Clinical Study

The Effects of Continuous Blood Purification for SIRS/MODS Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Received 4 April 2012; Accepted 2 May 2012

Academic Editors: D. Del Principe and I. C. Haznedaroglu

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Background. Continuous veno-venous hemofiltration (CVVH) has aroused great concern in recent years because its effect on clearing inflammatory mediators and its mechanism of clinical effects in the treatment of critical illness has also become a research direction. Objective. To evaluate the efficacy of continuous blood purification for systemic inflammatory response syndrome (SIRS)/multiple organ dysfunction syndrome (MODS) patients. Methods. A systematic review of the literature was undertaken to assess randomized controlled trials on CVVH. Results. 11 RCTs involving a total of 414 patients were included. Compared with the control group, CVVH for SIRS/MODS patients has several advantages including better effects on clearing the plasma inflammatory mediators IL-6 [SMD 3d = −0.45, 95%CI, (−0.83, −0.07), SMD 7d = −1.07, 95%CI, (−1.52, −0.62)], on plasma TNF-alfa [SMD 3d = −0.87, 95%CI, (−1.69, −0.04), SMD 7d = −1.42, 95%CI, (−2.49, −0.35)], lower white blood cell (WBC) count [MD = 2.61, 95%CI, (1.49, 3.73)], shorter hospital stays [MD = −7.21 days, 95%CI, (−10.68, −3.74)] and better stability of hemodynamics. However, there is no significant difference in the mortality rate [MODS:RR = 0.62, 95%CI, (0.38, 1.01), SIRS:RR = 0.75, 95%CI, (0.57, 1.08)]. Conclusions. The study showed that CVVH was able to eliminate inflammatory mediators (TNF-alfa, IL-6) in plasma effectively, lower WBC count and shorter hospital stays than conventional therapeutic measures.

1. Introduction

Continuous blood purification (CBP) has now been extensively employed for the management of systemic inflammatory response syndrome (SIRS), and even multiple-organ dysfunction syndrome (MODS) in critically ill patients [1]. To those patients, some treatments had been put forward targeting on them like monoclonal antibodies (such as anti-TNF antibody), receptor antagonists (such as anti-PAF), and soluble receptors (e.g., TNFR), yet none of these can prevent the release of inflammatory mediators satisfactorily nor remove existing inflammatory mediators, especially TNF-alfa, as a larger molecular weight trimer (54kd) has become a difficulty of internal clearance. Hemofiltration is commonly used in an intensive care unit setting which is also called continuous venovenous hemofiltration (CVVH) or continuous renal replacement therapy (CRRT). One of the important mechanisms of hemofiltration is that it may play a role in removed inflammatory mediators [2]. Amongst the mediators, the proinflammatory cytokines tumor necrosis factor (TNF-alfa) and interleukin-6 (IL-6) are thought to occupy a key position in the chain of events leading to shock.

Some trials support this view, but at the same time, some trials say there is no significant evidence found in the relationship between hemofiltration and inflammatory mediators [3, 4]. So there is still controversy regarding this problem.

The objective of this study is to evaluate the outcomes of CVVH versus control group for SIRS/MODS patients. Moreover, we investigated whether the use of CVVH would...
result in an improvement of mortality, total duration of hospital stays, white blood cell (WBC) count, and hemodynamic stability in patients, respectively.

2. Methods

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) was used to conduct data extraction.

2.1. Study Selection. We searched electronic databases from PubMed (1966–2011.10), the Cochrane Library (Issue 4, 2011), EMBASE (1974–2011.10), Science Citation Index (1974–2011.10), the China Journal Fulltext Database (1994–2011.10), Chinese Scientific Journals Fulltext Database (1989–2011.10), Chinese Biomedical Literature Database (1978–2011.10), with the terms (continuous venous hemofiltration), (continuous renal replacement therapy), (continuous arteriovenous hemofiltration), (continuous blood purification), in combination with the medical subject headings. Relevant articles referenced in these publications were downloaded from the databases. The related article function also was used to widen the search results. All abstracts, comparative studies, nonrandomized trials, and citations scanned were searched comprehensively. We also hand-searched the reference lists of every primary study for additional publications. Further searches were done by reviewing abstract booklets and review articles. Trials were included irrespective of the language in which they were reported.

2.2. Data Extraction. Each study was reviewed by 2 researchers for reliability of our meta-analysis. Only randomized controlled trials on CVVH versus conventional therapeutic measures for inflammatory mediators removal were included in the meta-analysis. Two researchers extracted data separately and if there was any controversial, it was confirmed by the third researcher.

2.3. Inclusion Criterion. The inclusion criteria for this analysis were randomized controlled trials that compared CVVH with conventional therapeutic measures about patients with critically inflammatory states (systemic inflammatory response syndrome or multiple-organ dysfunction syndrome) [5].

2.4. Exclusion Criteria. Trials were excluded if included patients were pregnant, younger than 18 years, in a moribund state, in chronic renal failure, or receiving immunosuppressive therapy.

2.5. Statistical Analysis. We summarized available data from all trials reporting results. Computing pooled risk ratios (RR) and their respective 95% confidence intervals by means of a fixed-effects meta-analysis model. For continuous data, the mean difference (MD) is recommended when all trials use the same scale to report their outcomes, while standardized mean difference (SMD) is more appropriate when trials use different scales to report their outcomes, just as data about effects on clearing the plasma inflammatory mediators in the following. All statistical analysis was performed with Review Manager (version 5.1). We used the chi2 statistic to assess heterogeneity between trials and the I^2 statistic to assess the extent of inconsistency. Subgroup analysis was intended to explore important clinical differences among trials that might be expected to alter the magnitude of treatment effect.

3. Results

From Figure 1 can be seen the flow chart of studies from initial results of publication searches to final inclusion [6–16]. 11 trials about CVVH versus conventional therapeutic evaluate the efficacy of inflammatory mediator removals encompassing a total of 438 patients which were retrieved from the electronic databases. Standard deviations were not reported in the majority of studies, where necessarily were estimated either by means of ranges or P values. Characteristics of each trial were given in Table 1. Included studies’ methodological quality was assessed using the Cochrane handbook in Table 2 [17].

3.1. Mortality: Statistical heterogeneity was basically well among studies (P = 0.25, I^2 = 22%) [6–14, 16]. There was no significant difference in mortality between CVVH and Control group (MODS: RR = 0.62, 95%CI, (0.38, 1.01), SIRS: RR = 0.75, 95%CI, (0.57, 1.08)) (Table 3).

3.2. Hospital Stay. Two studies reported the data of length of hospital stay [11, 14]. CVVH group was associated with significantly shorter hospital stays (MD = −7.21 days, 95%CI, (−10.68, −3.74)). Study Cole et al. [9] reported CVVH group shorten the length of stay in the ICU from a Kaplan-Meier analysis (Table 4).

3.3. CVVH versus Control on Plasma IL-6 Change. Three studies [10, 11, 15] reported at three-day and seven day followup, CVVH group had better effects than Control group on plasma IL-6 change [SMD_3d = −0.45, 95%CI, (−0.83, −0.07), SMD_7d = −1.07, 95%CI, (−1.52, −0.62)] (Table 5).

3.4. CVVH versus Control Group on Plasma TNF-Alfa Change. There was three trials [10, 11, 15] reported, CVVH versus control on plasma TNF-alpha, significant heterogeneity existed among trials (P = 0.07, I^2 = 69%), (P = 0.01, I^2 = 84%). CVVH group have better effects than Control group on plasma TNF-alpha change (SMD_3d = −0.87, 95%CI, (−1.69, −0.04)), (SMD_7d = −1.42, 95%CI, (−2.49, −0.35)) (Table 6).

3.5. WBC Count Reduction. WBC count reported in two trials was significantly reduced in CVVH group (MD = 2.61, 95%CI, (1.49, 3.73)) [13, 15] (Table 7).

3.6. Hemodynamic Variables. Two trials reported hemodynamic descriptive analysis stability [6, 7]. Riera et al. 1997
Trials identified as potentially relevant and screened for retrieval
- Cochrane Library (n = 47) - PubMed (n = 449)
- EMBASE (n = 805) - SCI (n = 351)
- WanFang Database (n = 111)
- The China Journal Fulltext Database (n = 173)
- Chinese Scientific Journals Fulltext Database (n = 201)

Excluded on the basis of title and abstract (n = 1896)

Potentially appropriate trials for more detailed assessment (n = 98)

Studies excluded with reasons (n = 87)
- Double records (n = 2)
- Incomplete information on outcomes (n = 44)
- Observational study (n = 34)
- Review articles (n = 7)

11 trials were included in this meta-analysis

**Figure 1**: Flow diagram of trial selection.

**Table 1**: Baseline characteristics of the included studies.

| Trials              | Sample size (n) | Country | Disease | Illness severity scores | Age | Filter membrane | Blood flow (mL/min) | Treatment            |
|---------------------|----------------|---------|---------|-------------------------|-----|----------------|---------------------|----------------------|
| Sander 1997 [6]     | 13/13          | Germany | SIRS    | 15.3 ± 1.4/13.9 ± 1.2A | 58 ± 3.0/52 ± 3.2 | AN69 | 150 mL/min     | CVVH* versus control |
| Sanchez Riera 1997 [7, 8] | 15/15       | Spain   | MODS    | 22 ± 7/21 ± 6A          | 36 ± 18/36 ± 14   | AN69 | 130 mL/min     | CVVH* versus control |
| Cole et al. 2002 [9] | 12/12         | Australia | MODS   | 21.8 ± 4/22.2 ± 6.4A   | Median (IQR) 65.5 (22.0)/68.0 (19.0) | AN69 | 200 mL/min     | CVVH* versus control |
| Liu et al. 2003 [10] | 24/26          | China   | MODS    | 25 ± 7/23 ± 7A          | 39 ± 11/37 ± 19   | AN69 +PS 200–250 mL/min | CVVH* versus control |
| Yang et al. 2004 [11] | 22/15         | China   | SIRS    | 14.8 ± 4.5/14.6 ± 4.7A | 44.6 ± 15.4/44.6 ± 15.4 | PS   | 150–200 mL/min | CVVH* versus control |
| Ding and Zhao 2007 [12] | 11/10        | China   | MODS    | 14.1 ± 3.6/14.1 ± 3.6A | 23–78/23–78      | PS   | Not reported   | CVVH* versus control |
| Yang and Hoyang 2008 [13] | 31/27        | China   | SIRS    | 18.6 ± 3.4/17.9 ± 2.7A | 31.5 ± 10.9/31.5 ± 10.9 | PS | 180–250 mL/min | CVVH* versus control |
| Peng et al. 2008 [14] | 17/15         | China   | SIRS    | 18.21 ± 2.58/17.65 ± 3.14A | 28–70/30–69 | AN69 | 250–300 mL/min | CVVH* versus control |
| Zhang et al. 2006 [15] | 30/30         | China   | SIRS    | Not reported            | 46.7 ± 18.3/46.7 ± 18.3 | PS | 150–200 mL/min | CVVH* versus control |
| Payen et al. 2009 [16] | 37/39         | France  | SIRS    | 11.6 ± 3.4/10.4 ± 2.9B  | 57.6 ± 12.6/58.6 ± 13.5 | PS | 150 mL/min     | CVVH* versus control |

MODS: multiple-organ dysfunction syndrome.
SIRS: systemic inflammatory response syndrome.
CVVH* group: CVVH + conventional therapeutic measures.
Control group: conventional therapeutic measures.
A: acute physiology and chronic health evaluation, APACHE II score; B: simplified acute physiology score, SOFA score.
fibroblasts. They are responsible for the systemic e
mination, chemotaxis, leukocyte adherence, and activation of
fever, production of cytokines, endothelial gene regula-
tion of cells to induce many similar inflammatory reactions:
release of cytokines and can improve prognosis [6]. However,
stage of MODS patients can decrease or break partly stop the
strategies for those diseases. CVVH treatment in the early
to inflammatory system have become ideal therapeutic
and keeping the balance of body proinflammatory system
decrease of inflammatory mediators’ body concentration,
in CVVH group. Removal of inflammatory mediators,
(TNF-alfa, IL-6) and WBC count is significantly reduced
rate. Meta-analysis also reports inflammatory mediators
inflammation, such as loss of appetite and increased heart
Payen et al. study suggests that early application of standard
can effectively, lower WBC count, shorten hospital stays,
erence in mortality between the two groups [6]. Some of the trials
as discontinued after There are some reasons like clinical heterogeneity, trial was discontinued after many patients
died, limited sample size and limited effect of CVVH can explain it. However, this is a very critical outcome and should
be studied carefully in following trials.
Length of hospital stay results from the studies included
in this meta-analysis showed that CVVH significantly
reduced length of hospital stay as compared with the control
group by 5.3 days. The results are due to the benefits of
removal of inflammatory mediators. Reducing length of stay
by this amount for every patient is likely to make a significant
difference to cost of patient care.
Two studies reported hemodynamic stability [6, 7].
During 48-hour followup, CVVH could keep hemodynamic
stability. However, to those SIRS/MODS patients, long-term
hemodynamic observation is needed.
All of the included studies offered adequate descriptions
of the randomization process. Only two studies offered allo-
cation concealment [7, 9]. Although blinding of patients and
caregivers may not be feasible in CRRT studies, allocation
concealment and blinding of data collectors and outcome
assessors are possible and desirable. However, blinding,
in all of the trials, was not stated, which would yield
selection bias and performance bias. Furthermore, only two
studies reported intention-to-treat analysis, which would
yield attrition bias [9, 16]. All studies reported incomplete
outcome data. Due to these methodological limitations, as
well as the statistical imprecision and heterogeneity, the
quality of evidence presented in this article is considered of
lesser quality.
Our meta-analysis also had its limitations. First, there
was inability to assess and estimate effects of baseline patient
characteristics because access to individual patient data was
limited. Second, different types of filter membranes used
may have had a different impact. The characteristics of the
membrane used in CVVH may be an important factor on
cytokine clearance. The use of different membranes may
lead to variable TNF and IL-6 extraction. Third, all of the
included studies focused on only two inflammatory medi-
ators, (TNF-alfa, IL-6). Perhaps other mediators like IL-1,
### Table 3: Mortality

| Study or subgroup | CVVH | Control | Risk ratio | Risk ratio |
|------------------|------|---------|------------|------------|
|                  | Events | Total | Events | Total | Weight | M-H, fixed, 95%CI | M-H, fixed, 95%CI |
| 5.1.1.MODS       |       |       |         |        |         |               |               |
| Sanchez Riera 1997 | 4     | 15     | 7       | 15     | 25.2%  | 0.57 (0.21, 1.55) |               |
| Cole et al. 2002 [9] | 4     | 12     | 4       | 12     | 14.4%  | 1.00 (0.32, 3.10) |               |
| Liu et al. 2003 [10] | 7     | 24     | 12      | 26     | 41.5%  | 0.63 (0.30, 1.34) |               |
| Ding and Zhao 2007 [12] | 2     | 11     | 5       | 10     | 18.9%  | 0.36 (0.09, 1.47) |               |
| **Subtotal (95%CI)** | **62** | **63** | **100.0%** | **0.62 (0.38, 1.01)** |       |               |               |
| **Total events**       | **17** | **28** |         |        |         |               |               |
| **Heterogeneity:** Chi-square = 1.27, df = 3 (P = 0.74); $I^2 = 0$
| **Test for overall effect:** Z = 1.91 (P = 0.06) |
| 5.1.2 SRS           |       |       |         |        |         |               |               |
| Sander et al. 1997 [6] | 9     | 13     | 12      | 13     | 27.5%  | 0.75 (0.51, 1.11) |               |
| Payen et al. 2009 [16] | 20    | 37     | 17      | 39     | 38.0%  | 1.24 (0.78, 1.97) |               |
| J. Yang and H. Yang 2008 [13] | 1     | 31     | 6       | 27     | 14.7%  | 0.15 (0.02, 1.13) |               |
| Peng et al. 2008 [14] | 0     | 17     | 2       | 15     | 6.1%   | 0.18 (0.01, 3.43) |               |
| Yang et al. 2004 [11] | 4     | 22     | 5       | 15     | 13.7%  | 0.55 (0.17, 1.70) |               |
| **Subtotal (95%CI)** | **120** | **109** | **100.0%** | **0.78 (0.57, 1.08)** |       |               |               |
| **Total events**       | **34** | **42** |         |        |         |               |               |
| **Heterogeneity:** Chi-square = 7.73, df = 4 (P = 0.10); $I^2 = 48$
| **Test for overall effect:** Z = 1.49 (P = 0.14)
| **Test for subgroup differences:** Chi-square = 0.63, df = 1 (P = 0.43), $I^2 = 0$
### Table 4: Hospital stay.

| Study or subgroup | CVVH Mean (SD) | Total | Control Mean (SD) | Total | Weight IV, fixed, 95%CI | Mean difference IV, fixed, 95%CI |
|------------------|----------------|-------|-------------------|-------|-------------------------|---------------------------------|
| Peng et al. 2008 [14] | 15.2 (5.8) | 17 | 20.5 (7.9) | 15 | 51.1% | −5.30 (−10.16, −0.44) |
| Yang et al. 2004 [11] | 18.3 (5.7) | 22 | 27.5 (8.6) | 15 | 48.9% | −9.20 (−14.16, −4.24) |
| **Total (95%CI)** | **39** | **30** | **100.0%** | **−7.21 (−10.68, −3.74)** |

Heterogeneity: Chi-square = 1.21, df = 1
(P = 0.27); $I^2 = 18\%$

Test for overall effect: Z = 4.07
(P < 0.00001)
| Study or subgroup | CVVH Mean | CVVH SD | Total | Control Mean | Control SD | Total | Weight | Std. mean difference IV, fixed, 95%CI | Std. mean difference IV, fixed, 95%CI |
|------------------|------------|--------|-------|--------------|-----------|-------|--------|----------------------------------|----------------------------------|
| **1.1.1 after 3 days** | | | | | | | | | | |
| Liu et al. 2003 [10] | 22 | 78.58 | 24 | 46 | 89.74 | 26 | 46.3% | −0.28 (−0.84, 0.28) | |
| Zhang et al. 2008 [15] | 8.99 | 4.59 | 30 | 13.43 | 9.3 | 30 | 53.7% | −0.60 (−1.12, −0.08) | |
| **Subtotal (95%CI)** | | | | | | | | | | |
| | 54 | | | 56 | | | 100.0% | −0.45 (−0.83, −0.07) | |
| **Heterogeneity: Chi-square = 0.67, df = 1** | | | | | | | | (P = 0.41); I² = 0% | |
| **Test for overall effect Z = 2.32 (P = 0.02)** | | | | | | | | | | |
| **1.1.2 after 7 days** | | | | | | | | | | |
| Liu et al. 2003 [10] | 31 | 78.58 | 24 | 32 | 93.58 | 26 | 65.0% | −0.01 (−0.57, 0.54) | |
| Zhang et al. 2008 [15] | −18.57 | 4.44 | 30 | −5.34 | 4.16 | 30 | 35.0% | −3.04 (−3.79, −2.28) | |
| **Subtotal (95%CI)** | | | | | | | | | | |
| | 54 | | | 56 | | | 100.0% | −1.07 (−1.52, −0.62) | |
| **Heterogeneity: Chi-square = 39.93, df = 1** | | | | | | | | (P < 0.00001); I² = 97% | |
| **Test for overall effect Z = 4.69** | | | | | | | | (P < 0.00001) | |
| **Test for subgroup differences: Chi-square = 4.28, df = 1 (P = 0.04), I² = 76.7%** | | | | | | | | | | |
| **Effect** | **Favours CVVH** | **Favours control** |
| Study or subgroup                  | Mean | SD  | Total | Mean | SD  | Total | Weight | Std. mean difference IV, random, 95%CI | Std. mean difference IV, random, 95%CI |
|-----------------------------------|------|-----|-------|------|-----|-------|--------|----------------------------------------|----------------------------------------|
|                                  |      |     |       |      |     |       |        |                                        |                                        |
| **2.1.1 after 3 days**            |      |     |       |      |     |       | 24     | 0.4 (−1.04, 0.09)                       | −0.48 (−1.04, 0.09)                     |
| Liu et al. 2003 [10]              | −0.4 | 1.32| 24    | 0.4  | 1.91| 26    | 53.9%  |                                        |                                        |
| Yang et al. 2004 [11]             | −24.5| 15.15| 22   | −3.6 | 15.95| 15    | 46.1%  |                                        |                                        |
| Subtotal (95% CI)                 | 46   | 41  | 100.0%| 0.48 (−1.04, 0.09) | −1.32 (−2.05, −0.59) | | |                                        |                                        |
| Heterogeneity: Tau² = 0.25; Chi-square = 3.23, df = 1 (P = 0.07); I² = 69% | | | | | | | |                                        |                                        |
| Test for overall effect Z = 2.05 (P = 0.04) | | | | | | | |                                        |                                        |
| **2.1.2 after 7 days**            |      |     |       |      |     |       |        |                                        |                                        |
| Liu et al. 2003 [10]              | −0.8 | 1.41| 24    | 0.8  | 2.08| 26    | 50.5%  | −0.88 (−1.46, −0.30)                     | −0.88 (−1.46, −0.30)                     |
| Zhang et al. 2008 [15]            | −46.7| 15.05| 30   | −16.3| 15.36| 30    | 49.5%  | −1.97 (−2.60, −1.35)                     | −1.97 (−2.60, −1.35)                     |
| Subtotal (95% CI)                 | 54   | 56  | 100.0%| 1.97 (−2.60, −1.35) | −1.42 (−2.49, −0.35) | | |                                        |                                        |
| Heterogeneity: Tau² = 0.50; Chi-square = 6.30, df = 1 (P = 0.01); I² = 84% | | | | | | | |                                        |                                        |
| Test for overall effect Z = 2.60 (P = 0.009) | | | | | | | |                                        |                                        |
| Test for subgroup differences: Chi-square = 0.65, df = 1 (P = 0.42), I² = 0% | | | | | | | |                                        |                                        |
| Study or subgroup          | CVVH Mean (SD) | Control Mean (SD) | Mean difference IV, fixed, 95%CI |
|---------------------------|----------------|-------------------|---------------------------------|
| J. Yang and ZH. Yang 2008 [13] | 5.56 (2.9)     | 2.67 (2.67)       | 2.89 (1.37, 4.41)               |
| Zhang et al. 2008 [15]   | 4.91 (3.2)     | 2.62 (3.3)        | 2.29 (0.65, 3.93)               |
| Total (95%CI)             | 60 (57)        | 57 (57)           | 100.0%                           |

Heterogeneity: Chi-square = 0.27, df = 1
(P = 0.60); I^2 = 0%

Test for overall effect: Z = 4.58
(P < 0.00001)
IL-8, platelet activating factor (PAF), and so forth, can be tested. Fourth, some data should be assessed using weighted mean differences, or only the descriptive analysis can be used. Finally, some of the inclusion studies were from China, so the results should be considered carefully when they were applied to other countries. Therefore, we still need more high-quality, multicenter, randomized, and controlled trials from other countries and regions.

5. Conclusions

All in all, CVVH could eliminate inflammatory mediators (TNF-alfa, IL-6) in plasma effectively, shorten hospital stays, and better stabilize of hemodynamics. This is worthy of further exploration and promotion. As an exogenous way of clearance, CVVH has aroused great concern because its effectiveness in other countries and regions. As an exogenous way of clearance, CVVH has aroused great concern because its effectiveness in other countries and regions.

Conflict of Interests

There is no financial support or relationships that may pose conflict of interests in this paper.

Acknowledgments

The first author the coauthors and all authors, who have contributed significantly. All authors are in agreement with the content of the paper.

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