Original Article

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Dermatology Section

Effectiveness of Corticosteroids Alone versus Corticosteroids and Cyclosporine in the Management of Patients with Severe Cutaneous Drug Reaction

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ABSTRACT

Introduction: Severe Cutaneous Adverse Reactions (SCADRs) are emergency dermatologic manifestations associated with high morbidity and mortality. Their management includes immediate withdrawal of suspected causal agent followed by prompt management with drugs such as corticosteroids, cyclosporine and cyclophosphamide.

Aim: To compare the effectiveness of corticosteroids alone versus cyclosporine and corticosteroids in management of SCADRs.

Materials and Methods: This was a prospective observational study carried out in Indoor patients of Dermatology Department, Civil Hospital Ahmedabad, Gujarat, India, from October 2019 to September 2022. Twenty six patients were diagnosed with SCADRs and grouped according to the treatment received in two groups: corticosteroids alone (group B), and corticosteroids along with cyclosporine (group A). The efficacy was assessed based on: the days of disease arrest, days of complete re-epithelialisation, duration of hospitalisation and final outcome. To know the prognosis of the patients, Score of Toxic Epidermal Necrosis (SCORTEN) score was used. Data was entered and analysed with the help of Microsoft excel ® 2019.

Results: There were 14 patients in group A and 12 in group B. In a total 26 cases majority were of Stevens-Johnson Syndrome (SJS) (50%) followed by SJS-Toxic Epidermal Necrolysis (TEN) (27%) TEN (15%), Drug Reaction with Eosinophilia and Systemic Symptom (DRESS) (8%). The mean duration of disease arrest was significantly shorter in group A (n=14) when compared to group B (n=12) (p-value <0.001**). Also, the time for complete re-epithelisation was significantly shorter in group A than group B (p-value=0.025*). While no significant difference between the two groups was observed in SCORTEN score. Mortality was 3/12 in group B, nil in group A.

Conclusion: Combination therapy with corticosteroids and cyclosporine leads to an early arrest of the disease progression, better prognosis and outcome in patients of SCADRs.

Keywords: Adverse drug reaction, Immunosuppressive drugs, Steven johnson syndrome, Toxic epidermal necrolysis

INTRODUCTION

An adverse cutaneous drug reaction is any undesirable change in the structure or function of the skin, its appendages or mucous membranes. It encompasses all adverse events related to drug eruption, regardless of the aetiology [1]. Adverse Drug Reactions (ADRs) are responsible for upto 7% of hospital admissions. Upto 30-45% of the ADRs are dermatology related, 2% of which may be severe and may have mortality rate as high as 10-30% [2]. Life-threatening severe cutaneous ADR are TEN, SJS, Acute Generalised Exanthematous Pustulosis (AGEP), and DRESS. Though rare in incidence, death rate can be as high as 25% in adults with TEN and even higher in older adults with very severe blistering. The death rate in children is estimated to be under 10% [3]. In SJS, the death rate is about 5%, while DRESS has a mortality rate of 10% [4]. About 200 drugs are implicated in this condition with highest relative associated with sulphonamides, Non Steroids Anti-Inflammatory Drugs (NSAIDs), allopurinol, antimetabolite like methotrexate, antiretroviral drugs, antiepileptics like phenobarbitone, phenytoin, carbamazepine, valproic acid etc., [5-7].

Management of SCADR consists of immediate cessation of an offending drug, definitive therapy and adequate supportive care [8]. Corticosteroids and immunosuppressive drugs like cyclosporine remains the mainstay definitive therapy for the management of SCADRs. Corticosteroids inhibit the epidermal apoptosis by several mechanisms like suppression of various cytokines, such as Tumour Necrosis Factor-α (TNF-α), Interferon (IF)-γ, Interleukin (IL) 6 and IL10 and inhibition of Fas-mediated keratinocyte apoptosis [8,9]. Cyclosporine acts by inhibiting the activation of CD4+ and CD8+ (cytotoxic) T-cells in the epidermis by suppressing IL2 production from activated T-helper cells which plays critical role in pathology of SCADRs. Intravenous Immunoglobulins (IVIG) and Anti-TNF-α agents have also been in use for treatment of SCADRs [10]. Various studies have been carried out to assess treatment efficacy in SCADR as they propose a significant risk of morbidity and mortality. However, all these therapies have variable success rates in terms of duration of hospitalisation, time taken for complete re-epithelialisation, and arrest of disease activities [8,9,11].

The Indian guidelines in 2016 recommended use of corticosteroids for 10-14 days may also be used either alone, or in combination with Cyclosporine [8]. Thus, the present study was undertaken to compare the effectiveness of corticosteroids alone versus cyclosporine and corticosteroids in management of SCADRs and to evaluate the causal drugs for SCADRs and their clinical outcome.

MATERIALS AND METHODS

It was a prospective observational study carried out in all the in-patient cases of Dermatology Department, Civil Hospital Ahmedabad, Gujarat, India, diagnosed with SCADRs for a period of 24 months October 2019 to September 2021. Following permission from Institutional Ethics Committee (Ref. No. EC/Approval/ 52/2020).

Inclusion criteria: Patients of all age groups and either gender diagnosed with SCADRs [12] by the clinician and willing to give written informed consent were enrolled in the study.

Exclusion criteria: Patients who refused to give written informed consent were excluded from the study.

Study Procedure

All the patients were visited everyday till their discharged/death, whichever was earlier. Information was obtained from the patients and/or his/her case papers and was recorded in Case Record Form (CRF). The treatment was decided by consultant (Dermatologist) as per diagnosis and clinical condition of the patient. Then later on patients were grouped into group A and B as follows:

Group A: Corticosteroids+Cyclosporine (cyclosporine 3-5 mg/kg/day oral suspension along with tapering doses of intravenous dexamethasone starting at 0.1 mg/kg/day)

Group B: Corticosteroids alone (intravenous dexamethasone at 0.1 mg/kg followed by oral prednisolone at 1 mg/kg/day) [8].

The data were analysed as per diagnosis, age, gender lag period for development of ADRs, presence of co-morbidity, causal drug group and causality analysis. The efficacy was assessed under outcome variable like days of disease arrest (defined by the time taken when new lesions cease to appear) [12], days of complete re-epithelialisation (defined by the time taken for complete healing of skin without any erosions) [5], duration of hospitalisation and outcome (death/recovered) [12].

SCORTEN is a scoring system for epidermal necrolysis, validated in the year 2000 in European population by Bastuji-Garin S et al., in patients of TEN and has been used in various parts of the world to evaluate the prognosis of SJS and TEN. A score from 1-7 predicts a probability of mortality from 3.2% to 90.0% [13]. The causality analysis of SCADRs was carried out using WHO-UMC causality assessment scale [14]. This scale gives the likelihood of relationship between drug and the suspected adverse reaction.

STATISTICAL ANALYSIS

Data was entered and analysed with the help of Microsoft excel ® 2019. The parameters between the groups were compared using student unpaired t-test and p-value less than 0.05 was considered statistically significant. The continuous variables were described in terms of {Mean and Standard Deviation (SD)} whereas, categorical variables were described in terms of percentage and number were compared using chi-square and p-value less than 0.05 was considered statistically significant.

RESULTS

Total 26 patients were enrolled in the study, 14 patients received a combination treatment of corticosteroid and cyclosporine (group A) whereas 12 received only corticosteroids (group B). Male to female ratio in group A was 1.33:1 and 1.4:1 in group B. Both groups were similar in age distribution. (Group A: 41.07±16.75 years, and group B: 40.91±16.27 years). Co-morbidities were present in nine patients in group A, whereas, seven patients in group B [Table/Fig-1]. The mean lag period for development of severe cutaneous ADR after drug intake was 9.10±3.66 days for group A, whereas it was 8.97±3.18 days for group B. Among the causal drugs antimicrobials (45.68%) were most common culprit drug in both the groups followed by antiepileptics (25.15%) and analgesics (18.52%) [Table/Fig-1].

Among antimicrobials cotrimoxazole, was the causal drug in four cases followed by levofloxacin, amoxicillin-clavulanic acid and nevirapine in three cases. Among antiepileptics, phenytoin contributed to six cases followed by carbamazepine three cases. In analgesic group most common causal drug diclofenac was observed in six cases. Ayurvedic medication was suspected to be the causal drugs in two cases. [Table/Fig-1] provides the details of the demographic characteristics, diagnosis and causal drugs in both the groups. The mean duration of disease arrest was significantly longer in group B (p-value <0.001**).

Also, the time for complete re-epithelisation was significantly shorter in group A than group B (p-value=0.025*). The mean duration of hospital stay was lesser in group A as compared to group B (p-value <0.046*). The predicted mortality in group A was 1.53 whereas observed mortality was zero (0/14) as per SCROTEN. For group B, predicted mortality was 2.102 whereas observed mortality was three (3/12). Mortality rate was higher in group B. [Table/Fig-2] depicts the comparison of the outcome variables among the two groups.

Variables	Group A (n=14)	Group B (n=12)	p-value
Age in years* (Mean±SD)	41.07±16.75	40.91±16.27	0.491
Male	8 (57.14%)	7 (58.33%)	0.498
Female	6 (42.85%)	5 (41.66%)	
Lag period in days* (Mean±SD)	9.10±3.66	8.97±3.18	0.621
Delay from disease onset to presentation to the hospital in days* (Mean±SD)	6.07±1.63	5.58±1.24	0.203
Co-morbidities	9	7	0.06
Diagnosis			
SJS	7	6	0.985
SJS-TEN	4	3	
TEN	2	2	
DRESS	1	1	
Causal drug groups antimicrobials	11 (44%)	9 (47.36%)	0.468
Antiepileptics	6 (24%)	5 (26.31%)	
Analgesics	4 (16%)	4 (21.05%)	
Antigout	2 (8%)	0 (0.00%)	
Others	2 (8%)	1 (5.2%)	
Causality analysis (WHO UMC [14])			
Probable	6	4	0.685
Possible	7	7	
Unassessable	1	1	

[Table/Fig-1]: Demographic details, diagnosis and causal drug groups.
*Student's unpaired t-test
Others: Chi-square

Variables	Group A (n=14)	Group B (n=12)	p-value (student's unpaired t-test)
Arrest of disease activity (Mean±SD) days	5.28±1.26	7.16±0.71	0.001
Complete re-epithelialisation (Mean±SD) days	10.85±2.46	12.53±2.46	0.025
Mean hospital stay (Mean±SD) days	12.85±2.38	14.33±2.01	0.046
Mortality			
Predicted	1.53	2.102	NA
Observed	0/14	3/12	

[Table/Fig-2]: Comparison of outcome variables.

DISCUSSION

The SCADRs are an important cause of morbidity, hospitalisation, increased health expenditure and even death [15]. This was a prospective study carried out at Department of Dermatology, Civil Hospital Ahmedabad, Gujarat, India. Twenty patients were included in the study. The aim of the study was to find out effectiveness of corticosteroid alone versus corticosteroid with cyclosporine in management of severe CADRs. Corticosteroid with cyclosporine was found to be more effective than corticosteroid alone in management of severe CADRs. Male preponderance was observed (57.6%) which was similar to study conducted by Thakur V et al., they have 53% of patients are of male gender [16].

The management of these SCADRs include early recognition of the condition, prompt withdrawal of the causal drug, meticulous supportive care, referral if required, initiation of specific therapy, management of complications, and prevention of future episodes [17]. A recent meta-analysis of systemic therapies in SJS/TEN concluded that corticosteroids and cyclosporine are most promising therapeutic options [18].

Till date systemic corticosteroids have remained the mainstay of therapy of SCADRs. The rationale behind the use of corticosteroids is that these conditions are immune-mediated processes, and corticosteroids are known to suppress the intensity of the reaction, prevent/decrease the necrolysis of the skin, cause a reduction in fever, and prevent damage to internal organs when administered at an early stage and in moderately high dosage. Although corticosteroids successfully control disease activity in SJS/TEN, they may be associated with increased rate of infective complications, delayed healing, and longer hospital stay [19]. The underlying pathology of most SCADRs involves activation of cytotoxic T-cells by a drug with the consequent release of granulysin and activation of caspase cascade resulting in keratinocyte apoptosis. Cyclosporine inhibits the activation of CD4+ and CD8+ (cytotoxic) T-cells in the epidermis by suppressing IL2 production from activated T-helper cells. Cyclosporine has also been shown to inhibit TNF-α production. TNF-α is another important cytokine which is involved in the amplification of apoptotic pathways implicated in SJS/TEN [20,21]. Generally, a dose of 3-5 mg/kg body weight, as oral capsules or solution, in two divided doses over 10-14 days is commonly used.

The mean duration of disease arrest was significantly shorter in group A with steroids with cyclosporines (p-value <0.001**) compared to group B which used corticosteroids alone. A similar study by Siddhabathumi N et al., had days of disease arrest as 3.18±1.32 (Mean±SD) days in patients treated with cyclosporine and corticosteroids [19] whereas a study by Singh GK et al., had days of disease arrest as 3.18 days in cyclosporine Group and 4.75 days in corticosteroid group [12]. Hence, corticosteroid with cyclosporine leads to arrest of disease earlier than corticosteroids alone. Mean time for complete re-epithelialisation was 10.85 days (SD=1.79) in cyclosporine with corticosteroid group whereas it was 12.53 days (SD=2.46) in corticosteroid group (p<0.05). A study by Rajput CD et al., noted days of complete re-epithelialisation as 17.1±2.63 (Mean±SD) days in cyclosporine Group and 24.25±5.82 (Mean±SD) days in corticosteroid group which was different from our study [5] whereas, it was 14.54±4.08 (Mean±SD) days in a study done by Siddhabathumi N et al., in corticosteroid and cyclosporine treated group [19]. The re-epithelialisation at an early basis decreases the risk of exposure of skin to the environment thereby decreasing the chances of secondary infection early healing and overall decrease in hospital stay [19].

In the present study, mean duration of hospitalisation was 12.85 days (SD=2.38) in cyclosporine with corticosteroid group vs 14.33 days (SD=2.01) in corticosteroid group (p<0.05). A similar study by Rajput CD et al., showed a hospitalisation as 20.5±3.17 (Mean±SD) days in cyclosporine Group and 25.50±10.6 (Mean±SD) days in corticosteroid group [5] whereas it was 18.09±5.02 (Mean±SD) days in a study by Siddhabathumi N et al., in corticosteroid and cyclosporine treated groups [19]. A study conducted by Singh GK et al., reported a duration of hospital stay as 18.09 days in cyclosporine Group and 26 days in corticosteroid group [12]. There are very limited studies comparing corticosteroid versus with corticosteroid combined with cyclosporine. The present study showed the addition of cyclosporine to corecostroid is beneficial. The lesser hospitalisation is beneficial for both the patients and the hospital setups which helps to decrease the resource utilisation and economically beneficial.

No mortality was observed in addition cyclosporine to corticosteroid whereas three (25%) patients died in corticosteroid. A similar study by Rajput CD et al., had zero mortality in cyclosporine group (n=11) and two deaths in corticosteroid group (n=10) [5] whereas, in study by Siddhabathumi N et al., in corticosteroid and cyclosporine reported zero mortality (n=12) [19]. A study done by Singh GK et al., had zero mortality in cyclosporine group whereas two deaths were observed in corticosteroid group (n=6) [12].

Despite being above similarities there were certain differences from other studies in terms of days of disease arrest, days of re-epithelialisation, duration of hospitalisation and outcome in the present study which can be due to various factors like the age of patients in various studies, associated comorbidities in patients, different dose selection of the drug, delay in presentation of the patients to the hospital and also the severity of the disease. However, based on the present study, combination of corticosteroid and cyclosporine is highly effective in management of SCADRs.

Limitation(s)

The present study had a few limitations, this being an observational study the diagnosis and treatment was decided by the dermatologist. The sample size of the study was limited.

CONCLUSION(S)

Highly effective results are observed with corticosteroid and cyclosporine combination therapy in patients of SCADRs in terms of faster rate of re-epithelisation, decreased duration of hospital stay and no mortality. However, future studies with larger sample size are warranted to establish this efficacy.

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