

Substitution of Citrate with Tissue Plasminogen Activator (rt-PA) for Catheter Lock Does Not Improve Patency of Tunneled Hemodialysis Catheters in a Randomized Trial

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Abstract

Background: The study aim was to establish if substitution of citrate with rt-PA for catheter lock once weekly can reduce the incidence of catheter-related blood stream infections (CR-BSI) or improve patency of tunneled hemodialysis catheters.

Methods: All incident patients undergoing insertion of a tunneled hemodialysis catheter were screened and included except those suffering infection or using oral anticoagulation. Study participants were randomized into two arms according to the solution applied as catheter lock: receiving either trisodium citrate (Citra-Lock™ 4%) only or rt-PA (Actilyse® 1mg/ml) on the middle session each week with citrate used on the first and third sessions. The incidence of CR-BSI (confirmed by positive blood culture), catheter non-function (complete obstruction), and malfunction (blood flow <250ml/min) was recorded. Statistical significance was tested with ANOVA, post hoc analysis was performed by means of multiple linear regression.

Results: Totally, 18 patients were included and followed during 655 hemodialysis sessions. No episode of CR-BSI was detected while 6 catheter non-functions (0.9% sessions) and 101 malfunctions (15.4% sessions) were recorded. The incidence of both events was equal between the study arms: 4 non-functions and 55 malfunctions in the rt-PA arm and 2 non-functions and 46 malfunctions in the citrate arm ($p=0.47$ and $p=0.24$, respectively). Additionally, the mean blood flow achieved did not differ significantly between the arms: $326\pm 1,8$ and $326\pm 1,9$ ml/min ($p=0.95$) in rt-PA and citrate arms, respectively. Post hoc analysis identified time elapsed since previous session ($\beta=0.12$, $p=0.005$) and malfunction on previous session ($\beta=0.25$, $p<0.001$) as significant factors affecting the occurrence of malfunction. By contrast, the study arm, rt-PA application on previous session, and catheter vintage did not enter the model.

Conclusion: Substitution of citrate with rt-PA for catheter lock does not reduce the incidence of catheter malfunction neither does it affect the blood flow achieved during hemodialysis. Catheter patency is related rather to the time interval between sessions and to previous malfunction (thus probably reflecting undefined individual factors). The incidence of CR-BSI within pre-selected hemodialysis population is sporadic (less than 1 per 4.3 patient years in our sample).

Trial registration: The study was registered on the ACTRN 12612000152820

Background

A number of guidelines and initiatives strongly recommend native arterio-venous fistulas (AVF) and discourage the use of catheters for chronic dialysis treatment [1-3]. This fistula first policy is based on evidence from large observational studies showing that the use of AVF is associated with the lowest (and catheters with the highest) risk of death from infection and cardiovascular disease [4-5]. However, in the contrast with this recommendation, the proportion of hemodialysis (HD) patients treated with central venous catheters (CVC) is increasing [6-7]. It is related to the aging of HD population and its

polymorbidity. The quality of vascular system is poor, the creation of AVF is difficult and the maturation is not successful enough. Up to 60% of AVFs fail immediately after surgery or fail to mature [8-9]. Noordzij et al. found that female patients and those > 80 years were least likely to start HD with an AVF according European renal registries between 2005 and 2009 [6].

An alternative to AVF for chronic HD treatment is tunneled CVC (tCVC). It can serve as a temporary access till the maturation of AVF or it is a definitive access for patients without the possibility for native one. The care for patients with tCVC means in particular prevention of exit site infection and catheter related blood stream infection (CRBSI) and care for catheter's patency. In addition, to common rules of asepsis, catheter locking solutions are used. These are solutions of various chemical composition that are instilled after termination of every HD procedure to tCVC of a volume precisely declared on the catheter. Evidence to guide catheter locking solutions is limited. In recent years, there has been a shift from the use of heparin to citrate solutions [10].

In 2011, Hemmelgarn with colleagues demonstrated a beneficial effect of once weekly used recombinant tissue plasminogen activator (rt-PA) on reducing the incidence of tCVC malfunctions and bacteremia [11]. At that time, rt-PA was compared with heparin locks. Later the same authors found a significant reduction in rate of rt-PA use for treatment of catheter malfunction using once weekly rt-PA as a locking solution, compared with thrice weekly heparin and citrate only [12]. Unlike the first study, there was no evidence of a significant effect on the occurrence of bacteremia (in the risk incident and prevalent HD patients). A certain limitation of the rt-PA lock is its higher cost (the difference of CAD\$962 per enrollment in the last mentioned study). We have decided to realize a prospective study to assess the effectiveness of rt-PA once per week as a locking solution, as compared with 4% citrate only, commonly used in our HD Center, for prevention of CRBSI and catheter dysfunction in our local condition.

Methods

The study was randomized, prospective and double blinded. All incident patients undergoing insertion of tCVC in the Hemodialysis Center at Charles University Teaching Hospital in Plzen were screened and included except those with exclusion criteria: anticoagulation treatment, INR more than 1.4, platelet less than $60 \times 10^9/l$, clinical symptoms of infection, known malignancy, catheter insertion in vena cava inferior region (femoral vein), bleeding complication in the prior 4 weeks before catheter insertion, major surgery in past 48 hours or scheduled for major surgery during next 6 months, active pericarditis and known allergy or intolerance to alteplase or trisodium citrate and pregnancy or breast - feeding. Study participants were randomized by block method into two arms (1:1, 4 patients in one block) according to the solution applied as catheter lock: 1. receiving either trisodium citrate (Citra-LockTM 4%) only or 2. rt-PA (Actilyse[®] 1 mg/ml, volume adjusted with saline to match the lumen) on the middle session each week with citrate used on the first and third sessions. The locks were prepared by an independent pharmacist, so both participants and medical staff were unaware of their compositions until the study end. Sample size calculation: The number of patients was calculated in relation to the primary endpoint of the study, which is the incidence of CRBSI at the end of the 6th month after the insertion of the

permcath. The basic hypothesis of the study is the assumption that rt-PA will lead to a reduction in the risk of CRBSI compared to sodium citrate. In the sodium citrate group, the incidence of CRBSI is assumed to be 15%. 65 (power = 0.80; alpha = 0.05) patients are needed to detect a reduction in incidence to 5% or less. Due to the assumption of patient losses from follow-up, the plan is to include 80 patients. Preliminary analysis of the results with a change of protocol was not planned.

The primary outcome was the incidence of CRBSI. The definition of definite CRBSI was 1. positive blood culture from catheter and peripheral blood and positive culture from discharge or aspirate from exit site or tunnel with identical organism or 2. positive blood culture and positive culture of catheter segment with identical organism or 3. positive blood culture and septic thrombophlebitis or 4. positive blood culture from peripheral blood and catheter (with the identical organism) that meet the criteria for differential time to positivity (DTP) = the positivity of catheter blood culture comes at least 2 hours earlier compared to peripheral blood. The definition of probable CRBSI was 1. two or more positive blood cultures (peripheral blood and catheter) with no evidence for source other than catheter or 2. single positive blood culture (peripheral blood or catheter) for G + coccus with no evidence for source other than catheter or 3. strong clinical suspicion of bacterial infection with the source in catheter (symptoms manifesting during dialysis procedure) with the necessary exclusion of other sources (urogenital and respiratory tracts) or 4. positive blood culture from peripheral blood and catheter (with the identical organism) that don't meet the criteria of DTP for definite CRBSI.

The secondary outcome was the incidence of catheter malfunction/obstruction that was defined as 1. maximal blood flow (BF) 250 ml/min and less for 30 min and more during one dialysis procedure (max arterial and venous pressure limits of - 250 mmHg and + 250 mmHg respectively) or 2. mean BF 250 ml/min and less during two consecutive dialysis procedures (max arterial and venous pressure limits of - 250 mmHg and + 250 mmHg respectively) or 3. reversal of catheter lines as a solution to start the dialysis with BF at least 200 ml/min (max arterial and venous pressure limits of - 250 mmHg and + 250 mmHg respectively) or 4. inability to initiate dialysis because of obstruction of catheter for at least 200 ml/min even after the reversal of catheter lines (max arterial and venous pressure limits of - 250 mmHg and + 250 mmHg respectively). Treatment-related adverse effects (bleeding, hypersensitivity) was recorded. The blood flow achieved (and sustained) during dialysis session was logged. Malfunctions were treated by application of Actilyse® 1 mg into one or both lumens according to study protocol.

The results are presented as arithmetical means (standard errors of the mean). Statistical significance was tested with ANOVA, post hoc analysis was performed by means of multiple linear regression. All calculations were performed using Statistica 8.0 (Stat Soft, Inc.) The study was registered at ANZCTR (ACTRN12612000152820) on the 3rd of February 2012 and approved by the local Ethics Committee at Charles University Teaching Hospital in Plzen. All participants were above 18 years of age and have signed an informed consent.

Results

Finally, 18 patients (mean age of 67 ± 15.1 years, 50% males), were included and followed during 655 hemodialysis sessions between March 2012 and December 2016. The main reason for retreat from the intended numbers was an unexpected absence of CRBSI episodes and a high proportion of patients meeting the exclusion criteria. While it made any analysis of the primary endpoint unfeasible (even in extended recruitment period), evaluation of the secondary endpoint was possible. No episode of CRBSI was detected making the incidence less than 1 in 4.3 patient years. However, it should be admitted that these figures may be underestimating the real occurrence due to selection bias. At the same time, 6 catheter non-functions (0.9% sessions) and 101 malfunctions (15.4% sessions) were recorded and no significant difference was found comparing the group with citrate and rt-PA (Fig. 1). The incidence of both events was equal between the study arms: 4 non-functions and 55 malfunctions in the rt-PA arm and 2 non-functions and 46 malfunctions in the citrate arm ($p = 0.47$ and $p = 0.24$, respectively). Additionally, the mean blood flow achieved did not differ significantly between the arms: $326 \pm 1,8$ and $326 \pm 1,9$ ml/min ($p = 0.95$) in rt-PA and citrate arms, respectively. Post hoc analysis identified time elapsed since previous session ($\beta = 0.12$, $p = 0.005$) and malfunction on previous session ($\beta = 0.25$, $p < 0.001$) as significant factors affecting the occurrence of malfunction (Table 1). Thus, administration of the rt-PA after the middle HD procedure did not affect the incidence of malfunction or tCVC afuction in our patients and did not affect the treated blood volume or blood flow during HD (Fig. 2, 3).

Discussion

Most valid recommendations prefer the native AVF as a vascular access for chronic dialysis treatment [1-3]. However, the number of patients with tCVC is high and, depending on the source, accounts for up to 80% of patients initiating HD treatment [13-15]. The main complications associated with the use of tCVC are infections and thrombotic occlusions [16]. The problem of patency reduces the effectiveness/adequacy of dialysis, and both of these complications increase the morbidity and mortality of dialyzed patients [17]. The frequency of the bacteremia is reported with rates of 2.7 per 1000 catheter days in the first month of catheter use and 0.4 per 1000 catheter days for > 12 months [18]. The target should be the rate lower than 1 episode of CRBSI per 1000 catheter days [19]. In our study, all patients were newly enrolled in the HD program, and the bacteremia rate of less than 0.64 per 1000 catheter days is therefore quite satisfactory, although it is burdened with no primary endpoint. However, in the context of the results of other studies, tCVCs may be considered relatively safe [11-12]. On the one hand, this is in contradiction with general recommendations (try to avoid tCVC rather). On the other hand, it has already been mentioned that for some certain type of dialysis population tCVC is a better alternative [20-21]. These include, in particular, patients of advanced age with severe sclerotic lesion, often with relatively short life perspectives or even considering palliative nephrology care. Under these circumstances, it is certainly not appropriate to set AVF in advance for many months, but it is better to wait for further course. If necessary, for initiating HD treatment, tCVC is the best and often lasting solution. We think our results with low incidence of CRBSI further supports this approach.

An important part of tCVC care is an aseptic approach in general and local exit site care. The aim of catheter locks is to ensure the patency of tCVC at the time between HD and, as far as possible, to reduce

possible infectious complications. In the context of these requirements, the composition of the locks has evolved over time. In the past, heparin was the most commonly used; in recent years, it has been seen to shift most often to citrate [10]. Higher citrate concentration (30%, 46.7%) were withdrawn by FDA for possible association with serious adverse effects, and citrate locks with the most commonly 4% concentration are currently used [22–23]. They appear to be safe and relatively inexpensive and have some antimicrobial activity [23–24]. For this reason, they are also the most recommended [25]. In the case of acute obstruction of tCVC, it is recommended to use fibrinolytic agent, e.g. rt-PA [3]. Thus, the question is whether regular fibrinolytic administration would further affect the malfunction of tCVC or the frequency of CRBSI. Because the major drawback of rt-PA is its high cost, it is usually used once a week. When compared to heparin locks, the beneficial effect of rt-PA administration was already shown [11]. In our study, we decided to verify the effect of rt-PA compared to citrate locks. However, during the 655 HD procedures in 18 patients, a significant difference was not found. The occurrence of malfunctions and afunctions was the same in both study arms. Using the linear regression, we found the length of interdialytic interval was the most important factor. The longer the interdialytic interval, the higher the risk of tCVC obstruction. And at the same time - if obstruction occurs once, the risk of every other obstruction is significantly higher.

A promising group for some time were locks containing antibiotic, but these are not yet generally recommended [26]. The main concern and problem are the risk of resistance. A certain alternative seems to be the lock that contains taurolidine. Taurolidine is an antimicrobial chemotherapeutic agent that acts through a chemical reaction with the microbial structure of the cell wall. It has an extremely wide microbial spectrum including methicillin- and vancomycin- resistant bacteria and unlike conventional antibiotics, the resistance has not yet been described [27]. However, the position of taurolidine on the field of catheter locks has to be verified by more prospective and randomized trials.

The weakness of our study is the fact that we have failed to include the required number of patients. We were confronted with strict exclusion criteria that eliminated most incident patients with tCVC. The second point was very low occurrence of primary outcome. On the other hand, we can say that the occurrence of CRBSI is low and tCVC is therefore relatively safe. They appear to be a good alternative to vascular access in patients, particularly with uncertain prognosis and exhausted own vascular system. This is in contradiction with common recommendations, but data from recent clinical practice tends to support this opinion.

Conclusion

Regular administration of rt-PA once a week does not affect the occurrence of obstruction / malfunction of tCVC compared to citrate locks only. With the low incidence of CRBSI in our study in general, we cannot say more about the impact on infectious complication. For us, tCVC appears to be relatively safe in recent years, and should be considered especially in the elderly population or patients with poor and uncertain prognosis, often in association with the devastated native vascular system. Until the results of larger

studies with catheter locks especially with taurolidine are available, there is a valid recommendation on the use of citrate locks.

Abbreviations

rt-PA – recombinant tissue plasminogen activator

CR-BSI – catheter related blood stream infection

HD - hemodialysis

AVF – arteriovenous fistula

CVC – central venous catheter

tCVC – tunneled central venous catheter

DTP – differential time to positivity

BF – blood flow

Declarations

Ethics approval and consent to participate is included in the text.

Consent for publication - „not applicable“.

The datasets during and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests - the authors declare that they have no competing interests

Funding – included in the text.

Authors' contributions -

PR - study protocol, registration, results and statistical analysis, manuscript preparation

JM - statistical analysis and results interpretation

LK – patients recruitment and randomization

JK – patients recruitment and randomization

JE – patients recruitment, consultant

TR – study design, consultant

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Table

Due to technical limitations, table 1 PDF is only available as a download in the Supplemental Files section.

Figures

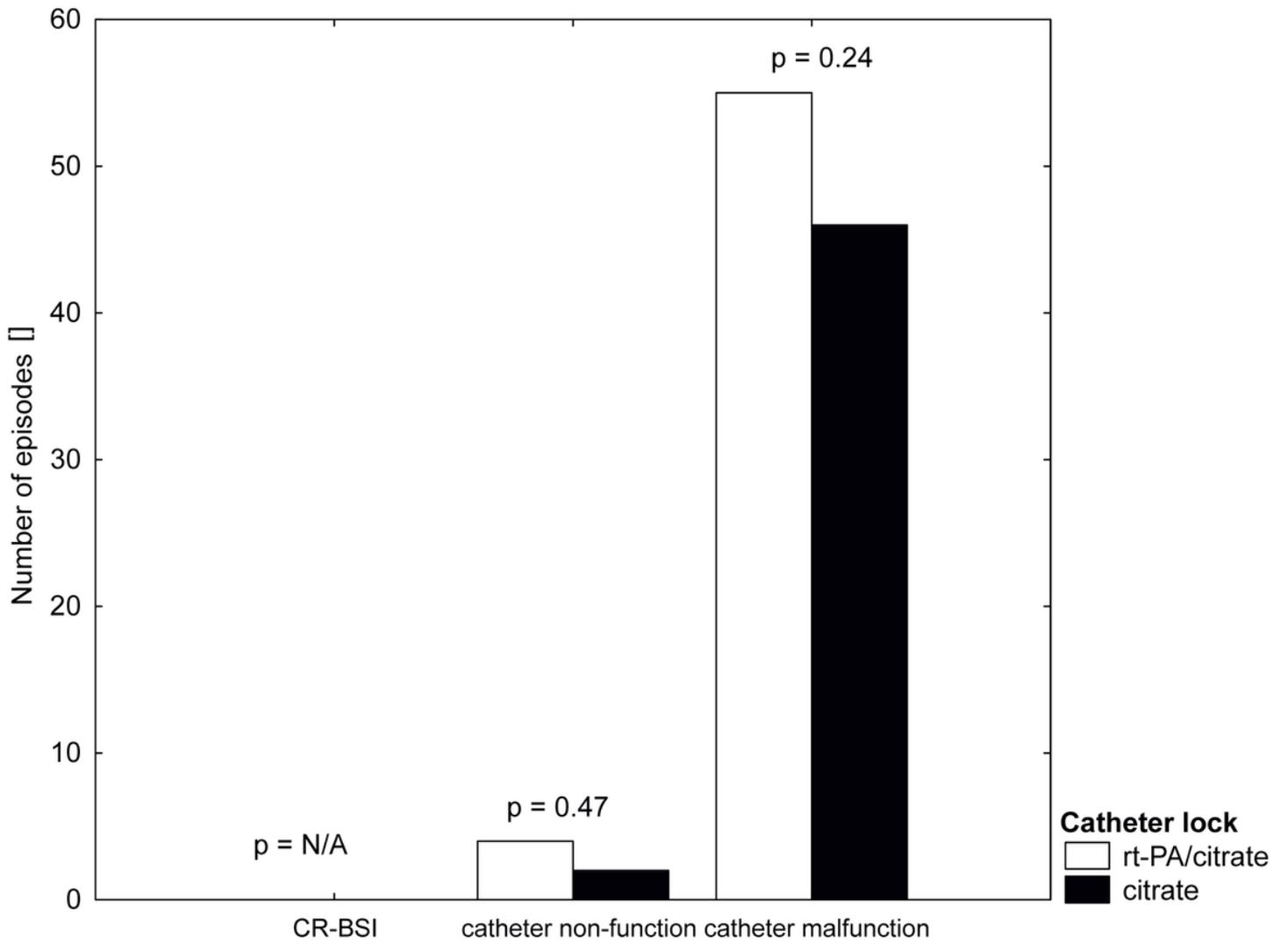


Figure 1

Primary (CR-BSI episodes) and secondary (catheter dysfunction) endpoints reached during the study

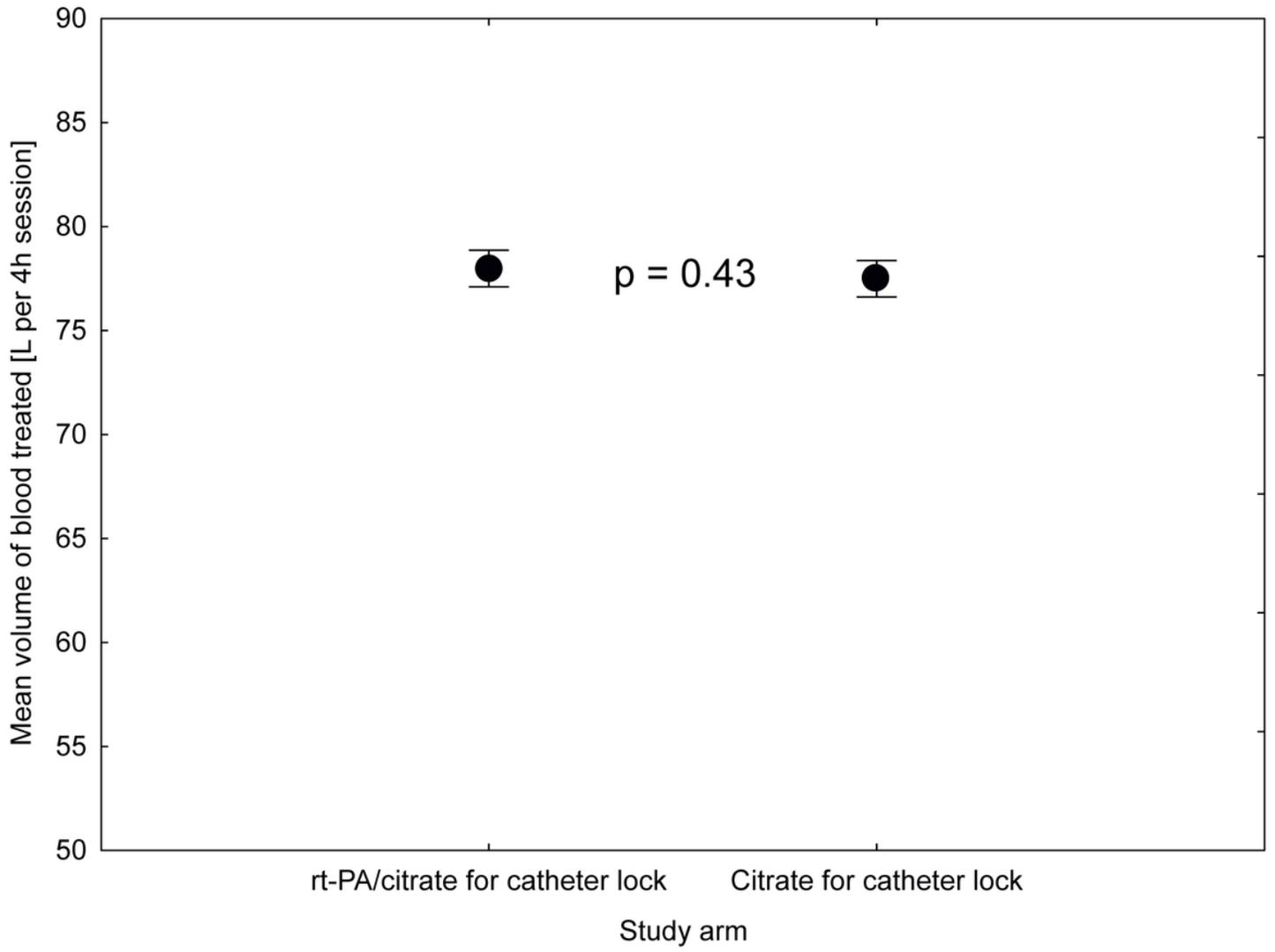


Figure 2

Mean volume of blood treated during HD session

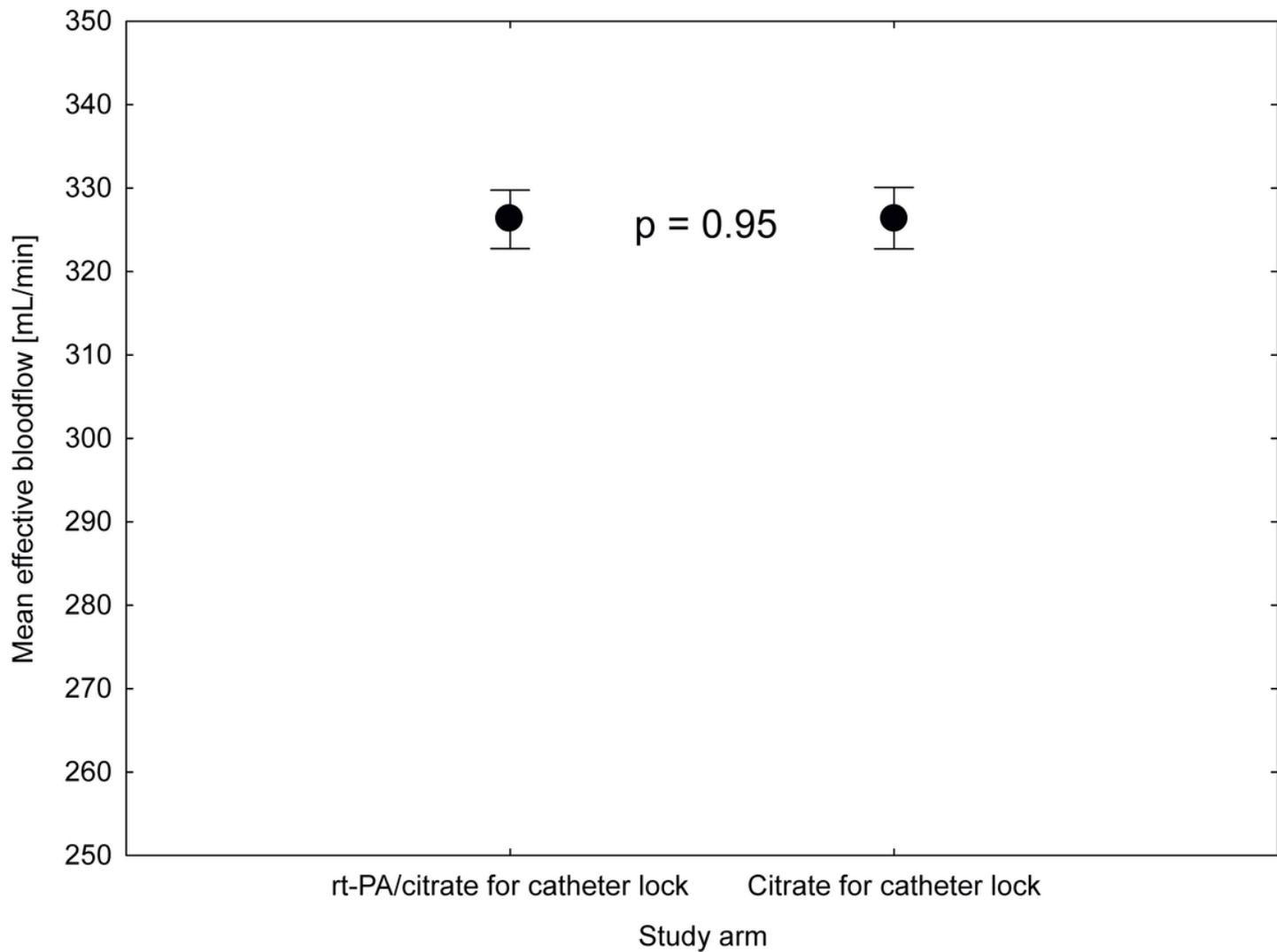


Figure 3

Mean effective blood flow achieved during HD session

Supplementary Files

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