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ORIGINAL ARTICLE

Tissue plasminogen activator versus heparin for locking dialysis catheters: A systematic review

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ABSTRACT

Background and Objectives: Hemodialysis catheters are commonly used when renal replacement therapy is initiated. These catheters have significant complications. Among "locking" solutions used in an attempt to decrease these complications is recombinant tissue plasminogen activator (rt-PA). This systematic review is to determine the efficacy of rt-PA versus heparin, the standard of care. **Materials and Methods:** A systematic review of randomized controlled trials studying rt-PA alone or rt-PA plus heparin versus heparin alone as locking agents for hemodialysis catheters, which included patients needed a temporary hemodialysis catheter for hemodialysis. We identified relevant trials through electronic databases and correspondence with experts. Two investigators independently reviewed potentially eligible trials and extracted data. **Results:** Three trials met the inclusion criteria. One trial reported an improved catheter malfunctioning in patients using rt-PA plus heparin to lock catheters (20.0%) versus heparin alone (34.8%). Another trial reported higher blood flow rate in hemodialysis catheters in patients who received rt-PA (231.6 ± 12.4 mL/min) compared with those who received heparin (206.9 mL/min). The third trial reported formation and weight of clots which were decreased by half in rt-PA group versus heparin group. **Conclusions:** In the few randomized trials that met our inclusion criteria, the use of rt-PA as a locking solution for hemodialysis catheters seems to be associated with fewer adverse events and catheter malfunctioning as compared with heparin. Our systematic review is limited by the few randomized trials addressing our question and the wide variety of outcome measures. Further prospective randomized trials are needed to confirm this conclusion.

Key words: Anticoagulants, catheter, dialysis, hemodialysis, heparin, prophylaxis, tissue plasminogen activator

INTRODUCTION

Among patients with end-stage kidney disease in the United States who undergo hemodialysis for renal replacement and to continue filtering the blood, 82% started their hemodialysis with a catheter.[1] Of these catheters, 25%–50% fail within the first year of insertion.[2-4] Most of these failures are related directly to either thrombosis or infection.[5] Infection risks include local catheter site infection and systemic bacteremia, which both require prompt removal of the catheter and appropriate intravenous antibiotic therapy.[6,7] Thrombosis, on the other hand, accounts for 10%–42% of catheter malfunctioning depending on catheter site;[8] for which thrombolytic agents, such as recombinant tissue plasminogen activator (rt-PA), are effective.[9] Heparin is routinely used as a "locking" solution for preventing thrombosis-related catheter malfunction.[10] Other agents, such as warfarin,[11] sodium citrate,[12,13] and low-molecular weight heparin,[14] have been studied for the same purpose.

rt-PA was first used as a prophylaxis in oncology patients with central venous catheters.[15,16] In small, randomized clinical trials, this agent was also studied as a locking

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solution for hemodialysis catheters,[17] and more recently in large and powered trials.[18,19] These studies showed significantly better outcomes with rt-PA than comparator solutions. In this systematic review, we summarized data on effectiveness reported in all published randomized control trials comparing rt-PA versus heparin as locking agents for hemodialysis catheters.

MATERIALS AND METHODS

Eligibility criteria

Studies that enrolled patients with end-stage renal disease who needed dialysis, using a hemodialysis catheter and allocated them at random either to rt-PA alone or rt-PA plus heparin versus heparin, using them as locking solutions, were eligible for review. Studies using rt-PA plus heparin versus heparin were considered eligible. Studies were included regardless of the size or language of publication. Observational studies were excluded. Cointerventions with any other anticoagulant were excluded. Due to limited studies available, we accepted all outcome measures reported to widen the findings of our search.

Information sources and search methods

A comprehensive literature search of electronic databases (MEDLINEÔ, EMBASE, and the Cochrane Library) was conducted, irrespective of the date of publication using the appropriate terms and text words. Key words used to build-up the search strategy were "tissue plasminogen activator," "heparin," and "catheter." The authors determined trial eligibility and extracted descriptive, methodologic, and outcome data from each eligible randomized controlled trial.

Selection of studies

Two authors (Firwana and Hasan) independently identified trials for inclusion. Initially, titles and abstracts of the records retrieved by the search were assessed in order to exclude those that were irrelevant. For the remaining records, full-text articles were retrieved and assessed in order to select trials that meet the inclusion criteria.

Control of bias assessment

Methodological quality was defined as the control of bias assessed through the reported methods in each individual trial.[20] Two reviewers independently assessed trial quality by examining three components: generation of allocation sequence (classified as adequate if based on computer-generated random numbers, tables of random numbers, or similar), concealment of allocation (classified as adequate if based on central randomization, sealed envelopes, or similar), and blinding (classified as adequate if the trial was described as double blind or had blinded outcome assessment). Disagreements between the reviewers were resolved by arbitration by a third author (Ferwana).

Data collection and extraction

This study was performed in accordance with the recommendations set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[21] Two reviewers extracted data from identified trials (Firwana and Hasan). We extracted prespecified data elements from each trial, including study design, agent used for locking hemodialysis catheter, baseline characteristics, sample size, outcome measures, period of the study, and other study characteristics. The number of events in each trial was extracted on the basis of the intention-to-treat approach.

Statistical analysis and measures of treatment effect

Our purpose was to perform a meta-analysis to assess relative risks to measure the effectiveness and harmfulness measures for hemodialysis catheters prophylaxis with rt-PA, I^2 statistics for heterogeneity of treatment effects, and subgroup analyses to adjust for different variables. Due to limited number of available studies and data availability on one hand, and due to both heterogenous outcome measures and different types of data represented on the other hand, the applicability of conducting pooled analyses and forest plots in this review was limited. There was no one similar outcome in at least two trials to combine the results. In one study, dichotomous results were reported, another study reported continuous data, and the last study reported odds ratios (ORs) only without providing detailed results for both study arms. Corresponding authors were contacted, with no additional data provided. Available raw data are obtained; the OR with 95% confidence intervals (CIs) was calculated for dichotomous data, mean differences (MDs) with 95% CI were calculated for continuous data. Analyses were conducted using features on RevMan version 5.0 (The Nordic Cochrane Center, Copenhagen, Denmark). We therefore used this systematic review to summarize available data in included trials assessing the use of rt-PA versus heparin as locking agents in hemodialysis catheter.

RESULTS

Selection and description of enrolled studies

The original search identified 122 potentially eligible citations, of which only 3 randomized trials were identified[17,18,22] [Figure 1], with a total of 246 studied participants [Table 1]. The enrolled patients in two of the studies were adult patients, with a mean age of more than 60 years; the third study had a pediatric population. Two of these studies were performed in Europe, while the third randomized trial was performed in Canada. Both Gittins *et al.* and

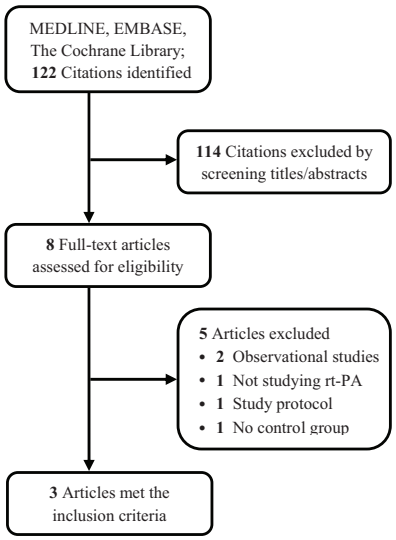

Figure 1: Flow chart of the systematic review

Schenk *et al.* compared rt-PA with heparin in a cross-over design, reporting the overall outcomes at the end of the two cross-over phases. Hemmelgarn *et al.* followed two treatment arms to the end the study period; one arm was getting rt-PA flushing once weekly plus heparin flushing twice weekly to lock catheters, where the other arm was receiving heparin alone thrice weekly.

In Hemmelgarn *et al.*, one outcome measure was hemodialysis catheter malfunction, which was defined as the first occurrence of any one of the following: inability to initiate dialysis owing to inadequate blood flow, mean blood flow of 250 mL/min or less during two consecutive dialysis treatments, or peak blood flow of 200 mL/min or less for 30 minutes during a dialysis treatment; and another outcome measure was catheter-related bacteremia. In Schenk *et al.*, outcome measures were mean blood flow rate, mean venous pressure, and arterial pressure. Gittins *et al.* reported on the weight of blood clot aspirated from the line at the start of the next dialysis session. The follow-up time assigned to complete each study, including both crossed arms, ranged from 10 weeks to 8 months [Table 1].

Risk of bias within studies

Regarding the methodological quality of these three studies, Hemmelgarn *et al.* described a well-conducted methodology, clear randomization, and blinding; the other two studies mentioned their studies to be randomized, but the methods for randomization or concealment were not specified. There was no early termination in either study due to study protocol. Funding sources were clear in two of the three studies [Table 1].

None of trials included reported on mortality or quality of life; this could be associated with the relatively short duration

Table 1: Description and quality assessment of included studies

Study ID	Year	Study location	Study design	No. of institutions	No. of subjects	Age (mean)	Primary outcomes	Type of data	Follow-up time (months)	Sequence generation	Allocation concealment	Blinding	Early termination	Selective outcome reporting	Funding
Hemmelgarn[18]	2011	Canada	RCT	11	225	63.24	Catheter malfunction	No. of events	6.0	Low risk	Low risk	Low Risk	Low Risk	High Risk	Not profit
Gittins[22]	2007	UK	RCT with cross-over	1	9	Children	Clot weight	Odds ratio	2.5	Low risk	Unclear	Low Risk	Low Risk	High Risk	Not profit
Schenk[17]	2000	Austria	RCT with cross-over	1	12	63.25	Flow,VP,AP	Mean ± SD	8.0	Low risk	Unclear	Unclear	Low Risk	High Risk	Unclear

RCT, randomized controlled trial;VP, venous pressure;AP, arterial pressure.

Table 2: Primary outcomes in Hemmelgarn *et al.*

	rt-PA (*n* = 110)	Heparin (*n* = 115)	Odds ratio	95% CI
Catheter malfunction	22 (20.0%)	40 (34.8%)	0.47	0.26 – 0.86
Catheter-related bacteremia	5 (4.5%)	15 (13.0%)	0.32	0.11 – 0.91

Table 3: Primary outcomes in Schenk *et al.*

	rt-PA (*n* = 10)	Heparin (*n* = 10)	Mean difference	95% CI
Blood flow rate (mL/min)	231.6 ± 12.4	206.9 ± 14.2	25.60	14.93 – 36.27
Venous pressure (mmHg)	140 ± 15.2	159.2 ± 20.7	-19.20	-33.73 – -4.67
Arterial pressure (mmHg)	–115.9 ± 12.7	–134.7 ± 25.8	18.80	2.53 – 35.07

Catheters and ports dysfunction is defined as failure to attain and maintain an extracorporeal blood flow of 300 mL/min or greater at a prepump arterial pressure more negative than –250 mm Hg; the exception is pediatric or smaller adult catheters that are not designed to have flows in excess of 300 mL/min.[23]

Table 4: Primary outcomes in Gittins *et al.*

	Odds ratio	95% CI
Clot formation*	0.42	0.25 – 0.71
Aspirate clot weight*	0.53	0.42 – 0.67

*Detailed numbers for both trial arms were not provided by authors; only odds ratios with 95% CI were available.

of follow-up. These outcomes are long-term outcomes, and the maximum period of follow-up among included trials was 8 months.

Tissue plasminogen activator effects

Catheter malfunction and blood flow rate

Both Schenk *et al.* and Hemmelgarn *et al.* reported on blood flow. Hemmelgarn *et al.* used blood flow rates as a criterion to detect their primary outcome, catheter malfunctioning (see above); where Schenk *et al.* reported the mean flow rates in both groups. In Hemmelgarn *et al.*, only 22/110 (20.0%) patients of the rt-PA group developed catheter malfunction, whereas that number was 40/115 (34.8%) in the heparin group; a reduction of risk by 47% (95% CI [26%–86%]) [Table 2].

Schenk *et al.* reported on mean blood flow rates and related venous and arterial pressures after using rt-PA and heparin for locking hemodialysis access.[17] The rate of blood flow in the rt-PA group was 231.6 ± 12.4 mL/min, whereas the rate of blood flow was 206.9 ± 14.2 mL/min, giving significantly higher rates of blood flow using rt-PA than using heparin as a locking agent, with a MD of 25.60 (95% CI 14.93–36.27). By the same measures, rt-PA-locked dialysis catheters causes significantly lower both venous pressure and arterial pressure (140 ± 15.2 mmHg and 115.9 ± 12.7 mmHg, respectively) when compared with heparin-locked catheters (159.2 ± 20.7 mmHg and 134.7 ± 25.8 mmHg); (MD= -19.20; 95% CI -33.73 to -4.67 and MD = 18.80; 95% CI 2.53 to 35.07, for venous and arterial blood flow, respectively) [Table 3]. Although mean blood flow rate was significantly better among patients on rt-PA than on heparin, worth noting that both of these blood flow rates are considered inadequate by standards for adult patients with end-stage kidney disease.[23]

Catheter-related infection

Only Hemmelgarn *et al.* reported on hemodialysis catheter-related bacteremia. Results showed that bacteremia had developed in 5/110 (4.5%) cases in the rt-PA group versus 15/115 (13.0%) cases in the heparin group, decreasing the risk of catheter-related bacteremia by 32% (95% CI [11%–91%]) [Table 2]. Schenk *et al.* reported on patients who developed local infection at catheter site, which was only one patient while he was on heparin; none of the patients developed either local infection of bacteremia while treated with rt-PA.

Clot weight and clot formation

Both Gittins *et al.* and Schenk *et al.* reported on clot formation, where only Gittins *et al.* looked at weight of aspirated clot in addition.[22] In Gittins *et al.*, available numbers show that children who received rt-PA in their dialysis catheters formed 42% fewer clots than children who received heparin; in addition, the weight of formed clots (rt-PA: 15 mg, heparin: 31 mg) was 16 mg (53%) lighter in the rt-PA group compared with the heparin group. We could not retrieve raw number of events to calculate significance [Table 4].

Schenk *et al.* reported that none of the patients had clots while on the rt-PA group, where clotting occurred in 20% of the patients in the heparin period. In patients with clotting formation, fibrinolysis with intracatheter 2 mg of rt-PA was necessary and was only needed in the heparin group.

DISCUSSION

Although all available data showed superiority for rt-PA over heparin, the overall results are not convincing; due to the small number of conducted randomized trials studying rt-PA versus heparin as locking solutions for dialysis catheters, the small number of participants in some of the conducted

studies, and the limited sources of homogenous data and point estimates among studies, we could not perform a meta-analysis combining homogenous data together to get pooled results to predict effectiveness. Given these limitations, we reported primary outcomes from each individual study, and reanalyzed them separately, to obtain an estimate of rt-PA effectiveness.

The use of heparin as a locking solution has been the standard of care in this era due to its efficacy, reasonable side effect profile, and cost-effectiveness.[24,25] In studies that used large central venous catheters for dialysis, heparin was shown to be superior to normal saline when used as a flush in dialysis catheters, keeping them more patent, decreasing the need of rt-PA to lyse formed clots within catheters, and improving catheter survival.[25-29] Conversely, some other studies showed that heparin flushed not to be different from normal saline; not to increase the duration of catheter use or to improve its functionality and may prolong aPTT significantly;[29,30] worth noting that these studies used smaller catheters either in peripheral intravenous catheters in children or as arterial catheters.

Clearly, in all enrolled studies, rt-PA was superior to heparin in all reported outcomes. The use of rt-PA reduced rates of developing malfunctioning in catheters locked with it; reduced rates of catheter-related bacteremia; provided good blood flow through catheters; and warrantees a better management for both venous and arterial pressures. Its use is also accompanied with less clot formation and less weight of these clots.[22]

The increased cost of using rt-PA could be one of the limitations in this largely Medicare population. Using rt-PA either every time or even once a week in a three-day week dialysis, rt-PA has been shown to be at least eight to nine times more expensive than using heparin three times a week.[17,18] However, as suggested by Hemmelgarn *et al.*, rt-PA may turn out to be cost-effective due to significantly decreased catheter malfunction and catheter-related bacteremia, fewer episodes of hospitalizations, and less serious adverse events without an increased incidence of major bleeding.

CONCLUSION

This systematic review shows that using rt-PA as a locking solution for hemodialysis catheters significantly reduces catheter-related bacteremia and catheter malfunctioning, improves venous and arterial blood flows, and is associated with less clot formation as compared with heparin; although the evidence is not convincing. Cost-effectiveness may be an issue for locking hemodialysis catheters with rt-PA. A need for adequately powered and long-term conducted randomized clinical trials to support or change the current results and knowledge of the effects of rt-PA for locking hemodialysis catheters still exists.

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