



The Comparison of Streptokinase, an Old Agent, Versus Reteplase for the Re-Tunnellisation of Blocked Cuffed Haemodialysis Catheter

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Abstract

Background/Aim: Catheter occlusion is the most common complication occurring in patients with end-stage renal disease (ESRD) who undergo haemodialysis. The management typically involves the use of local fibrinolytic agents. However, with the emergence of novel agents, the use of older agents has declined. The purpose of the study was to compare the effectiveness of reteplase versus streptokinase (SK) in resolving haemodialysis catheter occlusion.

Methods: This randomised clinical trial involved 100 patients with catheter occlusion who were equally divided into two groups of 50. One group received treatment with reteplase, while the other group received treatment with SK. The occluded catheter in the first group was instilled with 250,000 units (U) of SK, while the second group received 2 U of reteplase and the catheters were left in place for 2-6 h. Successful flushing of the catheter with a velocity of ≥ 200 rounds per minute was considered successful re-tunnelling. The study also evaluated the frequencies of re-injections and drug-related adverse effects.

Results: The success rate of SK versus reteplase did not differ significantly ($p = 0.48$). However, the required time to inject the agents to achieve appropriate luminal patency was statistically higher in the reteplase-treated group ($p = 0.018$). None of the patients experienced major adverse effects such as bleeding or anaphylactic reactions.

Conclusion: According to the findings of this study, both reteplase and SK resulted in significant recovery of luminal patency with no adverse effects. However, the lower frequency of re-injections required with SK to achieve successful rationalisation favoured the use of this agent over reteplase. Further studies are strongly recommended.

Key words: Streptokinase; Reteplase; Catheters; Fibrinolytic agents; Haemodialysis.

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Introduction

Central venous access devices (CVADs) refer to intravenous catheters placed within the central veins for temporary, semi-permanent, or permanent use, typically for haemodialysis in patients with end-stage renal disease (ESRD).¹ It is challenging for 30 % to 67 % of patients who experience occlusion of their haemodialysis catheters,

often due to the development of a fibrin sleeve or plug at the catheter tip. In such cases, fibrinolytic agents are used to dissolve the clot and reopen the catheter.²

Despite the availability of various thrombolytic options such as alteplase, reteplase and tenecte-

epase for managing different thrombotic events, these agents are expensive and not easily accessible, especially in low- to moderate-income countries.³ At present, alteplase is the preferred fibrinolytic agent approved for treating occluded central venous catheters.² However, research on the use of other thrombolytic agents is ongoing.

Retepase, a deletion mutant of recombinant tissue plasminogen activator, can directly activate plasminogen without complexing with plasminogen.⁴ Numerous studies in the literature have explored the use of 0.4 U reteplase per catheter port for 30–60 min, resulting in successful resolution of catheter dysfunction in approximately 85 % – 91 % of cases, with outcomes similar to those of alteplase.⁵

Streptokinase (SK), the first introduced thrombolytic agent, was isolated from β -haemolytic streptococci. Until 1990, it was used for catheter clearance; however, its related complications, such as anaphylaxis (0.1 %) and allergic reactions (5-15 %), led to its limited use.⁶ Over time, significant changes have been made in the molecular structure, chemical properties and drug delivery methods of SK, resulting in increased efficacy and reduced immunogenicity and adverse effects of this thrombolytic agent. Due to its low cost and high availability, SK is favoured in developing countries.⁷

The aim of the study was to investigate the therapeutic outcomes of reteplase versus SK for resolving catheter occlusion.

Methods

The current single-blinded randomised clinical trial was conducted on 100 patients admitted due to haemodialysis catheter occlusion at Alzahra Hospital, the tertiary medical centre affiliated with Isfahan University of Medical Sciences during 2019.

Participants eligible for inclusion were over 18 years old, had ESRD, were undergoing haemodialysis treatment, had catheters implanted for over 30 days before occlusion and experienced their first instance of catheter occlusion. Catheter occlusion was defined as difficulty in infusing or withdrawing fluid from the catheter conduit

using a 20 mL syringe, or inability to initiate haemodialysis with adequate flow.⁸

Patients with a previous history of central venous stenosis or thrombosis, any mechanical underlying cause for catheter occlusion, hypersensitive reactions to SK or reteplase, use of SK within the previous six months for any reason, high risk of bleeding (recent major surgery, intracranial or spinal injury, active bleeding, aortic aneurysm) lactating or pregnant were not included in the study.

Patients meeting the study criteria were included through convenience sampling until the desired number of participants was achieved. They were then assigned to two-member blocks and randomly allocated to one of the intervention groups using random allocation tables in Microsoft Excel. The patients were blinded to the medication that was administered.

Intervention and outcomes

The patients were divided into two groups, with 50 patients receiving 250,000 units of SK (*Vana Darou Gostar*, Iran) and 50 patients receiving 2 U of reteplase (*Osve Pharmacy*, Iran). The agents were instilled into the catheter and the lumens were not to be in contact with the agents for 6 h after SK and 2 h after reteplase injections.

The primary outcome of the study was to assess luminal patency and successful blood drawing from the catheter into a 20 mL syringe, as well as the possibility of appropriate haemodialysis at a velocity of ≥ 200 rounds per minute.

The secondary outcome included the frequency of thrombolytic use if the first injection did not lead to successful catheter lumen opening.

Data collection and analysis

Additional data on age, gender, duration of ESRD and the site of the embedded catheter were collected from medical records. The collected data were entered into the Statistical Package for Social Sciences (version 22, *IBM Corporation*, Armonk, NY, USA). Categorical statistics were reported as absolute numbers and percentages, while continuous variables were presented as mean and standard deviation. The Chi-square test or Fisher's exact test were used to compare categorical variables and the independent t-test was utilised to compare continuous variables. A p-value of less than 0.05 was considered to be statistically significant.

Results

In the current study, 100 patients in two equal 50-member groups were evaluated. The study population had the mean age of 60.48 ± 13.66 years (range: 19-89) and predominantly consisted of females (58 %). The most prevalent chronic medical diseases in the studied population were hypertension (70 %), diabetes mellitus (67 %), ischaemic heart disease (32 %) and hyperlipidaemia (23 %). Besides, the leading causes of ESRD included diabetes mellitus (64 %), hypertension (17 %), urinary tract infection (10 %), unknown (5 %), autoimmune disease (2 %) and cancer (2 %).

The studied patients were similar in terms of demographic, medical and clinical characteristics

including age ($p = 0.58$), gender ($p = 0.84$), comorbidities ($p > 0.05$), the aetiology of ESRD ($p > 0.05$), duration of ESRD ($p = 0.90$) and the site of implemented catheter ($p = 0.50$) (Table 1).

Table 2 shows the thrombolytic therapy related outcomes. Accordingly, the success rate of SK versus reteplase did not differ ($p = 0.48$). However, the required times to inject the agents in order to achieve appropriate luminal patency were statistically higher in the reteplase treated group ($p = 0.018$). None of the patients represented major adverse effects of the medications, bleeding and anaphylactic reaction.

Table 1: Demographic and clinical characteristics of the studied population

| Variables | Streptokinase treatment group (n = 50) | Reteplase treatment group (n = 50) | p-value |
|---|--|------------------------------------|----------|
| Demographic characteristics | | | |
| Age (year), mean \pm SD | 59.7 \pm 13.4 | 61.2 \pm 13.9 | 0.580 * |
| Gender (male), n (%) | 22 (44 %) | 20 (40 %) | 0.840 ** |
| Comorbidities, n (%) | | | |
| Hypertension | 32 (64) | 38 (76) | 0.190 ** |
| Diabetes mellitus | 38 (78) | 29 (58) | 0.056 ** |
| Ischaemic heart disease | 19 (38) | 13 (26) | 0.190 ** |
| Hyperlipidaemia | 12 (24) | 11 (22) | 0.810 ** |
| The aetiology of end-stage renal disease | | | |
| Diabetes mellitus | 34 (68) | 30 (60) | 0.400 ** |
| Hypertension | 10 (20) | 7 (14) | 0.420 ** |
| Urinary tract infection | 4 (8) | 6 (12) | 0.500 ** |
| Autoimmune disease | 0 (0) | 2 (4) | 0.490 # |
| Cancer | 0 (0) | 2 (4) | 0.490 # |
| Unknown | 2(4) | 3 (6) | > 99 # |
| Clinical characteristics | | | |
| ESRD duration (months), mean \pm SD | 28.0 \pm 33.1 | 27.2 \pm 33.9 | 0.90 * |
| Site of catheter, n (%) | | | |
| Jugular | 43 (86) | 44 (88) | 0.500 ** |
| Femoral | 7 (14) | 6 (12) | |

*: Independent t-test; **: Chi-square test; #: Fisher's exact test; SD: standard deviation; ESRD: end-stage renal disease;

Table 2: Streptokinase versus reteplase outcomes in the study population

| Variables | Streptokinase treatment group (n = 50) | Reteplase treatment group (n = 50) | p-value |
|--|--|------------------------------------|---------|
| Successful luminal patency, n (%) | 46 (92) | 43 (86) | 0.480** |
| Frequency of injections, mean \pm SD | 1.1 \pm 0.33 | 1.34 \pm 0.56 | 0.018* |
| Adverse effects, n (%) | | | |
| Bleeding | 0 (0) | 0 (0) | - |
| Anaphylactic reaction | 0 (0) | 0 (0) | - |

Independent t-test; **: Chi-square test; SD: standard deviation;

Discussion

Thrombosis formation in catheter lumens leading to their dysfunction is a common complication, accounting for 37-62 % of ESRD patients undergoing haemodialysis. Despite the high prevalence of this condition, the management and the choice of antithrombotic agents to dissolve the thrombosis with the least potential adverse effects remain a matter of debate. In presented study, aim was to compare the outcomes of two agents, SK versus reteplase. It was found that, despite both agents achieving a similar success rate in restoring appropriate haemodialysis through the patent lumens and having negligible adverse effects, fewer doses of SK were required to effectively dissolve the thrombosis and restore the function of the central venous catheter compared to reteplase.

In presented study, the use of reteplase to reopen the catheter lumen accounted for an 86 % success rate, similar to previous studies that reported a success rate of 85-91 % with the use of alteplase for occluded catheters. However, the specific protocols of these studies may have varied.⁵ Most of the studies in the literature applied a dwell time of 0.4 U of reteplase per catheter port for 30–60 min and reported promising outcomes.⁹⁻¹¹ Additionally, a study conducted by Hilleman and colleagues compared high-dose reteplase (2-3 U) with low-dose reteplase (0.5 U) and concluded that the high dose led to significantly superior outcomes than the low dose intervention (91 % versus 84 %).¹² A systematic review on various thrombolytic agents indicated that reteplase outperformed other agents in dissolving occluded catheters.¹³

SK is the oldest plasminogen activator agent used to restore function to occluded catheters. However, its associated complications, such as severe bleeding events and allergic reactions, have discouraged its routine use in this field.¹⁴ Recently, innovations have been applied to the production process of SK to improve its fibrinolytic characteristics, such as genetic manipulations, chemical modifications and domain fusions through the production of chimeric and conjugated SK proteins. These innovations, along with methods such as liposomal entrapment of SK or encapsulation in polyethylene glycol or chitosan nanoparticles, have resulted in the new generation SK with lower immunogenicity and improved fibrin-specific fibrinolytic properties.⁷

In this study, the dwell-lock technique of thrombolytic use, where the thrombolytic agent was instilled into the lumen and left for some hours or the procedure was repeated after an unsuccessful attempt for the first time, was proposed to minimise the potential adverse effects of using thrombolytic agents.¹⁵ This method was associated with no complications after the injections in presented study. Despite the emergence of more novel agents, recent studies have rarely examined SK in dissolving thrombosis. Tahir et al conducted a study in Pakistan comparing SK with urokinase in standard doses and reported successful outcomes for both approaches; however, SK was relatively superior with negligible complications.⁶ Another investigation by Wahaj et al compared high dose (375,000 U) versus low dose (225,000 U) SK to restore the patency of a blocked tunnel cuffed catheter. While both doses led to acceptable outcomes, the higher dose significantly led to superior re-canalisation in the first injection, although the success rate did not differ after the second injection.¹⁵

Conclusion

Older thrombolytic agents, such as SK and reteplase, have shown promise in unblocking haemodialysis catheters. The use of SK with a dwelling-lock technique led to successful outcomes with no complications and reteplase also showed favourable results. Due to the lower cost and the less frequent requirement for reinjection compared to reteplase, SK is preferred in this study. The conclusion suggests the need for further investigations to increase awareness and understanding of SK.

Ethics

The study protocol, which adhered to the tenets of the Helsinki Declaration, was initially proposed to the Isfahan University of Medical Sciences Ethics Committee and approved under the code number IR.MUI.MED.REC.1398.008, dated 17 April 2019. Patients were provided with written information and a verbal explanation about the study before giving their consent to participate. All participants signed a written consent form before taking part in the study.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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