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ORIGINAL ARTICLE

Continuous venovenous hemofiltration combined with hemoperfusion for toxic epidermal necrolysis: a retrospective cohort study

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ABSTRACT

Aim: The current treatments of toxic epidermal necrolysis (TEN) are limited to the discontinuation of a suspect medication and supportive measures. We conducted a retrospective study to evaluate the efficacy of adding continuous venovenous hemofiltration (CVVH) and hemoperfusion (HP) to the conventional treatment for TEN.

Methods: TEN patients who were admitted to our center between January 2008 and May 2016 were considered as candidates. The included patients were divided into the CVVH&HP group ($n = 34$) and the conventional group ($n = 34$) according to their accepted therapies during hospital stay.

Results: The patients in the conventional group had a significantly reduced 28-day survival proportion compared with patients in the CVVH&HP group (73.5 versus 91.2%, $p = .047$). The adjusted results demonstrated that the conventional group had a significantly higher risk of 28-day mortality as well. Moreover, patients in the CVVH&HP group were associated with significantly shorter hospital stay, rash, fever, and antibiotic durations. However, the addition of CVVH&HP to conventional treatment did not significantly increase the in-hospital cost.

Conclusions: In conclusion, CVVH&HP might be a safe and effective adjuvant therapy for TEN. Further well-designed studies are warranted to obtain robust evidence.

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Toxic epidermal necrolysis; Stevens–Johnson syndrome; continuous venovenous hemofiltration; hemoperfusion; glucocorticoids

Introduction

Toxic epidermal necrolysis syndrome (TEN) is a rare (0.4–1.2 cases per million per year) but acute life-threatening mucocutaneous disease with skin detachment over >30% of the total body surface area (TBSA). Skin detachment in <10% is purely Stevens–Johnson syndrome (SJS), and 10–30% TBSA is an overlap of SJS and TEN. TEN is often the result of an adverse drug reaction with cell apoptosis resulting in erosions of mucous membranes and extensive detachment of the epidermis. The mortality of TEN patients depends on the severity of disease and ranges from 30 to 90% (1–3).

Treatment of TEN includes the early discontinuation of suspect medications followed by multidisciplinary supportive measures to alleviate symptoms and prevent further complications of the disease (4). Several pharmacological therapies including steroids, intravenous immunoglobulin (IVIG), and cyclosporine have been used for the management of TEN. However, previous studies reported controversial results regarding the efficacy of these drugs. Thus, no consensus on the use of these drugs is available (4). Other pharmacological therapies, such as granulocyte colony stimulating factor (5,6), cyclophosphamide (7), N-acetylcysteine (8), antitumor necrosis factor antibodies (9) and ulinastatin (10), have demonstrated potential benefit for TEN patients. However, more studies are needed to evaluate the safety and efficacy of these drugs before the recommendation of them for routine clinical practice.

Plasmapheresis is a blood purification method that provides rapid and dramatic improvement in TEN patients (11–14). However, the use of plasmapheresis is limited by the requirement of abundant plasma. Hemosorption also called hemoperfusion (HP), is another type of blood purification that removes large inflammatory molecules and mediators. This method has been used in TEN patients since the 1980s. (15–17). However, evidence for the use of HP in TEN patients is limited to anecdotes. In 2014, Wang et al. (18) reported prompt improvement in general health and obvious blockage of disease progression in seven SJS and three TEN children who did not respond to intravenous methylprednisolone and IVIG. These results suggest that HP might be a useful adjuvant treatment for patients with severe SJS/TEN when initial treatment with glucocorticoid and IVIG fails (18).

Continuous venovenous hemofiltration (CVVH) is commonly used for the management of acute kidney injury (AKI). Moreover, CVVH effectively regulates the volume, acid–base, electrolyte balance, and inhibition of inflammatory cascade reaction, which are important for the management of TEN patients (19). Additionally, other mediators, including granulysin, Fas ligand (FasL), TNF-α and perforin/granzyme B, are considered as potential pathogenic factors of TEN that can be removed by CVVH (20,21). The combination of CVVH and HP (CVVH&HP) exhibits enhanced mediator clearance and theoretically would be more effective for TEN.

Our center managed various aspects of the TEN patients with CVVH&HP from 2008. Thus, we have access to patients who

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underwent conventional treatment alone and those who underwent both conventional treatment and CVVH&HP treatment.

Therefore, the purpose of our present study was to evaluate the efficacy of CVVH&HP combined with conventional treatment versus conventional treatment alone for the management of TEN in a retrospective cohort study.

Patients and methods

Our present study is a retrospective cohort clinical trial and has been approved by the ethics committee of our hospital. We conducted the present study following the Declaration of Helsinki. Data for the included patients were retrieved from the patient electronic medical records. TEN patients admitted to our hospital between January 2008 and May 2016 were considered as candidates. The following exclusion criteria were employed: (i) age $<$18 years, (ii) acute liver failure, (iii) AKI $\geq$ Stage 2, (iv) hyperkalemia (serum potassium $>$6.4 mmol/L), (v) CKD patients who underwent regular hemodialysis or peritoneal dialysis and (vi) patient with malignant diseases. Acute liver failure was diagnosed according to the American Association for the Study of Liver Diseases Clinical Practice Guideline for Acute Liver Failure, and the definition of acute liver failure includes evidence of coagulation abnormality (international normalized ratio, INR $>$1.5) and the degree of mental alternation (encephalopathy) (22). AKI was graded according to the KDIGO practice guidelines for AKI, and Grade 2 AKI was defined an increase in serum creatinine of 2.0 − 2.9-fold baseline values or urine volume $<$0.5 mL/kg/h for $\geq$12 h (23). Before CVVH&HP treatment, all patients received detailed information about the advantages and disadvantages of CVVH&HP treatment and provided written informed consent.

Conventional treatment

Conventional treatment included the discontinuation of suspect medication, fluid supplement, silver containing wound dressing, antibiotics, intravenous corticosteroids (IVCS) and IVIG (1.2–2 g/kg). Intravenous methylprednisolone (10–30 mg/kg/6 h) was used in all of the TEN patients without significant contraindication. The use of IVIG was determined by the doctor-in-charge.

CVVH&HP treatment

A detailed protocol of CVVH was previously published (24). Temporary vascular access was created by inserting a dual lumen catheter into the femoral vein or jugular vein. CVVH was performed by the Prismaflex HF 100 Set system (Gambro Hospal, Stockholm, Sweden) with 2 L/h replacement fluid and 200 mL/min blood flow. CVVH was continuously performed until the appearance of no new skin lesions and the healing of old lesions with visible re-epithelialization. HP was performed for 2 h per each 24 h of CVVH treatment using a HA330 (Zhuhai Jafron Biomedical Materials Co., Ltd., Zhuhai, Guangdong Province, China), which was installed before the hemofilter with a blood flow of 150–200 mL/min. Systemic heparin doses were adjusted depending on the patient's medical condition to maintain the circuit patency. During the CVVH treatment, coagulation function, serum electrolyte, blood gas, and renal function were routinely tested every 4 h. The use of CVVH&HP was prescribed by the doctor in charge according to his/her clinical experiences.

Outcome and definitions

The endpoints of our present study included the 28-day survival, hospital stay duration, rash duration, fever duration, antibiotic duration, in-hospital cost and adverse events related to CVVH&HP treatment. Patient 28-day survival time was calculated from the hospital admission to death by any cause or censored at the 28th day. The included patients were retrospectively followed-up by telephone or letter to June 2016. TEN-specific severity-of-illness scores (SCORTEN) were computed according to the age, malignancy, body surface area detached, tachycardia, serum urea, serum glucose and serum bicarbonate at the time of admission (25).

Statistical methods

Normally distributed continuous variables were described as the mean ± standard deviation and non-normally distributed variables were described as the median (range). The differences between groups for normally and non-normally distributed continuous were evaluated by the Student's *t*-test and Mann–Whitney rank tests, respectively. Categorical variables are presented as percentages and were compared using the χ^2 test or Fisher exact test. Classified variables were presented as median with full range. Accumulated survival proportions were computed by Kaplan–Meier curves and compared using the log-rank test. Risk factors of mortality were evaluated using the Cox regression model. Variables with $p < .01$ in univariate analyzes were incorporated into the multivariate analysis. Two-tailed $p < .05$ was considered statistically significant. All statistical calculations were conducted using SPSS 17.0 (SPSS, Chicago, IL).

Results

Patient selection

Between January 2008 and May 2016, 127 TEN patients were admitted to our center. Of these patients, 59 were excluded based on our exclusion criteria (Figure 1). In total, 68 patients were included in our present study. Of the included patients, 34 accepted conventional treatment alone, and 34 had additional CVVH&HP treatment.

Baseline characteristics

Table 1 presents the baseline characteristics of the included patients. All of the included patients exhibited $\geq$60% TBSA detachment, and most of them (72.1%) had $\geq$80% TBSA detachment. The median SCORTEN score was 2 (1–6). The numbers of patients who had 1, 2, 3 and 4 involved mucous membranes were 16, 15, 24 and 13, respectively. In addition, 12, 8 and 39 patients had liver injury, AKI and infection at the time of admission, respectively. During the hospital stay, all of the included patients accepted methylprednisolone treatment, and approximately half of them ($n = 30$, 44.1%) underwent IVIG treatment. Among the 34 patients underwent CVVH&HP treatment, the average CVVH time was 60.00 ± 25.10 h, and the median HP session was 2 (range: 1–5). The conventional group had less infection at the hospital admission (47.1 versus 67.7%, $p = .086$) than did the CVVH&HP group, but the difference was not significant. The two groups were not significantly different in the remaining baseline characteristics as well.

Patient survival

Within 28 days after the hospital admission, nine and three patients in the conventional group and CVVH&HP group died, respectively. The causes of death were cardiac shock, sepsis and

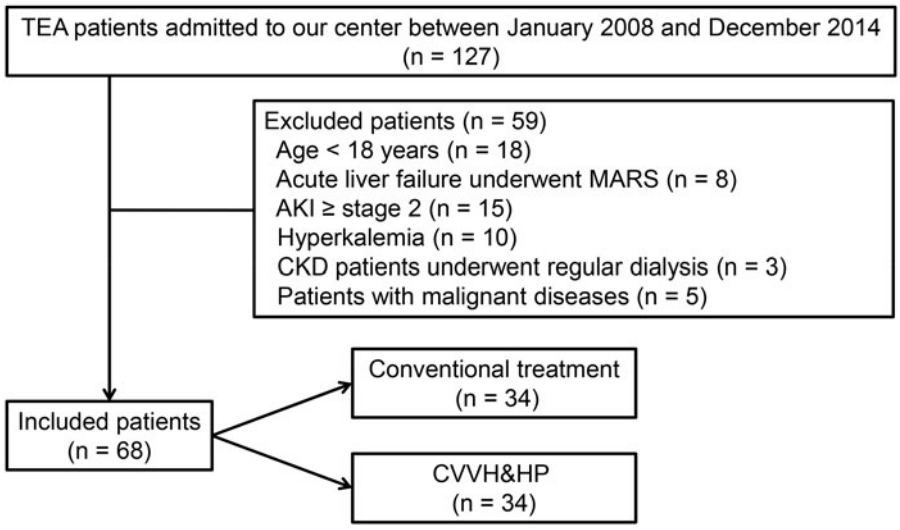

Figure 1. The patient inclusion flowchart.

Table 1. Baseline characteristics of the included patients.

Variables	Total ($n = 68$)	Conventional treatment ($n = 34$)	CVVH&HP ($n = 34$)	p values
Gender, male/female	36/32	18/16	18/16	1.000
Age, years	40.38 ± 16.71	42.06 ± 17.96	38.71 ± 15.43	.412
Heart rate, bpm	87.97 ± 16.57	86.53 ± 14.52	89.41 ± 18.51	.477
SCORTEN, median (range)	2 (1–6)	2 (1–6)	2 (1–5)	.378
Body surface area detached, %	77.94 ± 6.12	76.47 ± 5.71	79.41 ± 6.24	.064
No. involved mucous membranes, median (range)	3 (1–4)	3 (1–4)	2.5 (1–4)	.769
Acute liver injury, yes/no	12/56	4/30	8/26	.203
AKI, yes/no[a]	8/60	2/32	6/28	.132
Infection, yes/no	39/29	16/18	23/11	.086
WBC, 10^9/L	7.21 ± 4.67	8.23 ± 5.85	6.20 ± 2.83	.074
HGB, g/L	130.46 ± 21.64	133.50 ± 18.42	127.41 ± 24.33	.247
ALT, IU/L	51.53 ± 52.65	57.08 ± 58.28	45.97 ± 46.56	.388
AST, IU/L	49.87 ± 64.65	44.82 ± 35.96	54.91 ± 84.49	.524
Total bilirubin, μmol/L	23.76 ± 19.62	19.58 ± 14.71	27.93 ± 23.00	.079
INR	0.86 ± 0.10	0.86 ± 0.08	0.86 ± 0.11	.713
Serum creatinine, μmol/L	92.97 ± 20.78	90.76 ± 18.93	95.18 ± 22.55	.385
Blood urea nitrogen, mmol/L	7.55 ± 3.72	6.88 ± 3.32	8.21 ± 4.01	.141
Serum glucose, mmol/L	7.18 ± 2.51	7.20 ± 2.48	7.16 ± 2.57	.958
Serum bicarbonate, mmol/L	23.95 ± 3.13	23.67 ± 2.83	24.22 ± 3.43	.473
Serum potassium, mmol/L	4.00 ± 0.49	4.10 ± 0.45	3.89 ± 0.51	.087
IVIG, yes/no	30/38	12/22	18/16	.143
Methylprednisolone, mg	2275.00 ± 767.09	2335.29 ± 874.87	2214.71 ± 649.46	.521

ALT: alanine aminotransferase; bpm: beat per minute; HGB: hemoglobin; WBC: white blood cell.
[a]AKI patients were Stage 1.

MODS in two, three and seven patients, respectively. The two groups were not significantly different in the cause of death ($p = .522$). The 28-day accumulated survival in all patients was 82.4% (Figure 2(A)).

The 28-day accumulated survival proportions of the conventional treatment and CVVH&HP group were 73.5 and 91.2%, respectively. Patient survival significantly favored CVVH&HP treatment; however, the survival difference between the groups was not significant ($p = .047$, Figure 2(B)).

In the univariate Cox regression models, age ($p < 0.05$), SCORTEN score ($p < .05$), treatment (conventional versus CVVH&HP), aspartate transaminase (AST) and serum creatinine were the variables with p values $<.01$. When we adjusted the efficacy of CVVH&HP treatment by the two variables with p values $<.05$ (age and SCORTEN score) in the Cox regression model, the conventional group had a significantly higher mortality risk [hazard ratio (HR) = 38.843, 95% confidence interval (CI): 3.874–389.470, $p = .002$] compared with the CVVH&HP group. Age (HR = 1.070, 95% CI: 1.019–1.124, $p = .007$) and SCORTEN score (HR = 9.212, 95% CI: 2.500–33.942, $p = .001$) were identified as independent risk factors of patient survival as well. Additionally, we adjusted the results based on the variables with p values in the univariate analyzes <0.1, including SCORTEN score, age, AST and serum creatinine. The result demonstrated that patients in the conventional group had a significantly higher 28-day mortality risk (HR = 132.022, 95% CI: 6.316–2759.430, $p = .002$, Table 2) as well. SCORTEN score (HR = 14.448, 95% CI: 2.611–79.949, $p = .002$), age (HR = 1.090, 95% CI: 1.018–1.167, $p = .013$) and AST (HR = 1.008, 95% CI: 1.000–1.015, $p = .044$) were identified as independent risk factors of 28-day mortality in this model. The 28-day accumulated survival of the patients with SCORTEN scores ≤ 3 and >3 were 88.1 and 44.4%, respectively ($p < .001$, Figure 2(C)).

Other results

For the patients who were discharged alive, the median hospital stay duration was 13 days (range: 5–25 days) and 9 days

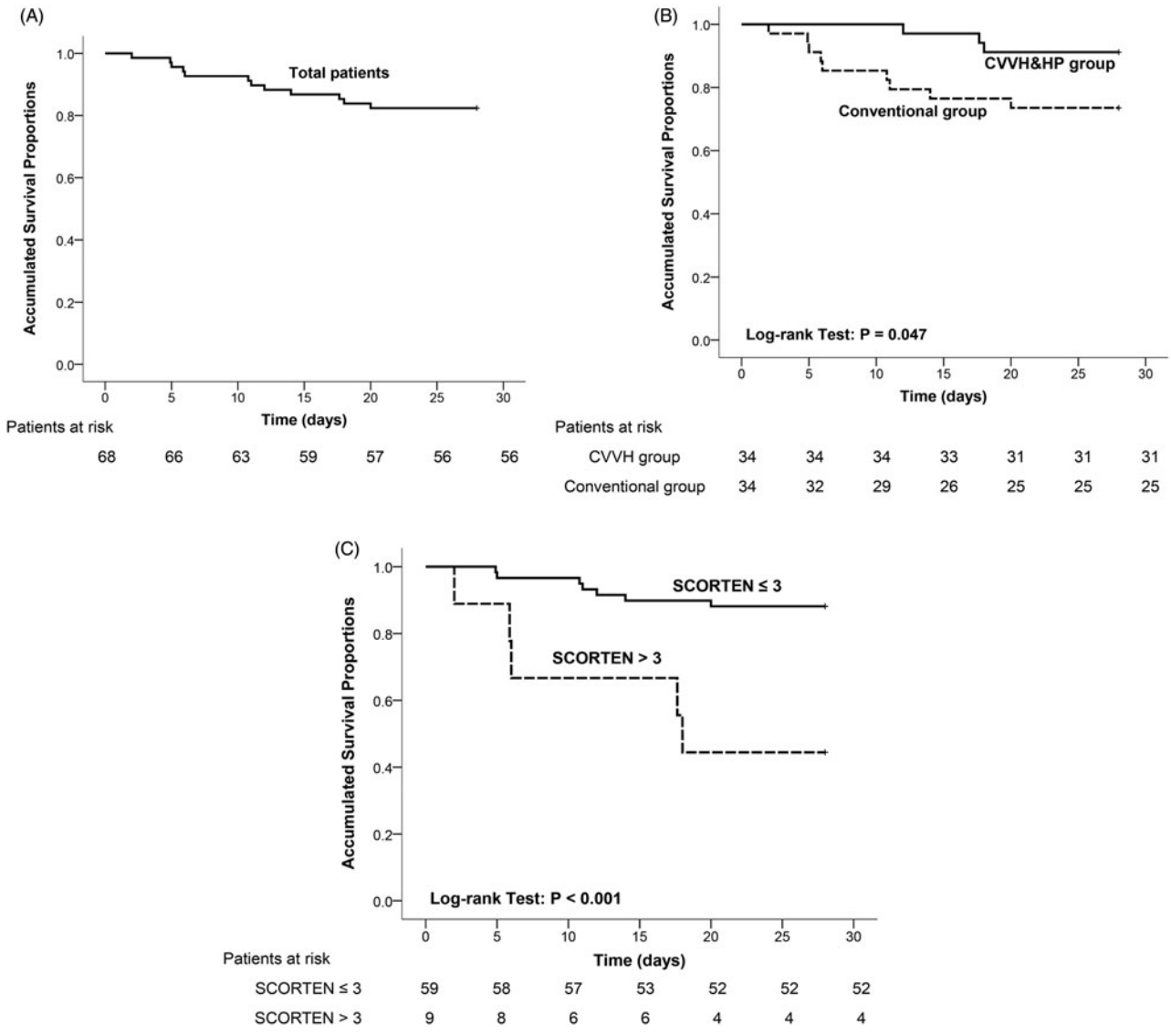

Figure 2. Survival curves of total patients (A), patients who underwent CVVH&HP combined with conventional treatment versus patients who underwent conventional treatment alone (B), patients with SCORTEN $\leq$3 versus patients with SCORTEN $>$3 (C).

(range: 4–18 days, $p = .002$, Table 3) for the patients in the conventional and CVVH&HP group, respectively. Additionally, patients in the CVVH&HP group had a significantly shorter rash duration [7 (range: 4–18) days versus 9 (range: 7–22) days, $p < .001$], fever duration [3 (range: 1–6) days versus 4 (range: 2–6) days, $p = .001$] and antibiotic duration [5 (range: 3–9) days versus 9 (range: 5–15) days, $p < .001$, Table 3]. The median in-hospital costs were 24454.75 RMB (range: 10442.48–122307.89 RMB) and 20358.81 (range: 4991.15–84093.20 RMB) for the CVVH&HP and conventional groups, respectively. The two groups did not exhibit significantly different in-hospital costs ($p = .136$, Table 3).

In the CVVH&HP group, two, two, four and five patients had hypotension, femoral vein thrombosis, arterial puncture and hematoma, respectively (Table 4). None of these CVVH&HP-related complications resulted in severe consequences, such as death, disability or treatment cessation.

Discussion

To the best of our knowledge, the present study is the first clinical trial to evaluate the efficacy of CVVH&HP combined with conventional treatment versus conventional treatment alone. Our present study found that (i) the addition of CVVH&HP to conventional treatment for TEN patients significantly reduced the 28-day mortality risk in the multivariate Cox regression models; (ii) TEN patients in the CVVH&HP group had significantly shorter hospital stay, rash, fever and antibiotic durations and (iii) the addition of CVVH&HP to conventional treatment was associated with the occurrence of CVVH&HP-related complications. However, none of the complications resulted in severe consequences.

Recommended treatments for TEN included the discontinuation of suspect medications and the use of supportive measures. The current literature dose not convincingly support the use of any adjuvant systemic therapy for TEN, and studies have demonstrate that the addition of steroids potentially benefited patient survival (26,27). Therefore, in our center, methylprednisolone is routinely used for the management of TEN patients. IVIG is another potentially effective adjuvant treatment. Current evidence regarding the efficacy of immunoglobulin for TEN is controversial. Prins et al. (28) suggested that high-dose IVIG improved patient survival, whereas Bachot et al. (29) did not report any benefit on patient mortality or progression from IVIG. The recent

Table 2. Risk factors of the 28-day patient mortality.

	Univariate Cox regression			Multivariate Cox regression		
Variables	HR	95% CI	*p* values	HR	95% CI	*p* values
Treatment, conventional versus CVVH	3.466	0.938–2.811	.062	132.022	6.316–2759.430	.002
Gender, male/female	0.794	0.252–2.501	.693	–	–	–
Age	1.059	1.023–1.097	.001	1.090	1.018–1.167	.013
Heart rate	1.006	0.972–1.040	.747	–	–	–
SCORTEN	2.423	1.541–3.811	<.001	14.448	2.611–79.949	.002
Body surface area detached, %	1.009	0.919–1.108	.847	–	–	–
No. involved mucous membranes	1.183	0.690–2.029	.541	–	–	–
Acute liver failure, yes/no	1.704	0.461–6.297	.424	–	–	–
AKI, yes/no	1.654	0.362–7.553	.516	–	–	–
WBC, <4.0 or >10.0 × 10^9/L	0.502	0.159–1.582	.239	–	–	–
HGB	1.016	0.988–1.045	.266	–	–	–
ALT	1.003	0.995–1.011	.454	–	–	–
AST	1.004	0.999–1.009	.087	1.008	1.000–1.015	.044
Total bilirubin	1.014	0.988–1.041	.292	–	–	–
INR	33.949	0.131–8775.892	.214	–	–	–
Serum creatinine	1.023	0.997–1.050	.083	1.031	0.986–1.079	.182
Blood urea nitrogen	0.934	0.787–1.107	.429	–	–	–
	0.970	0.757–1.242	.807	–	–	–
Serum bicarbonate, <22 or >27 mmol/L	0.433	0.140–1.343	.147	–	–	–
Serum potassium, <3 or >5 mmol/L	0.770	0.099–5.966	.802	–	–	–
IVIG, yes/no	1.227	0.389–3.869	.727	–	–	–
Methylprednisolone	1.000	0.999–1.001	.717	–	–	–

ALT: alanine aminotransferase; HGB: hemoglobin; HR: hazard ratio; WBC: white blood cell.

Table 3. Other outcomes.

Outcome	Conventional group	CVVH&HP group	*p* values
Hospitalized duration, days (range)	13 (5–25)	9 (4–18)	.005
Rash duration, days (range)	9 (7–22)	7 (4–18)	<.001
Fever duration, days (range)	4 (2–6)	3 (1–6)	.001
Antibiotic duration, days (range)	9 (5–15)	5 (3–9)	<.001
In-hospital cost, RMB (range)	20358.81 (4991.15–80062.04)	24454.75 (10442.48–122307.89)	.136

RMB: Ren Min Bi.

Table 4. Complications of CVVH&HP.

Variables	Incidence (%)
Hematoma	5 (14.71)
Arterial puncture	4 (11.76)
Femoral vein thrombosis	2 (5.88)
Hypotension	2 (5.88)

meta-analysis by Huang et al. (30) concluded controversial results as well. Accordingly, the addition of steroids with/without IVIG to supportive measures is the conventional treatment for TEN in our daily work. In our present study, IVIG was not identified as an independent risk factor for 28-mortality in the multivariate Cox model, which also challenged the routine use of IVIG for TEN.

The pathophysiological mechanisms of TEN were not studied very well given the lack of an appropriate animal model. TEN is thought to be a T cell-mediated disease with $CD8^+$ cells acting as the major mediator of keratinocyte death (31,32). The inappropriate activation of $CD8^+$ T cells exocytose granzyme B/perforin and granulysin activate other inflammatory cells, including macrophage, neutrophils, NK cell and B cell, and result in keratinocyte apoptosis (21). Some types of blood purification therapy could alleviate the inflammatory cascade reaction by cleansing inflammatory mediators, including granulysin, FasL, TNF-α and perforin/granzyme B. Several studies with small sample sizes suggested that plasmapheresis was a potentially effective blood purification therapy for TEN (11–14). However, the use of plasmapheresis is typically limited by the requirement of abundant plasma, especially in developing countries.

Our present study proved that the addition of CVVH&HP to conventional treatment significantly reduced the 28-day mortality risk. When we adjusted the results by SCORTEN score, age, AST and serum creatinine, CVVH&HP combined with conventional treatment significantly reduced the 28-day mortality risk. Based on the pathogenesis of TEN, the efficacy of CVVH&HP was most likely attributed to the clearance of the inflammatory mediators. We previously demonstrated that the combination of hemofiltration with HP (HA330 adsorbent) for acute hyperlipidemic pancreatitis patients was effective in the clearance of most of the inflammatory mediators, including IL-1, IL-2, IL-6, IL-8, IL-10 and TNF-α (33) Huang et al. (34,35) demonstrated that HP with HA330 was effective for the clearance of the plasma inflammatory mediators in sepsis patients. Furthermore, the effects of CVVH&HP on the reconstitution of the immune system, stabilization of the internal environment and preservation of organ function are also cited as potential mechanisms for survival improvement (36–38).

Further results demonstrated that the addition of CVVH&HP to conventional treatment significantly reduced rash and fever durations, indicating quicker recovery. Consequently, CVVH&HP reduced the hospital stay and antibiotic duration. The reduction of hospital stay duration and antibiotic duration likely decreased the patients' physiological status and the work of medical staff. The addition of CVVH&HP did not significantly increase the in-hospital cost, which is mainly attributed to the reduction of hospital stay duration and antibiotic duration.

Wang et al. (18) assessed the addition of HP to conventional treatment in seven SJS children and three TEN children who did not response to methylprednisolone (10–30 mg/kg, qd, 3 days) and IVIG (1 g/kg, qd, 2 days) treatment. Our patients in the CVVH&HP group had a shorter hospital stay duration and rash duration, indicating that the combination of CVVH&HP might be

more effective than HP alone. Because the patients in our study and patients in the Wang et al. (18) study were significantly heterogeneous in many important baseline characteristics, further studies are needed to evaluate the efficacy of CVVH&HP versus HP for TEN.

Potential disadvantages of the CVVH&HP combined with conventional treatment include the addition of CVVH&HP-related complications, including bleeding, hematoma, thrombosis, hypotension and heparin-induced thrombocytopenia. In our present study, several adverse events without severe consequences were observed in the CVVH&HP group. Most of the adverse events were related to vascular catheter deployment. The use of ultrasound-guided vascular assessment and the employment of regional citrate anticoagulation would reduce the incidence of these complications (39,40). More importantly, none of these adverse events resulted in severe consequences, which guaranteed the safety of CVVH&HP for TEN patients.

Our present study is associated with several limitations. First, this is a retrospective study. Even when the effect of CVVH&HP on patient survival was adjusted by several important parameters, it is impossible to balance the two groups as effectively as a randomized control trial. However, in a retrospective study, the data are obtained from actual clinical experiences, which is also important for evaluating the efficacy and safety of a treatment. Additionally, the worldwide morbidity of TEN is very low, and the occurrence of TEN is acute and unpredictable. Thus, it's difficult to perform a randomized control trial. Second, we did not include patients with SJS in our study, which limited the expansion of the results to these patients. Further prospective well designed studies are warranted to verify our findings.

Conclusions

In conclusion, the addition of CVVH&HP to conventional treatment for TEN could improve patient survival and reduce hospital stay, rash, fever and antibiotic durations. The safety of CVVH&HP is guaranteed by the absence of adverse events with severe consequences. CVVH&HP should be considered as an effective adjuvant therapy for TEN. Further well-designed studies are warranted for more robust evidence.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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References

1. Roujeau JC, Kelly JP, Naldi L, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. N Engl J Med. 1995;333:1600–7.
2. Bastuji-Garin S, Fouchard N, Bertocchi M, et al. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. J Invest Dermatol. 2000;115:149–53.
3. Palmieri TL, Greenhalgh DG, Saffle JR, et al. A multicenter review of toxic epidermal necrolysis treated in U.S. burn centers at the end of the twentieth century. J Burn Care Rehabil. 2002;23:87–96.
4. Schwartz RA, McDonough PH, Lee BW. Toxic epidermal necrolysis: Part II. Prognosis, sequelae, diagnosis, differential diagnosis, prevention, and treatment. J Am Acad Dermatol. 2013;69:e181–16, quiz 203–184.
5. Goulden V, Goodfield MJ. Recombinant granulocyte colony-stimulating factor in the management of toxic epidermal necrolysis. Br J Dermatol. 1996;135:305–6.
6. Jarrett P, Rademaker M, Havill J, et al. Toxic epidermal necrolysis treated with cyclosporin and granulocyte colony stimulating factor. Clin Exp Dermatol. 1997;22:146–7.
7. Frangogiannis NG, Boridy I, Mazhar M, et al. Cyclophosphamide in the treatment of toxic epidermal necrolysis. South Med J. 1996;89:1001–3.
8. Velez A, Moreno JC. 2002; Toxic epidermal necrolysis treated with N-acetylcysteine. J Am Acad Dermatol. 46:469–70.
9. Fischer M, Fiedler E, Marsch WC, et al. Antitumour necrosis factor-alpha antibodies (infliximab) in the treatment of a patient with toxic epidermal necrolysis. Br J Dermatol. 2002;146:707–9.
10. Inamo Y, Okubo T, Wada M, et al. Intravenous ulinastatin therapy for Stevens-Johnson syndrome and toxic epidermal necrolysis in pediatric patients. Three case reports. Int Arch Allergy Immunol. 2002;127:89–94.
11. Chaidemenos GC, Chrysomallis F, Sombolos K, et al. Plasmapheresis in toxic epidermal necrolysis. Int J Dermatol. 1997;36:218–21.
12. Yamada H, Takamori K, Yaguchi H, et al. 1998; A study of the efficacy of plasmapheresis for the treatment of drug induced toxic epidermal necrolysis. Ther Apher. 2:153–6.
13. Egan CA, Grant WJ, Morris SE, et al. Plasmapheresis as an adjunct treatment in toxic epidermal necrolysis. J Am Acad Dermatol. 1999;40:458–61.
14. Kostal M, Blaha M, Lanska M, et al. Beneficial effect of plasma exchange in the treatment of toxic epidermal necrolysis: a series of four cases. J Clin Apher. 2012;27:215–20.
15. Gonchar DI. [Hemosorption in the intensive treatment of Lyell's disease]. Anesteziol Reanimatol. 1983;6:61–2.
16. Muravko LS, Dorozhkova IA, Tolkachev BG. [Use of hemosorption in a 10-month-old infant with Lyell's syndrome]. Pediatriia. 1988;1:94.
17. Vozgoment OV, Griaznov VN, Medvedev SL. [Experience with the use of hemosorption in the intensive therapy of Stevens-Johnson syndrome in a child]. Anesteziol Reanimatol. 1989;6:46–7.
18. Wang YM, Tao YH, Feng T, et al. Beneficial therapeutic effects of hemoperfusion in the treatment of severe Stevens-Johnson syndrome/toxic epidermal necrolysis: preliminary results. Eur Rev Med Pharmacol Sci. 2014;18:3696–701.
19. Bellomo R, Tipping P, Boyce N. Continuous veno-venous hemofiltration with dialysis removes cytokines from the circulation of septic patients. Crit Care Med. 1993;21:522–6.
20. Peng Z, Pai P, Hong-Bao L, et al. The impacts of continuous veno-venous hemofiltration on plasma cytokines and monocyte human leukocyte antigen-DR expression in septic patients. Cytokine. 2010;50:186–91.
21. Schwartz RA, McDonough PH, Lee BW. Toxic epidermal necrolysis: Part I. Introduction, history, classification, clinical features, systemic manifestations, etiology, and

immunopathogenesis. J Am Acad Dermatol. 2013;69: e171–13, quiz 85–76.
22. Polson J, Lee WM. & American Association for the Study of Liver Disease. AASLD position paper: the management of acute liver failure. Hepatology. 2005;41:1179–97.
23. Kidney Disease Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for acute kidney injury. Kidney Inter. 2012;2:1–138.
24. Huang C, Zhang P, Du R, et al. Treatment of acute hypernatremia in severely burned patients using continuous venovenous hemofiltration with gradient sodium replacement fluid: a report of nine cases. Intensive Care Med. 2013;39:1495–6.
25. Guegan S, Bastuji-Garin S, Poszepczynska-Guigne E, et al. Performance of the SCORTEN during the first five days of hospitalization to predict the prognosis of epidermal necrolysis. J Invest Dermatol. 2006;126:272–6.
26. Brown KM, Silver GM, Halerz M, et al. Toxic epidermal necrolysis: does immunoglobulin make a difference? J Burn Care Rehabil. 2004;25:81–8.
27. Kardaun SH, Jonkman MF. Dexamethasone pulse therapy for Stevens-Johnson syndrome/toxic epidermal necrolysis. Acta Derm Venereol. 2007;87:144–8.
28. Prins C, Kerdel FA, Padilla RS, et al. Treatment of toxic epidermal necrolysis with high-dose intravenous immunoglobulins: multicenter retrospective analysis of 48 consecutive cases. Arch Dermatol. 2003;139:26–32.
29. Bachot N, Revuz J, Roujeau JC. Intravenous immunoglobulin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis: a prospective noncomparative study showing no benefit on mortality or progression. Arch Dermatol. 2003;139:33–6.
30. Huang YC, Li YC, Chen TJ. The efficacy of intravenous immunoglobulin for the treatment of toxic epidermal necrolysis: a systematic review and meta-analysis. Br J Dermatol. 2012;167:424–32.
31. Nassif A, Bensussan A, Boumsell L, et al. Toxic epidermal necrolysis: effector cells are drug-specific cytotoxic T cells. J Allergy Clin Immunol. 2004;114:1209–15.
32. Nassif A, Bensussan A, Dorothee G, et al. Drug specific cytotoxic T-cells in the skin lesions of a patient with toxic epidermal necrolysis. J Invest Dermatol. 2002;118:728–33.
33. Sun S, He L, Bai M, et al. High-volume hemofiltration plus hemoperfusion for hyperlipidemic severe acute pancreatitis: a controlled pilot study. Ann Saudi Med. 2015;35:352–8.
34. Huang Z, Wang SR, Su W, et al. Removal of humoral mediators and the effect on the survival of septic patients by hemoperfusion with neutral microporous resin column. Ther Apher Dial. 2010;14:596–602.
35. Huang Z, Wang SR, Yang ZL, et al. Effect on extrapulmonary sepsis-induced acute lung injury by hemoperfusion with neutral microporous resin column. Ther Apher Dial. 2013;17:454–61.
36. Ronco C, Tetta C, Mariano F, et al. Interpreting the mechanisms of continuous renal replacement therapy in sepsis: the peak concentration hypothesis. Artif Organs. 2003;27:792–801.
37. Saotome T, Endo Y, Sasaki T, et al. A case of severe acute pancreatitis treated with CTR-001 direct hemoperfusion for cytokine apheresis. Ther Apher Dial. 2005;9:367–71.
38. Kobe Y, Oda S, Matsuda K, et al. Direct hemoperfusion with a cytokine-adsorbing device for the treatment of persistent or severe hypercytokinemia: a pilot study. Blood Purif. 2007;25:446–53.
39. Zollo A, Cavatorta F, Galli S. Ultrasound-guided cannulation of the femoral vein for acute hemodialysis access with silicone catheters. J Vasc Access. 2001;2:56–9.
40. Bai M, Zhou M, He L, et al. Citrate versus heparin anticoagulation for continuous renal replacement therapy: an updated meta-analysis of RCTs. Intensive Care Med. 2015;41: 2098–110.