Dissertação

COMPARAÇÃO DE PARÂMETROS HEMODINÂMICOS ENTRE TERAPIA DE REPOSIÇÃO RENAL CONTÍNUA, INTERMITENTE E HÍBRIDA EM PACIENTES COM INSUFICIÊNCIA RENAL AGUDA: REVISÃO SISTEMÁTICA DE ENSAIOS CLÍNICOS RANDOMIZADOS

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Dissertação submetida como requisito para obtenção do grau de mestre ao Programa de Pós-Graduação em Ciências da Saúde, Área de Concentração: Cardiologia e *Ciências Cardiovasculares, da Universidade Federal do Rio Grande do Sul.*

Porto Alegre
2018

Russo, Diana da Silva
COMPARAÇÃO DE PARÂMETROS HEMODINÂMICOS ENTRE TERAPIA DE REPOSIÇÃO RENAL CONTÍNUA, INTERMITENTE E HÍBRIDA EM PACIENTES COM INSUFICIÊNCIA RENAL AGUDA: REVISÃO SISTEMÁTICA DE ENSAIOS CLÍNICOS RANDOMIZADOS / Diana da Silva Russo. -- 2018.
45 f.
Orientadora: Silvia Regina Rios Vieira.

Dissertação (Mestrado) -- Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Programa de Pós-Graduação em Ciências da Saúde: Cardiologia e Ciências Cardiovasculares, Porto Alegre, BR-RS, 2018.

1. Injúria Renal Aguda. 2. Terapia Intensiva. 3. Cuidados críticos. 4. Terapia Renal Substitutiva. I. Vieira, Silvia Regina Rios, orient. II. Título.

SUMÁRIO

RESUMO

Introdução: O uso de terapia de reposição renal (TRR) em pacientes com insuficiência renal aguda (IRA) na unidade de terapia intensiva (UTI) está associado a alta instabilidade hemodinâmica que leva a uma mortalidade intra-hospitalar de cerca de 50%. O objetivo deste estudo foi comparar parâmetros hemodinâmicos entre terapia de reposição renal contínua, intermitente e híbrida em lesão renal aguda. **Métodos:** Revisão sistemática realizada de acordo com o PRISMA e registrada no banco de dados PROSPERO. Ensaios clínicos randomizados envolvendo pacientes com LRA na UTI submetidos a RRT contínua, intermitente ou híbrida serão incluídos. Investigaremos os bancos de dados eletrônicos: PubMed, Embase e Cochrane. Dois revisores realizarão independentemente a seleção do estudo, avaliação da qualidade metodológica e extração de dados. **Resultados:** A maioria dos estudos não encontrou diferenças nos parâmetros hemodinâmicos em diferentes modalidades de RTT, com exceção de redução da freqüência cardíaca do grupo CVVH após 1 e 4 horas em comparação com o grupo IHD, aumento da pressão arterial sistólica após 0,5 e 2h de CVVH em contraste com IHD e doses significativamente maiores de Dobutamina em pacientes do grupo CVVHDF, quando comparados ao IHD. A MAP basal mais baixa, uma maior variação do MAP em diálise, maior número de pressores na linha de base e aumento da dose pressora durante a diálise foram associadas com menor tempo de sobrevivência; e uma maior variação do MAP em diálise negativamente foi correlacionada com a recuperação renal. **Conclusões**: Acreditamos que este estudo pode fornecer informações importantes para novos ensaios clínicos projetados especificamente para avaliar os parâmetros hemodinâmicos em diferentes tipos de RRT.

Palavras-chave: diálise renal, terapia de substituição renal, hemodinâmica, revisão sistemática.

INTRODUÇÃO

Injúria Renal Aguda (IRA) denota uma síndrome clínica de diminuição da função excretora renal e conseqüente diminuição da produção de urina, acumulação metabólica de ácido, creatinina e ureia, além de aumento de potássio e concentrações de fosfato[1].

O KDIGO (Kidney Disease Improving Global Outcome) Diretriz de prática clínica para IRA (Injúria Renal Aguda), a define através de um dos seguintes critérios: aumento da creatinina sérica ≤ 0,3 mg / dl em 48 horas; ou aumento da creatinina sérica ≤ 1,5 vezes em relação à basal, que é conhecido ou presumido ter ocorrido dentro dos 7 dias anteriores; ou volume de urina, 0,5 ml / kg / h por 6 horas[2] (Classificação vide Figura 02 Anexo I).

Pacientes com IRA utilizam mais recursos e têm maior tempo de permanência hospitalar, em parte devido ao efeito da Ira em órgãos-alvo: mais dificuldade em realizar o desmame de ventilação artificial, maior risco de sobrecarga de fluido com consequente aumento da mortalidade, insuficiência renal e recuperação mais prolongada[3]. Ela contribui, dessa forma, para o desenvolvimento de Injúria Renal Crônica e resultar em dependência dialítica.[1,3]

Um dos principais e mais utilizados métodos de tratamento da IRC é a hemodiálise, que é um processo terapêutico capaz de remover catabólitos do organismo e corrigir as modificações do meio interno por meio da circulação do sangue em equipamento idealizado para este fim[4]. No Brasil, é responsável pela sobrevida de aproximadamente 34.000 pessoas[5].

Mesmo com a segurança do procedimento e sua capacidade de manter a vida dos pacientes por longos períodos, vale mencionar que em 30% das sessões de hemodiálise pode ocorrer algum tipo de complicação decorrente desta modalidade terapêutica[6]. Essas complicações incluem: hipotensão arterial (como uma das principais), câimbras, náuseas e vômitos, cefaleia, dor no peito, dor lombar, prurido, febre e calafrios, diarreia, reações alérgicas, arritmia cardíaca, embolia gasosa, hemorragia gastrintestinal, problemas metabólicos, convulsões, espasmos musculares, insônia, inquietação, demência, infecções, pneumotórax ou hemotórax, isquemia ou edema na mão e anemia.[7,8]

REVISÃO DE LITERATURA

Conceitos sobre Injúria Renal

A maioria das etiologias da IRA pode ser prevenida por intervenções no indivíduo, nível comunitário, regional e hospitalar. Medidas eficazes devem incluir esforços a nível comunitário para aumentar uma consciência dos efeitos devastadores da AKI e fornecer orientação sobre estratégias preventivas, também como reconhecimento e manejo precoce.[9] É estimada em cerca de 20-200 por milhão de habitantes na comunidade, 7-18% dos pacientes no hospital e aproximadamente 50% dos pacientes admitidos na unidade de terapia intensiva (UTI).[10,11]

O KDIGO, define IRA através de um dos seguintes critérios: aumento da creatinina sérica ≤ 0,3 mg / dl em 48 horas; ou aumento da creatinina sérica ≤ 1,5 vezes em relação à basal, que é

conhecido ou presumido ter ocorrido dentro dos 7 dias anteriores; ou volume de urina, 0,5 ml / kg / h por 6 horas[2]

Sua etiologia varia com as condições de desenvolvimento humano, país desenvolvido e em desenvolvimento, além de idade. Em países desenvolvidos agora é encontrada em 45% pacientes admitidos em Unidade de Terapia Intensiva (UTI) e 20% dos pacientes hospitalizados.[12,13] Esta prevalência aumentada provavelmente reflete uma envelhecimento da população acometida por múltiplas comorbidades, que muitas vezes é manejada com múltiplos medicamentos[9]. Em contraponto, em países em desenvolvimento, está associada à pobreza, saneamento deficiente e higiene da água (doenças diarréicas), falta de educação e acesso a uma Infraestrutura urbana e sistema de saúde (abortos sépticos, mordidas de cobra, medicamentos naturais, tétano) e quebra de um equilíbrio ecológico de um sistema descontrolado e urbanização não planejada (leptospirose, febre amarela, abelhas e acidentes com lagartas).[9,14] Em crianças, mudou nas últimas décadas, sendo causada principalmente por de doenças renais intrínsecas, como síndrome hemolítica urêmica e glomerulonefrite e isquemia, ou por nefrotoxinas e sepse em crianças criticamente doentes[13].

De acordo com o KDIGO, a Ijnúria Renal pode ser classificada em IRA ou Injúria Renal Crônica (IRC). A primeira, caracteriza-se como uma diminuição abrupta na função renal, que ocorre durante um período de 7 dias ou menos, enquanto a segunda, como anormalidades na estrutura renal ou função que persistem por > 90 dias[15]. Propôs, ainda, o termo Doença Renal Aguda (DRA) como qualquer condição aguda que afeta a função renal incluindo IRA, eGFR <60ml/min/1,73m^2, uma diminuição da taxa de filtração glomerular em > 35%, um aumento de

creatinina sérica de > 50%, ou qualquer dano renal duradouro <3 meses[2]. Dessa forma, a DRA representa a janela de tempo em que pode-se iniciar intervenções para alterar a história natural de doença renal[16]. Figura 01 – Anexo 01.

Entre os mecanismos fisiopatológicos de IRA, a pré-renal há muito se diferenciou de outros subtipos, como a Necrose Tubular Aguda (NTA)[16]. Esta distinção pode se traduzir em diferenças em termos de recuperação renal e sugere que a IRA Transitória (IRAT) represente uma entidade separada, caracterizada por um aumento rapidamente reversível da creatinina sérica, enquanto uma IRA Persistente (IRAP), mais prolongada pode refletir estabelecimento de lesão estrutural[17], não apresentando recuperação dentro de 3 dias.

Um estudo comparou o prognóstico entre IRAP e IRAT. Nele, dois terços dos pacientes criticamente doentes com IRA apresentam a forma persistente. Embora a mortalidade aumente progressivamente com a duração da IRA, podendo ser um indicador potente da gravidade a injúria em vez de um marcador de mecanismos fisiopatológicos específicos[19].

Um total de 447 pacientes foram incluídos neste estudo, incluindo 283 pacientes (63,3%) com IRA na admissão (175 e 108 pacientes com IRAP e IRAT, respectivamente). Os pacientes com IRAP apresentaram IRA em Estágio 3 com maior frequencia (42,9% vs 30,6%; p = 0,04). A sobrevivência hospitalar foi de 76,2% (n = 125) em pacientes sem lesão renal aguda, 70,4% (n = 76) em pacientes com lesão renal transitória e 61,1% (n = 107) em pacientes com lesão renal aguda persistente[19].

O grupo de trabalho ADQI recomenda a presença de IRA persistente para iniciar avaliação e recomendação das opções de tratamento[16].

Terapia Renal Substitutiva (TRS)

Tradicionalmente, os nefrologistas vêm manejando a IRA com a hemodiálise intermitente (HDI). Se por um lado a rápida remoção de solutos e de volume é uma vantagem da HDI, por outro lado é também uma importante desvantagem para os pacientes gravemente enfermos em UTI, pois pode induzir hipotensão sistêmica em 20% a 30% dos casos[20] e instabilidade hemodinâmica em aproximadamente 10% dos pacientes. No entanto, a remoção de volume feita de maneira intermitente em sessões curtas pode induzir hipotensão intradialítica[21], o que potencialmente aumenta o risco de lesão renal recorrente. [20] Nesses casos, a terapia renal substitutiva contínua (TRSC) seria o tratamento preferencial, com vantagens clínicas potenciais.

Quando os pacientes com IRA necessitam de TRS as recomendações atuais do KDIGO são para administrar um volume de efluente de 20-25 ml / kg / h para TRSC ou para infundir um Kt / V de 3,9 por semana ao usar TRSI. A diálise peritoneal (DP) também deve ser considerada para IRA, particularmente nos países em desenvolvimento, porque é uma forma simples, eficaz, segura e relativamente barata de TRS.[2,22]

Em comparação com a TRSI, o início da TRSC em pacientes adultos críticos com adultos com IRA está associado com menor probabilidade de diálise crônica. [23]

Um ensaio controlado randomizado de diálise em IRA apontou vantagens potenciais de técnicas contínuas em relação à intermitente: a mortalidade geral na UTI e hospitalar foi de 50,6% e 56,6%, respectivamente. A terapia contínua foi associada a um aumento da mortalidade em UTI (59,5 vs 41,5%, P <0,02) e hospitalar (65,5 vs. 47,6%, P <0,02) em relação à diálise intermitente. O período médio de permanência da UTI mediana desde a consulta de nefrologia foi de 16,5 dias e a recuperação completa da função renal foi observada em 34,9% dos pacientes, sem diferenças significativas no grupo[24].

IRA recorrente pode ocorrer em cerca de 20% dos pacientes em UTI após o primeiro episódio de sepse relacionado à IRA. Esta recorrência aumenta a taxa de mortalidade independe da severidade da sepse ou estágio KDIGO do primeiro episódio de IRA. Médicos intensivistas devem estar atentos aos episódios recorrentes e registrar em prontuário cada novo episódio e incluí-los no escore de risco clínico da Unidade[25]. Dessa forma, apesar das potenciais vantagens da TRSC em relação à TRSI, não há evidências em relação a benefícios de sobrevida.[24]

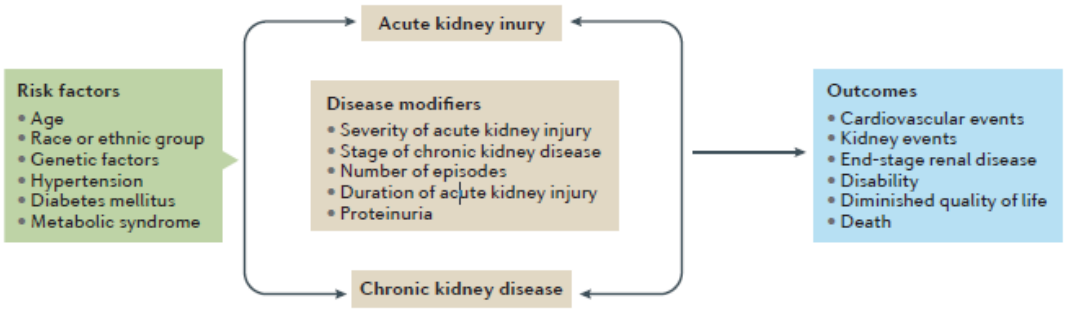
Sobre o uso de catecolaminas e o aumento da Pressão Arterial Média (PAM) no manejo da sepse, não está elucidado o quanto a pressão arterial média pode aumentar durante o choque séptico ao ponto de causar danos. Um estudo investigou a associação entre PAM, com valores ≤ 70mm Hg , mortalidade após 28 dias e doenças relacionadas ao choque séptico. Aparentemente, níveis de PAM ≤ a 70 mmHg não estão associados com aumento da sobrevivência em choques sépticos. Este aumento da PAM, com uso de altas doses de vasopressores, podem aumentar a mortalidade[26].

Em uma meta-análise do grupo Cochrane, publicado em 2007, a pressão arterial média foi o único parâmetro hemodinâmico clínico isso significativamente maior com TRSC do que com TRSI. Contudo, o número de episódios de hipotensão não era diferente.[27]

O custo da terapia para pacientes criticamente doentes precisa ser reconhecido nas decisões terapêuticas. Cuidados em UTI são extremamente caros. o menor custo de TRSC é adequado para países em desenvolvimento como o Egito[28]. O custo foi significativamente menor no grupo submetido a TRSC em comparação com o grupo TRSI (P <0,001). Este resultado correlaciona-se com um estudo prévio em que os autores relataram que o custo do TRSI foi mais que o dobro do de TRSC. [27] Isso também foi confirmado em outro multicêntrico e estudo multinacional.[27,29]

Anexos

Figura 01 – Relação entre Injúria Renal Aguda e Injúria Renal Crônica : A IRA e a IRC muitas vezes formam uma continuidade da doença ao não sendo entidades separadas. Os vários modificadores da doença e fatores de risco podem representam oportunidades para intervir e mitigar os pobres resultados associados a essas doenças.



Fonte: Chawla LS, Bellomo R, Bihorac A, Goldstein SL, Siew ED *et al.* **Acute Disease Quality Initiative Workgroup 16.** Nat Rev Nephrol. 2017 Apr;13(4):241-257. doi: 10.1038/nrneph.2017.2. Epub 2017 Feb 27

Figura 02 - Estágios da IRA segundo KDIGO

Stage	Definition
Stage 0*	A: Absence of criteria for B or C. B: Continued evidence of ongoing injury, repair and/or regeneration or indicators of loss of renal glomerular or tubular reserve C: Serum creatinine level <1.5 times baseline but not back to baseline levels B/C: Serum creatinine level <1.5 times baseline but not back to baseline levels, and continued evidence of ongoing injury, repair and/or regeneration
Stage 1	Serum creatinine level 1.5–1.9 times baseline
Stage 2	Serum creatinine level 2.0–2.9 times baseline
Stage 3	Serum creatinine level 3.0 times baseline or increase in serum creatinine to ≥353.6 μmol/l (≥4.0 mg/dl)‡ or ongoing need for renal replacement therapy

*Reflects that even when no apparent residual injury is present, the kidney might be vulnerable for some time after an episode of AKI. ‡Assumes the baseline serum creatinine level is <353.6 μmol/l (<4.0 mg/dl), and that an episode of AKI has occurred. AKD, acute kidney disease; AKI, acute kidney injury.

Fonte: Chawla LS, Bellomo R, Bihorac A, Goldstein SL, Siew ED *et al.* **Acute Disease Quality Initiative Workgroup 16.** Nat Rev Nephrol. 2017 Apr;13(4):241-257. doi: 10.1038/nrneph.2017.2. Epub 2017 Feb 27

Figura 03 – Índice Hazard para existência de IRA intra Unidade de Terapia Intensiva em relação à mortalidade.

	Vital status (intra-hospital)					Vital status (90-day)					Vital status (end of follow-up)				
	Survival (*N*)	Death (*N*)	HR	(95% CI)		Survival (*N*)	Death (*N*)	HR	(95% CI)		Survival (*N*)	Death (*N*)	HR	(95% CI)	
Including patients without AKI (*N* = 400)	298	102				290	110				212	188			
No AKI (*n* = 69)	62	7	1	–		61	8	1	–		47	22	1	–	
AKI = 1 (*n* = 252)	192	60	1.68[a]	0.74	3.82	188	64	1.54[a]	0.71	3.34	139	113	1.00[a]	0.61	1.63
AKI ≥ 2 (*n* = 79)	44	35	2.73[a]	1.15	6.51	41	38	2.57[a]	1.13	5.83	26	53	1.61[a]	0.93	2.77
Linear p trend			*0.006*					*0.005*					*0.021*		
Excluding patients without AKI (*N* = 331)	236	95				229	102				165	166			
AKI = 1 (*n* = 252)	192	60	1	–		188	64	1	–		139	113	1	–	
AKI ≥ 2 (*n* = 79)	44	35	2.48[b]	1.47	4.19	41	38	2.54[b]	1.55	4.16	26	53	1.97[b]	1.36	2.84

[a] HR = hazard ratio adjusted for sex, age, mechanical ventilation necessity, APACHE score, and baseline estimated glomerular filtration rate (GFR)
[b] HR = hazard ratio adjusted for sex, age, mechanical ventilation necessity, APACHE score, baseline estimated GFR, complete recovery and KDIGO stage

Fonte: Rodrigo E , Suberviola B, Santibáñez M et al, **Association between recurrence of acute kidney injury and mortality in intensive care unit patients with severe sepsis**. Journal of Intensive Care (2017) 5:28

Figura 04 – Características de pacientes sem IRA, com IRA Transitória e IRA Persistente

Variables	No AKI (*n* = 164)	Transient AKI (*n* = 108)	Persistent AKI (*n* = 175)	*p*[a]
Patient characteristics				
Male gender	90 (54.9%)	66 (61.1%)	122 (69.7%)	**0.02**
Age (yr)	55 (45–66)	68 (52–76)	67 (56–75)	**< 0.001**
Knaus score C or D (15)	51 (31.1%)	39 (36.1%)	71 (40.6%)	**0.03**
Logistic Organ Dysfunction score (range, 0–22) at admission (17)	4 (2–7)	6 (4–8)	7 (5–9)	**< 0.001**
Simplified Acute Physiology Score II at admission (16)	39 (29–52)	46 (37–57)	50 (36–62)	**< 0.001**
Chronic respiratory failure	39 (23.8%)	28 (25.9%)	30 (17.1%)	0.16
AKI risk factors, *n* (%)				
Chronic heart failure	19 (11.6)	25 (23.1)	36 (20.6)	0.27
Chronic kidney disease[b]	3 (1.8)	4 (3.7)	35 (20.0)	**< 0.001**
Sepsis	79 (48.2)	65 (60.2)	109 (62.3)	**0.02**
Diabetes mellitus	52 (31.7)	47 (43.5)	87 (49.7)	**0.003**
Nephrotoxic agent	61 (37.2)	32 (29.6)	59 (33.7)	0.43
Iodinated contrast agents	43 (26.4)	14 (13.0)	31 (17.7)	**0.02**
Aminoglycosides	14 (8.5)	16 (14.8)	37 (21.1)	**0.005**
Glycopeptides	4 (4.3)	5 (4.6)	10 (5.7)	0.82
Reason for ICU admission, *n* (%)				
Medical condition	145 (88.4)	102 (94.4)	162 (92.6)	0.17
Surgical emergency[c]	19 (11.6)	6 (5.6)	12 (6.7)	0.14
Acute respiratory failure	140 (85.4)	76 (70.4)	123 (70.3)	**0.002**
Shock	75 (45.7)	54 (50.0)	103 (58.9)	0.05
Coma	58 (35.4)	32 (29.6)	44 (25.1)	0.12
At ICU admission				
Diuresis, mL/kg/hr	1.05 (0.68–1.72)	0.94 (0.41–1.34)	0.57 (0.31–0.99)	**< 0.001**
ICU treatments during the first 3 days, *n* (%)				
Mechanical ventilation	124 (75.6)	66 (61.1)	113 (64.6)	**0.03**
Need for vasopressors	73 (44.5)	49 (45.4)	104 (59.4)	**0.010**
Renal replacement therapy	4 (2.4)	0 (0)	54 (30.9)	**< 0.001**
Acute Kidney Injury Network classification, *n* (%)				
No AKI	164 (100)	0 (0)	0 (0)	**< 0.001**
Stage 1	0 (0)	43 (38.8)	55 (31.4)	**< 0.001**
Stage 2	0 (0)	32 (29.6)	45 (25.7)	**< 0.001**
Stage 3	0 (0)	33 (30.6)	75 (42.9)	**< 0.001**

(*Continued*)

Variables	No AKI ($n = 164$)	Transient AKI ($n = 108$)	Persistent AKI ($n = 175$)	p*
Definition of AKI according to, *n* (%)				
Oliguria	0 (0)	16 (14.8)	21 (12)	**< 0.001**
Serum creatinine	0 (0)	78 (72.2)	101 (57.7)	**< 0.001**
Both	0 (0)	14 (13.0)	53 (30.3)	**< 0.001**
Baseline renal function (μmol/L)				
Previous serum creatinine	58 (48.75–69)	62 (47.75–71.75)	76 (58–107)	**< 0.001**
Backward creatinine calculation	61 (49.5–78.5)	68 (51–80)	80 (60–105)	**< 0.001**
Outcome, *n* (%)				
ICU survival	135 (82.3)	83 (76.8)	117 (66.9)	**0.004**
Hospital survival	125 (76.2)	76 (70.4)	107 (61.1)	**0.01**

AKI = acute kidney injury.
*p values represent the comparability across the three groups.
†Chronic kidney disease was defined as a creatinine clearance < 60 mL/min before ICU admission.
‡A single patient with persistent AKI was admitted following elective surgery.
Results are reported as median (interquartile range) or *n* (%). Values in boldface font are p values less than 0.05.

Fonte: Perinel S, Vincent F, Lautrette A, et al. **Transient and Persistent Acute Kidney Injury and the Risk of Hospital Mortality in Critically Ill Patients: Results of a Multicenter Cohort Study**. Crit Care Med. 2015 Aug;43(8):e269-75. doi: 10.1097/CCM.0000000000001077

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ARTIGO - Journal: Intensive Care Medicine
Impact factor: 12

Title page

Title:

Comparison of hemodynamic parameters among continuous, intermittent and hybrid renal replacement therapy in acute kidney injury: a systematic review of randomized clinical trials

Running title:
Hemodynamic parameters across RRT modalities in AKI

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Abstract

Purpose: The use of renal replacement therapy (RRT) in acute kidney injury (AKI) patients in the intensive care unit (ICU) is associated with high hemodynamic instability leading to an in-

hospital mortality of about 50%. The aim of this study was to compare hemodynamic parameters among continuous, intermittent and hybrid renal replacement therapy in acute kidney injury.
Methods: Systematic review conducted in accordance with the PRISMA and registered at the PROSPERO Database. Randomized clinical trials involving patients with AKI in the ICU submitted to continuous, intermittent or hybrid RRT will be included. We will investigate the electronic databases: PubMed, Embase and Cochrane. Two reviewers will independently carry out study selection, evaluation of methodological quality and data extraction.
Results: Most of the studies did not find differences in hemodynamic parameters across different RTT modalities, except a CVVH group heart rate decrease after 1 and 4 hours in comparison with IHD group, an increase in systolic blood pressure after 0.5 and 2h of CVVH in contrast with IHD, and doses significant higher of Dobutamine in patients from the CVVHDF group, when compared to IHD. Lower baseline MAP, greater MAP variation on dialysis, higher number of pressors at baseline, and increase in pressor dose during dialysis were associated with shorter survival time; and greater MAP variation on dialysis negatively was correlated to renal recovery.
Conclusions: We believe that this study can provide important insights for further clinical trials designed specifically to evaluate hemodynamic parameters across different types of RRT.

Key-words: Renal Dialysis, Renal Replacement Therapy, Hemodynamics, Systematic review.

Introduction

Acute kidney injury (AKI) is a frequent complication in the intensive care unit (ICU) and is independently associated with the development of end-stage renal disease and higher mortality rates [1,2]. Despite the significant advances in medical treatments, AKI requiring renal replacement therapy (RRT) in the ICU is associated an increased in-hospital mortality of about 50% [3,4]. Thus, it represents one of the most important and costly complications in ICU patients [1,2].

A wide array of methods is available nowadays for support of renal functional. RRT can be applied continuously, intermittently or still through hybrid modalities. Although the rigorous clinical practice guidelines available focusing on this conditions, clinical routines and outcomes still vary dramatically from institution to institution [5]. Debates exist regarding the RRT

modalities for critically ill inpatients with AKI [6], and no conclusive data on it is available to support clinical practice [7]. One of the most recurrent concerns about the use RRT in AKI patients is hemodynamic instability and, consecutively, its effects on morbimortality, especially when intermittent methods of RRT are used [7]. Previous studies in the literature have evaluated the impact of RRT on hemodynamic parameters, but results still seem to be controversial, and, to the best of our knowledge, no studies have consistently summarized these data into conclusive results.

Thus, in order to address this issue, we conducted this systematic review of randomized clinical trials to compare hemodynamic parameters among continuous, intermittent and hybrid modalities of renal replacement therapy in acute kidney injury.

Methods

Protocol and Registration

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [8] and is registered in the Prospero (International Prospective Register of Systematic Reviews) database [9].

Eligibility Criteria

We included only randomized clinical trials evaluating AKI patients undergoing continuous, intermittent and hybrid RRT and assessing the changes in hemodynamic parameters, as follows: heart rate, blood pressure and hypotensive episodes, and use of catecholamines. Only full peer reviewed publications were included. We excluded studies reporting results from the same population and articles published in languages other than English, Portuguese, and Spanish.

Information Sources

We searched the following electronic databases: PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL). In addition, we searched the references of the included articles manually, as well as we performed a citation analysis of the included studies using Google Scholar.

Search

The initial search comprised the Mesh terms "Renal Replacement Therapy", "Hemodiafiltration", "Renal Dialysis", "Hemodynamics", "Hypotension", "Heart Rate", "Catecholamines", followed by the related entry terms and other free terms. Additionally, we used the Cochrane highly sensitive search strategy for identifying randomized trials in PubMed [10] and Embase [11]. The complete search strategy used for the PubMed database is shown in Appendix 1.

Study Selection

Titles and abstract of the retrieved articles were independently evaluated by two reviewers. Abstracts which did not provide enough information regarding the eligibility criteria were kept for full-text evaluation. Reviewers independently evaluated full-text articles and determined study eligibility. Disagreements were solved by consensus.

Risk of bias

Risk of bias was evaluated by evaluating each study according to the Cochrane tool to assess risk of bias of randomized clinical trials [12]. The following items were considered: bias of selection (random sequence generation and allocation concealment), performance (blinding of participants and personnel), detection (blinding of outcome assessment), attrition (incomplete outcome data), reporting (selective reporting) and others. For practical reasons because of the nature of the interventions, blinding of patients and physicians administering the interventions (performance bias) were not considered in this systematic review, thus, we excluded this item from the tool to assess risk of bias.

Data Extraction

Two reviewers independently conducted the data extraction and disagreements were solved by consensus. General characteristics of the studies were collected, such as: authors names, institutions, year of publication, study design, study arms, interventions, outcomes, patients age, gender, levels of creatinine and urea, and severity-of-disease classifications systems such as the Acute Physiology and Chronic Health Evaluation (APACHE), Simplified Acute Physiology Score (SAPS), Sepsis-related Organ Failure Assessment (SOFA), and Therapeutic Intervention Scoring System (TISS)-28. In addition, we collect information specifically about the hemodynamic parameters, such as changes in heart rate, blood pressure including hypotensive episodes, use of catecholamines as well as the implications of these hemodynamic parameters on morbimortality. We used the software Web Plot Digitizer [13] to extract data from graphs when details on mean and SD were not available in the manuscripts.

In order to assess risk of bias of included studies, we extracted information about random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, and selective reporting.

Data Analysis

Descriptive analysis of studies was performed including study characteristics, risk of bias, and main results. Data was summarized into four categories: (1) Intermittent versus continuous RRT modalities, (2) Hybrid versus continuous RRT modalities, (3) Continuous versus continuous RRT modalities, and (5) other comparisons. Studies presented high heterogeneity in terms of outcomes definitions and measurement, thus, conduction of meta-analysis was not possible.

Results

Study Selection

The searches yielded a total of 3442 citations. After excluding duplicates and reviewing titles and abstracts, 16 studies were left for full-texts assessment. From those, 4 were excluded because they did not present any outcome of interest. Finally, 12 studies were included in this systematic review, as demonstrated in Figure 1.

Studies Characteristics

Of the 12 included studies, four were conducted in Germany, two in Egypt, and one in each of the following countries: France, Switzerland, United States, Croatia, India and Japan. Studies compared different types of RRT, including intermittent versus continuous, hybrid versus continuous, continuous versus continuous, among others. Total number of 1419 patients were assessed in this systematic review, including all types of intervention and comparisons. Table 1 demonstrates a summary of the characteristics of the studies, including age, gender, levels of creatinine and urea, as well as severity-of-disease classifications systems such as APACHE, SAPS, SOFA, and TISS.

Risk of bias

Most of the studies presented unclear risk of bias in relation to the assessed item. From the 12 included studies, seven presented unclear risk of bias in relation to random sequence generation, and 9 in relation to allocation concealment, which means there was insufficient information to permit judgement of ‘Low risk’ or ‘High risk’. In most cases, the studies did not mention the methods used for random sequence generation and allocation concealment. Thus, selection bias was not possible to be properly assessed. The same happened concerning detection bias, where 10 of the 12 studies were considered of unclear risk of bias. Only one study described outcome assessment as blinded and was considered of low risk of bias.

In relation to attrition bias, eight of the 12 included studies present low risk of bias, since no missing data was identified, or it does not appear to be related to the true outcome. The other four studies presented unclear risk of bias since there was insufficient reporting of attrition/exclusions to permit judgement. Risk of bias related to selective reporting was also unclear. None of the 12 studies referred a source where the study protocol could be assessed by readers, such as clinicaltrials.gov. Although the outcomes presented in the studies appear coherent with studies aims, it was not possible to exclude bias related to selective outcome reporting. Table 2 summarizes the assessment of risk of bias of included studies.

Comparison of hemodynamic parameters

Heart Rate

Two [14,19] of the six trials comparing intermittent versus continuous modalities of RRT evaluated differences in heart rate between the modalities. Study from Schefold et al (2014) [14] did not identify any differences between the groups when assessing heart rate from day 1 to day 21 after treatment. John et al (2001) [19] reported that CVVH group heart rate declined after 1 and 4 hours in comparison with IHD group. However, after 24h, heart rate had returned to baseline in the IHD group and the difference between both groups was no longer observed.

When comparing hybrid versus continuous modalities, two [20,22] of the three studies reported heart rate comparisons. None of the studies found differences in heart rate up to 24 days after intervention. Similarly, study from Badawy et al (2012) [24] comparing furosemide versus CVVHDF did not find differences between the groups in relation to heart rate, up to 72 hours after starting treatment. Table 3 summarizes data on heart rate comparisons from the included studies.

Blood pressure and hypotensive episodes

When comparing intermittent versus continuous modalities of RRT, four [14,16,17,19] of the six studies reported blood pressure comparisons between the groups. Only the trial from John et al (2001) [19] observed an increase in systolic blood pressure after 0.5 and 2h of CVVH in contrast with IHD. However, this difference was not observed after 24 hours of interventions. The other studies did not find differences between the groups in relation to blood pressure. Study from Nand et al (2010) [23] comparing CAVHDF versus CVVHDF observed an increase in MAP, in both groups, 24 hours after starting the treatments. None of the patients developed hypotension secondary to the procedures.

Incidences of hypotensive episodes varied from 5 to 60% among the included studies, but no differences among the RRT modalities were observed. Table 3 summarizes the data on blood pressure and hypotensive episodes comparisons between the groups reported in the included studies.

Use of catecholamines

In relation to the use of catecholamines, included studies presented distinct results. Among the studies comparing intermittent versus continuous modalities of RRT, Uehlinger et al (2005) [16] reported doses significant higher of Dobutamine in patients from the CVVHDF group, when compared to IHD. The same difference was not observed when evaluated doses of Adrenaline, Noradrenaline, and Dopamine. The other three studies [14,17,19] comparing the use of catecholamines between intermittent versus continuous modalities of RRT did not find any differences between the groups. The same was observed among the other comparisons. Table 3 summarizes the results on use of catecholamines in the included studies.

Implications of hemodynamic parameters on clinical outcomes

Included studies compared hemodynamic parameters among different types of RRT, however, most of them did not assess the impact of these changes on clinical outcomes such as

morbidity and mortality, except the studies from Augustine et al (2004) [17] and Uehlinger et al (2005) [16].

In Augustine et al (2004) study [17], a trial comparing IHD vs CVVHDF which included 40 patients in each group, the authors reported that, in univariate analysis, lower baseline MAP, greater MAP variation on dialysis, higher number of pressors at baseline, and increase in pressor dose during dialysis were associated with shorter survival time, HR 0.97 (95% IC 0.95 to 1.00, P=0.036); HR 1.04 (95% IC 1.01 to 1.08, P=0.032); HR 1.47 (95% IC 1.19 to 1.82, P<0.001); HR 1.91 (95% IC 1.07 to 3.41, P=0.028); respectively. When multivariate analysis was conducted, greater MAP variation on dialysis and higher number of pressors at baseline remained associated with decreased survival times. The study showed that for each 1 mmHg MAP on dialysis, the HR was 1.06 (95% CI 1.02 to 1.11; P=0.005) [17].

Additionally, the same study assessed the same variables in patients with renal recovery versus patients who died or were discharged still requiring dialysis therapy. Mean MAP variation on dialysis was 1.7±7.1 mmHg during initial dialysis in patients who did not recover renal function versus - 4.5±5.4 mm Hg in patients who did recover renal function (P=0.015). In patients with renal recovery, this represented a significant increase in MAP on dialysis versus baseline (P=0.038). Renal recovery did not correlate with baseline MAP, number of baseline pressors, or increased pressor dose on dialysis therapy. Logistic regression analysis demonstrated that a greater MAP variation on dialysis negatively correlate for renal recovery, OR 0.81 (95% IC 0.68 to 0.95, P=0.01) [17].

Uehlinger et al (2005) [16], in their trial comparing 55 patients undergoing IHD to 70 patients undergoing CVVHDF, demonstrated that treatment with catecholamines was a strong predictor of mortality, OR 4.3 (P=0.002) [16].

Discussion

This systematic review of randomized clinical trials aiming to compare hemodynamic parameters among continuous, intermittent and hybrid RRT in AKI patients summarized the

results of 12 previous trials. Most of the studies did not find differences between the groups in relation to heart rate, blood pressure, hypotensive episodes and use of catecholamines.

In relation to heart rate and blood pressure, one of the included studies [19] comparing CVVH to IHD reported differences between the groups up to 4 hours after intervention, however, the differences were not observed after 24h. Episodes of hypotension were observed across the studies with no differences between the RRT modalities. Hemodynamic instability frequently complicates maintenance of RRT in AKI patients. Clinical and pathological consequences vary from post-dialysis fatigue to more serious complications such as bowel ischemia, myocardial stunning, brain atrophy and access thrombosis [26,27], as well as loss of residual function over time [28,29]. In addition, the occurrence of hemodynamic instability can limit delivery of adequate RRT due to the need of terminating dialysis sessions early and/or reducing ultrafiltration goals [26,27].

Additionally, lower baseline MAP, greater MAP variation on dialysis, higher number of pressors at baseline, and increase in pressor dose during dialysis were demonstrated to be associated with shorter survival time; and greater MAP variation on dialysis negatively was found to correlate for renal recovery [17]. Even tough, diagnostic criteria for intradialytic hypotension is not totally clear in the literature [26].

In relation to the use of catecholamines, studies reported high doses of administration; only one study reported dose significant higher of Dobutamine in patients undergoing RRT with CVVHDF, when compared to IHD. The other studies did not find differences between the groups. Uehlinger et al (2005) demonstrated that treatment with catecholamines was strong predictor of mortality. Previous studies have reported that high-dose vasopressor is associated with increased mortality. Study from Wang et al (2011) [30] found that norepinephrine doses equal or above 0.3 μg/kg/min were independently linked to mortality, HR 1.77 (95% IC 1.23 to 2.52, P=0.001). Critically ill patients treated with high doses of norepinephrine before the initiation of CRRT have a very high mortality rate regardless of the stage of the AKI [30].

This study has some limitations. The heterogeneity across included studies did not allow to conduct meta-analysis to quantitatively summarize the results. Studies used different

definition and measurement of outcomes. In addition, most of studies included small sample size; however, this was the first systematic review to comprehensive summarize changes in hemodynamic parameters comparing different modalities of RRT.

In conclusion, most of the studies did not find differences in hemodynamic parameters among different types of RRT, except a CVVH group heart rate decrease after 1 and 4 hours in comparison with IHD group, an increase in systolic blood pressure after 0.5 and 2h of CVVH in contrast with IHD, and doses significant higher of Dobutamine in patients from the CVVHDF group, when compared to IHD. Lower baseline MAP, greater MAP variation on dialysis, higher number of pressors at baseline, and increase in pressor dose during dialysis were associated with shorter survival time; and greater MAP variation on dialysis negatively was correlated to renal recovery. We believe that this study can provide important insights for further clinical trials designed specifically to evaluate hemodynamic parameters across different types of RRT.

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Considerações finais

Em conclusão, a maioria dos estudos não encontrou diferenças nos parâmetros hemodinâmicos entre os diferentes tipos de RRT, com exceção da diminuição da freqüência cardíaca do grupo CVVH após 1 e 4 horas em comparação com o grupo IHD, aumento da pressão arterial sistólica após 0,5 e 2 h de CVVH em contraste com a IHD, e doses significativamente maiores de Dobutamina em pacientes do grupo CVVHDF, quando comparadas à IHD. A MAP basal mais baixa, uma maior variação do MAP em diálise, maior número de pressores na linha de base e aumento da dose pressora durante a diálise foram associadas com menor tempo de sobrevivência; e uma maior variação do MAP em diálise negativamente foi correlacionada com a recuperação renal. Acreditamos que este estudo pode fornecer insights importantes para novos ensaios clínicos projetados especificamente para avaliar parâmetros hemodinâmicos em diferentes tipos de RRT.

Table 1: Studies characteristics.

Study, Year of Publication	Country	Study Arms	Sample size	Age (Years - Mean±SD)	Gender male N (%)	Serum creatinine (mg/dl)	Serum urea (mg/dl)	APACHE-II score (Mean±SD)	SAPS-II score (Mean±SD)	SOFA score (Mean±SD)	TISS-28 score (Mean±SD)
Intermittent vs continuous modalities											
Schefold, 2014 [14]	Germany	IHD	128	60.8±13.4	81 (63.3)	3.64±2.3	159.7±86.5	28.5±7.9	66.1±18.1	13.2±3.9	45.0±10.3
		CVVH	122	62.3±14.5	75 (61.5)	3.57±1.9	156.7±77.1	28.8±9.6	63.8±17.6	13.0±4.0	47.1±10.3
Vinsonneau, 2006 [15]	France	IHD	184	65 (63-67)*	132 (72.0)	2.6 (2.4–2.7)*	186 (174-198)*	NA	64 (62–66)*	NA	NA
		CVVHDF	175	65 (63-67)*	129 (74.0)	2.5 (2.3–2.8)*	174 (156-186)*	NA	65 (65–67)*	NA	NA
Uehlinger, 2005 [16]	Switzerland	IHD	55	66 (18-85)**	40 (73.0)	2.0 (0.4-6.2)**	180.8 (37.8-345.9)**	NA	22 (21-110)**	NA	NA
		CVVHDF	70	67 (19-84)**	46 (66.0)	2.1 (0.8-3.9)**	152.5 (52.2-239.6)**	NA	55 (21-103)**	NA	NA
Augustine, 2004 [17]	United States	IHD	40	61.4±12.9	26 (65.0)	4.8±1.8	110.0±47.7	NA	NA	NA	NA
		CVVHDF	40	61.4±14.1	28 (70.0)	4.8±2.0	94.2±45.0	NA	NA	NA	NA
Gasparovic, 2003 [18]	Croatia	IHD	52	NA	NA	NA	NA	20.3±8.4	NA	9.8±4.7	NA
		CRRT	52	NA	NA	NA	NA	21.9±8.8	NA	11.0±3.9	NA
John, 2001 [19]	Germany	IHD	10	64.0±10.0	9 (90.0)	4.9±1.8	171.0±48.0	33.0±4.0	NA	NA	NA
		CVVH	20	59.0±12.0	17 (85.0)	5.2±2.6	158.0±63.0	34.0±5.0	NA	NA	NA
Hybrid vs continuous modalities											
Badawy, 2013 [20]	Egypt	EDD	40	46.0±18	28 (70.0)	3.70±1.1	NA	23.3±6.6	NA	NA	NA
		CVVHDF	40	49.0±17	24 (60.0)	3.00±1.0	NA	22.9±5.9	NA	NA	NA

Schwenger, 2012 [21]	Germany	SLED	115	66.6±12.6	72 (72.6)	2.59±1.3	132.7±59.7	31.3±8.7#	69.5±14.0##	NA	49.0±6.9
		CVVH	117	65.8±12.1	85 (72.7)	2.55±1.0	137.3±53.9	32.2±7.8#	67.6±16.7##		48.5±6.9
Kielstein, 2004 [22]	Germany	EDD	20	50.8±3.6	15 (75.0)	3.9±0.4	82.0±8.0	32.6±1.0	NA	NA	NA
		CVVH	19	50.1±3.2	12 (63.2)	3.5±0.4	83.0±10.0	32.3±1.2	NA	NA	NA
Continuous vs continuous modalities											
Nand, 2010 [23]	India	CAVHDF	15	39.9±14.5	7 (46.7)	4.68±1.78	232.4±71.5	101.1±11.7###	NA	NA	NA
		CVVHDF	15	43.3±12.7	9 (60.0)	6.89±3.82	239.6±75.4	101.1±23.3###	NA	NA	NA
Other comparisons											
Badawy, 2012 [24]	Egypt	Furosemide	20	62.0±14.0	12 (60.0)	1.40±0.7	NA	13.0±4.0	NA	NA	NA
		CVVHDF	20	64.0±11.0	14 (70.0)	1.40±0.8	NA	14.0±5.0	NA	NA	NA
Abe, 2011 [25]	Japan	SHDF	25	66.5±12.1	16 (64.0)	4.80±2.1	NA	20.0±4.3	NA	8.2±3.2	NA
		CVVHDF	25	65.3±13.1	17 (68.0)	4.60±2.3	NA	19.6±3.7	NA	8.1±2.0	NA

* mean (95% CI)
** median (range)
# Study used APACHE and not APACHE II
Study used SAPS and not SAPS II
Study used APACHE III
IHD: Intermittent haemodialysis, CVVH: Continuous venovenous hemofiltration, CVVHDF: Continuous venovenous hemodiafiltration, CRRT: Continuous renal replacement therapy, EDD: Extended daily dialysis, SLED: Sustained low-efficiency dialysis, CAVHDF: Continuous arteriovenous hemodiafiltration

Table 2: Risk of bias of included studies.

Study, Year of Publication	Selection bias		Detection bias	Attrition bias	Reporting bias	Other bias
	Random sequence generation (High, Low, Unclear)	Allocation concealment (High, Low, Unclear)	Blinding of outcome assessment (High, Low, Unclear)	Incomplete outcome data (High, Low, Unclear)	Selective reporting (High, Low, Unclear)	Other sources of bias (High, Low, Unclear)
Intermittent vs continuous modalities						
Schefold, 2014 [14]	Unclear	Low	Unclear	Low	Unclear	Low
Vinsonneau, 2006 [15]	Low	Low	Low	Low	Unclear	Low
Uehlinger, 2005 [16]	Low	Unclear	Unclear	Low	Unclear	Low
Augustine, 2004 [17]	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Gasparovic, 2003 [18]	High	High	Unclear	Unclear	Unclear	Unclear
John, 2001 [19]	Unclear	Unclear	Unclear	Low	Unclear	Low
Hybrid vs continuous modalities						
Badawy, 2013 [20]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Schwenger, 2012 [21]	Low	Unclear	Unclear	Low	Unclear	Low
Kielstein, 2004 [22]	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Continuous vs continuous modalities						
Nand, 2010 [23]	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Other comparisons						
Badawy, 2012 [24]	Unclear	Unclear	High	Low	Unclear	Unclear

Abe, 2011 [25]		Low	Unclear	Unclear	Unclear	Unclear	Unclear

Table 3: Synthesis of results.

Study, Year of Publication	Study Arms	Heart rate, bpm (Mean±SD)	Blood Pressure (Mean±SD)	Hypotensive episodes, N(%)	Use of catecholamines
Intermittent vs continuous modalities					
Schefold, 2014 [14]	IHD CVVH	IHD Group Day 1: 104.0±26.1 Day 3: 93.8±23.3 Day 5: 90.9±20.3 Day 7: 92.9±17.0 Day 10: 86.9±16.4 Day 15: 85.5±19.9 Day 21: 86.5±12.9 CVVH group Day 1: 105.2±21.3 Day 3: 93.6±22.3 Day 5: 90.0±20.4 Day 7: 87.5±19.5 Day 10: 89.7±18.1 Day 15: 93.1±17.2 Day 21:96.5±15.4 P=NS	Mean arterial pressure (mmHg) IHD Group Day 1: 73.3±16.5 Day 3: 76.5±17.6 Day 5: 76.9±15.9 Day 7: 82.2±16.7 Day 10: 78.1±17.2 Day 15: 83.3±11.9 Day 21: 70.0±15.1 CVVH group Day 1: 72.0±14.1 Day 3: 76.2±13.8 Day 5: 76.6±12.7 Day 7: 77.7±12.4 Day 10: 81.2±14.9 Day 15: 75.5±25.9 Day 21: 75.3±16.5 P=NS	NA	Cumulative vasopressor dose (g) Epinephrine IHD Group: 0.7 CVVH group: 0.6 P=0.96 Norepinephrine IHD Group: 19.1 CVVH group: 18.5 P=0.30 Dobutamine IHD Group: 150.2 CVVH group: 137.9 P=0.56
Vinsonneau, 2006 [15]	IHD CVVHDF	NA	NA	IHD group: 72 (39%) CVVHDF group: 61 (35%) Hypotension episode was defined as a systolic arterial pressure of 80 mm Hg or less or a fall greater than 50 mm Hg from the baseline value.	NA

Uehlinger, 2005 [16]	IHD CVVHDF	NA	Mean arterial pressure (mmHg) IHD Group Day 0: 75±2 Day 5: 74±2 Day 10: 78±2 Day 15: 79±2 Day 20: 85±2 Day 25: 81±3 CVVHDF Group Day 0: 72±1 Day 5: 76±2 Day 10: 77±2 Day 15: 74±2 Day 20: 75±3 Day 25: 75±3 Mean±SE	NA	Cumulative treatment days IHD Group: 455 CVVHDF Group: 510 Adrenaline N(%) of patients IHD Group: 15 (27) CVVHDF Group: 31 (44) P=0.06 N(%) of patient-days IHD Group: 21 (5) CVVHDF Group: 87 (17) Dose (µg/12h) IHD Group: 7350 (2-80500) CVVHDF Group: 4070 (56750) P=0.13 Noradrenaline N(%) of patients IHD Group: 28 (51) CVVHDF Group: 38 (54) P=0.72 N(%) of patient-days IHD Group: 129 (28) CVVHDF Group: 155 (30) Dose (µg/12h) IHD Group: 3300 (47-161350) CVVHDF Group: 4300 (10-143500) P=0.21 Dopamine N(%) of patients IHD Group: 7 (13) CVVHDF Group: 5 (7) P=0.37

					N(%) of patient-days IHD Group: 13 (3) CVVHDF Group: 11 (2) Dose (µg/12h) IHD Group: 33 (1-485) CVVHDF Group: 21 (2-156) P-0.13 Dobutamine N(%) of patients IHD Group: 19 (35) CVVHDF Group: 31 (44) P=0.36 N(%) of patient-days IHD Group: 76 (17) CVVHDF Group: 150 (29) Dose (µg/12h) IHD Group: 24 (12-425) CVVHDF Group: 32 (1-835) P<0.001
Augustine, 2004 [17]	IHD CVVHDF	NA	Mean arterial pressure (mmHg) IHD Group Pre-dialysis: 77.6±12.9 Intra-dialysis: 75.0±13.8 P=0.04 CVVHDF Group Pre-dialysis: 76.8±7.8 Intra-dialysis: 77.4±8.1 P=NS	NA	Pressors at baseline N(%) IHD Group: 22 (55) CVVHDF Group: 21 (52.5) P=NS No. of pressors at baseline (Mean±SD) IHD Group: 1.00±1.13 CVVHDF Group: 0.93±1.02 P=NS
Gasparovic, 2003 [18]	IHD CRRT	NA	NA	The article reports that there was no difference in total number of blood pressure drops between the two groups (data not shown).	NA

				Hypotension episode was defined as decrease greater than 10% from baseline.	
John, 2001 [19]	IHD CVVH	Baseline IHD Group: 108±13 CVVH Group: 114±17 P=NS Changes in 2 hours IHD Group: +9±8 CVVH Group: -3±11 Changes in 4 hours IHD Group: +9±8 CVVH Group: -2±12 P<0.01 Changes in 24 hours IHD Group: -3±7 CVVH Group: -9±22 P= NS	Systolic blood pressure (mmHg) Baseline IHD Group: 120±12 CVVH Group: 116±20 Changes in 0.5 hours IHD Group: -12±16 CVVH Group: +8±20 Changes in 2 hours IHD Group: 15±17 CVVH Group: +12±19 P<0.05 Changes in 24 hours IHD Group: -1±17 CVVH Group: +5±30 P=NS Similar responses were observed for MAP and DBP during both forms of renal replacement therapy (data not shown).	IHD Group: 6 (60) CVVH Group: 9 (45) Hypotension episode was defined as a decrease greater than 20% from baseline	Noradrenaline, mg/h (Mean±SD) Baseline IHD Group: 1.90±1.57 CVVH Group: 2.04±1.96 P=NS 0.5 hours IHD Group: 2.06±1.91 CVVH Group: 2.10±1.98 P=NS 2 hours IHD Group: 2.16±1.78 CVVH Group: 2.10±1.98 P=NS 4 hours IHD Group: 2.14±1.94 CVVH Group: 2.12±1.88 P=NS 24 hours IHD Group: 1.98±1.68 CVVH Group: 2.18±1.79 P=NS
Hybrid vs continuous modalities					
Badawy, 2013 [20]	EDD CVVHDF	Baseline EDD Group: 82±19 CVVHDF Group: 84±16 24 hours EDD Group: 77±17 CVVHDF Group: 85±11	Systolic blood pressure (mmHg) Baseline EDD Group: 123±15 CVVHDF Group: 119±14 24 hours	EDD Group: 2 (5) CVVHDF Group: 1 (25) Hypotension episode was defined as systolic blood pressure less than 80 mmHg	The article reports that the number of patients on vasopressors in both groups was comparable (data not shown).

		48 hours EDD Group: 76±15 CVVHDF Group: 78±12 72 hours EDD Group: 80±12 CVVHDF Group: 78±10 P=NS	EDD Group: 127±10 CVVHDF Group: 120±11 48 hours EDD Group: 118±17 CVVHDF Group: 126±9 72 hours EDD Group: 127±14 CVVHDF Group: 122±13 P=NS Diastolic blood pressure (mmHg) Baseline EDD Group: 64±13 CVVHDF Group: 63±11 24 hours EDD Group: 72±15 CVVHDF Group: 67±11 48 hours EDD Group: 70±11 CVVHDF Group: 74±13 72 hours EDD Group: 67±12 CVVHDF Group: 72±11 P=NS		
Schwenger, 2012 [21]	SLED CVVH	NA	Systolic blood pressure (mmHg) Pre-treatment SLED Group: 125.1±14.6 CVVH Group: 124.6±13.5 P=0.43 After treatment SLED Group:128.3±17.1	Mean±SD SLED Group: 1.5±1.4 CVVH Group: 1.8±1.6 P=0.07 A hypotensive episode was defined as an acute drop of systolic blood pressure below 80 mmHg	Article reports that vasopressors were not significantly different between groups (data not shown).

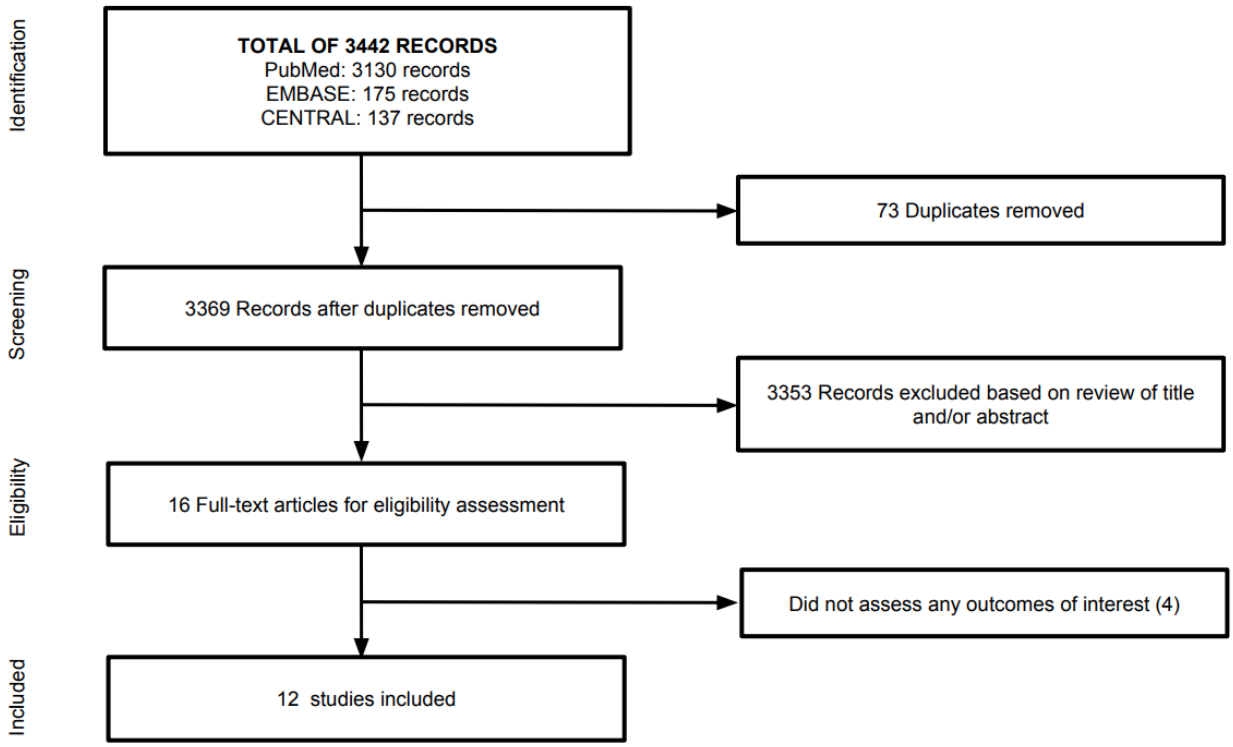
			CVVH Group: 124.3±15.6 P=0.05 Diastolic blood pressure (mmHg) Pre-treatment SLED Group: 60.7±10.7 CVVH Group: 60.7±10.0 P=0.42 After treatment SLED Group: 61.8±11.3 CVVH Group: 60.3±10.2 P=0.25	or greater than 20% from baseline.	
Kielstein, 2004 [22]	EDD CVVH	Baseline EDD Group: 105.3±15 CVVH Group: 97.3±6 6 days EDD Group: 97.3±11 CVVH Group: 95.4±5 12 days EDD Group: 95.0±12 CVVH Group: 87.0±5 18 days CVVH Group: 90.9±3 24 days CVVH Group: 87.0±4 P=NS	Mean arterial pressure (mmHg) Baseline EDD Group: 69.9±4 CVVH Group: 73.6±3 6 days EDD Group: 72.9±3 CVVH Group: 78.9±3 12 days EDD Group: 73.1±3 CVVH Group: 77.6±3 18 days CVVH Group: 76.6±3 24 days CVVH Group: 77.4±4 P=NS	NA	Norepinephrine, µg/kg/min (Mean±SD) Baseline EDD Group: 0.47±0.11 CVVH Group: 0.47±0.14 After 12 hours EDD Group: 0.45±0.12 CVVH Group: 0.42±0.13 After 24 hours CVVH Group: 0.39±0.13 P=NS
Continuous vs continuous modalities					
Nand, 2010 [23]	CAVHDF	NA	Mean arterial pressure (mmHg)	The article reports that none of the patients	The article reports that 18 the 30 patients were on vasopressor

	CVVHDF (A)		CAVHDF Group Baseline: 73.1±22.0 After 24 hours: 81.7±19.3 P<0.05 CVVHDF Group Baseline: 71.1±20.0 After 24 hours: 78.3±18.5 P<0.05	developed hypotension secondary to the procedure. In fact, there was improvement in hemodynamic parameters (data not shown).	support at the initiation of therapy, and requirement for dopamine, Dobutamine or nor adrenaline did not change significantly when it was measured at zero, one four, and 24 hours of HDF (no more data was shown).
Other comparisons					
Badawy, 2012 [24]	Furosemide CVVHDF	Furosemide Group Baseline: 72±16 24h: 79±12 48h: 81±11 72h: 80±17 P=NS CVVHDF Group Baseline: 79±13 24h: 73±15 48h: 78±11 72h: 82±8 P=NS	Systolic blood pressure (mmHg) Furosemide Group Baseline: 123±9 24h: 124±11 48h: 118±16 72h: 124±10 P=NS CVVHDF Group Baseline: 119±8 24h: 120±9 48h: 125±7 72h:121±10 P=NS Diastolic blood pressure (mmHg) Furosemide Group Baseline: 65±10 24h: 69±11 48h: 73±9 72h: 75±8 P=NS CVVHDF Group Baseline: 62±7 24h: 65±10	Furosemide Group: 0 CVVHDF Group: 1 (5) Hypotension episode as defined as systolic blood pressure of 80 mmHg or less	NA

			48h: 69±8 72h: 70±10 P= NS		
Abe, 2011 [25]	SHDF CVVHDF	NA	NA	SHDF Group: 12 (7.1) CVVHDF Group: 20 (9.8) P=0.32 Hypotension occurred that required discontinuation of the treatment.	Requirement of vasopressor support N(%) SHDF Group: 18 (10.5) CVVHDF Group: 26 (12.8) P=0.48

IHD: Intermittent haemodialysis, CVVH: Continuous venovenous hemofiltration, CVVHDF: Continuous venovenous hemodiafiltration, CRRT: Continuous renal replacement therapy, EDD: Extended daily dialysis, SLED: Sustained low-efficiency dialysis, CAVHDF: Continuous arteriovenous hemodiafiltration

Figure 1: Study flow diagram.



Appendix 1 - Pubmed search strategy

Search	Query	Items found
#20	Search (#5 AND #6 AND #19)	***3130***
#19	Search "Hemodynamics"[Mesh] OR "Hypotension"[Mesh] OR "Vascular Hypotension"[Title/Abstract] OR "Low Blood Pressure"[Title/Abstract] OR "Blood Pressure, Low"[Title/Abstract] OR "Hypotension, Vascular"[Title/Abstract] OR "Low Blood Pressure"[Title/Abstract] OR "Intradialytic Hypotension"[Title/Abstract] OR "Heart Rate"[Mesh] OR "Heart Rates"[Title/Abstract] OR "Rate, Heart"[Title/Abstract] OR "Rates, Heart"[Title/Abstract] OR "Pulse Rate"[Title/Abstract] OR "Pulse Rates"[Title/Abstract] OR "Rate, Pulse"[Title/Abstract] OR "Rates, Pulse"[Title/Abstract] OR "Cardiac Chronotropy"[Title/Abstract] OR "Chronotropy, Cardiac"[Title/Abstract] OR "Chronotropism, Cardiac"[Title/Abstract] OR "Cardiac Chronotropism"[Title/Abstract] OR "Heart Rate Control"[Title/Abstract] OR "Control, Heart Rate"[Title/Abstract] OR "Rate Control, Heart"[Title/Abstract] OR "Catecholamines"[Mesh]	862158
#6	Search (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] NOT (animals [mh] NOT humans [mh]))	3625237
#5	Search "Renal Replacement Therapy"[Mesh] OR "Therapy, Kidney Replacement"[Title/Abstract] OR "Replacement Therapy, Renal"[Title/Abstract] OR "Renal Replacement Therapies"[Title/Abstract] OR "Replacement Therapies, Renal"[Title/Abstract] OR "Therapies, Renal Replacement"[Title/Abstract] OR "Therapy, Renal Replacement"[Title/Abstract] OR "Replacement Therapy, Kidney"[Title/Abstract] OR "Kidney Replacement Therapies"[Title/Abstract] OR "Replacement Therapies, Kidney"[Title/Abstract] OR "Therapies, Kidney Replacement"[Title/Abstract] OR "Kidney Replacement Therapy"[Title/Abstract] OR "Hemodiafiltration"[Mesh] OR "Acetate-Free Biofiltration"[Title/Abstract] OR "Acetate Free Biofiltration"[Title/Abstract] OR "Acetate-Free Biofiltrations"[Title/Abstract] OR "Biofiltrations, Acetate-Free"[Title/Abstract] OR "Biofiltration, Acetate-Free"[Title/Abstract] OR "Biofiltration, Acetate Free"[Title/Abstract] OR "Hemodiafiltration"[Title/Abstract] OR "HDF"[Title/Abstract] OR "Continuous venovenous hemodiafiltration"[Title/Abstract] OR "CVVHDF"[Title/Abstract] OR "Renal Dialysis"[Mesh] OR "Dialyses, Renal"[Title/Abstract] OR "Renal Dialyses"[Title/Abstract] OR "Dialysis, Renal"[Title/Abstract] OR "Hemodialysis"[Title/Abstract] OR "Hemodialyses"[Title/Abstract] OR "Dialysis, Extracorporeal"[Title/Abstract] OR "Dialyses, Extracorporeal"[Title/Abstract] OR "Extracorporeal Dialyses"[Title/Abstract] OR "Extracorporeal Dialysis"[Title/Abstract]	202526