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Original Investigation

Citrate Versus Heparin Lock for Hemodialysis Catheters: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Background: Citrate solution has been suggested as an effective and safe catheter lock in hemodialysis. However, whether a citrate lock is superior to a heparin lock in preventing catheter-related infections and maintaining catheter patency is inconclusive.

Study Design: A systematic review and meta-analysis was performed by searching in PubMed, EMBASE, Ovid, the Cochrane Library, and Web of Science databases and major nephrology journals.

Setting & Population: Patients receiving hemodialysis with central venous catheters.

Selection Criteria for Studies: Randomized controlled trials comparing citrate locks with heparin locks in hemodialysis patients with central venous catheters.

Intervention: Locking central venous catheters with citrate locks.

Outcomes: Primary outcomes include catheter-related bloodstream infection (CRBSI), exit-site infection, catheter removal for poor flow, and thrombolytic treatment.

Results: 13 randomized controlled trials (1,770 patients, 221,064 catheter-days) met the inclusion criteria. Pooled analyses found that citrate locks could significantly reduce the incidence of CRBSI (risk ratio [RR], 0.39; 95% CI, 0.27-0.56; $P < 0.001$). Subgroup analysis showed that antimicrobial-containing citrate locks (citrate + gentamicin, citrate + taurolidine, and citrate + methylene blue + methylparaben + propylparaben) were superior to heparin locks in the prevention of CRBSI ($P < 0.001$, $P = 0.003$, and $P = 0.008$, respectively), whereas citrate alone failed to show a similar advantage ($P = 0.2$). Low- (1.04%-4%) to moderate-concentration (4.6%-7%) citrate locks were associated with decreased CRBSI incidence ($P < 0.001$ and $P = 0.003$, respectively), but patients receiving high-concentration (30%-46.7%) citrate and heparin locks had similar incidences ($P = 0.3$). The incidence of bleeding episodes (RR, 0.48; 95% CI, 0.30-0.76; $P = 0.002$) was significantly lower in patients receiving citrate locks, whereas both groups were similar in terms of exit-site infection ($P = 0.2$), catheter removal for poor flow ($P = 0.9$), thrombolytic treatment ($P = 0.8$), all-cause death ($P = 0.3$), catheter thrombosis ($P = 0.9$), mean catheter duration ($P = 0.2$), CRBSI-free catheter survival ($P = 0.2$), and catheter-related readmission ($P = 0.5$).

Limitations: All studies used in the meta-analysis were performed in Western countries. The applicability of our findings to other regions remains to be clarified.

Conclusions: An antimicrobial-containing citrate lock is better than a heparin lock in the prevention of catheter-related infection, while citrate alone fails to show a similar advantage. Citrate locks of low to moderate concentrations, rather than high concentration, were superior to heparin locks in preventing CRBSI. Citrate locks also might decrease bleeding episodes. No difference has been identified in the efficacy to prevent exit-site infection or preserve catheter patency between citrate and heparin locks.
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INDEX WORDS: Hemodialysis; lock solution; citrate; heparin; catheter-related bacteremia; antimicrobial solution; catheter lock; renal replacement therapy; exit-site infection; vascular access.

Central venous catheters (CVCs) are widely used in hemodialysis patients who have no permanent vascular access.[1] However, CVCs are prone to catheter malfunction and catheter-related infection (CRI), which includes catheter-related bloodstream infection (CRBSI) and exit-site infection. It is accepted practice to lock the CVC lumen with a heparin solution to prevent thrombosis and maintain catheter patency between dialysis sessions,[2] but heparin could increase the risk of systemic anticoagulation in case of inadvertent overfills of the lumen.[3]

Citrate is an anticoagulant that blocks the blood coagulation cascade by binding to calcium ions.

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If citrate leaves the catheter lumen, it would be metabolized rapidly into bicarbonates without causing systemic bleeding. The anticoagulation activity of citrate therefore is confined to the catheter, which potentially reduces the risk of bleeding episodes. Furthermore, citrate itself shows an antimicrobial effect,[4] and there is renewed interest in citrate lock solution for the prevention of CRIs.[5] At the same time, there have been concerns about citrate toxicity and arrhythmia in case of overfills, especially at high concentrations. A previous study found that 30% citrate solution was as effective as heparin in maintaining catheter patency by comparing premature catheter removals, and it was superior to heparin in preventing CRIs.[6] In contrast, citrate failed to show an advantage over heparin locks in 2 other randomized controlled trials (RCTs) in terms of CRI.[2,5] Results from studies comparing citrate with heparin locks remain inconclusive.

We performed a systematic review and meta-analysis to assess whether citrate locks are superior to heparin locks in the maintenance of catheter patency and the prevention of CRIs in patients receiving hemodialysis.

METHODS

Search Strategy

Two independent reviewers (Y.Z. and Z.L.) conducted a search in PubMed, EMBASE, Ovid, the Cochrane Library, Web of Science, and major nephrology journals. No language or date restrictions were imposed. We performed the last updated search on March 10, 2013. Search terms were as follows: "lock or filling solution" and "hemodialysis or dialysis or blood purification or renal replacement therapy." The exact search strategy used in the PubMed database is provided as an example in Item S1 (available as online supplementary material). Reference lists of identified articles were searched for relevant studies.

Study Selection and Data Abstraction

The inclusion criteria were as follows: (1) RCTs, (2) experimental arms receiving a citrate lock (with or without other antimicrobials) and control arms receiving a heparin lock alone, (3) reporting on CRI and/or catheter patency, and (4) sufficient data available to calculate a risk ratio (RR) or weighted mean difference with 95% confidence interval (95% CI). The following exclusion criteria were used: (1) studies focusing on lock solutions for dialysis vascular accesses other than CVCs, (2) studies dealing with the treatment of CRI and catheter malfunction rather than with prophylaxis, and (3) nonhuman studies. For studies with the same or overlapping data by the same authors, the most suitable studies with the largest number of cases or latest publication dates were selected.

Two investigators (Y.Z. and Z.L.) examined each study independently and recorded eligibility, quality, and outcomes, with disagreements resolved by discussion. We extracted the following study features: first author, publication year, country, intervention, mean age of patients, percentage of tunneled catheters, number of patients, number of catheter-days, intention-to-treat analysis, blinding, randomization method, and allocation concealment method. Missing data were requested from the authors.

Study Outcomes

The primary outcomes were: (1) CRBSI, defined as bacteremia without obvious sources other than the hemodialysis catheter; (2) exit-site infection, defined as the development of a purulent exudate or redness around the site not resulting from residual stitches; (3) catheter removal for poor flow; and (4) the need for thrombolytic treatments. Secondary outcomes included bleeding episodes, all-cause death, catheter thrombosis, CRBSI-free catheter survival, mean catheter duration, and catheter-related readmission. Incidence was presented as the number of episodes per catheter-day or per patient. Outcomes were extracted preferentially by intention to treat at the end of follow-up.

Quantitative Data Synthesis

For dichotomous variables such as CRBSI, rates of the experimental (citrate) and control (heparin) groups were expressed as RR and 95% CI. For the continuous variable (mean catheter duration), the pooled effects were expressed as weighted mean difference and 95% CI, which was calculated by multiplying the standard error to a coefficient $t_{0.05}$ associated with the degrees of freedom under t-distribution. Considering the inherited heterogeneity between these studies, we assumed the presence of statistical heterogeneity and used only a random-effects model (DerSimonian-Laird) before pooling the data. By using higher estimated variances and wider CIs, the random-effects model provided a more conservative estimate of an effect than a fixed-effects model. In the pooled-analysis, $P < 0.05$ was considered statistically significant.

We performed meta-regression analyses to assess the potential sources of heterogeneity. The small number of studies precluded the use of multivariable meta-regression. Selected characteristics were type of citrate lock solution, citrate concentration, blinding, and intention-to-treat analysis. A stratified analysis then was conducted according to results of metaregression analyses, as well as study characteristics considered to be clinically important.

For publication bias, Egger test was carried out for statistical assessment. Sensitivity analysis was conducted by sequentially deleting a single study each time in an attempt to identify the potential influence of the individual study. Data analysis was performed using Review Manager, version 5.0 (The Nordic Cochrane Centre, The Cochrane Collaboration), and Stata, version 10.0 (StataCorp LP).

RESULTS

Eligible Studies

The literature search yielded 347 potentially relevant records. By screening the abstracts, we removed 290 irrelevant studies. Then 57 articles were assessed further by full-text reading, of which 44 were excluded (Fig 1). Thus, 13 RCTs comparing citrate with heparin locks for hemodialysis CVCs were included in this systematic review and meta-analysis.[2,3,5-15]

The eligible studies were conducted from 1998 through 2012, with a total of 1,770 patients and 221,064 catheter-days involved. Five studies compared citrate alone with heparin locks, whereas 8 studies challenged mixtures of citrate and other antimicrobials (gentamicin, taurolidine, methylparaben, methylene blue, and propylparaben) against heparin locks. Studies were from North America, Europe, and Australia. Nine studies focused on tunneled catheters, and 2 studies, on nontunneled catheters, whereas