Short Communication

A Research Protocol on Efficacious Evaluation of Thrombus Recanalization Techniques Employing Pigtail Catheter *versus* Spray Catheter for Vessel Patency in Acute Iliofemoral Deep Venous Thrombosis — A Randomized Controlled Trial

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Background : Iliofemoral Deep Vein Thrombosis involves either partial or total occlusion of iliac and/or common femoral vein led by intravascular thrombus causing obstruction of resultant lumen. Venous valvular incompetence is one of the common factors leading to Deep Venous Thrombosis making it a vicious circle. Now-a-days, the concept of pharmacomechanical catheter directed thrombolysis is being utilised to treat Deep Venous Thrombosis of the lower limbs. The present study compares two thrombus recanalization techinques in iliofemoral deep vein thrombosis with respect to vessel patency.

Materials and Methods : In a randomised controlled parallel group trial, subjects (n=80) with acute iliofemoral Deep Venous Thrombosis will be enrolled into two groups A and B with 1:1 ratio of allocation. Group A will be subjected to spray catheter thrombus recanalization and group B will be subjected to pigtail catheter thrombus recanalization techniques. Follow-up will be on a periodic basis till 9 months. Primary outcome will be vascular patency representing anterograde flow across thrombosed vascular segment.

Purpose of the study : The outcomes of the current study will analyse the patency percentage of thrombosed iliofemoral venous segments after spray catheter and pigtail catheter thrombus recanalization techniques with respect to anterograde vascular flow.

Expected clinical implications : This study attempts to investigate the outcomes of two thrombus recanalization techniques at different points in the timeline up to 9 months with reference to vascular patency in terms of the anterograde flow across the thrombus site.

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***Key words* : Thrombus Recanalization, Pigtail Catheter, Spray Catheter, Vessel Patency, Acute Iliofemoral, Deep Venous Thrombosis.**

Iliofemoral Deep Vein Thrombosis involves either partial or total occlusion of iliac and/or common femoral vein led by intravascular thrombus causing obstruction of resultant lumen. This leads to elevation of venous blood pressure thereafter due to decreased luminal diameter. Resultant functional disability of affected leg is known to cause pain, cramps, hyperpigmentation, heaviness etc[1,2]. Post thrombotic syndrome thereafter is a known and notorious sequel due to functional disability along with anterograde venous flow obstruction[3-7].

Literature states that the more distal the thrombus is located, the better recanalization potential of the involved vessel there is if treated with anticoagulant therapy alone[8,9]. This may be attributed to the fact

Editor's Comment :

- This study protocol has been designed to examine the effectiveness of 2 methods for Deep Venous Thrombolysis - Conventional method using the spray catheter and the novel method which employs the pigtail catheter ie, Banode Mishra Thrombolysis technique.
- The main findings which are akin to the present study are to examine the vascular patency of the affected iliac vessels over a period of time to ensure long term effects.
- Any statistically significant difference in between the conventional and novel methods over the course of study will be key to indicating desired procedure selection for deep venous thrombosis.

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that the more proximal the site of thrombus in the venous vasculature, the more venous Blood Pressure it takes to propel the blood for the veins towards the heart and again, this puts the venous valves at extreme pressure. Venous valvular incompetence is one of the common factors leading to Deep Venous Thrombosis making it a vicious circle. Main outcome in question apart from long term follow up remains vessel patency at different points in the timeline[10-13].

It is stated clearly in literature that one of the most important factors contributing towards post thrombotic syndrome along the timeline is residual thrombus as a result of an incomplete thrombolysis treatment[14,15]. However, the recent advances mark the concept of utilising pharmacomechanical catheter directed thrombolysis to treat lower limb Deep Venous Thrombosis. Hence, the null hypothesis states that the thrombus recanalization techniques employing pigtail catheter will not be more efficacious than spray catheter for vessel patency in acute iliofemoral deep venous thrombosis and the alternate hypothesis states vice-versa.

The present study compares two thrombus recanalization techniques in the setting of iliofemoral deep vein thrombosis with respect to vessel patency in terms of the anterograde flow across the thrombus site.

Materials and Methods

Ethical Approval :

The study proposal was approved on consideration of ethical grounds by Institutional Ethics Committee, Datta Meghe Institute of Medical Sciences (deemed to be university) on 15th July, 2022 with letter reference number DMIMSU(DU)/IEC/2022/03. The present study has been registered in the Clinical Trial Registry India with the registration number CTRI/2022/12/047888. https://ctri.nic.in/Clinicaltrials/rmaindet.php?trialid=76868&EncHid=15032.46177&modid=1&compid=19

Study Design :

The present study will be carried out in the Department of Interventional Radiology, Acharya Vinoba Bhave Rural Hospital, Jawaharlal Nehru Medical College after approval obtained from Institutional Ethics Committee, Datta Meghe Institute of Higher Education and Research (declared as deemed to be university), formerly known as Datta Meghe Institute of Medical Sciences (deemed to be university). The participants will be duly informed about the aim, objectives and procedure pertaining to this research and will be included only after obtaining a statement of informed consent from them. A total of 80 cases will be enrolled and divided into 2 groups of 40 each.

Trial Design :

The study is a randomized parallel group controlled trial. The patients included for the research will be distributed into two independent groups – Group A and Group B. Group A will include patients getting the spray catheter based Deep Venous Thrombolysis while Group B will be assigned to be getting the pigtail catheter based Deep Venous Thrombolysis. The allocation of patients into these two groups will be based on computer generated randomization with concealment/blinding to be carried out by usage of sequentially numbered sealed envelopes.

Participants :

Those patients aged 16 to 75 years with acute ilio-femoral Deep Venous Thrombosis reporting to Department of Interventional Radiology, Acharya Vinoba Bhave Rural Hospital, Sawangi (Meghe), Wardha with absence of contraindications to thrombolytic treatment or no other cerebrovascular pathology related to fibrinolytic therapy, having life expectancy more than 6 months with no history of malignancy or addiction, those having given the statement of informed consent with symptoms of 21 days or less time duration will be enrolled[4,12]. Those patients with the history of recent major surgery, cerebrovascular accident and pregnancy will be considered under the exclusion criteria.

Sample Size Consideration :

Sample size was calculated using the Superiority (Parallel Design) Formula Using Proportion Difference as follows[16] :

$$n1 = \frac{(Z\alpha+z\beta)^2(p1(1-p1)+p2(1-p2)}{(\varepsilon-\delta)^2}$$

$Z\alpha$ = 1.64
α = Type I error
$Z\beta$ = 0.84
β = Type II error rate at 20%
Power $(1-\beta)$ = 80%
ε = True proportional difference
δ = Clinically Relevant difference (25%)
Considering true proportional difference ε =0
P1 = 60 %, P2 = 80 % (Assumed)
Here, True proportion difference Luminal Obstruction opening (Difference in Proportion ε) =0 % = 0
Clinically acceptable for Superiority (δ) single tail tailed = 25% = 0.25 (Expected)
P1 = 60% = 0.60
P2 = 85 % = 0.85(Assumed)
n1 = (1.64+ 0.84)^2* [(0.60*(1- 0.60)+ (0.85*(1-0.85)]/ (0.00 -0.25)^2 =36 for one group superiority
Total = 36 +36 =72, considering 10% Drop out rate ~ 8 = 40 +40 = 80
Therefore, the total number of cases which will be enrolled for the present study is 80, thereby including

40 cases in each study group.

Intervention Design :

Group A :

All the patients in Group A will be subjected to spray catheter (Cook Medicals LLC, USA) thrombus recanalization technique. The patients will be lying in prone position after the deployment of a filter in the inferior vena cava near the left renal vein's origin. The popliteal vein will be accessed by ultrasonography and punctured followed by insertion of a 7 French sheath (Translumina Therapeutics LLP, India). This will be followed by introduction of 0.035 hydrophilic guidewire (Blueneem Medical Devices Pvt Ltd., India) and intravascular catheter (Cook Medicals LLC, USA) over it and a venogram will be taken to assess the level and extent of intravascular thrombus load on digital subtraction angiography. A 5 French Cobra or Headhunter catheter (Cook Medicals LLC, USA) will be advanced over the guidewire up to the level of inferior vena cava crossing the thrombotic section. Then, there will be exchange of Cobra or Headhunter catheter with spray catheter over the hydrophilic guidewire through the sheath. The proximal tip of spray catheter will stay at the site of thrombus. Through the spray catheter, there will be administration of alteplase (10 ml alteplase in 50 ml normal saline). After 4 hours, spray catheter is exchanged over the hydrophilic guidewire with Judkins catheter (Translumina Therapeutics LLP, India) and mechanical aspiration of thrombus is carried out using a 50 ml syringe immediately followed by a post procedural venogram.

Group B :

All the patients in Group B will be subjected to pigtail catheter thrombus recanalization technique. The patients will be lying in prone position after the deployment of a filter in the inferior vena cava near the left renal vein's origin. The popliteal vein will be accessed by ultrasonography and punctured followed by insertion of a 7 French sheath. This will be followed by introduction of 0.035 hydrophilic guidewire and intravascular catheter over it and a venogram will be taken to assess the level and extent of intravascular thrombus load on digital subtraction angiography. A 5 French Cobra or Headhunter catheter will be advanced over the guidewire up to the level of inferior vena cava crossing the thrombotic section. Then, there will be exchange of Cobra or Headhunter catheter with pigtail catheter (Cook Medicals LLC, USA) over the hydrophilic guidewire through the sheath. The proximal tip of pigtail catheter will stay at the site of thrombus. This will be followed by forceful injection of alteplase (10 ml alteplase in 50 ml normal saline) through the pigtail catheter with rotation of the pigtail catheter by an angle of 90 degree and withdrawal by 1.5 to 2 cm distally. These steps will be repeated in succession till the entire thrombotic segment has been covered. After 4 hours, pigtail catheter is exchanged over the hydrophilic guidewire with Judkins catheter and mechanical aspiration of thrombus is carried out using a 50 ml syringe immediately followed by a post procedural venogram.

Outcome Measures :

The primary outcome for the present study will be extent of vessel recanalization and patency percentage based on the degree of luminal reduction. The success of catheter directed thrombolysis will be classified as success (>90%), partial success (more than 50% but <90%) and failure (<50%) where the said percentages are referring to the luminal area where venograms reveal robust anterograde flow across the thrombus site.

Follow-up :

Once the immediate pre-procedural (t_0) and post-procedural (t_4) venograms will have been taken, subsequent venograms will be recorded at further future patient visits at one (t_1), three (t_2), six (t_3), and nine (t_4) months as shown in Fig 1 after the discharge on colour doppler ultrasound or digital subtraction angiography. The follow-up measurements will be preserved electronically. During the trial, in case of the drop outs, the reasons will be recorded along with getting in contact with them as soon as possible and subjecting them to the projected follow up subsequently. The data regarding patient withdrawal as well as drop-out will be recorded and reflected in the final data analysis under the intention to treat principle of the analysis.

Blinding :

The intervention and outcome measure will be implemented by the Principal Investigator under the supervision of co-investigator.

Data Management :

The recorded data of the present trial will remain secured with restricted access upon permission for further analysis and reference by the researcher, the supervisor or the biostatistician.

Statistical Analysis :

The statistical analysis of the recorded data will carried out by IBM SPSS Statistics software (Version 27). Group effect will be calculated and compared by two-way analysis of variance (ANOVA). Significant difference thus shown, students t-test will be applied to calculate and compare in-group changes. Determination of significance will be made by a two-sided p value of less than 0.05. Baseline comparison

	STUDY PERIOD						
	Recruitment	Allocation	Post-allocation				Close-out
TIMEPOINT**	$-t_1$	Baseline t_0	t_1	t_2	t_3	t_4	t_x
ENROLMENT:							
Eligibility screen	X	X	X			X	X
Informed consent	X						
Allocation		X					
INTERVENTIONS:							
[Group A]		X	X	X	X	X	
[Group B]		X	X	X	X	X	
ASSESSMENTS:							
[Extent of Vessel Recanalization]		X	X	X	X	X	X
[Patency Percentage]		X	X	X	X	X	X

Fig 1 — SPIRIT Schedule for randomized parallel-group controlled trial, interventions, and assessments where t_0 is pre-procedural, t_1 is one month, t_2 is three months, t_3 is six months, and t_4 is nine months follow-up

will be carried out using Fisher's exact test, t-test or Mann-Whitney U test. Comparison of primary outcome will be carried out by application of Mann-Whitney U test upon the recorded data at the post-procedural venogram, 1 month, 3 months, 6 months and 9 months as per future patient visits. Intention to treat analysis principle will be used for the present study.

Discussion

Venous Thromboembolism has been a considerable concern in public health domain with high rates of pulmonary thromboembolism therein[17-19]. Deep venous thrombosis stands for approximately 66% of venous thromboembolism cases. A trial on Adjunctive Catheter-Directed Thrombolysis for Thrombus Removal (ATTRACT) demonstrated that catheter-directed pharmaco-mechanical thrombolysis (PCDT) did not lessen the frequency of post thrombotic syndrome but lowered its intensity during a 24-month period of follow-up and accelerated resolution of acute symptoms[12]. In a trial, the Catheter-Directed Venous Thrombolysis in Acute Iliofemoral Vein Thrombosis (CAVENT), thrombolysis was directed with catheter to reduce the post-thrombotic syndrome risk 2 and 5 years[10]. Pharmacomechanical catheter directed thrombolysis has been employed in various studies and randomized trials[10,12] noting its significant utility in easing the severity of acute symptoms[20]. This study attempts to investigate the outcomes of two thrombus recanalization techniques at different points in the timeline up to 9 months with reference to vascular patency in terms of the anterograde flow across the thrombus site.

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