TO ASCERTAIN THE EFFICACY, COST EFFECTIVENESS OF STREPTOKINASE AS INTRALUMINAL THROMBOLYTIC FOR OCCLUDED TUNNELED CATHETERS IN DIALYSIS PATIENTS OF A TERTIARY CARE HOSPITAL-A SINGLE CENTER EXPERIENCE

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ABSTRACT

Objective: To ascertain the efficacy, cost effectiveness and safety of streptokinase as intraluminal thrombolytic for occluded tunneled catheters in dialysis patients of a tertiary care hospital.

Study Design: Prospective quasi-experimental study.

Place and Duration of Study: Department of Nephrology, Pak Emirates Military Hospital Rawalpindi, from Aug 2018 to Jan 2019.

Methodology: The sample population comprised of 66 patients with occluded tunneled HD catheters who received either streptokinase in a dose of 250,000 unit or 375,000 units. Primary endpoint was the proportion of patients with occluded catheters achieving post-thrombolytic blood flow of ≥300 mL/min which persists for about 30min of hemodialysis. Safety endpoints included the adverse complications like bleeding or any serious allergic reaction.

Results: Out of 60 patients, 30 patients were treated with streptokinase in a dose of 375,000 units and 30 patients with 250,000 units of streptokinase. Hypertension and diabetes were the main causes of end-stage renal disease (50% vs 40%, p=0.08 and 33% vs 33%, p=0.38, respectively) jugular vein as main vascular access (54.8% vs 62.5%, p=0.57). Primary success was achieved in 60% in the first group and 42% in the second group, p=0.012. Patency was not achieved after the second dose in 10% in group-1 and 6.6% in the second group (p=0.31).

Conclusion: Streptokinase, although its efficacy as intraluminal thrombolytic agents is shrouded in disputation but still can be used as a robust and economical thrombolytic agent for occluded HD catheters in our country.

Keywords: Dialysis, Occluded tunneled catheters, Streptokinase, Thrombolytic agent.

INTRODUCTION

End stage renal disease is a humongous health problem worldwide and its prevalence is increasing at an unprecedented rate, afflicting about 13.1% of US population[1] whereas in Pakistan, its prevalence is about 12.5%[2]. The financial burden of ESRD, one of the paramount causes of atrocious compliance to therapy, ultimately leading to lamentable prognosis in majority of patients in our country. The average annual cost for management increases as per stage of disease ranging from USD 8091 (no CKD) to USD 46178 (CKD stage 4-5) and USD 87339 ESRD in patients under Medicare in USA[3]. The per capita annum for Pakistan currently stands at USD 1290.

Chronic kidney disease effectuate a robustious encumbrance on health care budget, with varied etiologies eventually emanating in irrevocable attrition of nephron number and function frequently leading to ESRD and requiring HD which is life sustaining procedure, therefore vascular access either through Tunneled catheter or AV fistula should be good enough to provide adequate blood flow rate Qb>300 ml/min[4]. This fact emphasizes the fact of proper counselling of patients for pre-emptive creation of AV fistula but because of the ongoing quagmire in the provision of vascular access and its astounding cost in creation will led more reliance on tunneled catheter for hemodialysis eventually. Nowadays, majority of the patients undergoing

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hemodialysis via tunneled catheter because of failure of multiple attempts of AV fistula[5] as 29% patients dialyzing through tunneled catheter in UK. Tunneled catheter are intricated mainly by thrombosis leading to catheter dysfunction and ultimately inadequate hemodialysis[6], which further adds towards the risk for mortality and morbidity.

There are mainly two types of catheter devices available, short term non-tunneled non-cuffed catheters and long term tunneled cuffed catheters (TCC). NCC (non-tunneled, non-cuffed catheters) should only be used for in-hospital managements and for a period not more than 2 week for internal jugular vein and 5 days for femoral catheters. For patients who are dialysis contingent for more than 2 week, TCC are the preferred vascular access due to boon of higher blood flow rates and lower rates of infections and accidental removal[7]. Both short term and long term complications are associated with TCCs. Long term complications including catheter malfunction and infections subsidised to the main causes of catheter dysfunction ultimately leading to catheter removal and replacement[4]. Catheter dysfunction is defined as failure to attain and maintain extracorporeal blood flow of about 300 ml/min[4]. Various techniques including intraluminal thrombolysis of TCC, with different protocols, after confirming correct tip placement have been used and documented in the literature. Drugs including streptokinase, urokinase, alteplase, tenecteplase, reteplase and alfimeprase have been attempted with different results and success rates[8-10]. Streptokinase and urokinase were historically preferred agents have now largely been discontinued in U.S, however remain agents of choice for our country due to cost effectiveness and ease of availability.

The rationale of this study was to assess the efficacy and cost effectiveness of 375,000 units of streptokinase as intraluminal thrombolytic agent as compared to 250,000 units of streptokinase for restoring the patency of occluded/malfunctioning hemodialysis catheters. It is assumed that dosing streptokinase at 375,000 units would provide better efficacy but more expenditure when compared to 250,000 units in a tertiary care hospital as literature review has revealed. There is quelling hefty economical burden in these patients especially in developing countries like Pakistan where people can't endure the pecuniary hardships of HD.

METHODOLOGY

This quasi-experimental study included 66 patients enrolled by non-probability purposive sampling, aged 18-65 years, with completely or partially occluded tunneled dialysis catheter having blood flow rate less than 300ml/min, who reported to Nephrology Dialysis Center of Pak Emirates Military Hospital Rawalpindi from August 2018 to January 2019. Patients with kinked or malpositioned catheters on Chest X-ray PA view, active bleeding from any site, major surgery within the last 02 months, history of allergic reaction to Streptokinase and its use within the last 7.5 years were excluded.

Subjects provided with a detailed description of the study and were inducted into the study after being approved from ethical committee and getting written informed consent. Dialysis was discontinued in patients with catheter dysfunction and catheter locked with pure heparin (according to volume of catheter) and patient admitted. Patients were randomly divided into two groups One group was being given 375,000 IU of streptokinase and the other group 250,000 units into each limb of catheter (volume mentioned on catheter) with continuous monitoring for about 03 hrs after which it was aspirated and blood flow checked. If good blood flow established , hemodialysis was initiated to check post thrombolysis blood flow. Patency was defined as blood flow of about 300ml/ min which persisted for about 30min during hemodialysis session after thrombolysis. Catheter was removed after failure to achieve patency with 3 attempts of Streptokinase. Estimated drug cost of streptokinase and Safety profile with different doses of thrombolytic also documented with complications like bleeding, allergic reaction etc.

All statistical analysis was performed using Statistics Package for Social Sciences version 21.0. Continuous variables were presented as means and standard deviation while discrete variables as frequency and percentages. The Fisher's exact test was used to do primary analysis by comparing proportions successfully finishing their dialysis and differences in pre-treatment blood flow rates with post treatment blood flow rates of patients. The *p*-value of ≤0.05 was considered to be statistically significant.

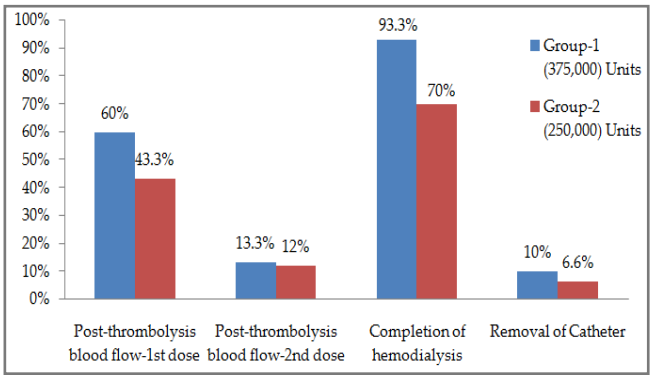

Figure: Efficacy of streptokinase results in group-1 (375,000 IU streptokinase) and group 2 (250,000 IU streptokinase) patients.

RESULTS

A total of 66 patients of CKD undergoing dialysis via tunneled catheter and with catheter dysfunction were approached to participate in the study. Of these, 6 patients were ineligible due to the exclusion criteria leaving 60 patients of which 30 (50%) patients received 375,000 units of streptokinase and 30 (50%) patients received 250,000 units of streptokinase. The mean age was 42 ± 11.56 years in the group-1 and 49 ± 10.44 years in the second group. All other characteristics of the study groups mentioned in the table-I. In group-1 patients, effective post thrombolysis blood flow rate achieved in 18 (60%) and 13 (43.3%) in group-2 patients (*p*=0.3019) (table-I). Group-1 patients more likely to complete hemodialysis compared to group-2 patients 28 (93.3%) versus 21 (70%), *p*=0.0419. Tunneled catheters were replaced in three patients in the

Table-I: Efficacy of streptokinase results in group 1 (375,000 IU streptokinase) and group 2 (250,000 IU streptokinase) patients.

	Completed dialysis post thrombolysis	**Not completing dialysis post thrombolysis**	***p*-value**
Group 1(375,000 IU streptokinase)	28 (93.3%	2 (6.66%)	0.0419
Group 2 (250,000 IU streptokinase)	21 (70%)	9 (30%)	
	Effective Blood Flow post-thrombolysis	**Effective blood flow not achieved post-thrombolysis**	
Group 1 (375,000 IU streptokinase)	18 (60%)	12 (40%)	0.3015
Group 2 (250,000 IU streptokinase)	13 (43.3%)	17 (56%)	

Table-II: Characteristics of the study group.

Characteristic	**Group-1 (n-30) (375,000 IU Streptokinase)**	**Group-2 (n-30) (250,000 IU Streptokinase)**	***p*-value**
Gender			
Male	51.8	56.8	0.31
Female	6	9	
Mean age	42	49	0.71
Underlying Disease			
Hypertension	16 (53.3%)	14 (46.6%)	0.38
Diabetes	8 (26.6%)	6 (20%)	0.08
Diabetes / Hypertension	3 (10%)	51(6.6%)	0.5
Chronic Glomerulosclerosis	2 (6.6%)	1 (3.33%)	0.01
Adult polycystic kidney disease	-	2 (6.66%)	0.7
Others	1 (3.33%)	2 (6.66%)	0.32
Jugular vein as main vascular access	54.8	62.5	0.57

375,000 units of streptokinase group 3 (10%) and two patients in the other group 2 (6.6%). Post thrombolytic effective blood flow was achieved after 2 attempts in four percent of group-1 patients 4 (13.3%) and 12 patients in group-2 patients 12 (40%) (figure). No episode of bleeding was observed in any group of patients however 1 patient in group-1 experienced minor reaction like flushing of face and chills (3.3%) but no major untoward effect observed with the other group. After applying fisher test analysis, it was observed that there is significant statistical difference between the treatment groups in terms of their efficacy, however no statistical difference observed in terms of side effect and cost effectiveness (table-II).

The average price of streptokinase of 1 vial containing 1.5 million units of streptokinase was 4900 Pak rupees, which yields 2 alliqouts of streptokinase (in a dose of 375,000) and 3 alliquots in case of 250,000 dose of streptokinase. The calculated cost for an aliquot of 375,000 dose is about 1225 Pak rupees while its about 816.6 Pakistan rupees for an alliqout of 250,000 dose while taking into consideration the average price of 1 vial of streptokinase.

DISCUSSION

We present the conspicuous and the first study so far published investigating the safety, cost and efficacy of intraluminal thrombolysis with streptokinase in occluded dialysis tunneled catheters. In contrary to the antecedent studies, role of alteplase, reteplase and urokinase in restoring the patency of occluded HD catheters have been well documented[8], however data on streptokinase and its dosing regimen for occluded HD catheters is exiguous and no randomized placebo controlled trial has been accomplished in humans to definitively apprise its worth in catheter dysfunction, though studies and trials accessible in animal model.

One year hemodialysis tunneled catheter survival estimated to be about 60% at 1 year and 51.5% at 3 years[9]. Catheter dysfunction due to thrombotic occlusion accounts for about 28% as mentioned in the largest strategic healthcare programs national database, 10 of which few enacted patency with thrombolytics that are non-invasive and cost effective. Thrombolytics including streptokinase alteplase, recombinant urokinase[11,12] all work by cleaving plasminogen to plasmin ultimately leading to clotlys is by breaking down fibrin. However alfimeprase, the newer thrombolytic agent act locally and produce fibrin degradation products directly, is under-going phase 3 trial for its potency as thrombolytic for occluded tunneled catheters.

Initially urokinase was considered to be only agent for long term catheter survival in 1998[12], later alteplase evolved, but despite that urokinase being cheaper than alteplase still being considered preferred in Europe as recommended by KDOQI[4].

Data on the intraluminal thrombolysis for tunneled dialysis catheter in impoverished countries remains scarce to provide a recommendation for the preferred agent and also on the optimal dosing to maintain catheter patency. Various retrospective and non-randomised prospective studies in the past, concluded good immediate success and better efficacy with reteplase and alteplase. One such retrospective study conducted by Hyman G, published in 2004 showed 85% of the patients completing hemodialysis session after reteplase administration while 70% able to achieve blood flow rate >250ml/min[10], but no study being conducted on streptokinase efficacy due to the unpropitious consequences, inspite of the cost-effective modality for catheter survival.

The primary patency achieved with t-PA is about 72%[13] while its about 80%[14] for urokinase, this is very much similar to streptokinase (60%) in our study. However, second treatment is required in 80% of patients with t-PA[13], while in our study second treatment was administered in 13.3% patients 1st group and 40% in the other group signifying high dose being the effective dose.

Many protocols for use of alteplase[12,14-16] recombinant urokinase, reteplase available.

According to Vercaigne *et al*, effective post-thrombolysis blood flow>300ml/min achieved in 82% of the patients administered alteplase push protocol than 65% of the patients with 2hr dwell protocol[20,21], but studies being carried out on their dose are lacking, likewise randomized control trials on streptokinase dose are also not available as it is associated with adverse consequences[2]. In our study, streptokinase in a dose of about 375,000 units had better success rate compared to streptokinase in a dose of 250,000 units.

There may be concern that the use of streptokinase as intraluminal thrombolytic, due to its antigenicity, will lead to an increased risk of sententious complications and other adverse events. In our study, no major complication observed as cited by Shavit *et al*[17], however we encountered only minor allergic reaction in 3.3% percent of patients which was more common in the first group. Our results are in congruence with the results of past literature[18,19].

Taking into account the fiscal cost of streptokinase, our results show monetary perk with a dose of 250,000 units as 01 vial of 1.5 million units will offer more than 03 alliquots, however, only 02 alliquots will be provided if 375,000 units of streptokinase used, this is in accordance with the prospective study being carried out by Haymond J, in 2005, on alteplase which also showed low dose (1mg/lumen dose) to be more cost effectivethan the high dose[13].

Our study has several important impediments. It is single center study without external corroboration including minuscule number of patients, of ephemeral duration and lacking comparison with the standard thrombolytic agent. As a result, they were not able to assess the impact of streptokinase on catheter survival which requires many months of follow up. Furthermore, lack of detailed evaluation of the etiology of catheter malfunction which will help us in recognizing patients in which it will be more fruitful curb the epilogue drawn from this study. Thus, we would galvanize researchers in the field to add all these variables in future trials for intraluminal thrombolysis of tunneled catheters. Clearly, our study highlights the need that vigorous effort in general is necessary to make great strides for revamping patient care (outcome) in such patients.

CONCLUSION

Streptokinase, although its efficacy as intraluminal thrombolytic agents is shrouded in disputation but still can be used as a robust thrombolytic agent for occluded HD catheters. Our study also revealed streptokinase to be economical for developing nations like Pakistan where outrageous prices in the market of newer armamentarium (i.e., other newer thrombolytics and catheter exchange procedure) will be extravagant for our population. Large randomized control trials needed as the sample size quite less to detect a difference from the newer agents.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

REFERENCES

1. Saran R, Li Y, Robinson B, Abbott KC, Agodoa LY, Ayanian J, et al. US renal data system 2015 annual data report: epidemiology of kidney disease in the United States. Am J Kidney Dis 2016; 67(3): S1-7.
2. Imran S, Shiekh A, Saeed Z, Khan SA, Malik AO, Patel J, et al. Burden of chronic kidney disease in an urban city of Pakistan, a cross-sectional study. J Pak Med Assoc 2015; 65(4): 366-69.
3. Golestaneh L, Alvarez PJ, Reaven NL, Funk SE, McGaughey KJ, Romero A, et al. All-cause costs increase exponentially with increased chronic kidney disease stage. Am J Manag Care 2017; 23(10-Suppl): S163-72.
4. John T, Thomas A. Kdoqi clinical practice guideline for Hemodialysis adequacy: 2015 update. Am J Kidney Dis 2015; 66(5): 884-930.
5. Pisoni RL, Zepel L, Port FK, Robinson BM. Trends in vascular access use, patient preferences, and related practices: an update from the US DOPPS practice monitor with international comparisons. Am J Kidney Dis 2015; 65(6): 905-15.
6. Miller LM, MacRae JM, Kiaii M, Clark E, Dipchand C, Kappel J, et al. Hemodialysis tunneled catheter noninfectious complications. Can J Kidney Health Dis 2016; 3(1): 1-10.
7. Pašara V, Maksimovic B, Gunjaca M, Mihovilović K, Lončar A, Kudumija B, et al. Tunnel led haemodialysis catheter and haemodialysis outcomes: a retrospective cohort study in Zagreb, Croatia. Bio Med J Open 2016; 6(5): e009757.
8. Kennard AL, Walters GD, Jiang SH, Talaulikar GS. Interventions for treating central venous haemodialysis catheter malfunction. Cochrane Database Syst Rev 2017; 10(1): CD011953.
9. Dinh LD, Nguyen DH. Vascular access for hemodialysis: Current practice in Vietnam. J Vascular Access 2018; 20(1): 20-23.
10. Hyman G, England M, Kibede S, Lee P, Willets G. The efficacy and safety of reteplase for thrombolysis of hemodialysis

catheters at a community and academic regional medical center. Nephron Clin Pract 2004; 96(2): c39-42.
11. Gunawansa N, Sudusinghe DH, Wijayaratne DR. Hemodialysis catheter-related central venous thrombosis: clinical approach to evaluation and management. Ann Vas Surg 2018; 51(1): 298-305.
12. Wójtowicz D, Cholewa D, Faba AM, Domańska B, Kokoszka J, et al. Diabetes decreases patency of tunneled catheters in hemodialysis patients after first effective thrombolysis with urokinase. Ren Fail 2018; 40(1): 384-89.
13. Haymond J, Shalansky K, Jastrzebski J. Efficacy of low-dose alteplase for treatment of hemodialysis catheter occlusions. J Vasc Access 2005; 6(2): 76-82.
14. Clase CM, Crowther MA, Ingram AJ, Cina CS. Thrombolysis for restoration of patency to haemodialysis central venous catheters: a systematic review. J Thromb Thrombolysis 2001; 11(2): 127-36.
15. Van Hulle F, Bonkain F, De Clerck D, Aerden D, Vanwijn I, Tielemans C, et al. Efficacy of urokinase lock to treat thrombotic dysfunction of tunneled hemodialysis catheters: A retrospective cohort study. J Vasc Access 2019; 20(1): 60-69.
16. Daeihagh P, Jordan J, Chen J, Rocco M. Efficacy of tissue plasminogen activator administration on patency of hemodialysis access catheters. Am J Kidney Dis 2000; 36(1): 75-79.
17. Shavit L, Lifschitz M. High dose urokinase for restoration of patency of occluded permanent central venous catheters in hemodialysis patients. Clin Nephrol 2010; 74(4): 297-302.
18. Hilleman D, Campbell J. Efficacy, safety, and cost of thrombolytic agents for the management of dysfunctional hemodialysis catheters: A systematic review. Pharmacother 2011; 31(10): 1031-40.
19. Pollo V, Dionízio D, Bucuvic EM, Castro JH, Ponce D. Alteplase vs. urokinase for occluded hemodialysis catheter: A randomized trial. Hemodial Int 2016; 20(3): 378-84.
20. Vercaigne LM, Zacharias J, Bernstein KN. Alteplase for blood flow restoration in hemodialysis catheters: A multicenter, randomized, prospective study comparing "dwell" versus "push" administration. Clin Nephrol 2012; 78(4): 287-29.
21. Marques MG, Maia P, Ponce P. Dialysis catheter malfunction. Port J Nephrol Hypert 2017; 31(3): 184-91.