, Pemphigus Vulgaris and Bullous Pemphigoid showed favorable responses. Immediate and delayed complications underline the need for vigilant management.

Key words: Autoimmune Bullous Diseases, Dexamethasone Methotrexate Pulse Therapy, Pemphigus, Bullous Pemphigoid, Treatment Response, Complications.

INTRODUCTION

Immunobullous disorders encompass a spectrum of heterogenous diseases classified based on clinical, histopathological, and immunopathological features, presenting both intra-epidermal and sub-epidermal variants.[1] Despite their rarity in the general population, these disorders can have a profound impact on an individual's quality of life, occasionally escalating to fatal outcomes for the affected patients.[2] Addressing the therapeutic challenges posed by immunobullous disorders is crucial for dermatologists, who are often pressured to achieve early remission and a steroid-free state.

The evolution of pulse therapy, characterized by the administration of drugs in large, intermittent doses to enhance therapeutic efficacy while minimizing adverse effects, has significantly influenced the management of various medical conditions.[3] Initially employed by Kountz and Cohn to prevent renal graft rejection, pulse therapy with corticosteroids found applications in diseases such as lupus nephritis, pyoderma gangrenosum, and rheumatoid

arthritis.[4]Notably, these therapies were reserved for emergency situations rather than serving as first-line treatments.

The introduction of Dexamethasone Cyclophosphamide Pulse (DCP) therapy by Pasricha et al marked a transformative milestone in the treatment of pemphigus, setting the stage for a paradigm shift in pulse therapy.[5] Dexamethasone, a corticosteroid, was strategically chosen for DCP therapy due to its notable attributes of cost-effectiveness and accessibility. This selection played a pivotal role in ushering in a new era for pulse therapy, making it more feasible for a broader patient population. The inherent qualities of Dexamethasone, such as its potent anti-inflammatory and immunosuppressive properties, contributed to its success in the treatment of pemphigus and paved the way for its application in other dermatological disorders.[6]

The ripple effect of the success of DCP therapy extended beyond pemphigus, gaining traction in the management of various dermatological conditions [7]. Autoimmune bullous disorders, characterized by blistering of the skin and mucous membranes due to an immune response against self-tissues, became one of the prominent beneficiaries of corticosteroid pulse therapy. Additionally, systemic sclerosis, systemic lupus erythematosus, dermatomyositis, pyoderma gangrenosum, toxic epidermal necrolysis, Steven Johnson's syndrome, lichen planus, alopecia areata, sarcoidosis, and systemic vasculitis were among the conditions where corticosteroid pulse therapy demonstrated efficacy.[8]

The current protocol for DCP therapy involves a carefully designed administration schedule. Patients receive 100mg of Inj. Dexamethasone in 500ml of 5% dextrose as a slow intravenous drip over 2 to 3 hours on three consecutive days. On the second day of the cycle, Inj. Cyclophosphamide at 500mg in 500ml of 5% dextrose is introduced through intravenous drip.[9] This structured regimen constitutes one cycle of DCP therapy, with cycles repeated at a 28-day interval, starting from the first day of the pulse. To maintain the therapeutic effect between pulses, patients are prescribed 50mg of oral Cyclophosphamide daily [9].

The versatility of DCP therapy is further highlighted by the availability of variations to suit individual patient needs. One such modification involves the replacement of Cyclophosphamide with Azathioprine at a daily dose of 50 mg. Alternatively, Methotrexate, administered at 10mg per week, offers another option for tailoring the therapy based on the patient's response and tolerance.[10]

The autoimmune bullous disorder, with its diverse manifestations, poses a considerable therapeutic challenge. While various modifications in DCP therapy have been proposed, the role of Methotrexate remains enigmatic, lacking conclusive evidence. Given the urgency to evaluate the efficacy and side effect profile of Dexamethasone Methotrexate Pulse therapy, our study aims to contribute meaningful insights into this unexplored dimension of immunobullous disorder management. This investigation represents a pivotal step toward addressing the lacunae in current treatment paradigms and offers potential avenues for enhancing patient outcomes.

MATERIALS AND METHODS

Study Setting: The study was conducted at the Skin Outpatient Department (OPD) of the Department of Dermatology, Venereology, and Leprology, Coimbatore Medical College and Hospital, Coimbatore. The research spanned from December 2018 to May 2020.

Study Design: This prospective study employed a longitudinal design to assess the efficacy of Dexamethasone Cyclophosphamide Pulse (DCP) therapy in patients with immunobullous disorders.

Study Participants: The selection of study participants for this research was carefully guided by inclusion and exclusion criteria to ensure a homogenous and representative cohort. Inclusion criteria encompassed newly diagnosed cases presenting with moderate to severe immunobullous disease, reflecting the focus on patients with a significant clinical burden. Additionally, participants were required to express a willingness to undergo monthly admission cycles, reflecting the unique and intensive nature of the proposed treatment approach.

Conversely, exclusion criteria were established to minimize confounding factors and potential risks. Patients with uncontrolled Diabetes Mellitus and Hypertension were excluded to maintain the integrity of the study outcomes. Individuals with a history of Myocardial infarction or compromised cardiac status were excluded due to potential risks associated with the proposed therapy. Hepatic or renal impairment, active Tuberculosis, and pregnancy or lactation were also grounds for exclusion, considering the potential impact of these conditions on patient safety and treatment outcomes. Further, the study excluded patients who refused to provide consent, ensuring ethical standards were upheld throughout the research process. Lastly, individuals previously on another treatment regimen were excluded to maintain the integrity of the study design, focusing on the specific intervention under investigation.

Sample Size and Sampling Technique: The study included patients attending the Skin OPD with immunobullous disorders during the stipulated period. The data was collected from a total of 18 patients. A systematic random sampling technique was employed.

Study Tools: The study tools used in this research are given below,

1. Clinical Evaluation: Details of the history and physical examination were meticulously recorded, with a focus on clinical features, Tzanck smear, and skin biopsy.
2. Weight Measurement: Patient weight was measured at enrollment and during subsequent admissions.
3. Disease Severity Grading: Disease severity was graded using the Fleischi criteria, where the number of bullae or erosions determined the classification as Severe (>40), Moderate (20–40), or Mild (<20). Severity in Pemphigus Foliaceus was also considered based on the involved body surface area.
4. Laboratory Evaluation: A comprehensive and systematic laboratory assessment was conducted at the onset of the study to gather essential baseline data on participants' health status. The battery of tests included in-depth analyses to provide a thorough understanding of the patients' overall well-being. These encompassed a complete hemogram, measuring parameters such as hemoglobin (Hb), total count (TC), differential count (DC), erythrocyte sedimentation rate (ESR), and platelet count. Additionally, blood sugar levels, blood urea, serum creatinine, and serum electrolytes were assessed to evaluate metabolic and renal functions. Liver function tests were employed to gauge hepatic health, while a urine routine examination provided insights into renal function. The presence of occult blood in stools was determined through a motion occult blood test, with additional scraping for Candida conducted if oral lesions were observed. Microbiological evaluations included pus culture and sensitivity, urine culture and sensitivity, and blood grouping and typing. Radiological investigations such as chest X-ray and Mantoux test were conducted to assess pulmonary health, complemented by ECG and cardiac evaluation to ensure cardiovascular well-being. Screening for sexually transmitted infections, including VDRL, and ELISA for HIV were integral components of the laboratory evaluation. Ophthalmology and Ear, Nose, and Throat (ENT) opinions were sought when deemed necessary, adding a multidisciplinary approach to the comprehensive assessment, enhancing the depth and breadth of the gathered data for a more holistic understanding of the participants' health profiles.

Study Methodology: The initiation of Dexamethasone Cyclophosphamide Pulse (DCP) therapy was a meticulously planned process, with particular attention given to controlling infections through systemic antibiotics, especially in cases where Candida scrapings were positive. In instances of Candida-positive findings, systemic antifungals, specifically Fluconazole (150mg orally biweekly for one week), were administered as a prerequisite before the commencement of DCP therapy.

The DCP therapy regimen was structured into four distinct phases, each playing a crucial role in the overall treatment approach. In Phase 1, patients received Inj. Dexamethasone (100mg dissolved in 500ml of 5% Dextrose) through slow intravenous infusion over 2 hours on three consecutive days, constituting one pulse. These pulses were then repeated every 4 weeks. Between pulses, patients were prescribed 10 mg Methotrexate once a week, and this phase continued until patients achieved remission. Remission, as defined by the disappearance of existing lesions and the absence of fresh lesions, served as a critical milestone.

Upon achieving remission, Phase 2 commenced, wherein Inj. Dexamethasone and 10 mg Methotrexate once a week were continued every month for a duration of 9 months. In Phase 3, the focus shifted to maintaining the progress with 10 mg Methotrexate once a week for an additional 9 months, while Inj. Dexamethasone was discontinued. Phase 4 marked the culmination of the treatment journey, with all medications being halted, and patients undergoing a follow-up period to assess the sustained effects of the therapy. This phased and systematic approach allowed for a comprehensive and structured management strategy, aiming to achieve remission while minimizing potential adverse effects associated with prolonged treatment.

Ethical Issues: Informed consent was obtained from all participating patients. The study adhered to ethical guidelines and was approved by the Institutional Review Board.

Statistical Analysis: The data analysis was carried out using IBM SPSS version 25. Descriptive statistics were employed to summarize patient demographics and clinical outcomes. Disease severity changes were analyzed using appropriate statistical methods.

RESULT

In this study, 18 cases of autoimmune bullous diseases, including Pemphigus Foliaceus, Pemphigus Vulgaris, and Bullous Pemphigoid, were treated with Dexamethasone Methotrexate Pulse therapy at the outpatient Department of Dermatology, Venereology, and Leprology, Coimbatore Medical College and Hospital. The investigation and treatment protocol involved repeated monthly laboratory evaluations, intermittent use of steroids and antibiotics based on individual needs, and careful monitoring.

The sociodemographic distribution of the study participants was analyzed, encompassing factors such as age, gender, and clinical types of autoimmune bullous diseases. A total of 18 participants were included in the study, with a mean age of 50 years. The age distribution revealed that the majority of patients fell within the age range of 41 to 50 years, comprising 33% of the total participants. Further breakdown showed 28% in the 31–40 age group, 22%

in the 51–60 age group, and 17% in the 61–70 age group. The age and gender distribution are given in Table 1.

Table 1: Age and gender distribution among the study participants

Age Group	Male	Female	Total
31 – 40	2	3	5
41 – 50	4	5	9
51 – 60	3	3	6
61 – 70	2	3	5
Total	11	14	25

Gender distribution indicated that out of the 18 participants, 44% were male and 56% were female. Analyzing the age and gender distribution together, it was observed that most patients in the study, irrespective of clinical type, belonged to the 41–50 age group. Specific breakdowns for Pemphigus Vulgaris, Pemphigus Foliaceus, and Bullous Pemphigoid were provided, showcasing variations in age and gender distributions within each clinical type.

In terms of clinical types, Pemphigus Vulgaris emerged as the predominant condition, representing 55% of the cases. Bullous Pemphigoid accounted for 28%, and Pemphigus Foliaceus constituted 17% of the study population. Severity grading using the Fleshchi et al. criteria revealed that 67% of the patients had severe disease, while 33% had moderate severity. The distribution of participants across different phases of treatment showed that the majority were in Phase 2 by the end of the study. Phase 1 accounted for 11.1%, Phase 3 for 38.8%, and no participants reached Phase 4 due to the study's relatively short duration.

The study participants were closely examined for the distribution of remission, with a focus on specific clinical types of autoimmune bullous diseases. For Pemphigus Foliaceus, 100% of patients attained remission within 6 months. In contrast, Pemphigus Vulgaris exhibited varied remission rates, with 30% achieving remission within 6 months and 80% within 9 months. Bullous Pemphigoid demonstrated a robust response, with 100% of patients achieving remission within 9 months.

When considering the gender distribution within Pemphigus Vulgaris, it was found that out of 10 patients, 40% were male and 60% were female. Further stratification based on age revealed that the majority of patients were in the 31–40 age group, with a mean age of 44.1 years. In Pemphigus Foliaceus, gender distribution showed that 67% were female, while 33% were male. Age distribution indicated that most patients were in the 41–50 age group, with a mean age of 54.3 years. Bullous Pemphigoid presented with a gender distribution of 40% male and 60% female. The majority of patients in this category fell within the 51–70 age group, with a mean age of 59.2 years.

The severity of diseases in Pemphigus Vulgaris was distributed as follows: 30% had moderate severity, and 70% had severe severity. In Pemphigus Foliaceus, 33% had moderate severity, and 67% had severe severity. Bullous Pemphigoid exhibited a distribution of 40% moderate severity and 60% severe severity.

Table 2: Immediate complications reported in study participants

Immediate Complications	No. of Patients	Percentage
Palpitations	2	11%
Diarrhea	2	11%
Hiccups	1	5%
Muscle Pain	1	5%
Vomiting	1	5%

Table 3: Delayed complications reported in study participants

Delayed Complications	Number of Patients	Average Number of Pulses	Percentage
Menstrual Irregularities	2	4	11%
Weakness	5	2.5	27%
Rise in FBS	3	6	16%
Infections	4	3	22%
Hair Loss	2	7	11%
Headache	1	3	5%
Taste	1	3	5%
Weight gain	4	7.5	22%
Arthralgia	1	8	5%
Increase in BP	3	3.5	16%

Sleep Disturbances	1	7	5%
Striae	1	6	5%
Blurring of vision	1	6	5%
Gastritis	3	3	16%

Note: FBS - Fasting Blood Sugar

Tables 2 and 3 summarize the immediate and delayed complications observed during the study, providing a clear overview of the occurrences and percentages associated with each complication

DISCUSSION

The present study investigates the efficacy of Dexamethasone Methotrexate Pulse therapy in treating autoimmune bullous diseases, specifically Pemphigus Foliaceus, Pemphigus Vulgaris, and Bullous Pemphigoid, within the outpatient Department of Dermatology, Venereology, and Leprology at Coimbatore Medical College and Hospital. The comprehensive investigation and treatment protocol, involving monthly laboratory evaluations, intermittent steroid and antibiotic administration, and vigilant monitoring, aimed to analyze the sociodemographic distribution, clinical types, severity, and remission patterns among the participants.

The sociodemographic analysis revealed a diverse participant pool of 18 cases, with a mean age of 50 years. The age distribution highlighted a concentration in the 41–50 age group, constituting 33% of the total participants. Interestingly, irrespective of clinical type, patients predominantly belonged to the 41–50 age group. Gender distribution demonstrated a slight predominance of females, comprising 56% of the participants. The amalgamation of age and gender data elucidated a commonality in the 41–50 age group across various clinical types were similar to the results obtained in a study done by Mahajan VK et al.[11]

Examining the clinical types, Pemphigus Vulgaris emerged as the predominant condition, representing 55% of cases, followed by Bullous Pemphigoid at 28%, and Pemphigus Foliaceus at 17%. Severity grading utilizing Fleshchi et al. criteria disclosed a predominance of severe disease (67%) over moderate severity (33%). The distribution across different treatment phases indicated that most participants reached Phase 2, with 11.1% in Phase 1 and 38.8% in Phase 3. The relatively short study duration precluded participants from reaching Phase 4. These were similar to the results obtained by Hassan I et al.[12]

The investigation of remission distribution within specific clinical types showcased distinct patterns. Pemphigus Foliaceus demonstrated a notable 100% remission rate within 6 months, while Pemphigus Vulgaris exhibited varying rates, with 30% achieving remission within 6 months and 80% within 9 months. Bullous Pemphigoid exhibited a robust response, with all patients attaining remission within 9 months.[13]

Further dissection of Pemphigus Vulgaris revealed a gender distribution of 40% male and 60% female, predominantly in the 31–40 age group with a mean age of 44.1 years. Pemphigus Foliaceus displayed a gender distribution of 67% female and 33% male, concentrated in the 41–50 age group with a mean age of 54.3 years. Bullous Pemphigoid manifested a gender distribution of 40% male and 60% female, with the majority in the 51–70 age group and a mean age of 59.2 years.

Severity analysis indicated that in Pemphigus Vulgaris, 30% had moderate severity, and 70% had severe severity. In Pemphigus Foliaceus, 33% had moderate severity, and 67% had severe severity. Bullous Pemphigoid demonstrated a distribution of 40% moderate severity and 60% severe severity.

Immediate complications, such as palpitations, diarrhea, hiccups, muscle pain, and vomiting, were observed in varying percentages, providing insights into the treatment's acute effects. Additionally, delayed complications, including menstrual irregularities, weakness, rise in fasting blood sugar, infections, hair loss, headache, taste alterations, weight gain, arthralgia, increased blood pressure, sleep disturbances, striae, blurring of vision, and gastritis, were meticulously documented, shedding light on the long-term effects associated with Dexamethasone Methotrexate Pulse therapy.[14]

This study contributes valuable insights into the sociodemographic distribution, clinical types, severity, remission patterns, and complications associated with Dexamethasone Methotrexate Pulse therapy in autoimmune bullous diseases. The findings underscore the importance of personalized treatment approaches, considering the diverse manifestations and responses observed across different clinical types.[15] Further research with larger cohorts and extended follow-up periods is warranted to consolidate these observations and enhance the understanding of optimal therapeutic strategies for autoimmune bullous diseases.

Limitations: Despite the valuable insights gained from this study, certain limitations must be acknowledged. The relatively small sample size of 18 participants may impact the generalizability of findings. Additionally, the study's duration limits the ability to observe long-term outcomes beyond Phase 3 of treatment. External factors, such as variations in individual responses and potential confounding variables, could influence the results. Moreover, the study's single-center design may introduce institutional bias.

CONCLUSION

This study on autoimmune bullous diseases, including Pemphigus Foliaceus, Pemphigus Vulgaris, and Bullous Pemphigoid, revealed significant insights.

The study demonstrated the effectiveness of Dexamethasone Methotrexate Pulse therapy in treating autoimmune bullous diseases, emphasizing the importance of considering disease severity for individualised treatment plans. The findings contribute valuable insights into the demographic and clinical characteristics, treatment outcomes, and complications associated with the pulse therapy approach.

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