Effects of Renal Replacement Therapy in Patients Receiving Extracorporeal Membrane Oxygenation: A Meta-Analysis

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The use of renal replacement therapy (RRT) in patients receiving extracorporeal membrane oxygenation (ECMO) is increasing, but the effect of RRT on ECMO is controversial. We performed a meta-analysis to determine whether RRT is related to higher mortality in patients receiving ECMO. We searched MEDLINE, EMBASE, the Cochrane Library, and KoreaMed and found 43 observational studies with 21,624 patients receiving ECMO and then compared inpatient mortality rates of patients receiving ECMO both with and without RRT. The risk ratio (RR) of mortality between patients receiving RRT and those not receiving RRT tended to decrease as the mortality of the group not receiving RRT increased. Among patients with RRT use rates of 30% and higher, the overall mortality rates for all patients receiving ECMO tended to decrease. We found that the increase in the RR for RRT tended to be greater the longer the initiation of RRT was delayed. We suggest that in patients receiving ECMO who have high RRT use rates, RRT may decrease mortality rates.

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Extracorporeal membrane oxygenation (ECMO) is an effective procedure that provides mechanical circulatory and pulmonary support for neonates, children, and adults with acute severe cardiopulmonary failure. Fluid overload and acute kidney injury are frequent complications of ECMO and the underlying disease process. Worsening volume overload or azotemia despite conventional medical treatment may lead to renal replacement therapy (RRT), such as peritoneal dialysis, intermittent hemodialysis, continuous venovenous hemofiltration, or hemodiafiltration. In 1 survey, the most common reasons leading to RRT in patients receiving ECMO were fluid overload, prevention of fluid overload, acute kidney injury, and electrolyte imbalances [1]. Continuous venovenous hemofiltration has been successfully applied in ECMO series to manage these problems in both venovenous and venoarterial ECMO [2–5]. Continuous RRT has treated acute kidney injury without further injury to the kidney and fluid overload in survivors who were receiving ECMO [6, 7]. Hemofiltration removes inflammatory proteins from the blood, demonstrating an antiinflammatory effect during cardiopulmonary bypass [8, 9]. However, many studies show that acute kidney injury and RRT in patients receiving ECMO were associated with increased mortality in both pediatric [10–15] and adult patients [16, 17]. Conversely, both Hoover and colleagues [2] and Blijdorp and associates [18] reported that there were no significant differences in mortality rates between patients receiving RRT and those not receiving RRT during ECMO. Therefore, we performed a systematic review and meta-analysis to determine whether RRT was related to higher mortality in patients receiving ECMO.

Patients and Methods

Data and Literature Sources

We used multiple comprehensive databases to find literature on the outcomes of patients receiving ECMO based on their RRT status. This study is based on the Cochrane Review methods [19, 20]. We searched MEDLINE (January 1, 1976–April 30, 2014), EMBASE (January 1,

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1985–April 30, 2014), the Cochrane Library (January 1, 1987–April 30, 2014), and KoreaMed (June 1, 1958–April 30, 2014). We put no restrictions on language or the year of publication in our search.

The following keywords and medical subject headings were searched through MEDLINE: extracorporeal membrane oxygenation (ECMO), extra corporeal membrane, extra-corporeal membrane, extra-corporeal life support, or extracorporeal life support (Appendix Table 1). The search methods used for MEDLINE were transferred to other databases. Identified articles were individually assessed for inclusion.

Study Selection

Inclusion of a study was independently determined by 2 reviewers (H.B. and S-S.H). The selection process consisted of 2 levels: at the first level we screened titles and abstracts of the identified studies, and at the second level we screened the full text. Studies were included in our meta-analysis if (1) all patients received ECMO and (2) there was documentation of inpatient mortality rates of ECMO both with and without RRT. We excluded studies if (1) they described only pharmacokinetic results, (2) they had no comparison or survival data, (3) the starting time of RRT was before the start of ECMO, or (4) they included the same study population as in other studies.

Data Extraction

The 2 reviewers (H.B. and S-S.H.) independently and blindly extracted data from each study using a predefined data extraction form. Any disagreement unresolved by discussion was then further reviewed by a third author (H.J.K).

The following variables were extracted from the studies: (1) mortality data, (2) demographics and clinical features (eg, age, weight, number of patients in each group, indications for ECMO), (3) Extracorporeal Life Support Organization (ELSO) registration status, (4) type of study, and (5) study period. If the aforementioned variables were not described in the study, we contacted the authors by e-mail to obtain the missing data.

Assessment of Methodological Quality

Two reviewers (H.B. and S-S.H.) blindly assessed the risk of bias in each study using the Newcastle-Ottawa Quality Assessment Scale [21], with any differences in opinion between the 2 authors resolved by a third reviewer (H.J.K.). We evaluated the studies based on the patients selected in the control (ECMO only) and intervention (ECMO with RRT) groups, the comparability between the 2 groups, the adequacy of follow-up, and the assessment of the outcomes. Based on these criteria, studies were scored from 0 to 9.

We assessed the possibility of publication bias using symmetry/asymmetry of funnel plots. When publication bias occurs, the funnel plot may be asymmetrical; hence, we evaluated asymmetry of the funnel plots using the trim and fill method [22] and Egger's test [23].

Statistical Analysis

The main focus of our review was the inpatient mortality rates in patients who had received ECMO with or without RRT. We extracted the number of total patients and deaths from each study and then used the Mantel-Haenszel method to calculate risk ratios (RRs) with the number of events in both the control and intervention groups.

Subgroup analysis was conducted based on age, indications for ECMO, mortality rates of control groups, case-matched studies, and the time that RRT was initiated. We conducted planned sensitivity analyses according to the study year, the total population, type of study, ELSO registration status, comparability, the degree of risk of bias, and the ECMO type.

Heterogeneity was estimated by calculating the I^2 statistic, which is the proportion of inconsistency between 2 studies arising from true difference rather than random error. I^2 values greater than 50% were considered heterogeneous. All cases, however, were analyzed through the random-effects model because they were observational studies. We used Stata, version 13.0 (StataCorp, College Station, TX), for these analyses.

Results

Identification of Studies

Our database search resulted in 17,177 articles (Fig 1). Of these, 11,880 publications were excluded because it was clear from the title and abstract that they did not fulfill

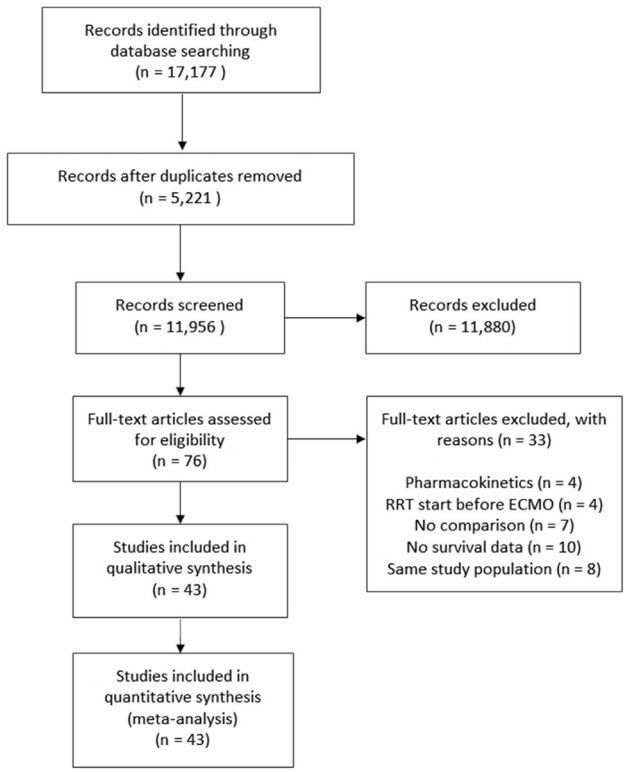

Fig 1. Flow diagram of study method. (ECMO = extracorporeal membrane oxygenation; RRT = renal replacement therapy.)

REVIEW