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**Title**

Extended daily dialysis versus intermittent hemodialysis for acute kidney injury: a systematic review

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**Contributions**

JAL was the guarantor. All authors contributed to the drafting of the manuscript, the development of the selection criteria, the risk of bias assessment strategy, data extraction criteria, and result interpretation and discussion. FBR developed the search strategy. JBN, FBR and MC conducted the report screening, study inclusion, and data extraction. FBR e JC performed the statistical analysis. JAL and JC provided expertise on acute kidney injury and on methodology. All authors read, provided feedback and approved the final manuscript.

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**Keywords**

Acute kidney injury, renal dialysis, systematic review

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To the Editor:

Acute kidney injury (AKI) occurs frequently during hospitalization[1] and is associated with deleterious effects[2,3]. The need for renal replacement therapy (RRT) in AKI is rising[4] and continuous RRT (CRRT), extended daily dialysis (EDD) and intermittent hemodialysis (IHD) are the most commonly used techniques in developed countries. Previous systematic reviews and meta-analysis have analyzed the use of RRT in AKI but failed to prove major outcome differences between CRRT and intermittent techniques, such as EDD and IHD[5-7]. Hemodynamic stability and the needed rate of solute clearance guide the clinical decision regarding dialytic modalities in AKI and evidence supporting the choice between IHD or EDD is limited[7]. Therefore, we aimed to systematically review published data comparing the safety and efficacy of EDD and IHD in AKI.

The protocol for this systematic review was pre-registered at PROSPERO (CRD42015025034) and the authors followed PRISMA guidelines (Annex S1). MEDLINE, CENTRAL (Cochrane Library), and clinicaltrials.gov were searched (June 2015) for studies comparing EDD and IHD in adult patients with AKI. Two independent authors selected studies, extracted data and evaluated the risk of bias. Primary outcomes were renal function recovery and mortality at 90 days. Secondary outcomes were intensive care unit (ICU) and hospital length of stay, hemodynamic stability, in-hospital mortality, and mortality at 30 days.

After deduplication 2735 studies were screened for eligibility, eight underwent full-text review and two were included[8,9] (Figure S1 - PRISMA flow diagram).

Study characteristics, baseline characteristics of patients and reported outcomes are summarized on Tables 1, 2, and 3, respectively. Both studies have an overall moderate risk of bias: Kumar et al[8] due to selection bias and Khanal et al[9] due to confounding bias, selection bias, reporting bias, and bias due to baseline imbalances.

Kumar and colleagues[8] describe a quasi-randomized study including 30 patients equally divided between arms. The mean age was 37.8 years (standard deviation (SD) 13.4), and most patients were women (n=23, 76.7%). The most frequent cause of AKI was sepsis (including 13 (43.3%) cases of obstetric sepsis), followed by hypovolemia. Extremely ill patients were excluded, less than half (n=13, 43.3%) of patients exhibited dysfunction of two organs and only six (20%) required vasopressor use. At 90 days follow-up, all had recovered renal function and no deaths were reported. A non-significant trend towards a greater rate of intradialytic hypotension was observed for IHD. However, the blood flow rate in EDD was occasionally reduced to 200ml/min in response to vital sign changes. No data is provided for ICU or hospital length of stay, or intradialytic need to start or escalate vasopressors.

Khanal et al[9] describe a retrospective cohort study comparing the three most frequently used RRT in AKI, with 118 patients undergoing EDD and 20 IHD. The mean age was 57.7 years (SD 7.97), and most patients were men (n=81, 58.7%). Sepsis and surgery were the most frequent causes of AKI. Patients had high baseline illness severity, with elevated mean APACHE IV acute physiology score (108.62, SD 37.96) and SOFA scores (12.40, SD 4.70) and rate of vasopressor use (n=118, 85,5%). Of note, patients undergoing IHD had a lower baseline rate of vasopressor use when compared with EDD. Hazard ratios (IHD *versus* EDD) adjusted for baseline and time-varying characteristics were 1.22 (95%CI: 0.33-4.43) for in-hospital death

and 2.22 (95%CI: 0.49-10.11) for 90-day mortality. No data is provided for renal function recovery, mortality at 30 days, or for outcomes related to in-session hemodynamic stability.

The two studies have disparate study designs and report on widely different populations, which compromises data aggregation and comparisons. The study by Kumar is interventional and its patients are characteristic of an underdeveloped country (young, with high rates of obstetric sepsis, hipovolemia, and malaria as causes of AKI), while Khanal reports on a severely ill population from a developed country. Also, Kumar's small sample size and less ill patients may contribute to the excellent endpoints achieved (no deaths and all recovered renal function). Finally, Khanal and colleagues indicate that IHD patients were slightly less ill than the EDD ones but this effect may be limited by the baseline and time-varying modeled statistical analysis used.

This systematic review gathers very low-quality evidence (i.e., any estimate of effect is very uncertain[10]) suggesting that IHD may lead to greater intradialytic hemodynamic instability than EDD, and that both interventions may carry similar in-hospital and 90-day risks of death. In the authors' opinion, no strong recommendations can be made. Notwithstanding, one important result is the confirmation that the available data on this topic is very scarce: there are only two published studies, both with moderate risk of bias, suboptimal designs and sample sizes, and that missed to report all relevant outcomes. To drive patient care strong evidence is essential and this systematic review highlights the pressing need for studies comparing the safety and efficacy of EDD and IHD in AKI.

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**Tables**

Table 1 – Characteristics of included studies

| Source | Study design | Study centers | Study period | Setting | Number of patients | Inclusion criteria | Definition of AKI | Definition of interventions | Reported causes of AKI | Follow-up | Outcomes |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Kumar et al | Quasi-randomized interventional study | 1; India | 2005-2006 | Hospital | 30 | >14 <60 years old<br>AKI<br>Absence of CKD<br>Absence of >2 failing organs | Serum creatinine≥2.0mg/dL or an increase in serum creatinine>50% over the baseline value | EDD: 8 hours per session, daily;<br>IHD: 4 hours per session, thrice a week. | Obstetric sepsis (43.3%)<br>Hypovolemia (36.7% )<br>Malaria (10%)<br>Other causes of sepsis (6.7%)<br>Nephrotoxicity (3.3% ) | 90 days | In-hospital mortality<br>Recovery of renal function |
| Khanal et al | Retrospective cohort study | 1; New Zealand | 2002-2008 | Intensive care unit | 138 | >16 years old<br>AKI or acute-on-chronic renal disease except if CKD on maintenance dialysis | RIFLE criteria | EDD: 8 to 10 hours per session, daily or on alternate days at physician discretion;<br>IHD: 4 to 6 hours per session, daily or on alternate days at physician discretion. | Sepsis (69.6%)<br>Postoperative (42%) | 90 days | In-hospital mortality<br>Mortality at 90 days |

AKI: acute kidney injury; CKD: chronic kidney disease; EDD: extended daily dialysis; IHD: intermittent hemodialysis; RIFLE: Renal Injury Failure Loss, End-stage kidney diseasE

Table 2 – Baseline characteristics of included patients

| | Kumar et al. | | Khanal et al. | |
|---|---|---|---|---|
| | IHD | EDD | IHD | EDD |
| Number of patients | 15 | 15 | 20 | 118 |
| Age [mean (SD); years] | 38.2 (12.2) | 37.3 (15.0) | 58.6 (17.6) | 57.6 (4.9) |
| Male [n (%)] | 4 (26.7) | 3 (25.0) | 11 (55) | 70 (59.3) |
| Baseline eGFR [mean (SD); ml/min/1.73m$^2$] | N/A | N/A | 59.8 (40.0) | 59.5 (29.4) |
| Cause of AKI | | | | |
| Sepsis [n (%)] | 7 (46.7) | 8 (53.3) | 14 (70.0) | 82 (69.5) |
| Postoperative [n (%)] | 0 (0.0) | 0 (0.0) | 6 (30.0) | 52 (44.1) |
| Nephrotoxicity [n (%)] | 1 (6.7) | 0 (0.0) | N/A | N/A |
| APACHE IV acute physiology score [mean (SD)] | N/A | N/A | 100.7 (35.5) | 108.9 (38.5) |
| APACHE IV risk of death in % [mean (SD)] | N/A | N/A | 68.3 (26.2) | 67.7 (28.2) |
| SOFA score [mean (SD)] | N/A | N/A | 10.6 (4.4) | 12.7 (4.7) |
| Organ dysfunction | | | | |
| 1 organ [n (%)] | 9 (60.0) | 8 (53.3) | N/A | N/A |
| 2 organs [n (%)] | 6 (40.0) | 7 (46.7) | N/A | N/A |
| Need of mechanical ventilatory support [n (%)] | 0 (0.0) | 0 (0.0) | N/A | N/A |
| Hemodynamic stability before dialysis | | | | |
| MAP [mean (min-max)] | 103.3 (89.9-109.9) | 101.9 (99.9-109) | N/A | N/A |
| Need of vasopressor drugs [n (%)] | 3 (20.0) | 3 (20.0) | 15 (75.0) | 103 (88.0) |
| Number of dialytic sessions | 82 | 140 | 55 | 413 |

EDD: extended daily dialysis; IHD: intermittent hemodialysis; SD: standard deviation; N/A: not available; eGFR: estimated glomerular filtration rate; AKI: acute kidney injury; MAP: mean arterial pressure.

Table 3 – Reported outcomes of included studies

| | Kumar et al | | | Khanal et al | | |
|---|---|---|---|---|---|---|
| | IHD | EDD | Effect measure* | IHD | EDD | Effect measure* |
| Renal function recovery [n (%)] | 15 (100) | 15 (100) | RR 1.00 (0.88-1.13) | N/A | N/A | N/A |
| Mortality at 90 days [n (%)] | 0 (0) | 0 (0) | RR 1.00 (0.07-14.55) | N/A | N/A | HR 2.22 (0.49-10.11) |
| Days in ICU [mean (SD)] | N/A | N/A | N/A | 11.2 (11.2) | 10.1 (9.5) | MD 1.1 (-4.10-6.30) |
| In-session hemodynamic stability | | | | | | |
| Hypotensive episodes [n (%)] | 6 (7.3) | 0 (0.0) | RR 13.00 (0.80-212.02) | N/A | N/A | N/A |
| Post-dialytic MAP [mean (min-max)] | 73 (70-79) | 78.6 (75-83) | Not estimable | N/A | N/A | N/A |
| In-hospital mortality [n (%)] | 0 (0) | 0 (0) | RR 1.00 (0.07-14.55) | N/A | N/A | HR 1.22 (0.33-4.43) |
| Mortality at 30 days [n (%)] | 0 (0) | 0 (0) | RR 1.00 (0.07-14.55) | N/A | N/A | N/A |

EDD: extended daily dialysis; IHD: intermittent hemodialysis; RR: risk ratio (95% confidence interval); N/A: Not available; HR: hazard ratio (95% confidence interval); ICU: intensive care unit; SD: standard deviation; MD: mean difference (SD); MAP: mean arterial pressure; *: IHD versus EDD