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SYSTEMATIC REVIEW

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Citrate versus heparin anticoagulation for continuous renal replacement therapy: an updated meta-analysis of RCTs

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Abstract *Purpose:* The purpose of this study was to evaluate the effect and safety of citrate versus heparin anticoagulation for continuous renal replacement therapy (CRRT) in critically ill patients by performing a meta-analysis of updated evidence. *Methods:* Medline, Embase, and Cochrane databases were searched for eligible studies, and manual searches were also performed to identify additional trials. Randomized controlled trials (RCTs) assessing the effect of citrate versus heparin anticoagulation for CRRT were considered eligible for inclusion. *Results:* Eleven RCTs with 992 patients and 1998 circuits met the inclusion criteria. Heparin was regionally delivered in two trials and systemically delivered in nine trials. Citrate for CRRT significantly reduced the risk of circuit loss compared to regional (HR 0.52, 95 % CI 0.35–0.77, $P = 0.001$) and systemic (HR 0.76, 95 % CI 0.59–0.98, $P = 0.04$) heparin. Citrate also reduced the incidence of filter failure (RR 0.70, 95 % CI 0.50–0.98, $P = 0.04$). The citrate group had a significantly lower bleeding risk than the systemic heparin group (RR 0.36, 95 % CI 0.21–0.60, $P < 0.001$) and a similar bleeding risk to the regional heparin group (RR 0.34, 95 % CI 0.01–8.24, $P = 0.51$). The incidences of heparin-induced thrombocytopenia (HIT) and hypocalcemia were increased in the heparin and citrate groups, respectively. No significant survival difference was observed between the groups. *Conclusions:* Given the lower risk of circuit loss, filter failure, bleeding, and HIT, regional citrate should be considered a better anticoagulation method than heparin for CRRT in critically ill patients without any contraindication.

Keywords
Continuous renal replacement therapy · Citrate · Heparin · Anticoagulation · Randomized controlled trial · Meta-analysis

Introduction

Continuous renal replacement therapy (CRRT) is commonly used for critically ill patients with acute kidney injury, severe metabolic disorder, refractory fluid overload, and certain drug intoxications. Clotting in the extracorporeal circuit shortens the filter and catheter lifespans, causes blood loss, and decreases solute clearance, consequently reducing the effectiveness of CRRT and increasing treatment cost and workload [1, 2].

Heparin can be systemically and regionally administrated for anticoagulation during CRRT. Systemic heparin was the classically used anticoagulation agent and had the advantages of low cost, easy administration, simple

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monitoring, and reversibility by protamine. However, systemic heparin increases the risk of bleeding in critically ill patients who already have an increased bleeding risk [3]. Regional delivery of heparin to the extracorporeal circuit and protamine to reverse its effect is an alternative to systemic heparin. Despite a reduction of the bleeding risk, regional heparin is associated with heparin-induced thrombocytopenia (HIT) risk similar to those of systemic heparin, and increased risks of protamine exposure and allergy [4, 5].

Regional citrate anticoagulation was first employed in hemodialysis in 1983 [6] and was introduced in CRRT in the 1990s [7]. Since then, the safety and efficacy of regional citrate anticoagulation have been extensively evaluated. Several randomized controlled trials (RCTs) have compared the efficacy and safety of citrate anticoagulation to those of heparin anticoagulation, and some of the results of those studies were controversial [8–10]. The recent Kidney Disease: Improving Global Outcomes (KDIGO) guideline, which was based on five earlier RCTs, has recommended regional citrate rather than heparin in patients who do not have contraindications for citrate [11].

Thereafter, two meta-analyses summarized the data of the same six RCTs [12, 13]. Although the two meta-analyses were not consistent in several data points of the included trials, they concluded that citrate anticoagulation could significantly reduce the risk of bleeding. However, they did not agree on whether citrate could improve circuit life-span compared to heparin. Additionally, both meta-analyses demonstrated significant inter-trial heterogeneity in the pooled effect of bleeding and circuit life-span. Therefore, the Canadian Society of Nephrology concluded that the data were insufficient to determine the most cost-effective anticoagulation method because of the uncertain improvement in filter life-span with citrate [14]. Recently, more RCTs [10, 15–18] with valuable data on citrate versus heparin anticoagulation for CRRT have been published. Therefore, we performed the present meta-analysis to summarize the updated evidence and evaluate the role of citrate anticoagulation for CRRT.

Materials and methods

Search and selection of studies

Two of the authors (M.B. and F.M.) independently performed the study searches and screens to identify eligible studies. Discrepancies were resolved by discussion and consensus. We searched the Medline, Embase, and Cochrane databases from inception to 6 April 2015. Eligible studies were identified using the following key terms: citrate, heparin, anticoagulation, CRRT, continuous renal replacement therapy, CVVH, continuous venovenous hemofiltration, CVVHD, continuous venovenous hemodialysis, CVVHDF, and continuous venovenous hemodiafiltration. We also manually reviewed the reference lists of the identified articles and the article lists of the relevant journals for additional studies. Additionally, we searched the International Clinical Trials Registry Platform (ICTRP, http://apps.who.int/trialsearch/Default.aspx) and ClinicalTrials.gov for gray trials. No language restriction was employed for the searches.

Studies with the following characteristics were candidates for inclusion: (1) the interventions were citrate versus heparin anticoagulation for CRRT and (2) the included patients were randomly assigned to the treatment groups. Studies with any of the following conditions were excluded: (1) quasi-random treatment assignment method (e.g., day of birth or date of admission), and (2) required data could not be extracted from the published results. When more than one publication reported the results from one study, only the publication with the most recent and complete data was included.

Data extraction

Two of the authors (B.M. and Z.M.) independently extracted the following data from each study using a predefined form: first author, publication year, included patients and circuit number, population characteristics, study design, inclusion and exclusion criteria, CRRT protocol, filter parameters, interventions, outcomes, and complications. The quality of each study was assessed using the Jadad score system, with 5 points representing a high-quality study and 0 points representing a low-quality study [19]. Discrepancies were resolved by discussion and consensus. The assessed outcomes included circuit loss (circuit termination for any reason), filter failure, catheter dysfunction, patient mortality, bleeding episodes, HIT, metabolic disturbances, and hypocalcemia. Filter failure was defined as the occurrence of filter clotting or high transmembrane filter pressure. If there was any need for additional data, then the corresponding authors were contacted.

Statistical analysis

Risk ratios (RRs) with 95 % confidence intervals (95 % CIs) were pooled for outcome which was reported as a binary variable. For the time-to-event outcome, hazard ratios (HRs) were pooled as the summarized parameter [20, 21]. Ln(HR)s and their standard errors (SEs) were calculated using the randomization ratio, number of analyzed patients, observed events, and expected events, HR and associated 95 % CI, log-rank variance, log-rank observed-minus-expected events, and *P* value of the log-

rank test [20, 22]. When these variables were not available, the survival curves were assessed to calculate the ln(HR)s and SEs using the easy-to-use calculations spreadsheet provided by Tierney et al. [20]. Subgroup analyses according to heparin delivery method (systemic or regional) were performed for circuit loss risk and bleeding risk.

A funnel plot and Begg's test were employed to assess the potential publication bias of the meta-analysis including 10 or more studies [23]. Heterogeneity among the included studies was evaluated using a Chi squared test and I^2 statistic and sensitivity analyses were performed to explore the source of heterogeneity. All of the pooled results were calculated using Review Manager software (version 5.3, Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2011). A P value less than 0.05 was considered to indicate a statistically significant difference. The results were calculated in random-effect models to yield controversial conclusions and were tested in fixed-effect models as well. The Mantel–Haenszel method was used for all of the binary endpoints and the inverse variance method was used for all of the time-to-event endpoints. Begg's test was performed using STATA 10 (Stata Corporation, College Station, TX, USA).

Results

Study inclusion

The study selection process is presented in Fig. 1. The numbers of studies identified in the Embase, Medline, and Cochrane databases were 398, 292, and 182, respectively. An additional two studies were identified by the manual searches. The searches of the two trial registry platforms identified no trials that had been completed and were unpublished. A total of 218 publications were excluded because they were duplicates among the databases or were repeat publications, resulting in the titles and abstracts of 656 studies being screened, and an additional 632 studies were excluded. Full-text review of the remaining 24 articles identified 11 RCTs with 992 patients and 1998 circuits that fulfilled all of the selection criteria.

Table 1 presents the characteristics of the included studies. Four studies [9, 15, 17, 24] were multicenter trials, four studies [9, 10, 15, 25] presented recurrent events data, and two studies [8, 26] had a crossover design. More than half of the included studies were published after 2010. The study participants of all included trials were acute kidney injury (AKI) patients requiring CVVH, and the median number of participants

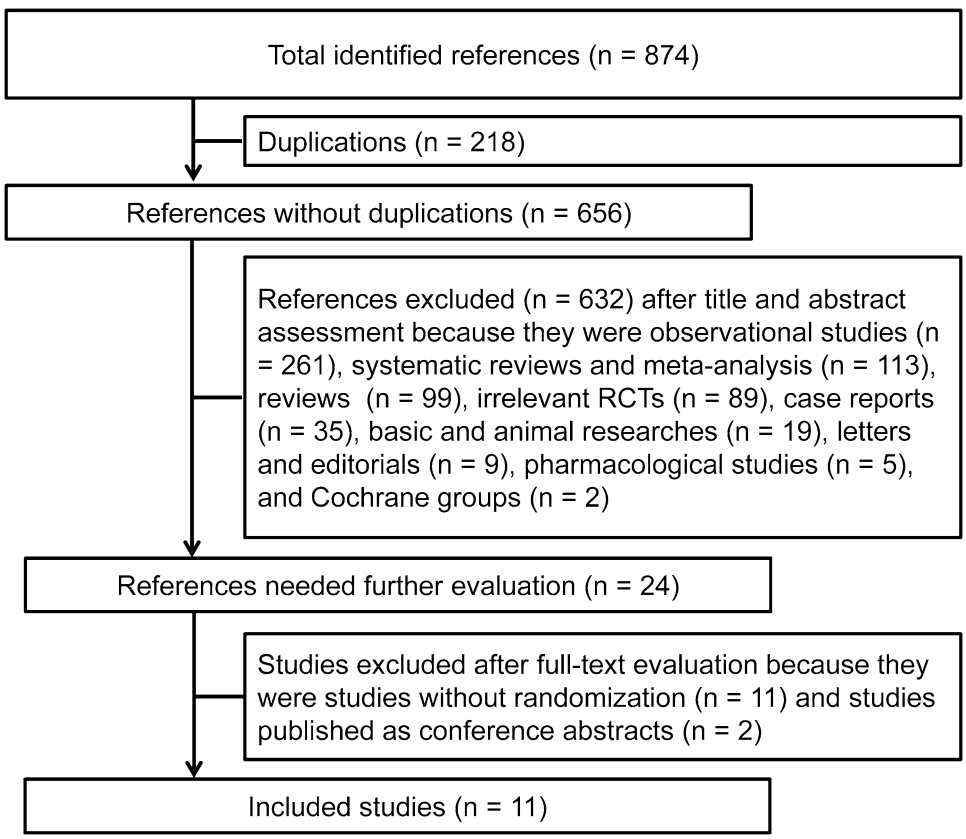

Fig. 1 Study inclusion flowchart

Table 1 Characteristics of the included studies

Study	No. of patients	No. of circuits	No. of centers	Crossover/ recurrent events	Inclusion	Exclusion	Age	Severity	Male/ female
Monchi et al. [8]	C: 8 H: 12	C: 26 H: 23	1	Yes/no	AKI	Liver cirrhosis, high bleeding risk	C: 67 (52–77) (IR) H: 64 (52–74) (IR)	SAPS C: 40 (31–53) (IR) H: 42 (33–55) (IR)	C: 11/1 H: 12/2
Kutsogiannis et al. [9]	C: 16 H: 14	C: 36 H: 43	2	No/yes	Adult, AKI,	Liver failure, contraindications to either intervention	C: 66.5 ± 14.5 (SD) H: 63.9 ± 21.2 (SD)	LOD C: 7.75 ± 3.53 (SD) H: 9.42 ± 2.31 (SD)	C: 7/9 H: 8/6
Betjes et al. [25]	C: 21 H: 27	C: 70 H: 72	1	No/yes	Adult, need for RRT	Acute liver failure, contraindications to either intervention	C: 57.8 ± 4.2 (SE) H: 55.2 ± 2.8 (SE)	SAPS C: 51.4 ± 4.1 (SE) H: 51.0 ± 2.6 (SE)	C: 19/8 H: 15/6
Fealy et al. [26]	C: 10 H: 10	C: 10 H: 10	1	Yes/no	AKI	Acute or chronic liver failure, contraindications to either intervention	71 (63.5–76.5) (IR)	SAPS: 41 (31–43) (IR) APACHE: 17 (15–21) (IR)	9/1
Oudemans-van Straaten et al. [27]	C: 97 H: 103	C: 97 H: 103	1	No/no	Adult, AKI	Liver cirrhosis, contraindications to either intervention, chronic dialysis, other therapeutic anticoagulation, HIT	C: 73 (67–79) (IR) H: 73 (64–79) (IR)	APACHE C: 28 (27–30) (95 % CI) H: 28 (27–29) (95 % CI) SAPS C: 59 (55–62) (95 % CI) H: 61 (58–64) (95 % CI)	C: 66/31 H: 70/43
Hetzel et al. [24]	C: 87 H: 83	C: 87 H: 81	9	No/no	Adult, AKI	Contraindications to either intervention, metabolic alkalosis, pregnancy or lactation, chronic dialysis, other therapeutic anticoagulation, HIT	C: 61.72 ± 15.29 (SD) H: 65.11 ± 12.46 (SD)	APACHE C: 21.8 ± 5.1 (SD) H: 22.04 ± 5.5 (SD) SOFA C:9.95 ± 2.9 (SD) H:9.95 ± 2.6 (SD)	C: 57/30 H: 59/24
Tiranathanagul et al. [18]	C: 10 H: 10	C: 10 H: 10	1	No/no	AKI	Acute or chronic liver failure, contraindications to either intervention, previous dialysis within 24 h, hypercalcemia, other therapeutic anticoagulation	C: 69.5 (32–78) (R) H: 75.5 (18–87) (R)	APACHE C:21 (18–29) (R) H:22 (15–29) (R)	C: 7/3 H: 5/5

Table 1 continued

Study	No. of patients	No. of circuits	No. of centers	Crossover/ recurrent events	Inclusion	Exclusion	Age	Severity	Male/ female
Schilder et al. [17]	C: 66 H: 73	C: 66 H: 73	10	No/no	Adult, need for CVVH	High bleeding risk, other therapeutic anticoagulation, HIT	C: 67 (36–87) (R) H: 67 (23–85) (R)	APACHE C: 23 (11–53) (R) H: 25 (6–43) (R) SOFA C: 10 (2–19) (R) H: 11 (3–18) (R)	C: 44/22 H: 49/24
Brain et al. [10]	C: 19 H: 11	C: 65 H: 156	1	No/yes	Adult, AKI	Contraindication to either intervention, BW <30 kg, pregnancy or lactation	C: 64 ± 13 (SD) H: 51 ± 17 (SD)	APACHE C: 80 (58–99) (IR) H: 61 (52.5–91.5) (IR)	C: 12/7 H: 7/4
Stucker et al. [16]	C: 54 H: 49	C: 54 H: 49	1	No/no	Adult, AKI	Liver failure, high bleeding risk, HIT	C: 60 ± 14 (SD) H: 65 ± 16 (SD)	APACHE C: 28 ± 9 (SD) H: 29 ± 9 (SD) SAPS C: 63 ± 18 (SD) H: 65 ± 18 (SD)	C: 32/22 H: 32/17
Gattas et al. [15]	C: 105 H: 107	C: 390 H: 467	7	No/yes	Adult, AKI	Liver failure, pregnant or breastfeeding, HIT, chronic dialysis	C: 66.4 ± 14.3 (SD) H: 66.8 ± 14.9 (SD)	APACHE C: 25.6 ± 7.6 (SD) H: 25.0 ± 6.9 (SD)	C: 74/31 H: 72/35

AKI acute kidney injury, *APACHE* acute physiology and chronic health evaluation, *BW* body weight, *C* citrate group, *CI* confidence interval, *CVVH* continuous venovenous hemofiltration, *H* heparin group, *HIT* heparin-induced thrombocytopenia, *IR* interquartile range, *R* range, *RRT* renal replacement therapy, *SAPS* simplified acute physiology score, *SD* standard deviation, *SE* standard err, *SOFA* sepsis-related organ failure assessment, *LOD* the logistic organ dysfunction score

was 48 (range 20–212). Liver failure, high risk of bleeding, and contraindications to heparin or citrate were employed as the exclusion criteria in most of the included trials.

Table 2 presents the characteristics of the interventions of the included RCTs. In nine studies, the doses of regional citrate used were 2.5–4.3 mmol/L blood flow [8, 15–18, 24–27], and in the remaining two studies, the citrate dose was adjusted according to the initial serum ionized Ca^{2+} ($ionCa^{2+}$) concentration [9, 10]. Heparin was systemically delivered in nine trials at various doses to maintain the activated partial thromboplastin time (APTT) between 45 and 80 s [8–10, 16–18, 24, 25, 27] and was regionally given in the remaining two trials [15, 26]. The CRRT model was CVVH in seven trials [8, 17, 18, 24–27] and CVVHDF in three trials [9, 10, 16]. In the remaining study, patients underwent either CVVH or CVVHDF [15]. The definitions of filter failure, bleeding, metabolic alkalosis, and hypocalcemia were not completely uniform but were comparable, and none of the included studies reported the definitions of HIT or catheter dysfunction (supplementary Table 1).

The Jadad scores of the included trials are presented in supplementary Table 3. Because the two interventions were significantly different, blinding was not practical and was not used in any of the included trials. Four trials did not describe the method used to generate the sequence of randomization, and two studies did not report the withdrawals and dropouts. The final Jadad scores were 2 and 3 in six trials and five trials, respectively.

Risk of circuit loss

Circuit loss was evaluated as a time-to-event endpoint in all of the included trials, except the study by Hetzel et al. [24]. HR and its 95 % CI were used to compute the ln(HR) and its SE in the trial by Gattas et al. [15], and P value and the number of events were used to evaluate the ln(HR) and its SE in the study by Oudemans-van Straaten et al. [27]. None of the remaining eight trials reported the data necessary to directly calculate ln(HR) and its SE. Therefore, the ln(HR)s and their SEs of those studies were assessed from the survival curves [8–10, 16–18, 25, 26].

Finally, the analysis of circuit loss risk included eight trials that used systemic heparin [8–10, 16–18, 25, 27] and two trials that used regional heparin [15, 26]. In the subgroup analysis of citrate versus systemic heparin anticoagulation with 953 filters, citrate filters had a significantly lower risk of circuit loss (HR 0.76, 95 % CI 0.59–0.98, $P = 0.04$, Fig. 2), with no significant inter-trial heterogeneity ($I^2 = 29$ %, $P = 0.20$). The citrate versus regional heparin subgroup included 877 filters and did not exhibit significant inter-trial heterogeneity ($I^2 = 0$ %, $P = 0.34$). The citrate group had a significantly lower risk of circuit loss than the regional heparin group (HR 0.52, 95 % CI 0.35–0.77, $P = 0.001$, Fig. 2). Subsequently, the summarized results of the two subgroups significantly favored the citrate group (HR 0.71, 95 % CI 0.56–0.90, $P = 0.006$, Fig. 2). Inter-trial heterogeneity ($P = 0.12$) and inter-subgroup heterogeneity ($P = 0.11$) were not significant in the total group analysis (Fig. 2). Fixed-effect meta-analyses did not result in different overall conclusions. Additionally, the funnel plot and Begg's test demonstrated a low risk of publication bias in the total group analysis (supplementary Fig. 1, $P = 0.653$). The sensitivity analysis excluding the two crossover trials [8, 26] and the four trials [9, 10, 15, 25] with recurrent events data did not result in different overall conclusions (supplementary Table 2).

Filter failure

Data on filter failure were available in six trials [8, 9, 15, 17, 25, 27]. The number of filter failures was 339 of the 685 citrate filters (49.5 %) compared with 471 of the 790 heparin filters (59.6 %). The pooled RR significantly favored the citrate group (RR 0.70, 95 % CI 0.50–0.98, $P = 0.04$, Fig. 2); however, the inter-trial heterogeneity was significant ($I^2 = 84$ %, $P < 0.001$). Similar results were observed in the fixed-effect meta-analyses. Sensitivity analyses were performed by sequentially excluding the study that used regional heparin [15], the study that used nadroparin [27], the studies with recurrent events data [9, 15, 25], the study with a crossover design [8], and the study with no definition of filter failure (supplementary Table 2) [17]. Additionally, subgroup analyses were performed according to the use of CVVHDF and Jadad score (supplementary Table 2). All of these analyses were associated with significant inter-trial heterogeneity.

Catheter dysfunction

The number of catheter dysfunctions was available in five trials [8, 9, 17, 25, 27]. In total, catheter dysfunction occurred in 27 of the 295 circuits with citrate anticoagulation (9.2 %) compared to 28 of the 314 circuits (8.9 %) with heparin anticoagulation. The risk of catheter dysfunction was similar between the two groups (RR 1.0, 95 % CI 0.52–1.91, $P = 0.99$, Fig. 2), with no significant inter-trial heterogeneity ($I^2 = 25$ %, $P = 0.26$). The results of the fixed-effect meta-analyses were consistent with those of the random-effect meta-analyses. Sensitivity analyses excluding the crossover trial [8] and the two trials with recurrent data [9, 25] did not result in different overall conclusions (supplementary Table 2).

Table 2 Interventions and follow-up duration of the included studies

Study	Citrate	Heparin	CRRT model	Pre-/post-filter dilution	Filters	Follow-up duration
Monchi et al. [8]	Citrate dose was 4.3 mmol/L of blood flow, serum ionCa^{2+} 1.05–1.15 mmol/L	Systemic heparin, bolus of 2000–5000 IU, APTT maintained at 60–80 s	CVVH 175 mL/min	Post-	1.6 m^2 polysulfone membrane (Arylane H6, HOSPAL Renal Care, Lyon, France)	NR
Kutsogiannis et al. [9]	Citrate dose was adjusted according to the ionCa^{2+}, post-filter ionCa^{2+} 0.25–0.35 mmol/L	Systemic heparin, bolus of 50 IU/kg, maintenance APTT at 45–65 s	CVVHDF 125 mL/min	Pre-	PRISMA M-100 AN69 (Gambro Renal Products, Montreal, Canada)	Discharge or death
Betjes et al. [25]	Citrate dose was 2.7 mmol/L blood flow, post-filter ionCa^{2+} 0.25–0.35 mmol/L	Systemic heparin, bolus of 3000–5000 IU, maintained APTT at 50–70 s	CVVH 150 mL/min	Post-	High-flux triacetate hemofilter (UF-205, Nipro Corporation, Osaka, Japan)	NR
Fealy et al. [26]	Citrate dose was 3.1 mmol/L of blood flow, serum ionCa^{2+} 1.1–1.3 mmol/L	Regional heparin (1500 IU/h) and protamine post-filter (15 mg/h), normal APTT	CVVH 150 mL/min	Pre-	1.3 m^2 APS650 polysulfone membrane (Asahi Medical, Tokyo, Japan)	NR
Oudemans-van Straaten et al. [27]	Citrate dose was 3 mmol/L blood flow, serum ionCa^{2+} 0.9–1.0 mmol/L	Systemic nadroparin, bolus of 2850 IU/h; maintenance of 380 IU/h, BW >100 kg: 3800 IU at initial, followed by 456 IU/h	CVVH 220 mL/min	Post-	1.9 m^2 cellulose triacetate membrane (UF 205, Nipro, Osaka, Japan)	90 days
Hetzel et al. [24]	Citrate dose was 4 mmol/L blood flow, post-filter ionCa^{2+} 0.25–0.30 mmol/L	Systemic heparin, 42 mL/kg/h	CVVH blood/HF-solution flow 3:1	Pre-	1.4 m^2 AV600S high-flux membrane, Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany	30 days
Tiranathanagul et al. [18]	Citrate dose was 2.5 mmol/L blood flow, serum ionCa^{2+} 0.9–1.2 mmol/L	Systemic heparin, a bolus of 1000 IU and a continuous infusion of 500 IU/h to keep APTT value of 1.5×	CVVH 120 mL/min	Pre-	1.5 m^2 polyethersulfone dialyzers (PureFlux PF-150H, Nipro Europe, Zaventem, Belgium)	60 days
Schilder et al. [17]	Citrate dose was 3 mmol/L blood flow, serum ionCa2^{+} 1.0–1.35 mmol/L	Systemic heparin prescribed individually, APTT maintained at 50 s	CVVH 180 mL/min	Pre-	NR	90 days
Brain et al. [10]	Citrate dose was adjusted according to arterial ionCa^{2+}, serum ionCa^{2+} 1.0–1.35 mmol/L	Systemic heparin, bolus of 5000 IU, APTT maintained at 50 s	CVVHDF blood flow depended on BW	Pre-	AN69 ST100 filters and Prismaflex M100 and ST150	28 days
Stucker et al. [16]	Citrate dose was 3 mmol/L blood flow, post-filter ionCa^{2+} 0.25–0.30 mmol/L	Systemic heparin, the dose of heparin was prescribed individually	CVVHDF 100–200 mL/min	Pre-	1 .5 m^2 high-flux membrane (ST-150; Gambro)	90 days
Gattas et al. [15]	Citrate doses were 2.5-3.3 mmol/L blood flow, serum ionCa^{2+} 1.0–1.2 or 0.91–1.1 mmol/L	Reginal heparin (1000 or 1500 IU/h), protamine (15 or 10 mg/h), normal APTT	CVVH or CVVHDF 150 or 200 mL/min	Pre-	Aquarius (Baxter) or Prismaflex system (Gambro)	Discharge or death

APTT activated partial thromboplastin time, *BW* body weight, *CVVH* continuous venovenous hemofiltration, *CVVHDF* continuous veno-venous hemodiafiltration, *ionCa*$^{2+}$ ionized Ca^{2+}, *NR* not reported

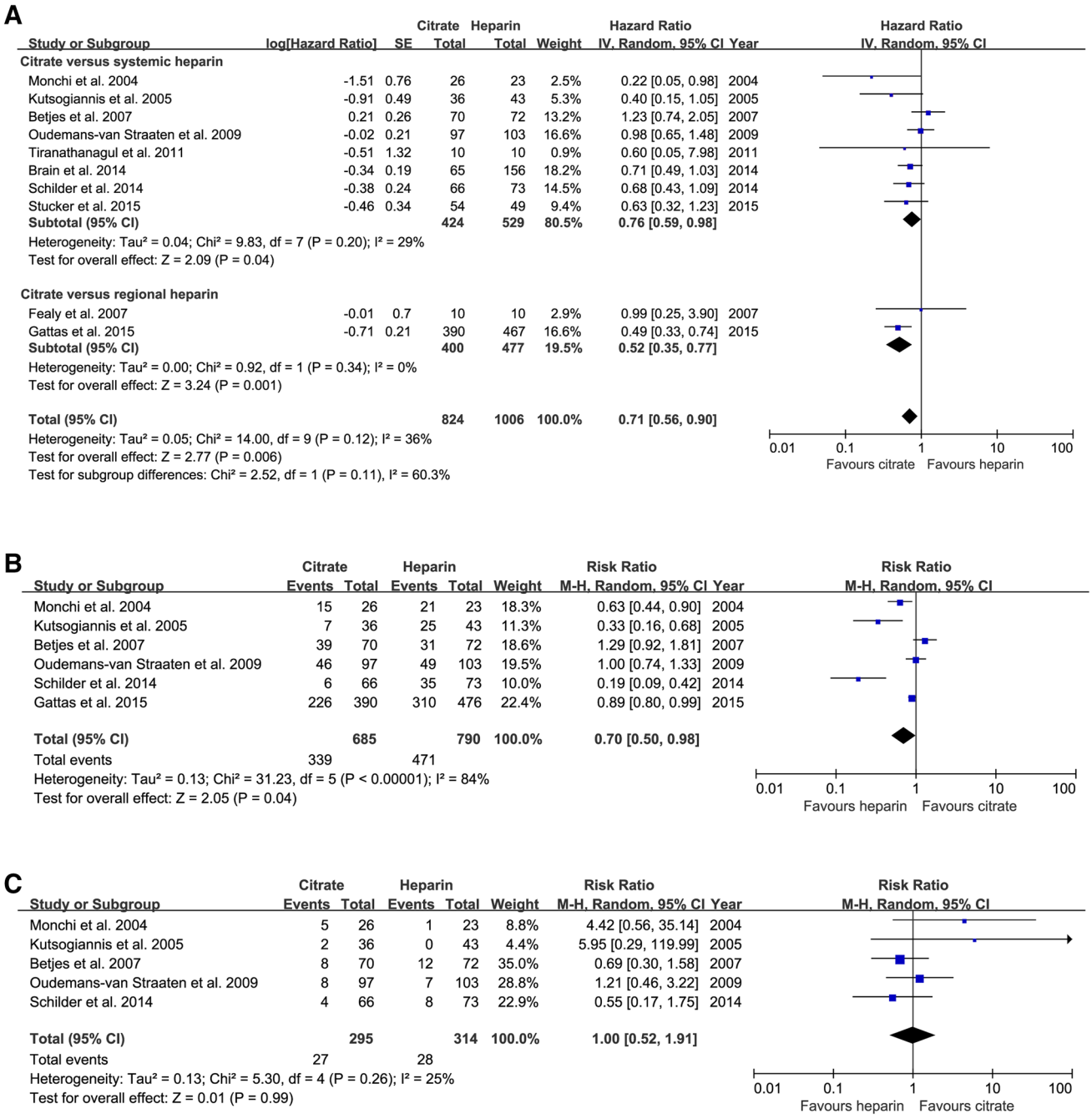

Fig. 2 Forest plot of comparisons: citrate versus heparin. Outcomes: **a** circuit loss, **b** filter failure, and **c** catheter dysfunction

Incidence of bleeding

All of the included trials evaluated the incidence of bleeding during the study period. In the nine trials that compared citrate to systemic heparin, 17 of the 378 citrate anticoagulation patients (4.5 %) developed a bleeding episode compared to 61 of the 382 systemic heparin anticoagulation patients (16.0 %) [8–10, 16–18, 24, 25, 27]. In this subgroup analysis, citrate anticoagulation reduced the bleeding risk by 64 % (RR 0.36, 95 % CI 0.21–0.60, $P < 0.001$, Fig. 3), and no significant inter-trial heterogeneity was observed among the trials ($I^2 = 0$ %, $P = 0.56$). In the two trials that compared citrate to regional heparin in a total of 232 patients, only one patient in the regional heparin group had one episode of bleeding during the study period [15, 26]. The

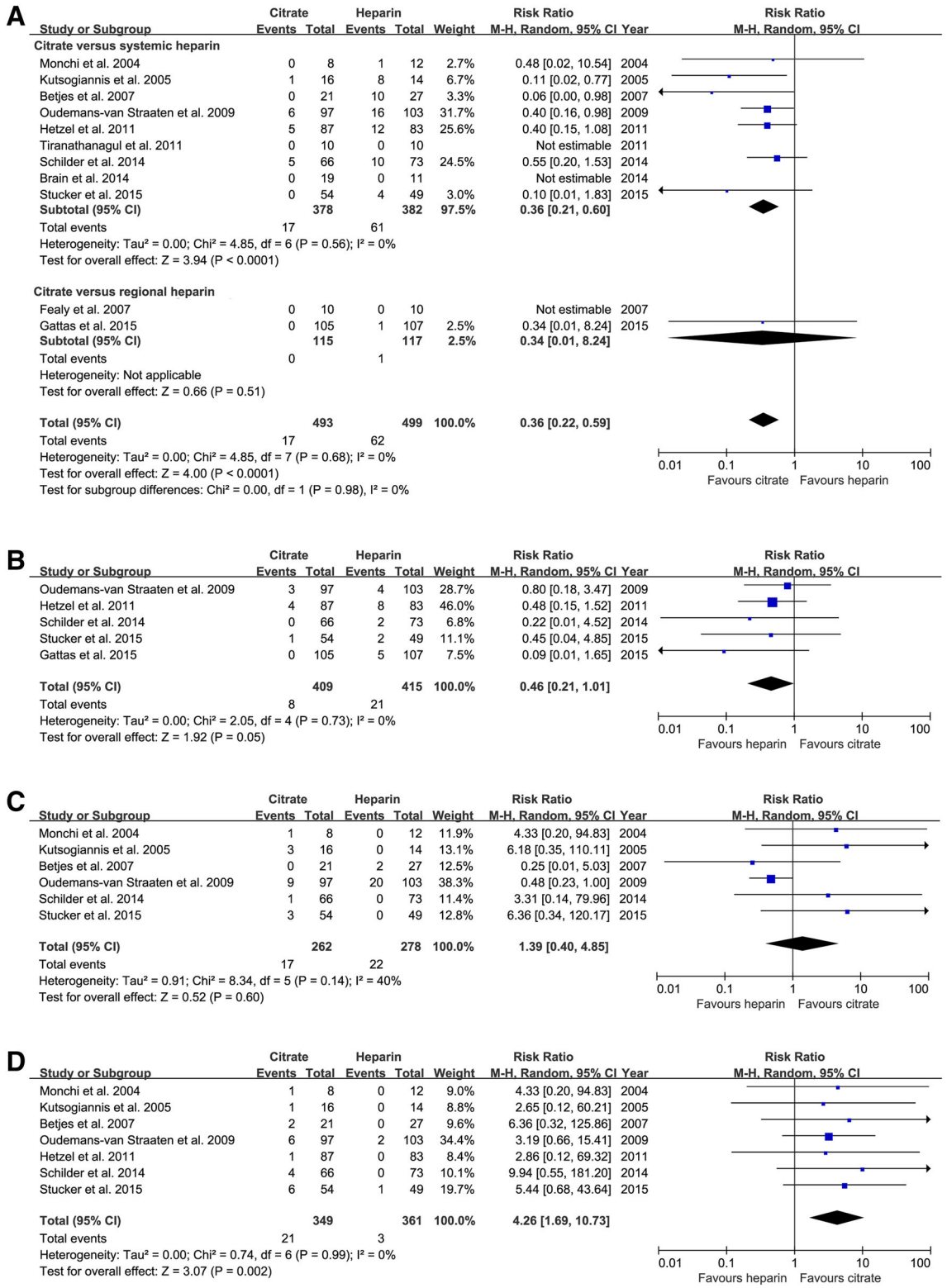

Fig. 3 Forest plot of comparisons: citrate versus heparin. Outcomes: **a** bleeding, **b** HIT, **c** metabolic alkalosis, and **d** hypocalcemia

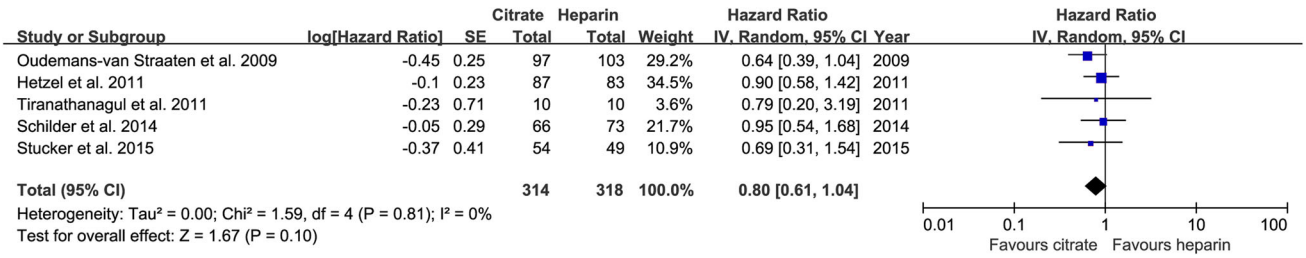

Fig. 4 Forest plot of comparisons: citrate versus heparin. Outcome: mortality

incidence of bleeding was not significantly different between patients who received citrate and regional heparin anticoagulation (RR 0.34, 95 % CI 0.01–8.24, $P = 0.51$, Fig. 3). Citrate anticoagulation reduced the bleeding risk by 64 % (RR 0.36, 95 % CI 0.22–0.59, $P < 0.001$, Fig. 3), with no inter-trial heterogeneity ($I^2 = 0$ %, $P = 0.68$). No heterogeneity was observed between the fixed-effect meta-analyses and the random-effect meta-analyses. No significant publication bias was identified by the funnel plot or Begg's test (supplementary Fig. 1, $P = 0.386$). The sensitivity analysis excluding the two crossover trials [8, 26] did not result in different overall conclusions (supplementary Table 2).

Heparin-induced thrombocytopenia

Data on HIT were available in five trials [15–17, 24, 27]. Citrate reduced the risk of HIT by 54 %, and this reduction was on the margin of statistical significance (RR 0.46, 95 % CI 0.21–1.01, $P = 0.05$) with no inter-trial heterogeneity ($I^2 = 0$ %, $P = 0.73$). No heterogeneity was observed between the fixed-effect meta-analysis and the random-effect meta-analysis.

Metabolic alkalosis

Data for the metabolic alkalosis endpoint were reported in six trials [8, 9, 16, 17, 25, 27]. The risk of metabolic alkalosis was not significantly different between the two interventions (RR 1.39, 95 % CI 0.40–4.85, $P = 0.60$), and the inter-trial heterogeneity was insignificant ($I^2 = 40$ %, $P = 0.14$). Similar results were observed in the fixed-effect meta-analyses. The sensitivity analysis excluding the crossover trial [8] did not result in different overall conclusions (supplementary Table 2).

Hypocalcemia

The number of patients with hypocalcemia during the study period was reported in seven trials [8, 9, 16, 17, 24, 25, 27]. Patients who underwent citrate anticoagulation had significantly higher risk of hypocalcemia (RR 4.26, 95 % CI 1.69–10.73) without significant inter-trial heterogeneity ($I^2 = 0$ %, $P = 0.99$). No hypocalcemia-related severe complications were observed in these trials. The results of the fixed-effect meta-analyses were consistent with those of the random-effect meta-analyses. The sensitivity analysis excluding the crossover trial [8] did not result in different overall conclusions (supplementary Table 2).

Mortality

Data on mortality were reported in seven trials [9, 15–18, 24, 27]. Of those trials, the ln(HR) and SE(ln(HR)) of patient mortality were available in five trials [16–18, 24, 27]. The ln(HR) and SE(ln(HR)) of the first month were calculated using the reported P value and the observed events in each arm for three trials [16, 17, 24] and using the survival curves for the remaining two trials [18, 27]. Mortality was not significantly different between citrate and heparin anticoagulation (HR 0.80, 95 % CI 0.61–1.04, $P = 0.10$, Fig. 4), and the inter-trial heterogeneity was insignificant ($I^2 = 0$ %, $P = 0.81$). No heterogeneity was observed between the fixed-effect meta-analysis and the random-effect meta-analysis.

Discussion

Our present meta-analysis with 11 RCTs demonstrated that regional citrate anticoagulation for CRRT was able to reduce the risk of circuit loss compared with heparin anticoagulation. Additionally, in the subgroup analyses, regional citrate anticoagulation was significantly superior in circuit loss risk to both regional and systemic heparin. Furthermore, patients undergoing citrate anticoagulation had lower incidences of filter failure, bleeding, and HIT. However, citrate anticoagulation was associated with an increased risk of hypocalcemia, although without hypocalcemia-related severe complications. The risk of catheter dysfunction, metabolic alkalosis, and death were not significantly different between the two

anticoagulation methods. Accordingly, the present meta-analysis suggests that regional citrate is most likely a better option than heparin for CRRT in critically ill patients.

The results of high-quality trials with approximately 2000 filters and 1000 patients were summarized in this meta-analysis. The sample size of this meta-analysis is three times larger than those of the previous meta-analyses by Zhang and Hongying [12] and Wu et al. [13]. Because of larger sample size the results of this meta-analysis are more reliable. Both of the two previously published meta-analyses employed mean difference to evaluate the pooled effect of citrate versus heparin on filter life-span and mortality [12, 13], which caused the information of censored participants to be lost. According to the PRISMA guideline for reporting systematic reviews and meta-analyses, HR is the most appropriate measure for pooling because both the number of deaths and the time to death are important when examining time-to-event outcomes [20, 21]. Therefore, we pooled the HRs of the circuit loss and mortality endpoints in this meta-analysis to present more reliable results. Owing to the enlarged sample size and appropriate analysis methods, almost all of the analyses were associated with low inter-trial heterogeneity. Additionally, no heterogeneity was observed between the fixed-effect meta-analyses and the random-effect meta-analyses. The subgroup analyses had consistent results for the circuit loss and bleeding endpoints. Additionally, the data were double-checked by two of our authors to prevent data error, and the reference lists of the identified articles and relevant journals were manually searched to decrease bias due to missing data. These advantages of the present meta-analysis guarantee the reliability of the findings presented here.

Citrate inhibits the clotting cascade at several levels by chelating Ca^{2+}. Studies have reported near total inhibition of coagulation when serum Ca^{2+} concentration is decreased to less than 0.33 or 0.25 mmol/L [28, 29]. The serum Ca^{2+} concentration can be easily targeted by careful adjustment of citrate dose according to Ca^{2+} concentration and blood flow. Therefore, if calcium replacement fluid is not tightly linked to calcium loss, citrate definitely has the potential to increase the incidence of hypocalcemia. However, no hypocalcemia-related severe complications were observed in the included trials. The anticoagulation effect of heparin is dependent on antithrombin, which is the most important endogenous inhibitor of thrombin and other coagulation factors [30]. However, the activation of coagulation and degradation by granulocyte-derived elastase in critically ill patients reduced the antithrombin concentration [31] resulting in heparin resistance. Furthermore, the occurrence of HIT also increased the filter clotting risk in heparin patients. All of these characteristics contributed to the reduction of circuit loss risk by more than a quarter in the citrate group compared to the heparin group.

It is regrettable that we could not obtain the HR of circuit loss risk from the study by Hetzel et al. [24]. The results of their study suggest that citrate was significantly superior to heparin in circuit life-span and were consistent with our pooled results of the remaining 10 trials. Therefore, the addition of the data from that study most likely would not have changed the conclusions reached.

Citrate also reduced the risk of filter failure. However, there was significant inter-trial heterogeneity without identified sources after careful sensitivity analyses, suggesting that unidentified factors caused the heterogeneity.

The reported bleeding incidences of heparin CRRT ranged from 10 to 50 %, with bleeding mortality rates as high as 15 % [32]. With careful adjustment of serum calcium concentration in the systemic circulation and preserved ability to metabolize citrate in the liver, muscle, and kidneys, the systemic coagulation system is minimally affected by the regional use of citrate [33]. The pooled results of this meta-analysis demonstrated that regional citrate anticoagulation for CRRT reduced bleeding risk by more than half compared with systemic heparin anticoagulation. Regional heparin was reported to have less influence on systemic coagulation function than systemic heparin [34, 35], and regional heparin anticoagulation had similar bleeding risk to regional citrate anticoagulation in our present meta-analysis.

Patients with liver failure and high bleeding risk were excluded in all of the included trials, which limited the application of the results to those subgroups. Several cohort studies proved that it was safe to use citrate in liver failure patients with careful monitoring of Ca^{2+} concentration and citrate accumulation [36–38]. The KDIGO guideline suggests to use regional citrate instead of regional heparin for patients with increased bleeding risk [11]. However, the strength of that recommendation and the quality of the evidence supporting it were of low grade. Further studies are needed to define an appropriate anticoagulation strategy for CRRT in patients with increased bleeding risk.

The present meta-analysis has several limitations. First, publication bias could not be completely avoided, even though comprehensive search strategies were used for the identification of eligible trials. There is a high risk of missing studies with negative results because they are less likely to be published. However, the additional searches of ICTRP and ClinicalTrial.gov did not identify any gray trials, and the funnel plot and Begg's test demonstrated high symmetry, which suggested a low risk of publication bias. Second, none of the included studies had high Jadad scores. The significant differences between the interventions did not allow for blinding, but most of the included trials adequately managed randomization and withdrawals. Therefore, the results of our meta-analysis are likely associated with a satisfactory evidence level. Third, the unavoidable variation in the inclusion criteria, endpoints definition, interventions,

CRRT technique, and data format among the included trials may have introduced bias into the pooled results. However, according to our clinical experience, we believe that the variations in these characteristics were acceptable for conducting this meta-analysis. Fourth, failure to identify the source of inter-trial heterogeneity of the filter failure endpoint after adequate sensitivity and subgroup analyses is another limitation of our present meta-analysis. Fifth, this meta-analysis did not adjust for competing risk, which may have yielded incomplete and potentially misleading conclusions [39]. Finally, the inclusion of crossover studies may have biased the results of this meta-analysis. However, the sensitivity analyses without the crossover studies did not result in different overall conclusions, which strengthens our findings.

Conclusions

Regional citrate anticoagulation for CRRT is more effective than systemic or regional heparin anticoagulation for decreasing the risk of circuit loss and filter failure and is safer than systemic heparin anticoagulation for the reduction of bleeding risk. Metabolic complications of citrate can be avoided by using an appropriate protocol and careful monitoring. Citrate-related hypocalcemia is rarely associated with severe complications and most likely can be reduced by further improvement of the citrate anticoagulation protocol. Therefore, citrate should be considered as the first choice for anticoagulation during CRRT in critically ill patients without increased bleeding risk or liver failure, and further studies are needed to evaluate the safety and efficacy of citrate for CRRT in these patient subgroups.

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Compliance with ethical standards

Conflicts of interest The authors have no potential conflicts of interest to disclose.

References

1. Fealy N, Baldwin I, Bellomo R (2002) The effect of circuit "down-time" on uraemic control during continuous veno-venous haemofiltration. Crit Care Resusc 4:266–270
2. Uchino S, Fealy N, Baldwin I, Morimatsu H, Bellomo R (2003) Continuous is not continuous: the incidence and impact of circuit "down-time" on uraemic control during continuous veno-venous haemofiltration. Intensive Care Med 29:575–578
3. Antonelli M, Bonten M, Chastre J, Citerio G, Conti G, Curtis JR, De Backer D, Hedenstierna G, Joannidis M, Macrae D, Mancebo J, Maggiore SM, Mebazaa A, Preiser JC, Rocco P, Timsit JF, Wernerman J, Zhang H (2012) Year in review in Intensive Care Medicine 2011. II. Cardiovascular, infections, pneumonia and sepsis, critical care organization and outcome, education, ultrasonography, metabolism and coagulation. Intensive Care Med 38:345–358
4. Carr JA, Silverman N (1999) The heparin-protamine interaction. A review. J Cardiovasc Surg (Torino) 40:659–666
5. Syed S, Reilly RF (2009) Heparin-induced thrombocytopenia: a renal perspective. Nat Rev Nephrol 5:501–511
6. Pinnick RV, Wiegmann TB, Diederich DA (1983) Regional citrate anticoagulation for hemodialysis in the patient at high risk for bleeding. N Engl J Med 308:258–261
7. Mehta RL, McDonald BR, Aguilar MM, Ward DM (1990) Regional citrate anticoagulation for continuous arteriovenous hemodialysis in critically ill patients. Kidney Int 38:976–981
8. Monchi M, Berghmans D, Ledoux D, Canivet JL, Dubois B, Damas P (2004) Citrate vs. heparin for anticoagulation in continuous venovenous hemofiltration: a prospective randomized study. Intensive Care Med 30:260–265
9. Kutsogiannis DJ, Gibney RT, Stollery D, Gao J (2005) Regional citrate versus systemic heparin anticoagulation for continuous renal replacement in critically ill patients. Kidney Int 67:2361–2367
10. Brain MJ, Roodenburg OS, Adams N, McCracken P, Hockings L, Musgrave S, Butt W, Scheinkestel C (2014) Randomised trial of software algorithm driven regional citrate anticoagulation versus heparin in continuous renal replacement therapy: the filter life in renal replacement therapy pilot trial. Crit Care Resusc 16:131–137
11. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group (2012) KDIGO clinical practice guideline for acute kidney injury. Kidney Inter 2:1–138
12. Zhang Z, Hongying N (2012) Efficacy and safety of regional citrate anticoagulation in critically ill patients undergoing continuous renal replacement therapy. Intensive Care Med 38:20–28
13. Wu MY, Hsu YH, Bai CH, Lin YF, Wu CH, Tam KW (2012) Regional citrate versus heparin anticoagulation for continuous renal replacement therapy: a meta-analysis of randomized controlled trials. Am J Kidney Dis 59:810–818
14. James M, Bouchard J, Ho J, Klarenbach S, LaFrance JP, Rigatto C, Wald R, Zappitelli M, Pannu N (2013) Canadian Society of Nephrology commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. Am J Kidney Dis 61:673–685
15. Gattas DJ, Rajbhandari D, Bradford C, Buhr H, Lo S, Bellomo R (2015) A randomized controlled trial of regional citrate versus regional heparin anticoagulation for continuous renal replacement therapy in critically ill adults. Crit Care Med 43:1622–1629

16. Stucker F, Ponte B, Tataw J, Martin P, Wozniak H, Pugin J, Saudan P (2015) Efficacy and safety of citrate-based anticoagulation compared to heparin in patients with acute kidney injury requiring continuous renal replacement therapy: a randomized controlled trial. Crit Care 19:9
17. Schilder L, Nurmohamed SA, Bosch FH, Purmer IM, den Boer SS, Kleppe CG, Vervloet MG, Beishuizen A, Girbes AR, Ter Wee PM, Groeneveld AB (2014) Citrate anticoagulation versus systemic heparinisation in continuous venovenous hemofiltration in critically ill patients with acute kidney injury: a multi-center randomized clinical trial. Crit Care 18:472
18. Tiranathanagul K, Jearnsujitwimol O, Susantitaphong P, Kijkriengkraikul N, Leelahavanichkul A, Srisawat N, Praditpornsilpa K, Eiam-Ong S (2011) Regional citrate anticoagulation reduces polymorphonuclear cell degranulation in critically ill patients treated with continuous venovenous hemofiltration. Ther Apher Dial 15:556–564
19. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ (1996) Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 17:1–12
20. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR (2007) Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 8:16
21. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 151:W65–W94
22. Parmar MK, Torri V, Stewart L (1998) Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 17:2815–2834
23. Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, Carpenter J, Rucker G, Harbord RM, Schmid CH, Tetzlaff J, Deeks JJ, Peters J, Macaskill P, Schwarzer G, Duval S, Altman DG, Moher D, Higgins JP (2011) Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 343:d4002
24. Hetzel GR, Schmitz M, Wissing H, Ries W, Schott G, Heering PJ, Isgro F, Kribben A, Himmele R, Grabensee B, Rump LC (2011) Regional citrate versus systemic heparin for anticoagulation in critically ill patients on continuous venovenous haemofiltration: a prospective randomized multicentre trial. Nephrol Dial Transplant 26:232–239
25. Betjes MG, van Oosterom D, van Agteren M, van de Wetering J (2007) Regional citrate versus heparin anticoagulation during venovenous hemofiltration in patients at low risk for bleeding: similar hemofilter survival but significantly less bleeding. J Nephrol 20:602–608
26. Fealy N, Baldwin I, Johnstone M, Egi M, Bellomo R (2007) A pilot randomized controlled crossover study comparing regional heparinization to regional citrate anticoagulation for continuous venovenous hemofiltration. Int J Artif Organs 30:301–307
27. Oudemans-van Straaten HM, Bosman RJ, Koopmans M, van der Voort PH, Wester JP, van der Spoel JI, Dijksman LM, Zandstra DF (2009) Citrate anticoagulation for continuous venovenous hemofiltration. Crit Care Med 37:545–552
28. Calatzis A, Toepfer M, Schramm W, Spannagl M, Schiffl H (2001) Citrate anticoagulation for extracorporeal circuits: effects on whole blood coagulation activation and clot formation. Nephron 89:233–236
29. James MF, Roche AM (2004) Dose-response relationship between plasma ionized calcium concentration and thrombelastography. J Cardiothorac Vasc Anesth 18:581–586
30. Hirsh J, Warkentin TE, Shaughnessy SG, Anand SS, Halperin JL, Raschke R, Granger C, Ohman EM, Dalen JE (2001) Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. Chest 119:64S–94S
31. Cohen JR, Sarfati I, Birnbaum E, Benacquista T, Wise L (1990) The inactivation of antithrombin III by serum elastase in patients with surgical infections. Am Surg 56:665–667
32. Martin PY, Chevrolet JC, Suter P, Favre H (1994) Anticoagulation in patients treated by continuous venovenous hemofiltration: a retrospective study. Am J Kidney Dis 24:806–812
33. Oudemans-van Straaten HM, Kellum JA, Bellomo R (2011) Clinical review: anticoagulation for continuous renal replacement therapy – heparin or citrate? Crit Care 15:202
34. Jaichenko J, Schustack A, Abraham D, Gotloib L (1987) Regional heparinization facilitates safe hemodialysis and/or hemofiltration in the critically ill patient. Am J Clin Pathol 87:556–557
35. Gordon LA, Perkins HA, Richards V (1956) Studies in regional heparinization. I. The use of simultaneous neutralization with protamine; preliminary studies. N Engl J Med 255:1025–1029
36. De Vico P, Messino V, Tartaglione A, Beccaris C, Buonomo C, Talarico D, Prati P, Sabato AF, Colella DF (2015) Safety and efficacy of citrate anti-coagulation continuous renal replacement therapies in post-cardiac surgery patients with liver dysfunction. Ther Apher Dial 19:272–278
37. Faybik P, Hetz H, Mitterer G, Krenn CG, Schiefer J, Funk GC, Bacher A (2011) Regional citrate anticoagulation in patients with liver failure supported by a molecular adsorbent recirculating system. Crit Care Med 39:273–279
38. Schultheiss C, Saugel B, Phillip V, Thies P, Noe S, Mayr U, Haller B, Einwachter H, Schmid RM, Huber W (2012) Continuous venovenous hemodialysis with regional citrate anticoagulation in patients with liver failure: a prospective observational study. Crit Care 16:R162
39. Beyersmann J, Gastmeier P, Schumacher M (2014) Incidence in ICU populations: how to measure and report it? Intensive Care Med 40:871–876