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Original Article

Comparison of Cyclosporine with Systemic Corticosteroid in Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis - A Pilot Study

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Abstract

Background: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening dermatological emergencies. Many immunosuppressive modalities have been tried with variable results.

Aims: This study aims to determine the efficacy of cyclosporine in cases of SJS and TEN and compare the efficacy with systemic corticosteroid in the same condition.

Materials and Methods: The study was conducted at a tertiary hospital from January 2015 to December 2017. SCORTEN was assessed at the time of admission. Total body surface area assessment was like any burn patients. Cyclosporine was administered in the dose of 4 mg/kg body weight in two divided dosage for 7 days and then tapered over another 7 days. Data were compared to a similar control series of SJS/TEN patients, managed by systemic steroids in the same time period.

Results: A total of 19 consecutive patients with a mean age of 32.09 and standard deviation ([SD] 16.17) were enrolled into cyclosporine group, which were compared to 19 patients with a mean age of 27.87 (SD 13.97) years in the corticosteroid group. The mean duration of reepithelialization was 14.54 (SD 4.08) and 23 days (SD 6.68) in cyclosporine and corticosteroid group, respectively. Mean hospital stay was 18.09 (SD 5.02) and 26 (SD 6.48) days in cyclosporine and corticosteroid group, respectively. Total mortality was 9. A total of 3 patients died in the cyclosporine group with 2 male and 1 female, compared to 6 deaths occured in corticosteroid group 4 female, 2 male.

Conclusion: This study definitely suggests that cyclosporine has encouraging role in the management of uncomplicated cases of SJS, SJS-TEN overlap, or TEN, but randomized control trails are needed for further confirmation.

Key words: Cyclosporine, Dexamethasone, Drug reaction, Scorten, Stevens Johnsons syndrome, Toxic epidermolytic necrosis

INTRODUCTION

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening dermatological emergencies mainly due to drugs characterized by peeling of skin along with hemorrhagic crusting of lips and erosions of oral and genital mucosa.[1] Worldwide, the average annual incidence of TEN is 0.4–1.3 cases per million populations. The mortality rate of SJS and TEN is high, approximately 5% for SJS and 30% for TEN.[2] Now, SJS, SJS-TEN overlap, and TEN are considered a spectrum of the same condition having common risk factors and causes, differentiated only by the extent of the body surface area (BSA) involved. Patients with epidermal detachment involving <10% of BSA are classified as having SJS, more than 30% BSA as TEN, and 10–30% as SJS/TEN overlap.

Apoptosis is believed to be the primary mechanism responsible for keratinocyte death in SJS/TEN. Two pathways have been proposed to support this theory. The first theory proposes that cytotoxic T-cells are activated by an inciting drug, which leads to the release of granzyme B

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and perforin, thereby activating the caspase cascade that ultimately results in keratinocyte apoptosis. The second theory proposes that Fas-Fas ligand binding activates caspase 8, which results in nuclease activation and the widespread skin blistering characteristic of this severe drug reaction.

A prognostic score called SCORTEN has been validated to demonstrate its ability to specifically predict patient outcome in SJS and TEN.[3] Even though some uncertainty still persists on effector mechanisms of TEN, the resemblance to graft rejection provided a rationale for using the immunomodulating agents. There are several studies illustrating variable results in the management of SJS/TEN. These included corticosteroids, plasmapheresis, cyclophosphamide,[4] and thalidomide. Fas-Fas ligand and cytotoxic T-cell which play a key role in the pathogenesis of SJS/TEN are, respectively, blocked by intravenous immunoglobulin (IVIG) and cyclosporine.[5] Thus, theoretically making, IVIG and cyclosporine effective drugs in the management of SJS/TEN.[6-8] Several case reports have suggested encouraging results with IVIG in management of SJS/TEN. However, a study by Bachot *et al.*[9] did not show any improvement with IVIG. In Indian subcontinent, managing SJS/TEN by IVIG is not cost-effective. In addition, there is no double-blinded controlled trial, which suggests IVIG superior than other modalities. Several case reports and case series revealed encouraging result of the use of cyclosporine in stopping disease progression and to prevent the mortality.[8,10] In Indian subcontinent, systemic steroids have traditionally been used to manage this condition due to its experience of use, easy availability, and cost-effectiveness despite having multiple complications.[11] This study was designed to evaluate the efficacy of cyclosporine and compare the results with patients who were managed by systemic steroids in tertiary healthcare setting.

MATERIALS AND METHODS

This was an open, pilot, and uncontrolled study. The study was conducted at Baba Raghav Das Medical College, Gorakhpur, from January 1, 2015, to December 30, 2017. A total of 38 patients were enrolled in the study during this period. All cases fulfilling clinical diagnoses of SJS, SJS-TEN overlap, and TEN, Figures 1-3 were included into the study. Exclusion criteria were prior treatment with any other immunosuppressive drugs, history of intolerance to cyclosporine, uncontrolled diabetes mellitus, human immunodeficiency virus (HIV) positivity, and cases of multiorgan failure and sepsis. It was decided in protocol that cyclosporine will be stopped if there is the development of high blood pressure with a diastolic pressure >110 mmHg and creatinine ≥150% of initial value. Irrespective of the clinical spectrum of disease (SJS/SJS-TEN overlap/TEN) cyclosporine was administered in solution form in the dose of 4 mg/kg body weight in two divided dosage for 7 days, then 2 mg/kg body weight in two divided dosage for another 7 days. If there was no requirement of cyclosporine, it was to be stopped after 7 days of therapy. No other immunosuppressant was administered. Cases of SJS, SJS-TEN overlap, and TEN were managed in the general ward of the Department of Dermatology. It was proposed in the protocol that if there is clinical deterioration in the cases of SJS/SJS-TEN overlap, those would be managed in the burn center having intensive care facility. Barrier nursing, ambient temperature of 30°C, fluid and electrolyte balance, and high calorie-containing diets were considered in each patient. Injectable antibiotics were considered in strongly suspected or evident sepsis mostly managed on azithromycin or linezolid.

Figure 1: (a) Typical hemorrhagic crusting on lips in a patient with toxic epidermolytic necrosis (b) bullous eruptions and erythema on trunk in a patient with Stevens-Johnson syndrome

Figure 2: Detached skin of the hand in a patient with toxic epidermal necrolysis

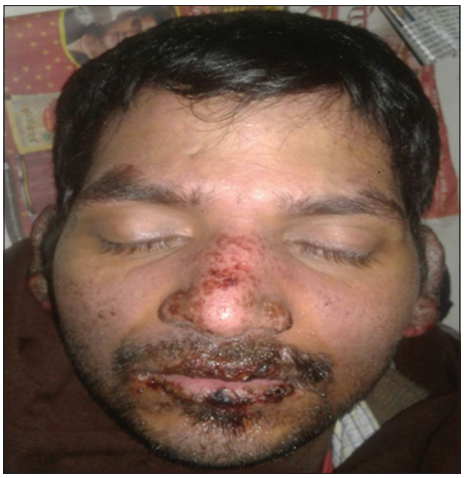

Figure 3: Involvement of the face in a patient of toxic epidermal necrolysis

The patients were evaluated clinically daily for the entire period of hospitalization. Data were filled as per predesigned pro forma. Efficacy of cyclosporine was assessed by the average number of days in stabilization of disease progress, rate of reepithelization of skin, duration of hospitalization, tolerance to treatment, and rate of mortality at 1 month in comparison with the predicted death estimated by the SCORTEN at the time of admission. The actual death rates were compared to the predicted rates by standardized mortality ratio analysis (sum of observed deaths/sum of expected deaths) × 100. The SCORTEN calculation was as per the study of Bastuji-Garin *et al.*[3] Stabilization of disease was defined when new lesions cease to appear. Progression of disease was evaluated by any increase in erosions, blistering, and positive Nikolsky's sign. Reepithelization was defined as complete healing of the skin without any erosion. Total BSA (TBSA) assessment was like any burn patients, following rule of nine. Monitoring of patients was like well-established Intensive Care Unit protocol. We compared the data with a side-by-side study with the patients admitted to our hospital during the same period who were managed with systemic steroids in similar setup. The inclusion and exclusion criteria remained the same as it was considered for the cyclosporine therapy except the fact these patients were managed by systemic steroid. These patients were treated with injectable dexamethasone 2 ml twice a day for 2 consecutive days tapered to 2 ml once in morning and 1 ml once in evening for 2 days, followed by 1 ml twice a day for 2 days then stopped by giving to 1 ml once in morning.

RESULTS

A total of 19 cases of SJS/TEN were seen from January 1, 2015, to December 30, 2017, who were treated by cyclosporine. No patient was dropped out from the study because of adverse effects of cyclosporine. A total of 19 consecutive patients (12 men and 7women) were enrolled; they were aged 32.09 ± 16.17 years (mean ± standard deviation [SD]) M: F (12:7). Mean ± SD delay between onset and admission was 2.63 ± 0.67 days (range 1–4). There was no intolerance to cyclosporine. Five cases of SJS were given cyclosporine only for 7 days due to marked improvement in the clinical condition. Rest in other cases, full 14 days course, as proposed in the protocol, was given three patients died (2 male and 1 female); however, there was no long-term complication in patients who survived the episode.

There were a total of 19 cases of SJS, SJS-TEN overlap, and TEN from January 1, 2015, and December 30, 2017, who were treated by corticosteroid. Mean delay between the onset of the disease and admission was 2.16 (SD 0.75) days. 6 patients died under this treatment regimen (4 female and 2 male). Only one case developed long-term complication that is corneal ulcer with symblepharon.

Based on the SCORTEN system, 7.39 patients were expected to die in patients treated by cyclosporine. While in patients treated by corticosteroid, 8.8 patients were expected to die. The comparison of mortality rate along with SCORTEN is depicted in Table 1.

The age and initial TBSA, which might have interfered with the clinical outcome, were also analyzed. There were no statistically significant differences ($P > 0.05$). The time from the onset of the disease to admission was also not significantly different ($P > 0.05$). However, cyclosporine had significantly reduced the time to the arrest of progression of SJS/TEN ($P = 0.04282$), the total reepithelization time ($P = 0.009956$), and hospitalization stay ($P = 0.02597$) in comparison to corticosteroid. Those, who survived the disease, both drugs were tolerated well by the patients. Only one patient treated by cyclosporine developed corneal ulceration with symblepharon, which was statistically insignificant ($P > 0.05$).

DISCUSSION

The Cochrane review on intervention for TEN revealed only one randomized controlled trial. This trial compared the effectiveness of thalidomide with placebo. The only trial available used thalidomide, but this trial did not show any benefit from treatment compared against placebo but highlighted increased chances of dying from the treatment. Role of steroids in the management of TEN has been controversial. Several studies had shown possible benefit of corticosteroids. However, of late, most of the studies criticized the use of corticosteroids stating it not only prolongs the hospital stay but also makes patients susceptible for complications. A retrospective analysis of 289 patients from the EuroSCAR study found no benefit from corticosteroids or IVIG compared to supportive care alone.[12] Even the combination therapy of IVIG and

Table 1: Data of mortality of patients of SJS/TEN managed by cyclosporine and corticosteroid

SCORTEN	Expected mortality %	Cyclosporine group			Corticosteroid group		
		Number of patients	Number of death		Number of patients	Number of death	
			Predicted	Actual		Predicted	Actual
0–1	3.2	5	0.16	0	3	0.96	0
2	12.3	4	0.50	0	5	0.61	0
3	35.3	3	1.0	0	4	1.41	0
4	58.3	5	2.93	1	4	2.3	2
5-7	90	3	2.8	2	4	3.6	4
TOTAL	19	19	7.39	3	19	8.8	6

TEN: Toxic epidermal necrolysis, SJS: Stevens-Johnson syndrome

corticosteroid did not find any significant decrease in the mortality rate. In the paucity of data on effective drug for SJS/TEN, prompt withdrawal of causative drugs should be a priority when managing such cases. Garcia-Doval *et al.* have shown that the earlier the causative drug is withdrawn, the better the prognosis and that patients exposed to causative drugs with long half-lives have an increased risk of dying. To identify the culprit drug(s), it is important to consider the chronology of administration of the drug and the reported ability of the drug to induce SJS/TEN. The reported ability or likelihood of a drug being the cause of SJS/TEN can be found in PubMed/MedLine or other appropriate sources such as the Litt's drug eruption reference manual. SJS/TEN is a life-threatening condition, and therefore, supportive care should be an essential part of the management strategy.

Our study was distinct in the way; it had evaluated the efficacy of cyclosporine and compared historically to corticosteroids. It highlighted few important results. Cyclosporine was well tolerated by all the patients. There were three deaths in the patients managed by cyclosporine while there were five deaths in the corticosteroid group. All these results were statistically significant with $P < 0.05$. The only complication noted was a corneal ulceration and symblepharon formation. High survival in cyclosporine group could be explained by probable mechanism of action of this drug, which targets cytotoxic T-cell, which plays an important role in the apoptosis of keratinocytes. Other probable explanation could be better patient selection by excluding patients of multiorgan failure, sepsis, and HIV, which are the groups who succumb to death very fast when they develop SJS/TEN.

Recently, Valeyrie-Allanore *et al.*[12,13] conducted an open, phase II trial to determine the safety and possible benefit of cyclosporine. A total of 29 patients were included in the trial (10 SJS, 12 SJS-TEN overlap, and 7 TEN), and 26 completed the treatment with cyclosporine administered orally (3 mg/kg/d for 10 days) and tapered over a month. The prognostic score predicted 2.75 deaths and none occurred ($P = 0.1$). There was no comparison with any historical group of corticosteroid. This study suggested that both the death rate and the progression of detachment seemed lower than expected, suggesting a possible usefulness of cyclosporine in SJS and TEN.

A case series reported by Arevalo *et al.*[14] in which 11 patients treated enterally with cyclosporine 3 mg/kg daily observed a rapid epithelialization with no significant toxicity in comparison with patients treated with cyclophosphamide and corticosteroids combined. Similar findings were noted by Reese *et al.* in four patients with SJS/TEN who were managed by cyclosporine.

This study provided an excellent result with cyclosporine; however, comment on its efficacy cannot be made due to inherent constraint of the study design. An open, uncontrolled study with very small sample size in each group and selection of uncomplicated cases is obvious limitations of this study, which may have favored the better outcome of cyclosporine. A large, double-blind, placebo-controlled, randomized trial would be more appropriate to confirm its efficacy, which is not only unpractical but also unethical. Like most of the recent studies, our study also finds the use of corticosteroid in the management of SJS/TEN cause prolong hospital stay and increase in the mortality rate. This study definitely suggests that cyclosporine has encouraging role in the management of uncomplicated cases of SJS and SJS-TEN.

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