How Wise is Early Dialysis in Critically-Ill Patients?

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Acute Kidney Injury (AKI)

- A common condition in ICU patients
- Associated with high mortality and morbidity
- Renal Replacement Therapy (RRT) is the cornerstone of the management of severe AKI

Indications for Renal Replacement Therapy (RRT)

- A: Acidosis
  - Not responsive to bicarbonate
- E: Electrolyte abnormalities
  - Hyperkalemia, hyperphosphatemia
- I: Intoxication
  - Boric acid, ethylene glycol, lithium, methanol, phenobarbital, salicylate, theophylline
- O: Fluid overload
  - Symptomatic pulmonary edema
- U: Uremia
  - Pericarditis, weight loss

Modalities of Dialysis

- Hemodialysis
  - Intermittent for end-stage kidney disease

- Peritoneal dialysis

- Continuous renal replacement therapy (CRRT) for AKI
  - Continuous venovenous hemofiltration (CVVH): Removes fluid and solutes by convection rather than by diffusion
  - Continuous venovenous hemodialysis (CVVHD): Dialysate flows countercurrent to blood flow, and solute is removed by diffusion
  - Continuous venovenous hemodiafiltration (CVVHDF): Ultrafiltration and dialysis; solute is removed by both convection and diffusion. Requires both replacement fluid and dialysate

Previous Studies on RRT

- Heterogenous
- Dose of RRT
- Method of RRT
- Unequivocal need for RRT in patients with severe AKI and life-threatening complications
- Undefined need for RRT in patients with severe AKI and no life-threatening complications
- Undefined time to initiate RRT

Optimal Time to Initiate RRT?

5.3: TIMING THE INITIATION OF RRT

5.3.1: We suggest that dialysis be initiated when one or more of the following are present: symptoms or signs attributable to kidney failure (serositis, acid-base or electrolyte abnormalities, pruritus); inability to control volume status or blood pressure; a progressive deterioration in nutritional status refractory to dietary intervention; or cognitive impairment. This often but not invariably occurs in the GFR range between 5 and 10 ml/min/1.73 m^2. (2B)

Kidney Disease: Improving Global Outcomes (KDIGO). Available at http://kdigo.org/home/guidelines/

Early versus Delayed Dialysis

- Early Dialysis
  - Better control of fluid and electrolyte status
  - Removal of uremic toxins
  - Prevention of complications
    - Gastric hemorrhage
    - Metabolic encephalopathy
- Delayed Dialysis
  - Time for stabilization of patient's status before RRT is started and may avoid the need for such support

What Is The Evidence?

Wierstra et al. Critical Care (2016) 20:122
DOI 10.1186/s13054-016-1291-8

Critical Care

RESEARCH   **Open Access**

The impact of "early" versus "late" initiation of renal replacement therapy in critical care patients with acute kidney injury: a systematic review and evidence synthesis

Benjamin T. Wierstra[1], Sameer Kadri[2], Soha Alomar[2], Ximena Burbano[2], Glen W. Barrisford[2] and Raymond L. C. Kao[2,3*]

Conclusion: Early RRT in critical illness and AKI does not improve patient survival or confer reductions in ICU or hospital LOS

Early RRT? Delayed RRT?
Early RRT? Delayed RRT?

She loves me
She loves me not

Artificial Kidney Intervention in Kidney Injury (AKIKI)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit

Stéphane Gaudry, M.D., David Hajage, M.D., Frédérique Schortgen, M.D., Laurent Martin-Lefevre, M.D., Bertrand Pons, M.D., Eric Boulet, M.D., Alexandre Boyer, M.D., Guillaume Chevrel, M.D., Nicolas Lerolle, M.D., Ph.D., Dorothée Carpentier, M.D., Nicolas de Prost, M.D., Ph.D., Alexandre Lautrette, M.D., Anne Bretagnol, M.D., Julien Mayaux, M.D., Saad Nseir, M.D., Ph.D., Bruno Megarbane, M.D., Ph.D., Marina Thirion, M.D., Jean-Marie Forel, M.D., Julien Maizel, M.D., Ph.D., Hodane Yonis, M.D., Philippe Markowicz, M.D., Guillaume Thiery, M.D., Florence Tubach, M.D., Ph.D., Jean-Damien Ricard, M.D., Ph.D., and Didier Dreyfuss, M.D., for the AKIKI Study Group*

N Engl J Med 2016;375:122-33

ELAIN Trial

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury
The ELAIN Randomized Clinical Trial

Alexander Zarbock, MD; John A. Kellum, MD; Christoph Schmidt, MD; Hugo Van Aken, MD; Carola Wempe, PhD; Hermann Pavenstädt, MD; Andreea Boanta, MD; Joachim Gerß, PhD; Melanie Meersch, MD

JAMA 2016;315(20):2190-99

AKIKI vs. ELAIN

Hypothesis

AKIKI	ELAIN
• Observational and indirect data suggest that there may be survival benefit or harm from early RRT. They formed a hypothesis that delayed RRT would confer an absolute survival benefit of at least 15%	• Evidence from various observational studies and formed a hypothesis that early RRT would confer an absolute survival benefit of 18%

Study Design

AKIKI	ELAIN
• Unblinded, prospective, multicenter, open-label, two-group randomized trial between Sep 2013 – Jan 2016 • 31 centers in France (80% Medical ICUs)	• Single-center randomized controlled trial between August 2013 and June 2015 • 1 center in Germany (mostly surgical, 47% cardiac patients)

Inclusion Criteria

AKIKI	ELAIN

• N = 620
• > or = 18 years with KDIGO Stage 3 (> 3x baseline SrCr or SrCr >354 micromol/L with acute increase of 4.4; UO < 0.3 mL/Kg/hr for 24 hrs or anuria for > 12 hrs)
• Admitted to ICU with AKI similar to Acute Tubular Necrosis
• Critically unwell:
  • Receiving invasive mechanical ventilation, catecholamine infusion or both
• Sequential Organ Failure Assessment (SOFA) score (early vs. delayed) = 10.9 vs. 10.8
	• N = 231
	• 18 – 90 years with KDIGO Stage 2 (> 2x baseline SrCr or UO < 0.5 mL/Kg/hr for 12 hrs despite resuscitation)
	• Plasma Neutrophil Gelatinase Associated Lipocalin (NGAL) > 150 ng/mL
	
	• Critically unwell:
	  • Mechanical ventilation or vasopressor
	
	• SOFA score = 15.6 vs. 16
	• APACHE II = 30.6 vs. 32.7

Kidney Disease: Improving Global Outcomes (KDIGO) Classification

GFR Category	Description	GFR (mL/minute/1.73 m^2)
G1	Kidney damage with normal or high GFR	≥ 90
G2	Kidney damage with mildly decreased GFR	60–89
G3a	Mildly to moderately decreased GFR	45–59
G3b	Moderately to severely decreased GFR	30–44
G4	Severely decreased GFR	15–29
G5	Kidney Failure	< 15

Kidney Disease: Improving Global Outcomes (KDIGO). Available at http://kdigo.org/home/guidelines/

Exclusion Criteria

AKIKI
• Pre-existing renal failure CrCl < 30 mL/min
• BUN > 112 mg/dL
• K > 6 mmol/L or > 5.5 mmol/L despite Rx
• pH < 7.15 in the context of either pure metabolic acidosis ($PaCO_2$ < 35 mm Hg) or mixed acidosis ($PaCO_2$ = or > 50 mm Hg)
• Acute pulmonary edema due to fluid overload causing severe hypoxemia

ELAIN
• Pre-existing renal disease eGFR < 30 mL/min

Intervention Arms

AKIKI
• **Early-strategy group**   • Started within < 6 hrs of stage 3 AKI
• **Delayed-strategy group**   • RRT started if any of the above abnormalities (exclusion criteria) develops or if oliguria or anuria lasted for more than 72 hrs   • 51 % patients received delayed RRT at a median 57 hrs post randomization (p < 0.001)
• Choice of RRT, duration, interval between sessions, device settings, anticoagulation, was left to the physician's discretion

ELAIN
• **Early RRT**   • Started within 8 hrs of stage 2 AKI
• **Delayed RRT**   • Within 12 hrs of stage 3 AKI
• 91% patients received delayed RRT at a median 27 hrs post randomization
• Choice of RRT: CVVHDF to all

Results

AKIKI
• Primary Endpoint: 60-day mortality early vs. delayed 48.5% vs. 49.7% (p=0.79)
• Secondary Endpoints: • Duration of RRT: NR   • Median RRT-free days: 17 vs. 19 (p < 0.001)   • Rate of catheter related infections : 10% vs. 5 % (p=0.03)   • Diuresis (p<0.001)   • Hypophosphatemia: 22% vs. 19% (p = 0.03   • LOS, Mechanical ventilation free days, other outcomes : NS

ELAIN
• Primary Endpoint: 90-day mortality early vs. delayed 39.3% vs. 54.7% (p=0.03)
• Secondary Endpoints: • Median time from full eligibility to RRT initiation: 6hrs vs. 25.5 hrs (p < .001)   • Recovery of renal function at d90: 53% vs 38.7% (p=0.02)   • Duration of RRT: 9d vs. 25d (p=0.04)   • LOS: 51 d vs.82 d (p<0.001)   • Requirement of RRT after d 90, ICU LOS, organ dysfunction: NS   • Duration of mechanical ventilation: 125.5 vs. 180 (p = 0.002)

Limitations

AKIKI
• Patient selection: Severe acute kidney injury   • KDIGO stage 3 and lower SOFA scores   • 51% of patients received Intermittent HD while 85% required vasopressor → external validity   • No blinding

ELAIN
• Early AKI stage with more serious systemic disease   • Surgical patients   • NGAL > 150 ng/mL vs. NGAL > or = 400 ng/mL in ongoing trial   • Single center   • Power?   • HR for 90-day mortality: crude or adjusted?

Early Dialysis: Wise or Not Wise?

- **AKIKI**: In sick patients that are medical or surgical with sepsis, then *we don't know* if early or delayed RRT is the right therapy

- **ELAIN**: In really sick patients on a surgical intensive care unit, then *we cautiously think* very early CVVHDF is the right therapy

Ongoing Trials

- Need for larger RCTs
- IDEAL ICU (France)
  - Barbar SD et al. Impact on mortality of the timing of renal replacement therapy in patients with severe acute kidney injury in septic shock: the IDEAL-ICU study (Initiation of Dialysis Early versus Delayed in the Intensive Care Unit): study protocol for a randomized controlled trial

- SMARRT-AKI
  - Smith OM et al. Standard versus Accelerated Initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI): study protocol for a randomized controlled trial

A Hard Nut to Crack?

- Consider objective markers to inform future need for RRT that are translatable to routine bedside practice

- Is early RRT incrementally harmful?

- Integrate clinician's impression of the patient's global condition and trajectory rather than creatinine thresholds and urine output alone

Role of the Renal/Dialysis Pharmacist

RRT Timing??

Medication History/Review

Patient and Staff Education

Medication Reconciliation

Protocols (anemia, phosphate)

Drug Dose Adjustment (CrCl/ dialyzable Rx)

Monitoring Patient Lab Test Results

Monitoring and Reporting Adverse Drug Reactions

1. Nephrol Dial Transplant 2012:1-8
2. Intl J Clin Pharm 2012;34:569-78

Questions?

Thank You!

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