Early Versus Late Initiation of Renal Replacement Therapy in Critically Ill Patients With Acute Kidney Injury After Cardiac Surgery: A Systematic Review and Meta-analysis

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Objective: **To investigate the impact of early versus late renal replacement therapy (RRT) on mortality in patients with acute kidney injury (AKI) after cardiac surgery.**

Design: **Meta-analysis of 9 retrospective cohort studies and 2 randomized clinical trials extracted from the Medline engine from 1950 to 2013.**

Setting: **University medical school.**

Participants: **841 Patients.**

Interventions: **None.**

Measurements and Main Results: **A total of 841 patients were studied. Pooled estimates of the odds ratio with 95% confidence interval using a random-effect model were conducted as well as the heterogeneity, publication bias, and sensitivity analysis. Primary outcome was 28-day mortality, and secondary outcome was the intensive care unit (ICU) length of stay. The 28-days mortality rate was lower in the early RRT group (OR = 0.29, 95% CI, 0.16-0.52, p < 0.0001, NNT = 5). Heterogeneity was high (I2 = 56%), and publication bias was low. Secondary outcome suggested 3.9 (1.5-6.3) days shorter ICU stay in the early RRT group, p < 0.0001, with extremely high heterogeneity (I^2 = 99%), and low publication bias. Specifically, studies before 2000 and studies with mortality less than 50% in the late RRT group reported significantly higher odds ratio and mean difference than overall value favoring early RRT.**

Conclusion: **Early initiation of RRT for patients with AKI after cardiac surgery revealed lower 28-days mortality and shorter ICU length of stay. However, this was based on 11 studies of various qualities with very high heterogeneity of results. Defining treatment guidelines needs further research with a larger and better database.**

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KEY WORDS: cardiac surgical procedures, renal replacement therapy, acute kidney injury, critical illness, meta-analysis

ACUTE KIDNEY INJURY occurs in up to 42% of patients undergoing cardiac surgery, with approximately 1% of all patients requiring dialysis.[1] Not only is AKI associated with a prolonged intensive care unit (ICU) admission and hospital stay, but it also can result in a higher mortality rate.[2–4] The proposed mechanism for the development of AKI is perioperative hypotension and subsequent vasoconstrictor therapy leading to impaired renal perfusion. Other causes such as prolonged exposure to cardiopulmonary bypass, hypothermia, hemolysis, and postoperative reperfusion also have been proposed.[5] Thus, multiple interventions have been applied after cardiac surgery to reduce AKI, which include IV fluids, steroid medications, diuretics and renal replacement therapy (RRT).[6,7] Among these, RRT has been shown to be the most effective way to achieve the extracorporeal removal of waste products such as urea and creatinine in order to provide an optimal condition for kidney recovery.[8]

Unfortunately, there is no consensus on the timing of RRT initiation. Several studies focused on timing for initiation of RRT for AKI;[9–19] however, due to the complexity and variations of underlying causes, it is still difficult to generate a clear guideline to start RRT on each specific patient. Among the several studies on RRT timing, the definition of early versus late also differs. Currently, there are controversial data for outcome analysis for early and late RRT in cardiac surgery. Therefore, the authors conducted a systematic review and meta-analysis assessing whether early initiation of RRT would lead to better survival rate, less dialysis dependence, less duration of RRT as well as shorter ICU stay. The authors hypothesized that morbidity and mortality are reduced in early RRT after cardiac surgery.

METHODS

Database Search

The authors performed a computerized search to identify relevant published original studies (1950 to August 2013). Medline, Cochrane Library, and EMBASE databases were searched using medical subject headings (MeSH) and keywords. This search was last updated on January 1, 2013 and was not limited to English language or publication type. MeSH terms were "cardiovascular surgical procedures, thoracic surgery, coronary artery bypass, early vs. late dialysis, renal replacement therapy, mortality, kidney diseases and acute kidney injury." Keywords were "acute renal failure, acute kidney injury, renal replacement therapy, early vs. late, mortality, coronary artery bypass, and cardiothoracic surgery." Table 1 shows the number of studies found.

Study Selection

An initial eligibility screen of all retrieved titles and abstracts was conducted, and only studies reporting RRT for patients with AKI were selected for further review. The following specific criteria were used for final selection: (1) retrospective or prospective cohort studies as well as randomized control trials (RCT), (2) studies reporting patients with AKI specifically after cardiac surgery, and (3) studies showing clear comparison of early versus late RRT initiation with direct effect on mortality. Studies without clear comparison and outcomes or experimental studies were excluded. A restriction of English only was imposed on study selection. Two reviewers (YL and JP) independently examined the studies, and disagreement was resolved by discussion.

Data Extraction

Characteristics of each study were extracted, which included the last name of first author, publication year, country of study, study period, study design, population settings, the number of the patients, and percentage of male and mean age in the early and the late group.

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Table 1. Basic Characters of Studies Selected

Author	Country	Study Period	Study Design	Population Setting	No. of Patients		Male (%)		Mean Age (Year)	
					Early	Late	Early	Late	Early	Late
Bouman[9] (2002)	Netherlands	1998-2000	Randomized Control Trial	Cardiac Surgery	35	36	57	61	70 ± 10	67 ± 13
Demirkilic[10] (2004)	Turkey	1992-2001	Retrospective Cohort Study	Cardiac Surgery	34	27	79	77	NR	NR
Elahi[11] (2004)	United Kingdom	2002-2003	Retrospective Cohort Study	Cardiac Surgery	36	28	67	71	70 ± 8.7	68 ± 9.7
Fernandez[12] (2011)	Spain	2007	Retrospective Cohort Study	Cardiac Surgery	101	102	NR	NR	NR	NR
Iyem [13] (2009)	Turkey	2004-2007	Retrospective Cohort Study	Cardiac Surgery	95	90	37.8	35.5	64.5 ± 5.2	62.3 ± 6.4
Ji[14] (2009)	China	Before 2009	Retrospective Cohort Study	Cardiac Surgery	34	24	64.7	58.3	64 ± 10	62 ± 10
Manche[15] (2008)	Malta	1995-2006	Retrospective Cohort Study	Cardiac Surgery	56	15	NR	NR	66 ± 9.1	63.7 ± 10.9
Sugahara[16] (2004)	Japan	2001-2002	Retrospective Cohort Study	Cardiac Surgery	14	14	64.3	64.3	65 ± 3	64 ± 3
Durmaz[17] (2003)	Turkey	1999-2001	Randomized Control Trial	Cardiac Surgery	21	23	76.2	82.6	58.1 ± 12	54.3 ± 11.3
Lange[18] (1987)	United States	1980-1983	Retrospective Cohort Study	Cardiac Surgery	17	19	70.6	52.6	68 ± 14	69 ± 9
Kleinknecht[19] (1972)	France	1966-1970	Retrospective Cohort Study	Cardiac Surgery	10	10	NR	NR	46	46

Another table to summarize the definition of early and late initiation was generated. Finally, RRT modality, pre-RRT creatinine, and blood urea nitrogen (BUN) level and Acute Physiology and Chronic Health Evaluation II (APACHE II) score from each study were extracted. The following outcomes included hemodialysis-free percentage, duration of RRT in days, ICU length of stay (LOS) in days, and mortality at 28 days for both early and late groups.

Quality Assessment

The quality of each study was evaluated using the checklist developed by Downs and Black,[20] which included 27 questions based on the study's reporting, external validity, bias, confounding, and power. Each question gave a score of 0 or 1, and the overall score ranges from 0 to 27. Studies with scores of 23 or higher were considered to be high quality, 18 to 23 were moderate quality, and scores of 18 or below were low quality.

Statistical Analysis

RevMan 5.2 was used to calculate the odds ratio (95% confidence interval) for each study, overall mortality, and mean difference of ICU length of stay. Pooled analysis was performed using the Der Simonian and Laird random-effects model.[21] I^2 was used to assess statistical heterogeneity with a value below 30% meaning low heterogeneity, a value between 30% and 50% meaning moderate heterogeneity, and a value above 50% meaning high heterogeneity. A random-effect model was used for all analyses. Publication bias was assessed using Egger's regression test[22] and Begg and Mazumdar[23] methods, using a funnel plot. Sensitivity was evaluated with meta-regression analysis in order to avoid extreme outcome variation from each specific pre-defined characteristic as well as study sample size, study design, RRT modality, quality score, study period, and late RRT group mortality rate.

RESULTS

Study Selection

After careful examination of titles and abstracts, a total of 1,217 citations were identified from databases with only 15 selected for full-text review. Four papers were excluded from review due to the following reasons: (1) AKI developed from conditions other than cardiac surgery (n=2).[24,25] (2) There was lack of clear comparison between early and late RRT (n = 2).[26,27] Only 11 publications were finalized for this meta-analysis (Fig 1).

Study Characteristics

Table 1 includes the basic characteristics of the studies selected. One notable finding was the mean age difference that was 46 to 80 before 2000 and 60 to 78 after 2000. The percentage of male patients did not vary among different study periods. Of the selected studies, 9 were retrospective cohort studies, and 2 were randomized clinical trials. According to the scoring system from Downs and Black, 4 studies were of high quality, 3 of intermediate quality, and 4 of poor quality, as shown in Table 2. Common quality problems were inadequate followup, publication bias, and outcome definition inconsistency. The definition of early and late initiation of RRT for each specific study is outlined in Table 2. Several studies used urine output, time elapsed after surgery, and diuretics use for low urine output for defining early versus late renal failure. For the 7 studies using serum BUN and creatinine level as cutoff values, the early group had BUN ranging from 27 to 212 mg/