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Successful treatment of toxic epidermal necrolysis using plasmapheresis: A prospective observational study

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ABSTRACT

Toxic epidermal necrolysis (TEN) is a rare, severe, life-threatening skin disease and it requires urgent critical care, including admission to the intensive care unit (ICU). It is characterized by fatal sequelae and high mortality. Currently, insufficient evidence exists to support the use of any systemic adjuvant therapy, such as cyclophosphamide, intravenous immunoglobulin (IVIg), or corticosteroids. However, plasmapheresis has been increasingly valued by clinicians due to its significant efficacy and little adverse side effects. To assess the efficacy of such treatment, 28 patients who were diagnosed with TEN or SJS/TEN overlap were continuously recruited in the ICU from February 2009 to August 2016. These patients including both children and adults were randomly divided into two groups based on whether or not plasmapheresis therapy was performed after admission, which resulted in a plasmapheresis group (n = 13) and a non-plasmapheresis group (n = 15). Severity of the disease and the efficacy of treatments were evaluated by the severity-of-illness score for TEN. The results indicated that plasmapheresis may be superior to conventional therapies, such as IVIg or corticosteroids. Furthermore, plasmapheresis combined with other treatments might not be advantageous compared to the effect of plasmapheresis alone.

1. Introduction

Toxic epidermal necrolysis (TEN) is a rare, severe, life-threatening skin disease characterized by extensive exfoliation of the epidermis and skin mucous membrane that is accompanied by systemic disturbances [1]. It is mainly induced by adverse drug reactions arising mostly from antibiotics, anti-retroviral therapies, allopurinol, anti-convulsants, or nonsteroidal anti-inflammatory drugs (NSAIDs) [2,3]. The vital characteristics of TEN include low morbidity, fatal sequelae, and high mortality in the intensive care unit (ICU). In a narrow sense, TEN is the most severe skin disease with maximum epidermal detachment of ≥30% body surface area (BSA) after admission. As a milder form of TEN, patients with SJS/TEN overlap exhibit less severe skin damage, which affects approximately 10%–30% of their body surface compared to >30% in TEN [4]. Although many studies have stressed the importance of the early diagnosis and rapid withdrawal of causative drugs and active adjuvant therapy, the best administrative strategy for controlling pathological progress and reducing the mortality of TEN remains controversial [1,5].

A literature review returned no convincing evidence to support the use of any systemic adjuvant therapy. A previous study has demonstrated that intravenous immunoglobulin (IVIg) could inhibit Fas-FasL mediated keratinocyte apoptosis in vitro [6]. Unfortunately, this was not consistent with the finding that IVIg failed to improve the survival rate of patients with TEN [1]. Moreover, because of their rapid anti-inflammatory effects, corticosteroids have become another popular treatment option for TEN [3,7]. However, systemic corticosteroids increase the risk of sepsis, which accelerates multiple organ damage and leads to higher mortality [8].

A range of other therapies, such as plasmapheresis, cyclophosphamide, cyclosporine, pentoxifylline, *N*-acetylcysteine, ulinastatin, and infliximab, have also been used in the treatment of TEN [9]. However, there is no clear and compelling evidence that supports the use of any

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of the above systemic adjuvant therapies. Although plasmapheresis is increasingly used by doctors in the ICU and researchers due to its significant advantages in reducing the mortality of TEN and shortening hospital stays, no results from prospective observational studies or randomized controlled trials have been provided [10,11]. In this study, we prospectively reviewed a group of 28 patients with TEN or SJS/TEN overlap admitted to the ICU. The basic clinical information of patients, the therapeutic effect, as evaluated using scores, and total medical expenditures were compared among different groups to confirm the effectiveness of plasmapheresis therapy.

2. Materials and methods

2.1. Design and study population

Twenty-eight patients with TEN or SJS/TEN overlap who were admitted to the ICU of the second affiliated hospital of Xi'an Jiaotong University from February 2009 to August 2016 were prospectively recruited. According to the 2016 United Kingdom guidelines for the management of SJS/TEN in adults, TEN is defined as epidermal detachment of >30% of the BSA, and SJS/TEN overlap is defined as detachment of 10%–30% of the total BSA [12]. Patients with a maximum epidermal detachment of 10–30% of the BSA were also incorporated into the TEN group in this study [1].

2.2. Group and treatments

All patients were randomly divided into either the plasmapheresis group (n = 13) or the non-plasmapheresis group (n = 15) on the basis of whether plasma exchange was performed after admission. Subsequently, the plasmapheresis group was further divided into two subgroups: the pure plasmapheresis group, whose members were treated with plasmapheresis alone (n = 6), and the co-plasmapheresis group, whose members were treated with plasmapheresis in combination with glucocorticoids and/or IVIg (n = 7). In addition, Plasmapheresis therapy was performed only once in all occasions with 1000 ml of Ringer-Locke and 2000–3000 ml of plasma at a rate of 1000 ml an hour. Glucocorticoids and IVIg were given according to the latest guidelines [12].

2.3. Effect evaluation

The primary efficacy end-point was the response rate as evaluated by the change in the severity-of-illness score between admission and discharge as well as the recovery velocity index (RVI). The severity-of-illness score was established for this study to evaluate the efficacy after the therapy. It is a rating scale that scores ophthalmic lesions, lip/oral lesions, cutaneous lesions and general condition, with a total score ranging 0–39 (see Supplementary Table 1) [13]. Recovery velocity index (RVI) is calculated using the differences in TEN score between admission and discharge divided by the time of hospital stay. This reflects the speed of recovery from illness. The secondary efficacy end-point included changes over time in the severity-of-illness score on the 4th, 7th, 10th, and 20th days of the treatments. The above scores were evaluated as short-term treatment outcomes. Additionally, total expenditures in the hospital were also calculated.

2.4. Statistical analysis

Standard descriptive statistics were used to describe the study sample. We first conducted a normality test and assessed the homogeneity of variance for all variables. An independent-sample *t*-test was used to analyze continuous data that were normally distributed. Two-independent-sample test in the nonparametric tests (namely the Mann-Whitney *U* test) was used for quantitative data that was non-normally distributed and the Chi-square test was used for binary variables between different groups. The statistical results are presented as percentages for discrete variables and as means ± standard deviation or median (P25, P75) for continuous variables. All data were analyzed using SPSS V.22.0.

3. Results

There were no statistical differences with respect to the children/adult ratio, male/female ratio, and stripping area after admission between the plasmapheresis group and non-plasmapheresis group (Table 1). We found no statistical difference in the severity-of-illness score on the 1st and 4th day after admission between the two groups. However, the scores of the plasmapheresis group were lower than those of the non-plasmapheresis group on the 7th, 10th, and 20th day of admission [12.00 (10.00, 18.50) vs 19.00 (13.00, 33.00), $P = 0.025$; 6.50 (4.00, 7.75) vs 26.00 (10.25, 32.75), $P < 0.001$; 2.63 ± 2.82 vs 20.30 ± 12.53, $P = 0.001$; respectively] (Fig. 1). Furthermore, score change between admission and discharge also demonstrated a significant difference between the two groups (28.23 ± 4.91 vs 12.50 ± 13.19, $P < 0.001$).

Furthermore, we created a recovery velocity index (RVI) of TEN to evaluate the recovery rate of TEN by treatment. Notably, the rate of recovery in the plasmapheresis group was higher than in the non-plasmapheresis group (2.49 ± 1.02 vs 0.88 ± 0.99, $P < 0.001$). However, in subgroup analysis, in addition to the stripping area after admission [23.00(17.25,36.75) vs 40.00(35.00,50.00), $P = 0.035$], there were no statistical differences with respect to age, gender, the system score, RVI and total expenditure between the pure plasmapheresis group and co-plasmapheresis group ($P > 0.05$) (see Supplementary Table 2). The Supplementary Table 3 shows the original data for all patients.

4. Discussion

TEN is a severe cutaneous disease characterized by epidermal detachment and mucus erosion with a mortality rate of over 30% and an annual incidence of approximately 0.4–1.2 cases per million individuals [14]. This high mortality results not only from the extensively denuded skin area but also from the systemic complications, such as sepsis, disseminated intra-vascular coagulation (DIC), and multiple organ failure. The disorder is mainly induced by adverse drug reactions, which include antibiotics, anticonvulsants, anti-retroviral drugs, NSAIDS, and allopurinol [15]. Therefore, it is obligatory for these patients to discontinue the relevant agents and receive supportive therapies in the intensive care unit [3].

There is an abundance of clinical anecdotes that indicate a therapeutic benefit of corticosteroids, IVIg and plasmapheresis; however, these therapies are not supported by prospectively observational or randomized controlled experiments. In the current study, we observed that plasmapheresis therapy might be superior to IVIg, corticosteroids, or even a combination of the two. Furthermore, the single plasmapheresis strategy was found to be just as effective as combination therapy that included plasmapheresis and IVIg and/or glucocorticoids regarding the extent and speed of the reduction in the TEN score and total expenditure.

Previously, it has been reported that extensive keratinocyte apoptosis plays a critical role in the pathogenesis of TEN, where the soluble Fas ligand, perforin and granzyme have been implicated in triggering keratinocyte apoptosis or necrosis. However, a recent study found that granulysin is believed to be a key mediator of this process [12]. Although there is evidence for the use of IVIg in the acute management of SJS/TEN at the recommended dose of 2–3 g/kg, other findings have indicated that this type of treatment was less favorable as there was no survival benefit when compared with supportive care alone [16]. Corticosteroids administration was once regarded as a promising and effective treatment that could quickly relieve the clinical symptoms of TEN [17]. However, other reports have proposed that systemic corticosteroids might increase the risk of sepsis [12,18].