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# Comparison of antimicrobial and thrombolytic central venous catheter lock solutions in preventing catheter-related complications in hemodialysis: a randomized controlled trial

## Poređenje antimikrobnih i trombolitičkih rastvora za zatvaranje centralnih venskih katetera u prevenciji komplikacija povezanih sa kateterima kod bolesnika na hemodijalizi: randomizovano kontrolisano ispitivanje

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**Abstract**

**Background/Aim.** Central venous catheters (CVC) in hemodialysis (HD) patients are associated with serious complications, particularly catheter-related bloodstream infection (CRBSI) and thrombosis, leading to increased morbidity and mortality. The aim of this study was to evaluate the effectiveness of three different catheter lock solutions in preventing major catheter-related complications. **Methods.** This prospective, randomized, controlled, single-center study, conducted between June 2018 and June 2023, included 96 adult HD patients. Depending on the solutions they received, the patients were equally divided into three groups: gentamicin-citrate twice weekly plus taurolidine/urokinase after the third weekly session (TAURO); gentamicin-citrate three times weekly (GENTAM); unfractionated heparin 5,000 international units/mL three times weekly (HEPARIN). Lock solutions were administered for a minimum of three months post-CVC insertion and continued until catheter removal. Measured outcomes included CRBSI incidence, catheter thrombosis, and adverse events. **Results.** Over the course of 10,770 catheter-days, eight CRBSI episodes were recorded, with *Staphylococcus aureus* as the most common pathogen (50%). The incidence of CRBSI (*per* 1,000 catheter-days) was 0.27 in the TAURO group, 0.83 in the GENTAM group, and 1.15 in the HEPARIN group, without statistical significance ($p = 0.526$). Thrombosis incidence was similar across groups (1.09–1.15; $p = 0.990$). Cox proportional hazards analysis revealed no significant differences, although the TAURO group demonstrated a trend toward lower CRBSI risk compared to the HEPARIN group (hazard ratio = 0.236; 95% confidence interval 0.026–2.116). **Conclusion.** None of the evaluated lock regimens significantly reduced the risk of CRBSI or thrombosis. Nonetheless, the lowest CRBSI incidence was observed in the TAURO group, suggesting a potential benefit that warrants confirmation in larger, multicenter studies.

**Keywords:**
**anticoagulants; bacteremia; catheter-related infections; catheterization, central venous; fibrinolytic agents; renal dialysis; thrombosis.**

**Apstrakt**

**Uvod/Cilj.** Centralni venski kateteri (CVK) kod bolesnika na hemodijalizi (HD) povezani su sa ozbiljnim komplikacijama, posebno bakterijemijom povezanom sa kateterom (BPSK) i trombozom, što dovodi do povećanog morbiditeta i mortaliteta. Cilj rada bio je da se proceni efikasnost tri različita rastvora za zatvaranje katetera u sprečavanju većih komplikacija povezanih sa kateterom. **Metode.** Ova prospektivna, randomizovana, kontrolisana studija sprovedena u jednom centru, od juna 2018. do juna 2023. godine, obuhvatila je 96 odraslih bolesnika na HD. U zavisnosti od rastvora koji su primali, bolesnici su bili ravnomerno podeljeni u tri različite grupe: gentamicin–citrat dva puta nedeljno uz taurolidin/urokinazu nakon treće nedeljne dijalize (TAURO); gentamicin–citrat tri puta nedeljno (GENTAM); nefrakcionisani heparin 5 000 internacionalnih jedinica/mL tri puta nedeljno (HEPARIN). Rastvori za zatvaranje katetera su primenjivani najmanje tri meseca nakon plasiranja CVK i njihova primena je nastavljena do uklanjanja katetera. Praćeni ishodi obuhvatali su incidenciju BPSK, trombozu

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katetera i neželjene događaje. **Rezultati.** Tokom 10 770 „kateter-dana" registrovano je osam epizoda BPSK, a najčešći uzročnik bio je *Staphylococcus aureus* (50%). Incidencija BPSK (na 1 000 „kateter-dana") bila je 0,27 u TAURO grupi, 0,83 u GENTAM grupi i 1,15 u HEPARIN grupi, bez statističke značajnosti ($p$ = 0,526). Incidencija tromboze katetera bila je slična u svim grupama (1,09–1,15; $p$ = 0,990). Koksova analiza proporcionalnih rizika nije pokazala značajne razlike, iako je TAURO grupa pokazala trend ka manjem riziku od BPSK u poređenju sa HEPARIN grupom (*hazard ratio* = 0,236; 95% interval poverenja 0,026–2,116). **Zaključak.** Nijedan ispitivani režim rastvora za zatvaranje katetera nije značajno smanjio rizik od BPSK ili tromboze. Ipak, najniža incidencija BPSK zabeležena je u TAURO grupi, što ukazuje na potencijalnu korist koju treba potvrditi u većim, multicentričnim studijama.

**Ključne reči:**
**antikoagulansi; bakterijemija; kateter, povezane infekcije; kateterizacija, centralna, venska; fibrinolitici; bubreg, dijaliza; tromboza.**

## Introduction

Vascular access is essential for effective hemodialysis (HD), yet it also represents its most fragile component. While arteriovenous fistulas (AVF) remain the gold standard due to their superior long-term outcomes, temporary central venous catheters (CVCs) for dialysis are still widely used in incident HD patients in Serbia, with a prevalence of 63.5% according to data from the Serbian National Vascular Surgery Registry, due to their ability to provide immediate vascular access [1]. However, frequent failures in primary AVF creation and the rise in marginal fistulas have resulted in many patients depending on prolonged CVC use. Long-term use of CVC leads to complications, the most common of which are CVC dysfunction and thrombosis, and a high rate of catheter-related bloodstream infections (CRBSI) [2, 3]. The risk of sepsis in patients dialyzed *via* a CVC is two to five times higher than in patients with AVF and arteriovenous grafts (AVG), and initial septic episodes can double the incidence of adverse cardiovascular events such as myocardial infarction and congestive heart failure [3, 4]. These complications often necessitate catheter replacement, further limiting available vascular access options.

Preventive strategies for catheter-related complications have traditionally focused on using unfractionated heparin as a lock solution. However, high concentrations [5,000–10,000 international units (IU)/mL] raise concerns about systemic anticoagulation and promote *Staphylococcus* (*S.*) *aureus* biofilm formation in a dose-dependent manner [5, 6]. As an alternative, trisodium citrate (TSC) offers both anticoagulant and antimicrobial properties without systemic effects. *In vitro* studies have shown that the use of TSC reduces the formation of biofilms inside dialysis catheters [5]. Different concentrations of TSC have been tested, with 4% TSC being safe and effective in preventing catheter thrombosis, but it did not lead to the expected reduction in the incidence of CRBSI [5, 7]. Several studies have explored the addition of antibiotics to anticoagulant lock solutions to reduce the incidence of CRBSI [8, 9]. Moran et al. [8] reported a significant decrease in CRBSI rates (0.28 episodes *per* 1,000 catheter-days) using a gentamicin and 4% TSC combination, compared to heparin (1,000 IU/mL). While this combination reduced CRBSI, it showed no benefit in preventing thrombotic complications. A meta-analysis by Lai et al. [9], including 17 randomized controlled trials, confirmed a significant reduction in CRBSI with citrate-based locks compared to heparin [relative risk: 0.48; 95% confidence interval (CI): 0.31–0.73; $p$ = 0.001]. Subsequent studies have highlighted citrate-based lock solutions combined with antimicrobial agents as the most effective strategy for preventing catheter-related infections [5]. Other research has focused on reducing catheter thrombosis. Weekly use of thrombolytics, such as recombinant tissue plasminogen activator (1 mg) or urokinase (25,000 IU) dissolved in 4% TSC with taurolidine (taurolock-urokinase), combined with standard anticoagulants twice weekly, was associated with reduced thrombosis and less frequent catheter replacement [5, 10].

There were no data regarding the preventive use of urokinase (25,000 IU) dissolved in 4% TSC with taurolidine (taurolock-urokinase) combined with gentamicin-citrate antibiotic catheter locks.

The aim of this study was to compare the effects of a combination of prophylactic catheter lock solutions to gentamicin-citrate three times a week or heparin on the incidence of catheter-related complications (CRBSI and catheter-related thrombosis – CRT).

## Methods

This was a randomized controlled trial with an open-label approach that included 96 adult patients with end-stage chronic kidney disease undergoing HD at the Clinic for Nephrology and Clinical Immunology, University Clinical Center of Vojvodina, Novi Sad, Serbia, from June 2018 to June 2023.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University Clinical Center of Vojvodina (No. 00-20/243, from February 22, 2018). Written informed consent was obtained from all participants prior to enrollment.

Participants were excluded if they had confirmed malignancy, significant bleeding within the previous four weeks, clinical or laboratory signs of active infection, psychiatric illness, pregnancy, or were receiving concomitant therapy affecting thrombogenicity.

Temporary double-lumen, polyurethane, non-tunneled catheters (REF CV 12122 F, 16 cm; Arrow International, Pennsylvania, USA) were inserted by anesthesiologists or nephrologists using a modified Seldinger technique under strict aseptic conditions.

Patients were randomly assigned in a 1:1:1 ratio to receive interdialytic catheter locking with either gentamicin-citrate twice weekly plus taurolidine/urokinase after the third

weekly session (TAURO group), gentamicin-citrate three times weekly (GENTAM group), or unfractionated heparin 5,000 IU/mL three times weekly (HEPARIN group). Patients in all three groups were predominantly male, with no significant differences in age or the underlying cause of end-stage kidney disease.

Patients underwent thrice-weekly 4-hr bicarbonate HD using high-flux polysulfone capillary membranes (1.1–1.3 m²), with a blood flow rate of 250–300 mL/min, a dialysate flow of 500 mL/min, and standard bicarbonate dialysate.

Following each dialysis session, both lumens were locked with the assigned solutions appropriate to the randomized group. Lock solutions were prepared by dialysis nurses at the end of each session and instilled into the catheter lumen according to protocol. Gentamicin-citrate lock was prepared by mixing 0.2 mL of gentamicin (40 mg/mL; 2 mL) with 3 mL of 4% TSC solution (IntraLock®, Fresenius Medical Care, Bad Homburg, Germany) in a sterile syringe. This solution contains gentamicin 2.5 mg/mL and 4% TSC. TauroLock™-U25,000 (TauroPharm GmbH, Waldbüttelbrunn, Germany) is a commercially available product that contains taurolidine, 4% TSC, and 25,000 IU urokinase *per* vial. When used as a catheter lock solution, unfractionated heparin (5,000 IU/mL; Heparin Galenika 25,000 IU/5 mL, Galenika A.D., Belgrade, Serbia) was prepared from the original ampoule and instilled in a volume recommended by the catheter manufacturer using a 2 mL syringe. Lock volumes adhered to manufacturer recommendations, and catheter lock solutions were administered for at least 3 months after CVC insertion or until one of the predefined outcomes occurred.

During follow-up, catheter care was performed at each dialysis session following infection control protocols. Catheters were disinfected with chlorhexidine and 70% alcohol. Exit sites were treated aseptically with hydrogen peroxide, iodine, or Codan (colorless alcohol-based solution), and covered with 3M™ Tegaderm™ Transparent Film Dressing (Saint Paul, Minneapolis, USA) or sterile gauze [11]. If signs of local infection were observed, venous blood samples for hemocultures and catheter exit site swabs were collected. Swabs were sent for microbiological analysis using standard culture and biochemical identification techniques [12]. In the case of systemic infection signs, blood was sampled from both catheter lumens and a peripheral vein (10–20 mL *per* sample), and inoculated into commercial blood culture bottles (Himedia HiCombi HiSafe, 40 mL, HiMedia Laboratories, Thane, India). Cultures were processed using the BacT/Alert® 3D system (bioMérieux, Marcy-l'Étoile, France) for continuous monitoring. At the end of the study, after aseptic catheter removal, the distal 5 cm tip was placed in a sterile container and processed using standard microbiological techniques [12]. Catheter tip colonization was determined using a semi-quantitative technique [2].

The primary outcomes were the occurrence of CRBSI, exit-site infections, and CRT, within 90 days post-CVC insertion (or until AVF maturation if longer). Patients were censored at catheter removal or death. CRT and CRBSI were defined according to the 2019 Kidney Disease Outcomes Quality Initiative (KDOQI) vascular access guidelines [2]. Since non-tunneled CVCs were used, thrombosis was further defined as the inability to initiate dialysis after previous successful use or to maintain a blood flow rate ≥ 150 mL/min during three consecutive dialysis sessions. Patients with CRBSI continued follow-up unless the catheter was removed. No patient experienced more than one episode of CRBSI. The number of catheter-days was calculated from CVC insertion to removal. The incidence of CVC thrombosis and CRBSI was expressed as events *per* 1,000 catheter-days, using the formula: (number of events/total catheter-days) × 1,000.

Detailed patient laboratory data are presented in Table 1 of Azasevac et al. [13].

*Statistical analysis*

The data were evaluated using descriptive statistics (mean values and standard deviations). Group differences

**Table 1**

**Demographic and clinical characteristics at baseline by study group**

| Parameters | Group | | | *p*-value |
|---|---|---|---|---|
| | TAURO | GENTAM | HEPARIN | |
| Gender | | | | |
| male | 14 | 14 | 14 | 1.0 |
| female | 18 | 18 | 18 | |
| Age, years | 58.6 ± 15.3 | 60.4 ± 12.2 | 62.1 ± 14.6 | 0.1 |
| Cause of ESKD | | | | |
| diabetes | 10 (31.3) | 11 (34.4) | 11 (34.4) | 0.9 |
| hypertension | 11 (34.4) | 12 (37.5) | 9 (28.1) | 0.8 |
| polycystic kidney disease | 3 (9.4) | 3 (9.4) | 3 (9.4) | 1.0 |
| glomerulonephritis | 5 (15.6) | 2 (6.3) | 2 (6.3) | 0.4 |
| chronic pyelonephritis | 0 (0) | 1 (3.1) | 3 (9.4) | 0.1 |
| other | 3 (9.4) | 3 (9.4) | 4 (12.5) | 0.9 |
| Clinical characteristics | | | | |
| overweight and obesity | 17 (53.1) | 21 (65.6) | 17 (53.1) | 0.5 |
| CKD vintage, year | 5.0 ± 4.4 | 4.9 ± 4.7 | 4.5 ± 4.8 | 0.9 |
| antiplatelet drugs | 18 (46.0) | 18 (46.0) | 16 (50.0) | 0.9 |

**ESKD – end-stage kidney disease; CDK – chronic kidney disease.**
**All values are given as numbers (percentages) or mean ± standard deviation.**
***Note*. TAURO group – gentamicin-citrate twice weekly plus taurolidine/urokinase after the third weekly session; GENTAM group – gentamicin-citrate three times weekly; HEPARIN group – unfractionated heparin 5,000 international units/mL three times weekly.**

were tested with the *t*-test or Mann-Whitney *U* test for two groups, and analysis of variance or Kruskal-Wallis test for three or more groups. Categorical data were compared using the Chi-square test. Survival was analyzed using the Kaplan-Meier method and the log-rank test. Cox proportional hazards regression was used to examine the association between predictor variables and the occurrence of key catheter-related complications, with hazard ratios (HR) and 95% CI reported. A $p$-value < 0.05 was considered statistically significant.

## Results

*Baseline demographic, clinical, and laboratory data*

A total of 96 patients (32 *per* group) were enrolled, and no patient was lost to follow-up or discontinued the catheter-lock solution. The mean patient age was 60.35 ± 14.25 years; 56.3% were male, without significant differences between groups. Approximately one-third of the study population had diabetes mellitus, with comparable rates of diabetic kidney disease across the three treatment groups. Together with arterial hypertension, diabetic kidney disease was the leading underlying cause of chronic kidney disease. Analysis of anthropometric parameters revealed that more than half of the study participants were overweight or obese (BMI > 25 kg/m²). Baseline demographic and clinical characteristics of the study population, presented by study group, are summarized in Table 1.

Among the patients included in this study, the majority (86 patients) received a CVC for the initiation of renal replacement therapy with HD, making it their first vascular access. A smaller proportion began HD *via* a functional AVF or AVG, with CVC placement required only after thrombosis of the existing access. One patient was initially treated with peritoneal dialysis and underwent CVC insertion upon transition to HD. Regarding CVC positioning, the majority of catheters were inserted *via* the right internal jugular vein (90.6% vs. 84.4% vs. 84.4%), followed by the left internal jugular vein (6.3% vs. 9.4% vs. 12.5%). There was no statistically significant difference in the distribution of jugular vein catheter placements among the three groups ($p$ = 0.693).

Regarding laboratory findings, parameters were mostly similar across the three groups (TAURO, GENTAM, HEPARIN), with no statistically significant differences observed in white blood cells, hemoglobin, platelets, creatinine, albumin, calcium, phosphorus, ferritin, transferrin, CRP, or fibrinogen levels ($p$ > 0.05). However, parathyroid hormone (PTH) levels differed significantly between the groups, with mean values of 428 ± 304, 412 ± 334, and 263 ± 231 pg/mL, respectively ($p$ = 0.03).

Across 10,770 catheter-days, median catheter dwell time was similar: 125.94 ± 87.48, 113.44 ± 35.68, and 108.59 ± 37.84 days, respectively ($p$ = 0.831).

*Catheter-related bloodstream infection*

The CRBSI rate was lowest in the TAURO group (0.27 episodes/1,000 catheter-days), compared to the GENTAM group (0.83 episodes/1,000 catheter-days) and the control HEPARIN group (1.15 episodes/1,000 catheter-days), although the difference was not statistically significant ($p$ = 0.526). All isolated pathogens causing CRBSI were gram-positive. In 87.5% of cases, a single organism was isolated, while polymicrobial growth was identified in 12.5%. The most common pathogen was *S. aureus* (50.0%). Table 2 presents the distribution of isolated CRBSI pathogens across study groups.

The average interval from catheter insertion to CRBSI onset was 45.47 ± 38.93 days. While the TAURO group exhibited the longest duration prior to infection (115.99 ± 58.61 days), compared to the HEPARIN (37.75 ± 35.37 days) and GENTAM (33 ± 24.27 days) groups, this difference did not reach statistical significance ($p$ = 0.212) (Table 3). The total number of catheter-days until CRBSI onset was 935. There was no statistically significant difference in cumulative CVC

**Table 2**

**Distribution of pathogens isolated from catheter-related bloodstream infections by study group**

| Pathogen | Group | | | Total |
|---|---|---|---|---|
| | TAURO | GENTAM | HEPARIN | |
| *Staphylococcus* species, coagulase-negative | 1 (12.5) | 1 (12.5) | 1 (12.5) | 3 (37.5) |
| *Staphylococcus aureus* | 0 (0) | 2 (25.0) | 2 (25.0) | 4 (50.0) |
| Polimicrobic flora | 0 (0) | 0 (0) | 1 (12.5) | 1 (12.5) |
| Total | 1 (12.5) | 3 (37.5) | 4 (50.0) | 8 (100) |

**All values are given as numbers (percentages).**

**Table 3**

**Number and time to onset of catheter-related complication following catheter insertion by study group**

| Catheter-related complication | Group | | | *p*-value |
|---|---|---|---|---|
| | TAURO | GENTAM | HEPARIN | |
| CRBSI | 1 (3.12) | 3 (9.37) | 4 (12.5) | 0.385 |
| Time to CRBSI onset, days | 115.99 ± 58.61 | 33 ± 24.27 | 37.75 ± 35.37 | 0.212 |
| Exit-site infections | 24 (75.0) | 26 (81.2) | 19 (59.4) | 0.968 |
| Time to exit-site infections onset, days | 141.47 ± 111.747 | 122.19 ± 36.694 | 107.05 ± 32.667 | 0.344 |
| Catheter-related thrombosis | 4 (12.5) | 4 (12.5) | 4 (12.5) | 1.000 |
| Time to catheter-related thrombosis onset, days | 67.75 ± 14.886 | 99.50 ± 49.568 | 132.00 ± 57.486 | 0.182 |

**CRBSI – catheter-related bloodstream infection; n – number. For other abbreviations, see Table 1.**
**All values are given as numbers (percentages) or mean ± standard deviation.**

survival free from CRBSI between the antibiotic lock groups (TAURO and GENTAM) and the control HEPARIN group (log-rank test, $p = 0.38$) (Figure 1). Cox proportional analysis regarding the occurrence of CRBSI showed the following results: HR (HEPARIN vs. TAURO) = 0.236 (95% CI: 0.026–2.116), $p = 0.197$; HR (HEPARIN vs. GENTA) = 0.737 (95% CI: 0.165–3.292), $p = 0.689$; HR (TAURO vs. GENTA) = 3.115 (95% CI: 0.324–29.95), $p = 0.325$.

*Exit-site infections*

A total of 89 exit-site infections were documented during the follow-up period, corresponding to an overall incidence of 8.26 episodes *per* 1,000 catheter-days. The cumulative number of catheter-days until the first recorded exit-site infection was 7,219. The number of exit-site infections and the time to their onset by group are presented in Table 3. The incidence of exit-site infections was 8.45 episodes/1,000 catheter-days in the TAURO group, 10.46 in the GENTAM group, and 5.75 in the HEPARIN group ($p = 0.078$). Regarding the frequency of exit-site infections *per* patient, 23 (23.9%) patients experienced one episode, 27 (28.1%) experienced two episodes, and 4 (4.2%) experienced three or more episodes. The remaining 42 (43.7%) patients did not develop any exit-site infections during the study period. There was no statistically significant difference in cumulative CVC survival free from exit-site infections between the antibiotic lock groups (TAURO and GENTAM) and the control HEPARIN group ($p = 0.21$) (Figure 2). Cox proportional analysis for exit-site infections occurrence showed no significant associations with lock type: $HR_{TAURO\ vs.\ HEPARIN} = 1.384$ (95% CI: 0.687–2.787) ($p = 0.362$), and $HR_{GENTAM\ vs.\ HEPARIN} = 1.836$ (95% CI: 0.925–3.641) ($p = 0.082$).

*Catheter thrombosis*

The overall incidence of CRT was 1.11 events *per* 1,000 catheter-days, with a total of 1,197 catheter-days until thrombosis occurred. The incidence of CVC thrombosis in

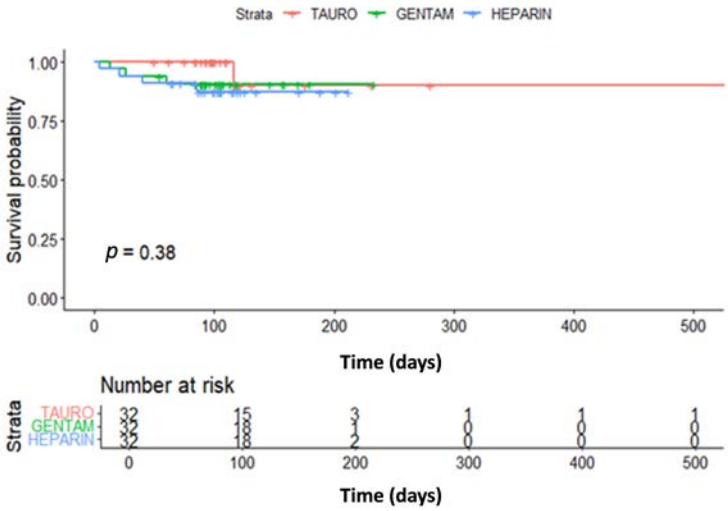


**Fig. 1 – Kaplan-Meier analysis of cumulative catheter-related bloodstream infection-free catheter survival among the three catheter lock groups. For abbreviations, see Table 1.**

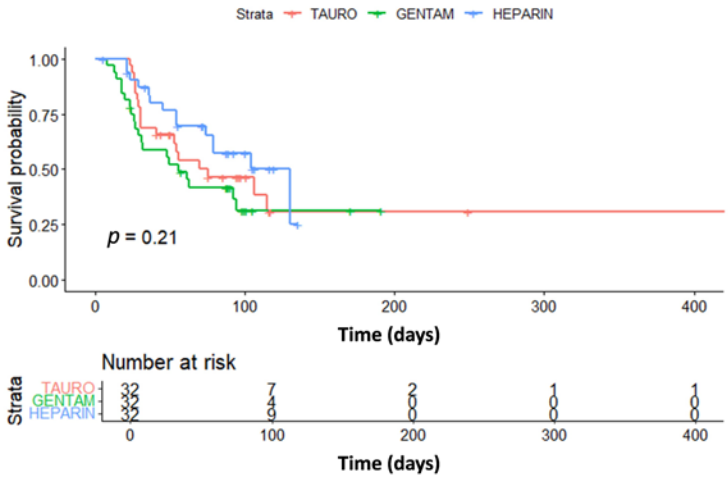


**Fig. 2 – Kaplan-Meier analysis of cumulative exit-site infection-free central venous catheter survival among the three catheter lock solution groups. For abbreviations, see Table 1.**

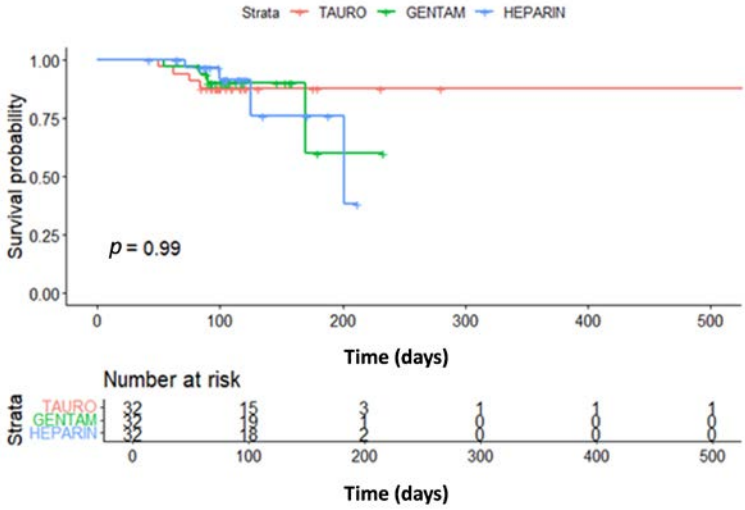


**Fig. 3 – Kaplan-Meier analysis of cumulative thrombosis-free catheter survival among the three catheter lock solution groups.**
**For abbreviations, see Table 1.**

the TAURO group was 1.09/1,000 catheter-days, 1.10/1,000 catheter-days in the GENTAM group, and 1.15/1,000 catheter-days in the control HEPARIN group ($p = 0.990$). The mean time to CRT onset was $99.75 \pm 48.81$ days, with the number of thrombosis and time to onset by groups presented in Table 3. Cumulative catheter survival without thrombosis was not significantly different between groups receiving anticoagulant and fibrinolytic locks (TAURO and GENTAM groups) compared with the HEPARIN group ($p = 0.990$) (Figure 3). The Cox proportional model regarding the development of CVC thrombosis in relation to the lock type showed the following result: $HR_{TAURO\ vs.\ HEPARIN} = 0.958$ (95% CI: 0.239–3.838) ($p = 0.952$); $HR_{GENTA\ vs.\ HEPARIN} = 1.002$ (95% CI: 0.249–4.032) ($p = 0.997$); $HR_{TAURO\ vs.\ GENTA} = 1.082$ (95% CI: 0.267–4.379) ($p = 0.912$).

*Adverse effects*

No differences were observed in the distribution of gentamicin-resistant strains after completion of the tested lock regimens and removal of the CVC ($p = 0.799$). No symptoms were recorded that would indicate toxicity from the administered drugs or solutions.

## Discussion

Despite frequent complications, the use of temporary CVCs for dialysis remains remarkably high among incident HD patients in Serbia [1]. Depending on the dialysis center, the incidence of CRBSIs associated with CVCs ranges from 1.0 to 6.2 episodes *per* 1,000 catheter-days [7], while the incidence of CRT is reported to be 0.5 to 3.0 episodes *per* 1,000 catheter-days when heparin is used as the locking solution [2]. To prevent CRBSIs and CRT, the KDOQI guidelines for vascular access recommend the use of anticoagulant agents such as heparin or citrate. In centers with a high incidence of these complications, or in high-risk patients with a history of recurrent infections and/or thrombosis, the guidelines suggest combining these agents with thrombolytics and antibiotic locks to further reduce the risk of recurrence [2]. These combinations have yielded varying degrees of success in reducing the incidence of both CRBSIs [5, 8, 9] and CRT [5, 11]. To the best of our knowledge, this is the first study to use a combination of gentamicin-citrate and taurolock-urokinase to prevent catheter-related complications, aiming to reduce both infections and thrombosis in HD patients. Although the use of these catheter locks showed a non-significant trend toward reducing CRBSIs compared to other solutions, it did not prove superior in preventing catheter thrombosis.

As noted in previous studies, diabetes may contribute to CRBSI risk [3]. In our study, about one-third of patients had diabetes, with similar rates of diabetic kidney disease across groups. Mohazzab et al. [14] identified obesity as a potential risk factor for catheter dysfunction and thrombosis in tunneled dialysis catheters. Notably, in the present study, over half of the patients in each group were overweight, with a balanced distribution among the groups. Analysis of biochemical parameters revealed that the only significant difference between the groups was a higher PTH level in the TAURO group compared to the HEPARIN group. However, according to the literature, PTH is not considered a recognized risk factor for the development of CRBSI or CVC thrombosis [5, 14–17].

In our study, over 90% of CVCs were inserted *via* the right internal jugular vein, followed by the left internal jugular vein. Previous studies have shown that right internal jugular access is associated with longer catheter survival, but potentially higher risk of bacteremia due to prolonged use [18]. In contrast, femoral vein catheterization has been linked to an increased risk of CRBSIs [15, 19, 20], likely due to its anatomical proximity to the perineum, a moist area conducive to bacterial growth. Prolonged catheter duration further increases the risk of infection, regardless of the insertion site [18–20].

Catheters in the TAURO group had the longest median duration (125.9 days), compared with the GENTAM (113.4 days) and HEPARIN (108.6 days) groups, although the difference was not statistically significant. Compared to published data, the duration of catheter use in our study was notably longer. Prior studies have reported much shorter average lifespans for temporary CVCs, ranging from 6 to 58 days, depending on catheter type and insertion site [20–22]. For instance, Stolić et al. [22] reported a much shorter average duration of $17.4 \pm 13.2$ days, with most catheters placed in the femoral vein. Weldetensae et al. [21] found a mean duration of $57.9 \pm 95.5$ days for the first catheter, irrespective of insertion site. In contrast, Van Oevelen et al. [23] demonstrated significantly longer durations for tunneled and precurved non-tunneled jugular catheters, while Slovenian data showed that precurved non-tunneled catheters used as long-term access remained functional for over 9 months on average [24]. As expected, tunneled permanent catheters have the longest duration, typically ranging from 504 (366-3,802) days [25]. Our findings suggest that the catheter locks used in the TAURO group may contribute to enhanced catheter longevity.

The overall incidence of CRBSIs in our study was 0.74/1,000 catheter-days, with the lowest rate (*per* 1,000 catheter-days) observed in the TAURO group (0.27), followed by the GENTAM group (0.83), and the HEPARIN group (1.15), though without statistical significance. Notably, this represents a marked reduction compared to a previous study conducted at our center between 2012 and 2015, in which the CRBSI incidence associated with heparin locks (5,000 IU/mL) was 3.72/1,000 catheter-days [26]. This improvement likely reflects better adherence to vascular access guidelines and catheter care protocols, which may have contributed to the lower infection rates even in the control (HEPARIN) group. Additionally, another study from our region have reported CRBSI rates affecting 3.7% to 4.8% of patients during the 2003–2006 period [22]. International data show a wide range of CRBSI incidence with temporary catheters locked with heparin (3.55–7.74/1,000 catheter-days), and reduced infection rates when precurved catheters or gentamicin-heparin locks were used [19, 21, 23, 24]. Antibiotic-based catheter locks, particularly those containing gentamicin-citrate, have been shown to reduce CRBSI incidence, with reported effectiveness ranging from 31% to 100% [27]. Although randomized trials investigating taurolidine-urokinase combinations have not reached statistical significance, a meta-analysis including this agent reported a favorable trend in reducing infection rates [10, 28]. All CRBSI isolates in our study were gram-positive organisms, with *S. aureus* responsible for 50% of cases, consistent with findings reported in the literature [29]. Although gentamicin primarily targets gram-negative bacteria, none of these organisms were identified in our patients. Similarly, no gram-negative pathogens were isolated in the HEPARIN control group, consistent with previous data from our center, where gram-negative bacteria represented only 6.4% of all CRBSI isolates [26].

In contrast to a meta-analysis by Sheng et al. [30], which demonstrated that citrate-based lock solutions significantly reduced the incidence of catheter exit-site infections compared to heparin at 5,000 IU/mL, our study found the highest incidence in the GENTAM group and the lowest in the HEPARIN group ($p = 0.078$).

The incidence of CRT did not differ across groups, with an overall incidence of 1.11 events *per* 1,000 catheter-days. These rates are lower than previously reported thrombosis incidences associated with heparin locks, which reach up to 3.0 events/1,000 catheter days [2]. Previous study using 4% TSC as an anticoagulant reported catheter thrombosis rates of around 3.2 events *per* 1,000 catheter-days [24]. However, one meta-analysis concluded that citrate locks, regardless of concentration or combination with antimicrobials such as gentamicin, did not significantly reduce catheter malfunction [30]. In contrast, a separate meta-analysis found that urokinase combined with 4% TSC and taurolidine significantly reduced the incidence of catheter thrombosis compared to heparin locks [28].

This study has several limitations, including a relatively small sample size and a single-center design, which limit the generalizability of the findings. A notable strength of our study is the novel application of antimicrobial and thrombolytic lock combinations for the prevention of CRBSI and catheter thrombosis. Although the observed reductions in complication rates were not statistically significant, the results suggest potential benefit in high-risk populations and settings with high CRBSI incidence.

## Conclusion

The findings of this study indicate that the use of gentamicin-citrate in combination with taurolock-urokinase is safe and feasible in routine clinical practice. While no statistically significant reductions in catheter-related complications were observed, the consistent trend toward lower catheter-related bloodstream infection rates and enhanced catheter longevity supports further investigation. Future multicenter studies with larger sample sizes are needed to validate these results and guide individualized catheter care strategies in hemodialysis patients.

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