Canadian Society of Nephrology/ Société canadienne de néphrologie CSN/SCN

CANADIAN JOURNAL OF KIDNEY HEALTH AND DISEASE
Journal canadien de la santé et de la maladie rénale

Clinical Research Protocol

Canadian Journal of Kidney Health and Disease
Volume 12: 1–5

DOI: 10.1177/20543581241312631
journals.sagepub.com/home/cjk

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Definitions of Hemodynamic Instability Related to Renal Replacement Therapy in Critically Ill Patients: A Systematic Review Protocol

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Abstract

Background: Hemodynamic instability related to renal replacement therapy (HIRRT) is a common complication affecting critically ill patients that require renal replacement therapy (RRT). There is currently no consensus regarding the definition of HIRRT in critically ill patients. In this context, the impacts of HIRRT on clinical outcomes such as mortality or renal recovery in critically ill patients are unclear.

Objective: The primary objective of this proposed systematic review is to evaluate the association between HIRRT and clinical outcomes, as reported within randomized control trials in the literature. The secondary objective of this systematic review is to compare rates of HIRRT, according to various definitions used by randomized controlled trials, across different RRT modalities used to treat critically ill patients, with the goal of paving the way toward a common definition of HIRRT for future research.

Design: Systematic review and meta-analysis

Measurements: The rates of HIRRT, mortality, and renal recovery will be reported according to each definition of HIRRT

Patients: Critically-ill adults with acute kidney injury admitted to intensive care units

Methods: The search strategy will be developed to identify articles in Medline, MEDLINE In-Process, EMBASE, and Cochrane CENTRAL Registry. We will include randomized control trials examining renal replacement therapy in critically ill patients. This will include intermittent hemodialysis (iHD), all forms of prolonged intermittent RRT (PIRRT), and continuous renal replacement therapy (CRRT). Only articles that report a definition of HIRRT and the rates of HIRRT will be included in our analysis. Two reviewers will independently screen all articles for inclusion and exclusion. Data extraction and quality assessment will be also performed in duplicate. All disagreements will be resolved through discussion or a third reviewer.

Limitations: The heterogeneity in the definitions of HIRRT and outcome reporting may limit the ability to perform meta-analysis and perform comparisons in the rates of HIRRT between RRT modalities.

Conclusions: This systematic review aims to assess the association between HIRRT and important clinical outcomes. In doing so, we will identify definitions of HIRRT within the current literature and the rates of HIRRT associated with these definitions. HIRRT can result in early discontinuation of dialysis, organ injury from hypoperfusion, and may negatively impact mortality and renal recovery in critically ill patients. This systematic review will synthesize the impact and frequency of HIRRT reported in the literature and, in doing so, may help determine the extent to which common definitions of HIRRT might be recommended for standardized use in future research related to HIRRT.

Systematic Review Registration: PROSPERO registration number: CRD42023396550.

Abrege

Contexte: L'instabilité hémodynamique liée à la thérapie de remplacement rénal (IHTRR) est une complication fréquente chez les patients gravement malades qui ont besoin d'un traitement de suppléance rénale (TSR). Actuellement, il n'existe aucun consensus pour la définition de l'IHTRR chez les patients en état critique. Dans ce contexte, les conséquences de l'IHTRR sur les évènements cliniques comme la récupération rénale ou la mortalité chez les patients aux soins intensifs sont mal connues.

Objectifs: L'objectif principal de la revue systématique proposée est d'évaluer l'association entre la TSR et les évènements cliniques, telle que rapportée dans les essais contrôlés randomisés dans la littérature. L'objectif secondaire est de comparer les taux d'IHTRR, selon les différentes définitions utilisées dans les essais randomisés contrôlés, entre les différentes

modalités de TSR utilisées pour traiter les patients en réanimation; ceci dans le but d'ouvrir la voie à une définition commune de l'IHTRR pour les recherches futures.
Conception: Revue systématique et méta-analyze
Mesures: Les taux d'IHTRR, de mortalité et de récupération rénale seront rapportés selon chacune des définitions de l'IHTRR
Sujets: Des adultes en état critique, atteints d'insuffisance rénale aiguë, admis aux soins intensifs
Méthodologie: La stratégie de recherche sera élaborée pour répertorier les articles dans Medline, MEDLINE in Process, EMBASE et le Cochrane CENTRAL Registry. Nous inclurons les essais contrôlés randomisés examinant la thérapie de suppléance rénale chez les patients aux soins intensifs, soit l'hémodialyse intermittente (HDi), toutes les formes de TSR intermittente prolongée (TSRip) et la thérapie continue de remplacement rénal (TCRR). Seuls les articles qui rapporteront une définition et des taux pour l'IHTRR seront inclus dans notre analyze. Deux réviseurs examineront de façon indépendante tous les articles pour les inclure ou les exclure. L'extraction des données et l'évaluation de la qualité seront également effectuées en double. Tous les désaccords seront résolus par discussion ou par l'intervention d'un troisième réviseur.
Limites: L'hétérogénéité des définitions de l'IHTRR et de la publication des résultats pourrait limiter la capacité à réaliser une méta-analyze et à effectuer des comparaisons entre les taux d'IHTRR des différentes modalités de TSR.
Conclusion: Cette revue systématique vise à évaluer l'association entre l'IHTRR et des résultats cliniques importants. Ce faisant, nous recenserons les différentes définitions de l'IHTRR dans la littérature existante, ainsi que les taux d'IHTRR associés à ces définitions. L'IHTRR peut entraîner l'arrêt précoce de la dialyze et des lésions des organes cibles dues à l'hypoperfusion, en plus d'avoir un possible effet négatif sur la mortalité et la récupération de la fonction rénale chez les patients aux soins intensifs. Cette revue systématique résumera la fréquence et les conséquences de l'IHTRR rapportées dans la littérature et, ce faisant, pourrait aider à déterminer dans quelle mesure une définition commune de l'IHTRR pourrait être recommandée pour une utilization normalisée dans les futures recherches en lien avec cette complication.

Keywords
intensive care unit, hemodialysis, renal replacement therapy, hemodynamic instability related to renal replacement therapy

Received August 11, 2024. Accepted for publication November 8, 2024.

Introduction

Acute kidney injury (AKI) is an independent risk factor for morbidity and mortality in critically ill patients, occurring in 20% to 50% of patients in the intensive care unit (ICU) with upward of 15% requiring renal replacement therapy (RRT).[1,2] While RRT can be life-sustaining when needed, RRT often precipitates or worsens hemodynamic instability. Hemodynamic instability related to RRT (HIRRT) occurs during all forms of RRT commonly used in ICU including intermittent hemodialysis (iHD), various forms of prolonged intermittent renal replacement therapy (PIRRT), and continuous renal replacement therapy (CRRT). HIRRT is reported to complicate 10% to 70% of iHD treatments and 19% to 43% of CRRT treatments in the literature, though definitions of HIRRT vary in published studies.[3]

While HIRRT has been associated with increased mortality and decreased renal recovery, few studies have directly evaluated the impact of HIRRT on clinically important outcomes.[4-6] Nonetheless, the concept that CRRT is less likely to cause HIRRT than intermittent RRT modalities (and, as a result, may also allow for more overall fluid removal) is the primary basis for its preferential use in hemodynamically unstable patients.[2]

There is currently no consensus definition for HIRRT in critically ill patients. For patients with end-stage renal disease on maintenance hemodialysis, the Kidney Disease Outcomes Quality Initiative (K-DOQI) established the definition of intradialytic hypotension as a decrease of $\geq$20 mmHg in systolic blood pressure or decrease of $\geq$ 10 mmHg in mean arterial pressure, associated with symptoms related to intradialytic hypotension.[7] However, this definition is not applicable to critically ill patients as they may have hypotension prior to starting RRT due to their concurrent illness and they frequently receive vasoactive medications to treat hypotension. In addition, critically ill patients are often unable to

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report symptoms of hypotension due to severe illness, sedation, and/or intubation.

At present, the absence of an established definition of HIRRT makes evaluating the occurrence and impacts of HIRRT in critically ill patients challenging. It also limits comparability of interventions across trials.[6] As such, we seek to undertake a systematic review to establish the impact of HIRRT on mortality and renal recovery according to various definitions of HIRRT that have been used in randomized controlled trials involving critically ill patients. We also seek to assess the rate of HIRRT according to various definitions across RRT modalities. In doing so, we also seek to evaluate the extent to which different definitions of HIRRT have been used across trials with the goal of informing potential standardization of future reporting of HIRRT outcomes.

Methods

This protocol is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA-P) guidelines and the checklist can be found in Additional File 1 in the Supplemental Material.[8] This protocol was also registered with the International Prospective Register of Systematic Reviews (PROSPERO): CRD42023396550.

Eligibility Criteria

Types of studies. This systematic review will include randomized control trials (RCTs) that assess renal replacement therapy in critically ill patients. Given the vast number of research studies in this field, this review focuses on the highest quality of evidence informing current clinical practice by limiting to only RCTs. Specifically, these will include only original, peer-reviewed, full text literature. Only articles in English will be included.

Patient populations. Studies that involve patients with AKI who are critically ill, defined as patients in both medical as well as surgical ICUs, and are undergoing RRT (including iHD, all forms of PIRRT and CRRT). This study will be limited to adults aged 18 years or older.

Interventions/control. The interventions of interest are dialysis-related and encompass all RRT modalities, including: dose of RRT; timing of initiation; modality comparison trials; interventions to reduce HIRRT/augment ultrafiltration. Studies were included in this review if they received an intervention of interest.

Outcomes. The primary outcomes of interest in this systematic review are mortality and renal recovery (across all definitions used) in relation to the proportion of RRT treatments complicated by HIRRT (across varying definitions of HIRRT). The articles will need to report data on mortality and/or kidney recovery, and the rate of HIRRT, for each treatment group, to be included in the review.

Search Strategy

A search strategy was developed by an information specialist (LS) to systematically search Medline and MEDLINE in Process, EMBASE, and the Cochrane CENTRAL, all via the Ovid platform. All databases were searched from database inception to October 2024. The search was peer-reviewed according to the Peer Review of Electronic Search Strategies (PRESS) guidelines by another librarian (PF).[9] No language exclusions or other restrictions were included in the search strategy, although only articles in the English language were included in the review at the article screening stage. The search strategy is reported in Additional File 2 in the Supplemental Material. All references identified by the search strategy will be entered into EndNote (version 20.3, Clarivate Analytics Inc., Philadelphia, PA) citation manager for processing. Additional supplemental searching will be performed by manually reviewing the bibliographies of eligible studies, as well as a search of clinical trial registries (the National Institutes of Health [https://clinicaltrials.gov] and the World Health Organization International Clinical Trials Registry Platform [https://www.who.int/clinical-trials-registry-platform]).

Study Selection and Screening

After removal of duplicates in Covidence, all articles will undergo screening within the systematic review software, Covidence (Veritas Health Information Ltd., Melbourne Australia). Article screening will be performed in 2 stages: title and abstract screening followed by full text screening. The Supplementary Materials, study protocols, and additional files will be reviewed for additional information if necessary. Screening will be performed in duplicate, with all disagreements resolved through discussion or with the help of a third reviewer if disagreement persists following discussion between the primary 2 reviewers.

Data Extraction

Data extraction will be performed by 2 reviewers independently on all articles included in the review. Any disagreements will be resolved through discussion between reviewers or if disagreement persists, using a third reviewer. A data extraction form will be developed to gather the following details:

- Bibliographic details: author, year of publication, citation.
- Study characteristics: study setting (geographical area as well as location such as ICU and acute care step-down unit), study arms, study design, follow-up period, study objective.

- Baseline sample characteristics: number of study participants, mean age, sex, inclusion/exclusion criteria, comorbidities, clinical condition leading to ICU admission (ie, medical and surgical).
- Interventions and co-interventions: type of renal replacement therapy modality, RRT-associated interventions, blinding, dropouts.
- Outcomes: primary and secondary outcomes that were assessed (including mortality and renal recovery rates), adverse outcomes such as rates of HIRRT, and definitions of HIRRT. The units of measurement of each outcome will be recorded, and include but are not limited to the rates of HIRRT, proportion of patients experiencing HIRRT, timing of HIRRT, and percentage of blood pressure drop during dialysis (if measured), according to each definition of HIRRT.

Quality Assessment

The quality of RCTs will be critically appraised using the Cochrane Risk of Bias 2 Tool.[10] The tool will be applied by 2 independent reviewers and disagreements resolved via discussion or a third reviewer. Studies will be reported as unknown, low, medium, or high risk of bias. Inclusion of studies will not be limited based on quality assessment. The strength of the evidence with respect to the impact of HIRRT on mortality and kidney recovery will be evaluated according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.[11]

Data Synthesis

The data will be narratively synthesized using thematic analysis. This synthesis will be performed based upon common definitions of HIRRT within the literature and the renal replacement therapy modality that was used. If there is sufficient numeric data regarding outcomes with homogeneity for the definitions of HIRRT, quantitative analysis may be performed. A meta-analysis of the rates of HIRRT stratified by RRT modality and definition of hemodynamic instability will be performed if there is sufficient homogeneity amongst studies, such as 3 or more articles using the same definition of HIRRT, dialysis modality and unit of measurement. Potential units of measurement include but are not limited to the number/frequency of dialysis sessions affected by HIRRT and number/percentage of patients who experienced HIRRT. Random effects models will be used for the mean differences and the inverse variance method will determine the weights of the meta-analyses. Forest plots will be developed to outline the outcome of the meta-analyses.

Given that this study does not seek to assess the direct impact of a particular study intervention but rather, the association between HIRRT and other outcomes (ie, mortality and kidney recovery), a formal analysis will also be undertaken to evaluate the association between particular HIRRT definitions and outcomes if there is sufficient data. More specifically, if 3 or more studies that demonstrate a statistically significant difference in the incidence of HIRRT using same definition of HIRRT and have a common outcome (or outcomes) of interest then a formal meta-analysis will be undertaken to determine the pooled relative risk of that particular outcome (or outcomes) as was done by Coca *et al.* (2016) to investigate the association between short-term changes in serum creatinine (various definitions) and long-term chronic kidney disease and mortality outcomes.[12]

Whenever possible, study authors will be contacted in cases of missing data to request supplemental data and sensitivity analyses will be performed to assess the potential impact of missing data. Publication bias will be assessed through visual examination of the funnel plot and use of the Egger test.[13] Data analyses will be performed using Review Manager 5.3 (RevMan, The Cochrane Collaboration, Oxford, United Kingdom).

Protocol Amendments

Any changes to or deviations from the protocol will be outlined in an addendum explaining the new changes with justifications regarding the changes. These amendments will also be included in the final article.

Discussion

Hemodynamic instability related to renal replacement therapy is a frequent complication of RRT in critically ill patients, one that can result in early termination of dialysis treatments and may have detrimental impacts on clinical outcomes. However, there remains a gap in research in this area, with much of the literature regarding hypotension during renal replacement therapy derived from outpatients on stable regimens of iHD.[14] Some research suggests that HIRRT in critically ill patients results in a higher risk of mortality and decreased rates of renal recovery.[14]

Strengths and Weaknesses

This review is the first in its field to synthesize data on the definitions of HIRRT in the literature and seek to pave the way toward a common definition of HIRRT. Current research on the clinical impacts of HIRRT is limited by the significant heterogeneity in the literature regarding the definition of HIRRT. There is no consensus regarding the definition of HIRRT, rendering it difficult to compare rates of HIRRT across studies, evaluate the impacts of HIRRT on clinical outcomes, and identify strategies to mitigate HIRRT. This review will apply high quality systematic review methodology according to PRISMA guidelines to perform a comprehensive search and provide novel data in addressing this gap.

One of the limitations in this review is the heterogeneity of HIRRT definitions as well as outcomes may limit the ability to perform meta-analysis, however narrative and thematic synthesis can still provide valuable contributions to the field.

Conclusions

The present review aims to synthesize what is currently known regarding the impact of HIRRT on mortality and kidney recovery. We also seek to evaluate the rates of HIRRT across RRT modalities. In doing so, we may identify significant heterogeneity across definitions of HIRRT employed by major RCTs examining RRT modalities and interventions in critically ill patients which would highlight the need for a common definition of HIRRT. As such, this study could also help pave the way toward a common definition of HIRRT and encourage standardization of outcomes reporting for future trials evaluating the RRT modalities and related interventions.

Abbreviations

AKI, acute kidney injury; CRRT, continuous renal replacement therapy; HIRRT, hemodynamic instability related to renal replacement therapy; ICU, intensive care unit; iHD, intermittent hemodialysis; K-DOQI, Kidney Disease Outcomes Quality Initiative; PIRRT, prolonged intermittent renal replacement therapy; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PRESS, Peer Review of Electronic Search Strategies; PROSPERO, International Prospective Register of Systematic Reviews; RCT, randomized control trial; RRT, renal replacement therapy.

Author Contributions

JZW, LS, PF, SH, and EGC were all involved in the study conception and design of the study. JZW drafted the manuscript. All authors provided critical feedback. EGC supervised the project. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical considerations

Ethics approval was not required.

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Supplemental Material

Supplemental material for this article is available online.

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