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The Role of Oral Cyclosporine in the Management of Steven Johnson Syndrome and Toxic Epidermal Necrolysis: A Retrospective Multicentric Observational Study

Rajnish Kumar¹, Rashmi Singh^{2*}, Uday Kumar Udayan³

¹Senior Resident, Department of Skin and VD, Darbhanga Medical College and Hospital, Laheriasarai, Bihar, India

²Assistant Professor, Department of DVL, Heritage Institute of Medical Sciences, Bhadwar, Varanasi, Uttar Pradesh, India

³Assistant Professor and Head, Department of Skin and VD, Darbhanga Medical College and Hospital, Laheriasarai, Bihar, India

***Corresponding Author:** Rashmi Singh, Assistant Professor, Department of DVL, Heritage Institute of Medical Sciences, Bhadwar, Varanasi, Uttar Pradesh, India; E-mail: sweetrashmi4364@gmail.com

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Abstract

Background: SJS and TEN are severe life threatening muco-cutaneous reactions characterised by extensive epidermal sloughing with mucosal erosions.

Objective: The main objective of this study was to observe the effectiveness of cyclosporine in reducing the mortality and healing time of lesions in patients of SJS and TEN.

Methods: The present work was designed as a retrospective tertiary urban hospital based, observational study during the period from March 2019 to Feb 2020. Detailed history, physical examination including cutaneous examination was done at the time of admission and the assessment of lesions using SCORTEN scoring was done at baseline, on day 3 and on tenth day of cyclosporine. All the routine investigations were done in each case. As per hospital records, oral cyclosporine in the dose of 5 mg/kg body weight per day was given to each patient for ten days.

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Results: Out of 18 patients, 10 patients were of TEN, 6 patient of SJS/TEN overlap and 2 patients were of SJS. Females were predominant in the study (females: males: 2:1). The most common culprit drug identified was phenytoin (50%) followed by carbamazepine and lastly NSAIDs. Mean SCORTEN at the time admission was 2.6 and it was observed to decrease following cyclosporine. Epidermal detachment was found to reduce by 4th day and complete re-epithelisation was seen around 15th day in majority of the patients.

Conclusions: Oral cyclosporine was found to be effective in reducing mortality and improving overall prognosis and re-epithelisation i.e complete healing of skin without any erosion, in patients of SJS/TEN.

Keywords

SJS/TEN; SCORTEN; Cyclosporine; Prognosis; Re-Epitheliasation

Introduction

Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are severe, drug reactions affecting both skin and oral as well as genital mucosa leading to large areas of denuded skin and threatens life in all age groups. Though, mostly SJS and TEN are drug induced but sometimes, these may result from infections like mycoplasma. The common culprit drugs include antiepileptics, sulfonamides, β -lactam antibiotics, NSAIDs and allopurinol. It is a fatal form of drug induced hypersensitivity reactions [1].

Earlier, both were considered to be different entities clinically but now they are included under same heading, the only difference being of extent of skin denudation. The term SJS is used when the body surface area is less than 10%, SJS/TEN overlap when the BSA is between 10 to 30% and TEN, when the body surface area involved is more than 30%. [2]. The diagnosis is usually obvious clinically and histopathology not required routinely but if done – apoptosis of keratinocytes is the hallmark finding [3]. Though, SJS/TEN can occur in any age group but is more commonly seen in women ratio being 1.5: 1 [4].

Cyclosporine is a potent immunosuppressant isolated from soil fungus *trypocladium inflatum* gams. Cyclosporine acts by inhibiting calcineurin inhibitors and thus reducing IL-2. It inhibits IFN- γ produced by T- Lymphocytes and reduces keratinocytes activity.

The main aim of our study is to find the role of cyclosporine in treatment of patients of SJS and TEN.

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Methods

The study was done retrospectively using previous records from drug reaction register of the departments of in-patients of SJS and TEN admitted in the Department of Dermatology in Darbhanga Medical College, Bihar and in Heritage Institute of Medical College, Bhadvar, Varanasi, over a period of 1 year from March 2019 to Feb 2020. Approval from the institute's ethical committee was taken.

The details of the clinical and demographic informations of 18 patients of SJS and TEN were recorded in tabular form which included their SCORTEN scores. The names of all the culprit drugs responsible for SJS and TEN were noted.

Intensive supportive care given to patients of both SJS and TEN as per record included - Fluid and electrolyte balance, vitals (pulse, blood pressure, temperature and urine output), nutritional supplementation and wound care. The ophthalmologist consultation was routinely done for eyes to prevent infections, scarring and vision loss. The drug reaction wounds were dressed routinely with topical antibiotics, bactigrass and dry gauge.

Cyclosporine was given orally in the dose of 5 mg/kg body weight/day for ten days.

The involvement of epidermis in terms of Total Body Surface Area (TBSA) was noted daily in printed charts to determine the date of arrest of progression and of complete re-epithelisation.

SCORTEN, is a validated scoring method for severity of SJS and TEN and helps in predicting the mortality in such patients. The score is calculated with 1 point per variable: Age > 40 years, TBSA > 10 %, presence of malignancy, heart rate > 120 beats/min, blood urea > 10 mmol/l, serum bicarbonate < 20 m eq/l and glucose > 14 mmol/L.

Using this criteria, score was calculated at the time of admission, on day 3 and after 10 days of receiving oral cyclosporine therapy and its efficacy was assessed in terms of healing of lesions and mortality of the patients.

Results

A total of 18 patients were included in the study of which 2 patients were of SJS, 6/18 of SJS and TEN overlap and 10/18 were of TEN (Table 1-3).

Disease Entity	No. of Cases
SJS	2
SJS/TEN Overlap	6
TEN	10

Table 1: Number of cases with different disease entity.

Age Group	No. of Cases
15-30	4
30-45	9
45-60	3
60 and above	2

Table 2: Age groups. Mean age of the patient was 42.4 years.

Sex	No. of Cases
Males	6
Females	12

Table 3: Patient genders. 66% of the patients were females whereas 34 % were males.

In the present study phenytoin was the most common culprit (50%) followed by carbamazepine (22.2%) and NSAID (16.6%) whereas causative agent could not be identified in rest of the cases.

Patients who developed TEN due to phenytoin were those patients who either had history of seizures or history of fall. Time interval between use of phenytoin and development of TEN was around 4-6 weeks in 6 patients while it was 3-4 weeks in 3 patients (Table 4).

Culprit Drug	No. of Cases
Phenytoin	9
Carbamazepine	4
NSAID	3
No Clear Cut History	2

Table 4: Results with different drugs testes on patients.

Mucosal Involvement

The oral mucosa was involved in almost all the patients, followed by genital mucosa followed by conjunctiva (Table 5).

Mucosal Involvement	No. of Cases
Oral	18
Genital	10
Conjunctival	8

Table 5: Mucosa was involvement in patients.

Mean SCORTEN at the time of admission was 2.6 (range 0-5) and it decreased following the treatment. SCORTEN score on 3rd day of admission was 1.9 and on day 10 it was less than one. Most patients improved significantly following therapy.

One patient developed hypertension following therapy and he was managed with ACE inhibitors, three patients complained of gastrointestinal upset in the form of nausea, vomiting and diarrhoea, in these patients doses was reduced by 1 mg/kg body weight following which they tolerated the drug. No patient died during a follow up period of 3 months.

The mean BSA (Body Surface Area) of epidermal detachment was reduced around fourth day and complete re-epithelization was observed in a mean interval of 15 days (Table 6) (Fig. 1-6).

SCORTEN	At The Time Of Admission (Mean)	On Day 3	On 10 th Day
	2.6	1.9	< 1

Table 6: Mean SCORTEN.

SCORTEN SCORE AT THE TIME OF ADMISSION DAY 0

atient rofile	AGE/SEX	AGE > 40 Year	TBSA > 10 %	Presence of Malignancy	HR > 120 beats/mi n	Serum Bicarbonate < 20 m Eq/L	B.UREA > 10 mmol/ L	GLUCOSE > 14 mmol/L	TOTAL SCORE
	18/F	0	1	0	1	0	1	0	3
	44/F	1	1	0	0	0	0	1	3
	29/F	0	1	0	1	0	0	0	2
	43/F	1	0	0	0	1	0	0	2
	27/F	0	1	0	0	0	1	0	2
	64/M	1	1	1	0	0	0	1	4
	39/M	0	1	0	0	0	0	1	2
	37/F	0	1	0	1	0	1	0	3
	56/F	1	0	1	0	0	0	1	3
0	58/M	1	1	0	0	0	0	0	2
1	48/F	1	1	0	1	0	0	0	3
2	28/F	0	1	0	1	0	0	0	2
3	65/F	1	1	1	0	0	0	1	4
4	41/M	1	1	0	0	0	0	0	2
5	42/M	1	1	0	0	0	0	1	3
5	42/F	1	1	0	0	0	0	0	2
7	39/F	0	1	0	1	0	0	1	3
8	44/M	1	1	0	0	0	0	0	2

Average SCORTEN ON DAY 0 - 2.6

SCORTEN SCORE ON DAY 3

atient rofile	AGE/SEX	AGE > 40 Year	TBSA > 10 %	Presence of Malignancy	HR > 120 beats/mi n	Serum Bicarbonate < 20 m Eq/L	B.UREA > 10 mmol/ L	GLUCOSE > 14 mmol/L	TOTAL SCORE
	18/F	0	1	0	0	0	1	0	2
	44/F	1	1	0	0	0	0	1	3
	29/F	0	1	0	1	0	0	0	2
	43/F	1	0	0	0	0	0	0	1
	27/F	0	1	0	0	0	1	0	2
	64/M	1	0	1	0	0	0	0	2
	39/M	0	1	0	0	0	0	1	2
	37/F	0	1	0	0	0	1	0	2
	56/F	1	0	1	0	0	0	0	2
0	58/M	1	1	0	0	0	0	0	2
1	48/F	1	1	0	0	0	0	0	2
2	28/F	0	1	0	1	0	0	0	2
3	65/F	1	1	1	0	0	0	0	2
4	41/M	1	1	0	0	0	0	0	2
5	42/M	1	0	0	0	0	0	1	2
5	42/F	1	1	0	0	0	0	0	2
7	39/F	0	1	0	1	0	0	0	2
8	44/M	1	0	0	0	0	0	0	1

Average SCORTEN ON DAY 3 - 1.9

SCORTEN SCORE ON DAY 10

Patient profile	AGE/SEX	AGE > 40 Year	TBSA > 10 %	Presence of Malignancy	HR > 120 beats/min	Serum Bicarbonate < 20 mEq/L	B.UREA > 10 mmol/L	GLUCOSE > 14 mmol/L	TOTAL SCORE
	18/F	0	0	0	0	0	0	0	0
	44/F	1	0	0	0	0	0	0	1
	29/F	0	0	0	0	0	0	0	0
	43/F	1	0	0	0	0	0	0	1
	27/F	0	0	0	0	0	1	0	1
	64/M	1	0	1	0	0	0	0	2
	39/M	0	0	0	0	0	0	1	1
	37/F	0	0	0	0	0	1	0	1
	56/F	1	0	1	0	0	0	0	2
0	58/M	1	0	0	0	0	0	0	1
1	48/F	1	0	0	0	0	0	0	1
2	28/F	0	0	0	0	0	0	0	0
3	65/F	1	0	1	0	0	0	0	2
4	41/M	1	0	0	0	0	0	0	1
5	42/M	1	0	0	0	0	0	0	1
6	42/F	1	0	0	0	0	0	0	1
7	39/F	0	0	0	0	0	0	0	0
8	44/M	1	0	0	0	0	0	0	1

Average SCORTEN ON DAY 10 - 0.9 i.e <1.

Figure 1: Baseline Photo of SJS.

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Figure 2: Photo at day10 after use of Cyclosporine in SJS.

Figure 3: Baseline Photo of SJS.

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Figure 4: Photo at day 10 of Cyclosporine in SJS.

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Figure 5: Baseline Photo.

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Figure 6: Photo of child of SJS at day10 of Cyclosporine.

Discussion

SJS/TEN are serious dermatologic emergencies caused mostly following hypersensitivity to drugs. In our study age of the patients was widely distributed (range -14 to 65) mean age being 42.4 years and had a female predominance. We found more cases of TEN (10 out of 18) as

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compared to SJS and SJS/TEN overlap. In our study, most common drug responsible for SJS/TEN, was found to be phenytoin followed by NSAIDs. However exact pathogenesis is not fully known it is suggested that on exposure to these drug or its metabolite, predisposed individuals develop immune reaction that leads to apoptosis of keratinocytes that furthcauses the epidermal detachment and mucosal erosion as well. This keratinocytes cell death leads to epidermal separation at dermo-epidermal junction [6].

While, few studies mention Fas receptor activation via Fas ligand leading to apoptosis in SJSandTEN, others suggest it to be mediated by TNF- α , perforin and granzyme B [7].

In SJS/TEN as there is epidermal detachment in sheets, the barrier function of the skin is lost. This leads to disturbance of fluid, protein, and electrolyte balance resulting in hypovolaemic shock and local and systemic infection with the threatening of sepsis, often leading to multiorgan failure - the most important causes of death and to avoid this, our focus should be on restoration of skin and mucosal barrier function and simultaneously preventing the adverse effects of already lost skin barrier [8]. Apart from withdrawal of the offending drug and intensive supportive care, there are no general accepted guidelines for the specific treatment of SJS/ TEN. The few of many treatment options available include intravenous immune globins, plasmapheresis, thalidomide, and short courses of high-dose corticosteroids in early SJS/TEN .These treatment modalities and also cyclosporine hit directly on to the apoptotic pathway involved in SJS/TEN probably due to their immunosuppressive and immune-modulatory nature [9].

The efficacy oral cyclosporine was evaluated according to arrest of further epidermal or mucosal detachment, healing time in days, outcome and sequelae. The patients stabilized after an average of fourth days, while total re-epithelialization was reached after around 15 days. No patient died during a follow up period upto 3 months. We calculated SCORTEN as validated predictive score for the outcome in SJS/TEN.

This study shows good results with cyclosporine in managing patients with SJS/TEN. Few studies have also shown efficacy of cyclosporine in SJS/TEN. In one study by Valeyrie-Allanore, et al., safety and possible benefits of cyclosporine was evaluated and it suggested that mortality and progression of epidermal detachment seemed lower than expected [10].

Arevalo, et al., in a case series found out rapid re-epithelisation with no significant toxicity at a dose of 3 mg/kg body weight of cyclosporine [11]. The cyclosporine is a good and safe alternative to steroids in treating cases of drug reaction especially SJS and TEN in all age groups and our study very well supports this. This further helps in reducing the hospital stay and hospital related infections and other issues faced by the patients and their attendants.

Conclusion

This retrospective study done by us in support to the use of cyclosporine in treatment of SJS/TEN and that it reduces both the mortality and healing time in such patients. Further, the study also clearly shows how cyclosporine helps in speedy reepithelization of skin and mucosa.

Conflict of Interest

There is no conflict of interest to declare.

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