Timing of Renal Replacement Therapy Initiation in Acute Renal Failure: A Meta-analysis

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Background: Some studies have suggested that early institution of renal replacement therapy (RRT) might be associated with improved outcomes in patients with acute renal failure (ARF).

Study Design: A systematic review and meta-analysis of randomized controlled trials and cohort comparative studies to assess the effect of early RRT on mortality in patients with ARF.

Setting & Population: Hospitalized adult patients with ARF.

Selection Criteria for Studies: We searched several databases for studies that compared the effect of "early" and "late" RRT initiation on mortality in patients with ARF. We included studies of various designs.

Intervention: Early RRT as defined in the individual studies.

Outcomes: The primary outcome measure was the effect of early RRT on mortality stratified by study design. The pooled risk ratio (RR) for mortality was compiled using a random-effects model. Heterogeneity was evaluated by means of subgroup analysis and meta-regression.

Results: We identified 23 studies (5 randomized or quasi-randomized controlled trials, 1 prospective and 16 retrospective comparative cohort studies, and 1 single-arm study with a historic control group). By using meta-analysis of randomized trials, early RRT was associated with a nonsignificant 36% mortality risk reduction (RR, 0.64; 95% confidence interval, 0.40 to 1.05; $P = 0.08$). Conversely, in cohort studies, early RRT was associated with a statistically significant 28% mortality risk reduction (RR, 0.72; 95% confidence interval, 0.64 to 0.82; $P < 0.001$). The overall test for heterogeneity among cohort studies was significant ($P = 0.005$). Meta-regression yielded no significant associations; however, early dialysis therapy was associated more strongly with lower mortality in smaller studies ($n < 100$) by means of subgroup analysis.

Limitations: Paucity of randomized controlled trials, use of variable definitions of early RRT, and publication bias preclude definitive conclusions.

Conclusion: This hypothesis-generating meta-analysis suggests that early initiation of RRT in patients with ARF might be associated with improved survival, calling for an adequately powered randomized controlled trial to address this question.

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INDEX WORDS: Acute renal failure; ARF; dialysis; hemodialysis; continuous renal replacement therapy; timing; prophylactic; early; late; intensive; mortality; meta-analysis.

The potential impact of renal replacement therapy (RRT) on clinical outcomes in patients with acute renal failure (ARF) has been a subject of intensive investigation, as previously reviewed.[1] Several factors to consider in RRT include modality, dialyzer membrane, timing of initiation, and level of intensity and adequacy of the therapy. The link between these interconnected RRT-related variables and clinical outcomes has remained largely unexplored except for the dialyzer membrane[2-4] and RRT modality used,[5-8] with several meta-analyses yielding conflicting results.[9]

In patients with ARF, the goal of RRT is to attain solute clearance and fluid balance while waiting for kidney function to recover. Timely institution of RRT is fundamental to achieving this goal. Current indisputable indications for

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initiating RRT include persistent hyperkalemia, severe acidosis, and hypervolemia that are unresponsive to conservative measures; uremic serositis; bleeding diathesis; and severe encephalopathy.[10]

"Early" or "prophylactic" RRT was introduced more than 5 decades ago[11-20] and was used to describe the initiation of dialysis therapy before nitrogenous waste products reached some arbitrary predefined "critical" blood value, irrespective of clinical indications. Relatively few studies primarily addressed the role of "early" versus "late" initiation of RRT for the reduction of complications of the uremic syndrome in patients with ARF. Old reports suggested that early initiation of dialysis therapy might improve survival.[11-22] However, in more recent years, very few studies have confirmed these findings.[23-34] To provide a comprehensive review of these studies, we conducted a systematic review and meta-analysis to examine whether early initiation of RRT confers better survival and to explore heterogeneity among studies. We also explored whether early initiation of RRT is associated with improved kidney function recovery rates.

METHODS

Search for Relevant Studies

We searched the medical literature for clinical studies examining the timing of RRT and mortality in patients with ARF, starting in 1960 because the first artificial kidney (Kolff twin coil tank) became commercially available in 1956[35] and the concept of prophylactic dialysis was not introduced until 1960.[14] Primary sources used to identify clinical studies included: (1) a MEDLINE literature search in PubMed using the MeSH database search terms "kidney failure, acute," "renal insufficiency, acute," "dialysis," "renal dialysis," "peritoneal dialysis," "renal replacement therapy," "kidney, artificial," and "kidney failure, acute/therapy" limited to human clinical studies published from 1960 through October 2006; (2) a literature search in the Cochrane Central Register of Controlled Trials using the same search terms during the same period; (3) a manual search of proceedings from the annual meetings of the American Society of Nephrology (1999 to 2006), review articles on the dialytic management of ARF, and study references; and (4) a manual search in the Latin American and Caribbean Health Sciences Literature database or Literatura Latino Americana e do Caribe em Saúde (LILACS). English, French, Spanish, Italian, and Portuguese language studies were included in the search.

Selection Criteria

Studies examining the effect of timing of RRT initiation in patients with ARF on clinical outcomes, namely mortality, were selected. We excluded studies primarily designed to examine the effect of RRT dose or frequency/intensity. To minimize the effect of publication bias, we included full-length published articles and scientific abstracts. If investigators published more than 1 report on the same study, data from the most inclusive report were retrieved. Studies lacking a historic or contemporaneous control group were excluded.

Data Extraction

Two authors (V.F.S. and B.L.J.) extracted the data independently, and differences were resolved in a conference. The primary outcome for this analysis was all-cause mortality, which was summarized for each treatment group in individual studies. If quantifiable, a secondary outcome of recovery of kidney function, defined by the investigators of the individual studies, was also summarized.

Quality Assessment

Study quality was assessed by using a previously published method with some modification.[7] In brief, each question in this quality instrument was given a score of 1 to 5, in which 1 corresponded to poor and 5 corresponded to excellent methods. Scores for each question were totaled and divided by the number of relevant questions within each domain (enrollment, intervention, and outcome) to produce a domain score of 1 to 5. The enrollment domain addressed the selection process, specification of inclusion and exclusion criteria, quality of randomization, or comparability of groups in nonrandomized studies. The intervention domain addressed comparability of the 2 treatment arms in regard to RRT modality, dose, dialyzer membrane, and cointerventions. The outcome domain addressed the relevance of the outcome variable, including survival, renal recovery, and length of stay, as well as data analysis quality and follow-up and attrition information. The mean score of all 3 domains was calculated and used as a surrogate for overall quality assessment.

Statistical Methods

The primary analysis was restricted to randomized and quasi-randomized trials, and the secondary analysis, to comparative cohort studies. For each study, risk ratio (RR) with 95% confidence interval (CI) was computed for mortality and recovery of kidney function in the early- versus late-RRT-initiation group. The pooled RR for mortality was compiled by using a random-effects model.[36] This model assigns a weight to each study based on both within-study variance and between-study heterogeneity. Heterogeneity among studies was analyzed by using a χ^2 test on N-1 *df,* with α of 0.10 used for statistical significance. To attempt to explain heterogeneity, sensitivity analyses were performed with exploratory subgroup analyses. Student *t*-test was used to compare subgroups. Random-effects model meta-regression was performed to examine the relationship of the RR to several covariates, including year of study publication, patient mean