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Review

Safety and Efficacy of Catheter Direct Thrombolysis in Management of Acute Iliofemoral Deep Vein Thrombosis: A Systematic Review

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Purpose: Catheter direct thrombolysis (CDT) has been shown to be an effective treatment for deep venous thrombosis. The objective of the review is to improve safety and efficacy of the CDT by using ward based protocol, better able to predict complications and treatment outcome through monitoring of haemostatic parameters and clinical observation during thrombolysis procedure.

Materials and Methods: MEDLINE, EMBASE, CENTRAL and Web of Science were searched for all articles on deep venous thrombosis, thrombolysis and correlations of clinical events (bleeding, successful thrombolysis) during thrombolysis with hemostatic parameters to March 2016. The risk of bias in included studies was assessed by Cochrane Collaboration's tool and Cochrane Risk of Bias Assessment Tool: for Non-Randomized Studies of Interventions.

Results: Twenty-four studies were included in the review and we found that improving safety and efficacy of CDT by using ward based protocol depending on eight factors; strict patient selection criteria, types of fibrinolytic drugs, mode of fibrinolytic drug injection, biochemical markers monitoring (fibrinogen, D-dimer, activated partial thromboplastin time, plasminogen activator inhibitor-1), timing of intervention, usage of intermittent pneumatic calf, ward monitoring and thrombolysis imaging assessment (intravascular ultrasound). These factors may help to improve safety and efficacy by reducing total thrombolytic drug dosage and at the same time ensure successful lysis. There is a marked lack of randomized controlled trials discussing the safety and efficacy of catheter direct thrombolysis.

Conclusion: CDT can be performed safely and efficiently in clinical ward, providing that careful nursing, biochemical monitoring, proper selection and mode of infusion of fibrinolytic drugs, usage of Intermittent pneumatic calf and adequate thrombolysis imaging assessment are ensured.

Key Words: Ilio-femoral deep vein thrombosis, Catheter direct thrombolysis, Hemorrhage, Bio-chemical markers

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INTRODUCTION

1) Background

Venous thromboembolic (VTE) disease is very common in the western world with an incidence of 1.6 per 1,000 persons per year [1]. It has been estimated that 25,000 people in the UK die every year from hospital-acquired VTE [2].

Deep vein thrombosis (DVT) is an important clinical condition as it may result in thromboembolism to the lungs pulmonary embolism (PE) or post thrombotic syndrome (PTS). The mainstay of treatment is anticoagulation, which reduces the risk of thrombus propagation and subsequent embolism. Anticoagulation however doesn't accelerate the rate of thrombolysis, which continues at the natural rate. Thrombolytic therapy has been shown to have a role in treatment but is not widely used, as majority of patients are unsuitable to receive it.

DVT may develop spontaneously in healthy individuals but there are also known risk factors that can predispose its development [3]. Most risk factors influence one or more of the components of virchow's triad (vessel wall damage, stasis of blood and hypercoaguability) and in particular, many are associated with an element of hypercoaguability.

The American College of Chest Physicians Committee has recommended treatment strategies for thrombus removal in patients with acute DVT to reduce acute symptoms and post-thrombotic morbidity. It was the opinion of the guideline committee that if catheter direct thrombolysis (CDT) were available, it would be preferable to operative venous thrombectomy, assuming that patients are at low risk for bleeding [4].

The Committee has addressed the importance of correcting underlying venous lesions after successful CDT and recommended that the same intensity and duration of anticoagulant therapy be used in these patients as in comparable patients who did not undergo CDT, thereby underscoring the importance of avoiding rethrombosis.

The objectives in treatment of acute DVT are to prevent thrombus extension, early recurrence, death from PE and late recurrences and long-term consequences such as the development of PTS and chronic pulmonary hypertension.

Currently, most of the patients who have CDT procedure are likely to be monitored in high dependency unit (HDU) which might lead to delay of thrombolysis and also add to the cost of the procedure.

The aim of the review is to understand the mechanism of clot dissolution in CDT and the possibility of improving safety and efficacy of the procedure by using ward based protocol, better able to predict complications and treatment outcome through monitoring of haemostatic parameters and clinical observation during thrombolysis procedure.

2) Research hypothesis

① Null hypothesis

There is no benefit in the use of a ward based protocol for catheter based thrombolysis and stenting in improving efficacy and safety of the treatment of acute iliofemoral DVT.

MATERIALS AND METHODS

This review was written following guidance of the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement [5].

Prior to the start of this review, Current Controlled Trials, Clinical Trials, and World Health Organization International Clinical Trials Registry Platform were searched for ongoing trials: none was found.

We also searched the International Prospective Register of Systematic Reviews for ongoing systematic reviews or meta-analyses: none was found.

A comprehensive search was conducted of the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE via PubMed, MEDLINE via OvidSP, and EMBASE via OvidSP addressing the safety and efficacy of CDT in management of acute iliofemoral DVT, role of haemostatic parameters in prediction and prevention of bleeding complication during thrombolysis and the role of ward based clinical observations in improving safety and efficacy.

In order to maximize sensitivity of the search a combination of the following keywords was used: "DVT", "deep venous thrombosis", "thrombolysis", "activated partial thromboplastin time (aPTT)", "safety", "efficacy", "D-dimer", "plasminogen activator inhibitor-1 (PAI-1)", "tissue plasminogen activator (tPA)", "iliofemoral", "fibrinogen" and "CDT".

1) Eligibility criteria

① Participant

Studies of participants diagnosed with acute iliofemoral deep venous thrombosis at any age.

② Intervention

Hemostatic parameter monitoring and clinical observation during thrombolysis procedure for iliofemoral DVT.

③ Outcomes

Improve safety and efficacy of CDT by reducing bleeding complication incidence and improve clinical outcome.

④ Study design

Randomized controlled trials (RCTs), controlled trials and cohort studies are eligible for inclusion provided that data from a comparison group are reported. Case series and case reports are excluded from the review owing to the high potential for bias in these study designs. Case-control studies (except where nested as part of a cohort study) and economic evaluations are also excluded.

⑤ Language

English language.

2) Data extraction (selection and coding)

Two independent reviewers were involved in both study selection and data extraction. There was no blinding of the reviewers. Data extraction was carried out independently and in duplicate by the study investigators in review manager.

Disagreement was resolved by review team discussion and the article was excluded, if any of the eligibility criteria were not met. Results of data extraction were compared, and any discrepancies were resolved by consensus among researchers and arbitration by an additional independent researcher.

Data were extracted using a standardized data collection form, covering; general information (study identifier, year of publication of the last report, study period, country of origin, source of funding and type of publication), study characteristics (aim of the study, study design, inclusion and exclusion criteria, recruitment procedures used; e.g., details of randomisation, blinding and unit of allocation), participant characteristics (age, gender, ethnicity, disease characteristics and co-morbidities), intervention and setting (systemic thrombolysis, continuous CDT, single bolus CDT), and outcome data and result (unit of assessment for every hemostatic parameters and grade of thrombolysis, statistical test used, definition used in the study, unit of measurement, number of participant enrolled, number of withdrawals, exclusion, lost follow up and summary of outcome data and results of study analysis; e.g., odd ratio [OR], risk ratio [RR] and confidence intervals, P-value).

3) Risk of bias (quality) assessment

We assessed risk of bias in included studies using the Cochrane Collaboration's tool [6], which addresses six specific domains: allocation sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias. Non-randomized studies risk of bias was assessed using Cochrane Risk of Bias Assessment Tool: for Non-Randomized Studies of Interventions (ACROBAT-NRSI) [7].

4) Quality assessment

The abstracts of all identified articles were reviewed, and the studies that are deemed suitable were selected for review.

Each article is then examined to ensure that it meets eligibility requirements and quality per threshold. Essentially every piece of research is critically appraised with a view to eliminating biased studies.

5) Result of the search

The search based on the five electronic databases retrieved 1,343 potentially relevant records. After removing duplicates and unsuitable abstracts, 294 titles and abstracts remained for screening: 272 were found ineligible. Finally articles included in review are 24 of which 2 randomized controlled trial. Details of article selection are shown in Fig. 1.

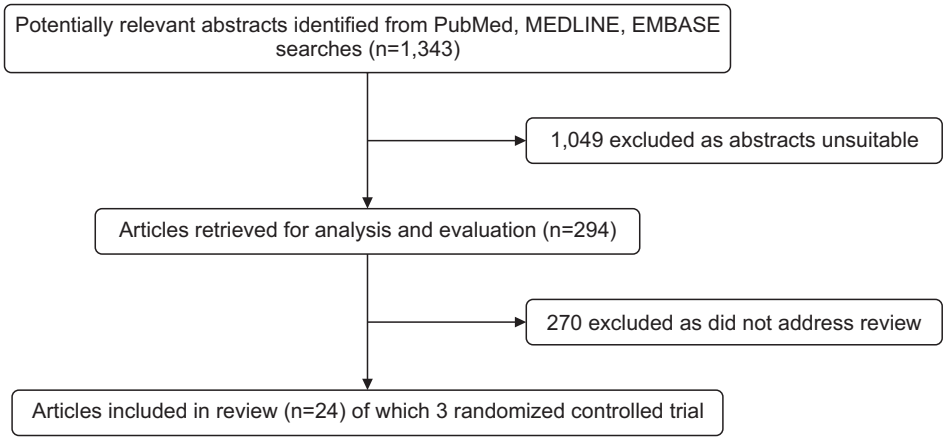

Fig. 1. Flowchart demonstrating article selection process.

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6) Included studies

① We included two RCTs (235 participants)

Cavent trial [8] representing the first RCT in this area and aimed to evaluate whether additional CDT with altepase improved the functional outcome by reducing PTS development following acute iliofemoral DVT comparing it to standard treatment (anticoagulation).

Grünewald et al. [9] representing the only RCT on patients undergoing thrombolytic therapy for deep venous thrombosis that correlate between hemostatic parameters and clinical event such as therapeutic outcome and bleeding complications.

Bovill et al. [10] is a RCT that discuss the outcome of thrombolytic treatment of acute myocardial infarction however we included it in the review as there were no other studies regarding DVT thrombolysis discussing the relationship between hemostatic parameters and clinical events specially DD and fibrinogen during thrombolysis.

② Other studies included were 20 prospective studies

Fourteen studies comparing between CDT plus anticoagulation versus anticoagulation alone in management of acute deep venous thrombosis [11-23].

One study [24] investigates the loco-regional thrombolytic effect by studying hemostatic parameters.

Two studies [25,26] discussed daily catheter-directed single dosing of tPA in treatment of acute deep venous thrombosis of the lower extremity. Lozier et al. [27] focus also on biochemical dynamics relevant to the safety of low-dose, intraclot altepase for DVT.

One study [27] evaluates the efficiency and safety of intermittent pneumatic compression during CDT for DVT using low dose urokinase by comparing it with CDT alone.

One study [28] assess the feasibility of identifying DVT characteristics with contrast enhanced magnetic resonance venography (MRV) and correlate [29] this finding with clinical outcome of thrombolysis.

One study [30] is a cohort study comparing between intravascular ultrasound (IVUS) and standard, single-plane, transfemoral venography were performed in 304 consecutive limbs during balloon dilation and stenting of an obstructed iliac venous segment.

One systematic review [31] discussed the outcome (success rate and bleeding incidence) of systemic thrombolysis and CDT in management of lower limb DVT by analyzing 13 RCTs and 19 cohort studies, respectively.

7) Risk of bias in included studies

The assessment of risk of bias of included RCT is summarized in Fig. 2.

In general terms, risk of bias was judged to be low both in sequence generation and sequence concealment.

Cohort studies included in the systematic review were assessed according to ACROBAT-NRSI seven domains, 2 pre-intervention (bias due to confounding, bias in selection of participants into the study), at intervention (bias in measurement of interventions) and post-intervention (bias due to departures from intended interventions, bias due to missing data, bias in measurement of outcomes and bias in selection of the reported result).

Chang et al. [25] and Lozier et al. [26] are prospective studies, which discuss the outcome of single bolus altepase in management of acute lower limb DVT (calf veins, popliteal vein, iliofemoral vein and inferior vena cava thrombo-

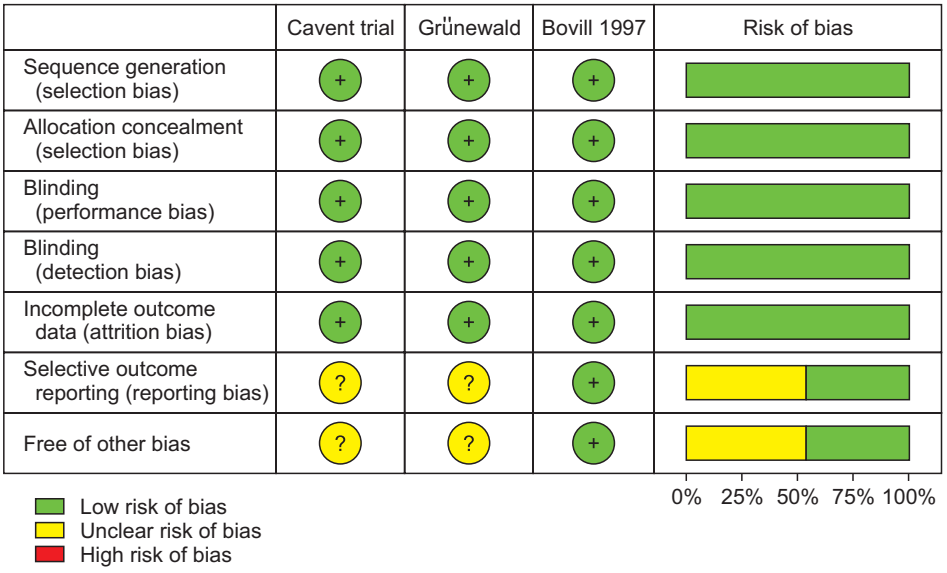

Fig. 2. Risk of bias in the included randomized controlled trials.

sis), and there is moderate risk of bias as good outcome may be related to including cases with calf vein and popliteal vein thrombosis low thrombus burden (selection bias).

Other prospective studies [12-22,24,32,33] show low risk of bias.

RESULTS

Bleeding is the main CDT complication and occurred in 5% to 10% of cases with most located at the venous access site [34,35].

The review discusses the potential factors that may improve safety and efficacy during thrombolysis procedures.

We divided these factors into eight factors; patient selection criteria, fibrinolytic drugs, mode of fibrinolytic drug injection, biochemical markers, timing of intervention, intermittent pneumatic calf compression (IPCC), ward monitoring and thrombolysis imaging assessment.

1) Patient selection criteria

Most of the bleeding complications probably occur as a result of action of thrombolytic drugs at sites of vascular injury or malformation. This is why most of the studies agree that strict exclusion criteria for local thrombolysis can improve safety and avoid bleeding complication.

Society of Intervention Radiology (SIR) [36] produced its standards for endovascular thrombus removal of lower limb DVT and divided the contraindication to pharmacologic CDT into absolute contraindication and relative contraindications:

① Absolute contraindications

Active internal bleeding or disseminated intravascular coagulation.

Recent cerebrovascular event (including transient ischemic attacks), neurosurgery (intracranial, spinal), or intracranial trauma (less than three months).

Absolute contraindication to anticoagulation.

② Relative contraindications

Recent cardiopulmonary resuscitation, major surgery, obstetrical delivery, organ biopsy, major trauma, or recent eye surgery (less than seven to ten days), intracranial tumour, other intracranial lesion, or seizure disorder.

Uncontrolled hypertension: systolic >180 mmHg, diastolic >110 mmHg.

Recent major gastrointestinal bleeding (less than three months).

Serious allergic or other reaction to thrombolytic agent, anticoagulant, or contrast media (not controlled by steroid/antihistamine pretreatment).

Severe thrombocytopenia.

Known right-to-left cardiac or pulmonary shunt or left heart thrombus, massive PE with hemodynamic compromise.

Suspicion for infected venous thrombus.

③ Other relative contraindications

Renal failure (estimated glomerular filtration rate <60 mL/min), pregnancy or lactation, severe hepatic dysfunction, bacterial endocarditis and diabetic hemorrhagic retinopathy.

Most of the trials advice similar contraindication, however, Cavent and adjunctive catheter-directed thrombolysis trials [8] added others exclusions criteria in addition to the one mentioned by SIR like life expectancy less than 2 years, chronic non-ambulatory status and haemoglobin less than 9; international normalized ratio more than 1.6 before warfarin.

2) Types of fibrinolytic drugs

All of the plasminogen activators share the potential of inducing plasmin action on fibrin, with an associated greater or lesser effect on plasma fibrinogenolysis (lytic state).

Currently approved fibrinolytic drugs include streptokinase, anistreplase, urokinase, recombinant tPA, two recombinant derivatives of tPA, reteplase [37] and tenecteplase [38].

There are small numbers of studies to compare different fibrinolytic drugs regarding safety and efficacy. Grünewald and Hofmann [11] is a retrospective single center study of 72 patients (82 limbs) study comparing alteplase, reteplase and urokinase found no difference between safety and efficacy of the 3 drugs. However, alteplase and reteplase were significantly less expensive than urokinase ($P<0.001$ and $P<0.01$, respectively), the same result has been confirmed by Sugimoto et al. [39] which found no statistical difference between altepase and urokinase thrombolysis success rates. However, tPA was significantly ($P<0.05$) less expensive and faster than urokinase.

The use of tenecteplase in the peripheral system is few, and these studies are not well controlled. Assent-2 trial [41] is a double-blinded RCT comparing between single bolus tenecteplase (30–50 mg according to bodyweight) and less than 6 hour duration rapid infusion of alteplase (≥100 mg) for treatment of acute myocardial infarction showed that tenecteplase has fewer non-cerebral bleeding (26.43% vs. 28.95%, $P=0.0003$) and less need for blood transfusion (4.25% vs. 5.49%, $P=0.0002$) than those treated with alte-

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pase.

From the data above, we can see that there are not enough studies to compare between fibrinolytic agents. However, the high specificity of alteplase and tenecteplase [40,41] to fibrin make them theoretically more safe and efficient than urokinase and streptokinase as we avoid systemic lytic effect.

The longer half-life of tenecteplase, high resistant to inactivation by PAI-1 and the less affinity to DD may lead to improving safety by avoiding systemic lytic effect and at the same time theoretically we can give it as a single bolus that will be more comfortable as the patient is not bed bound and can start mobilizing after the end of thrombolysis. However, there is a lack of the studies comparing between tenecteplase and other tPA in the management of acute lower limb DVT, although, it shows promising results in the management of acute myocardial infarction.

3) Mode of fibrinolytic drug injection

There are various techniques for fibrinolytic drug administration including systemic thrombolysis, continuous CDT and single bolus CDT.

In this review, we compare the three different techniques in view of safety and efficacy.

① Systemic thrombolysis

Initial attempts to treat acute DVT with thrombolytic therapy were by the peripheral administration.

Camerota and Kagan [35] has reported thirteen studies since 1968, pool analysis shows that there is complete or significant lysis in 45% of cases, partial lysis in 18% None or worse in 37%.

Out of the thirteen studies, 11 studies discussed bleeding complication with systemic thrombolysis and showed that minor bleeding complication happened in 28.5% of cases and major bleeding occur in 26.23%.

② CDT (continuous infusion)

Pool analysis of 14 studies [12-22,24] (440 patients) including Cavent trial [8] for patients who received only CDT using either urokinase and tPA from 1994 for acute lower limb DVT shows complete lysis in 64% of limbs treated, partial lysis in 29.55% and no lysis in 4% of cases. Minor bleeding and major bleeding complication in 5.7% and 4% of cases respectively.

③ Single bolus CDT

The strong fibrin affinity of recombinant tissue plasminogen activator tPA theoretically obviates continuous infusion or replacement of tPA after direct intrathrombic injection.

Chang et al. [25] is a cohort (non randomized) pilot study of 12 patients with acute DVT ranging from inferior vena cava thrombosis to bilateral calf vein thrombosis to unilateral popliteal and calf vein thrombosis, which evaluate single daily catheter-directed injection of tPA as a thrombolytic treatment for acute DVT of the lower extremity. Significant or complete lysis was achieved in 11 of the 12 extremities, and one has 75% lysis. Although the average total dose of altepase was 106 mg, bleeding complications were minor. No patient had a decrease in hematocrit of greater than 2% or decrease in hemoglobin of more than 1 g, and no patient required blood transfusion.

In 2011, Lozier et al. [26] conducted a prospective study of 30 patients using single bolus tPA (maximum dose used was 10 mg of alteplase per dose), and inherited thrombophilic traits were identified in 13 patients (43%) and 7 patients has iliofemoral DVT, and the remaining 23 patients (77%) had femoral popliteal DVT.

Venograms performed the day following last thrombolytic treatment showed that antegrade venous flow was restored in 29 of 30 patients (97%) using an average total dose of 19.7 mg (range, 8-38 mg) of alteplase over an average of 2.7 treatments (range, 1 to 4 treatments or days) for an average dose of 7.3 mg tPA/day. There were no major bleeding complication and minor bleeding in 3/30 (10%) had hematoma at catheter insertion site.

Analysis of the previous data shows that, CDT has better clinical outcome than systemic thrombolysis with significant decrease in risk of both minor bleeding (RR, 0.38; OR, 0.34) and major bleeding (RR, 0.05; OR, 0.12) (Fig. 3).

Single bolus CDT shows promising results in acute iliofemoral DVT, as it can help to reduce the cost of treatment with same efficacy and also more comfortable as the patient is not bed bound and can start mobilizing one hour after the end of thrombolysis; however, these studies may be biased (moderate risk of bias) as good outcome may be related to including cases with calf vein and popliteal vein thrombosis (low thrombus burden).

4) Biochemical markers

The role of haemostatic parameters measurement in the prediction of bleeding complication and treatment outcome during thrombolysis is not clear yet.

Endogenous fibrinolysis is regulated at two levels. PAIs, particularly the type 1 form (PAI-1), which prevent excessive plasminogen activation by regulating the activity of tPA [42-44].

PTTs, fibrinogen and DD level are the main haemostatic parameters measured during thrombolysis in most of the

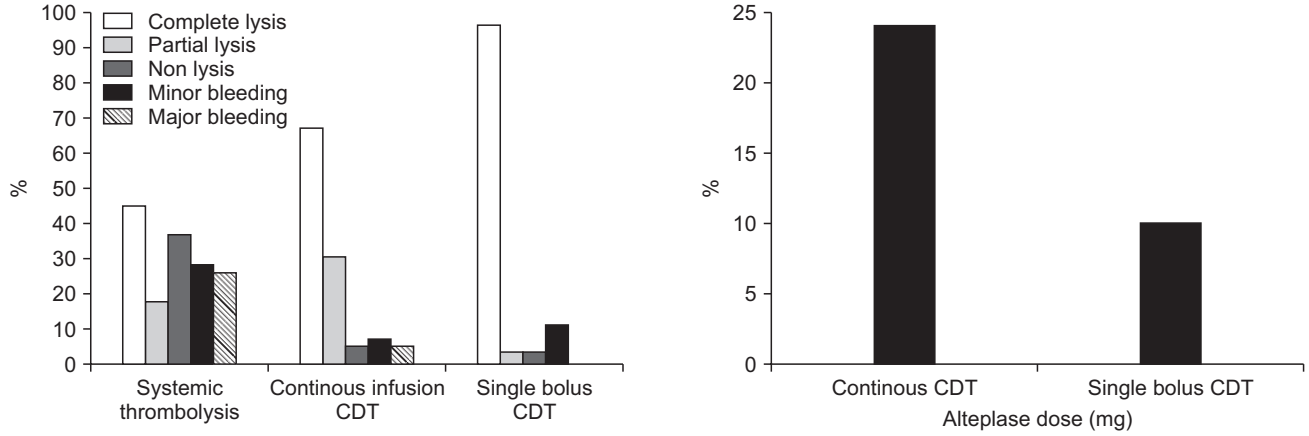

Fig. 3. The difference between systemic, continuous infusion catheter direct thrombolysis (CDT) and single bolus CDT from safety and efficacy plus average total amount of alteplase used per day.

studies.

There are few other studies discussing the role of others haemostatic parameters like PAI-1, systematic tPA, plasminogen and alpha2–anti plasmin activity.

① D-dimer

D-dimer (DD) is one of the Fibrin degradation products and resulted from the action of tPA on fibrin [45-47].

DD has been identified in the blood of patients with various thrombotic or thrombolytic disorders [46].

DD level during thrombolysis procedure has 3 phases:

Phase 0: DD level rises abruptly by the time tPA administration is complete.

Phase 1: DD reaches a plateau level that indicates continuous thrombolysis. Phase 1 duration in continuous CDT is up to 2 days while in single bolus CDT is 8 hours [26].

Phase 3: DD level significantly decrease at the third day of continuous CDT in most of the studies and after 8 hours in single bolus thrombolysis [26].

Failure to achieve the initial peak (phase 0) of DD level may indicate failing of thrombolysis therapy. However, coordination with venogram finding is required.

Grünewald et al. [9] discussed the correlation between clinical events and hemostatic parameters during systemic thrombolysis in lower limb DVT and shows that persistent high level or plateau of DD and fibrinogen degradation products (FDPS) during thrombolysis indicate either;

(1) Increase bleeding tendency and it is supported by the biochemical fact that DD has affinity as potent as fibrin as a stimulator of plasminogen activation by alteplase. So persistent high DD leads to increase plasminogen and alteplase activity and in turn increase bleeding tendency, this finding is supported by Bovill et al. [10] that correlate between bleeding incidence and haemostatic parameters and found that there were a correlation between high peak DD level and bleeding tendency (P=0.007) during systemic thrombolysis in acute myocardial infarction.

(2) Resistant thrombus as the patient most probably will be procoagulant and interpretation with venogram result needed to confirm it.

② Fibrinogen

Thrombolysis agent has local and systemic fibrinolytic activity, although CDT act locally on fibrin but also thrombolytic agent can escape systemically and cause lysis of soluble fibrinogen.

There are a small number of retrospective and prospective non-randomized studies trying to link between fibrinogen levels and bleeding complication.

Grünewald et al. [9] found that there is no relationship between fibrinogen level and bleeding incidence or treatment success (P=0.06).

Bovill et al. [11] found that that low nadir fibrinogen levels associated with bleeding complication (P=0.005) and recommended to keep fibrinogen level between 100-150 mg/dL.

Vandelli et al. [48] discussed the correlation between increase of the risk of intracerebral hemorrhage after intravenous thrombolysis for acute ischemic stroke and low fibrinogen level. Fibrinogen levels were determined at 2 hours after therapy: patients were classified as belonging to 'low fibrinogen group' if levels decreased to less than 2 g/L and/or by 25% or more. Bleeding rate in the low fibrinogen group was significantly higher (43.9%) than that in the normal fibrinogen group (9.5%; OR, 7.43; P<0.001). The result of this study may not correlate with the DVT thrombolysis

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and intracerebral bleeding risk may be high due to nature of the disease (ischemic stroke).

In view of the previous studies, there is no clear evidence to correlate between fibrinogen level and bleeding incidence or treatment success in management of iliofemoral DVT.

③ Plasminogen activator inhibitor-1

Experimental study was conducted by Carmeliet et al. [49] who observed PAI-1 level on mice blood after PAI-1 gene alteration and relation to resolving jugular vein induced thrombus. He found that disruption of the PAI-1 gene in mice (low PAI-1 level) appears to induce a mild hyperfibrinolytic state and a greater resistance to venous thrombosis but not to impair hemostasis.

Grünewald et al. [9] observed that during continuous systemic tPA infusion there was significant decrease of PAI-1 from day 3 to day 5 and PAI-1 level was significantly lower in patients with bleeding comparing to those without (P=0.01), suggesting that serial measurements of PAI-1 might help to predict bleeding and prevent it (level 2 evidence).

The effect of single bolus tPA on PAI-1 level was discussed by Lozier et al. [26] and shows that PAI-1 fell to essentially undetectable levels immediately after completion of alteplase administration. As tPA activity decreased over the following one to two hours, mean PAI-1 levels rose rapidly and by the eight-hour time point were three times the baseline values (Fig. 3).

Other study conducted by Grünewald et al. [24] comparing locoregional to systematic thrombolysis observed that there is a rapid decrease in PAI level to immeasurable value at the time of thrombolytic agent injection (1st therapeutic cycle) with gradual increase in value of PAI-1 over the following cycles to reach normal or elevated level at therapeutic cycle three.

PAI-1 level remains low through the treatment in continuous tPA infusion which according to Carmeliet et al. [49] can induce a mild hyperfibrinolytic state and a greater resistance to venous thrombosis but not to impair hemostasis.

However, if PAI-1 levels persistently decrease significantly (reach zero level), bleeding is likely to happen.

In single bolus altepase, the rebound increase in PAI-1 level either locoreginally or systemically to normal or three fold of normal level may lead to increase safety by opposing the active tPA but also may affect negatively the thrombolysis process.

So, monitoring and maintaining PAI-1 level at low level (above zero level) may improve both safety and efficacy of CDT (level 3 evidence).

④ Activated partial thromboplastin time

SIR [36] recommended blood draws for hematocrit, platelet count and PTT at least every 12 hours.

During CDT, the intravenous heparin dose should be adjusted to keep aPTT at 1.2 to 1.7 times prolongation, that is, at 40s to 60s [8].

Proper matching of the anticoagulation level to each patient according to bleeding risk should be considered. For example, young, healthier patients can tolerate more robust heparin and rTPA than elderly or debilitated patient. However, we have to make sure that aPTT level values are not above therapeutic level during thrombolysis to avoid unnecessary bleeding [36].

5) Ward monitoring

CDT is a safe procedure but ward monitoring is one of the important factors that can help to improve safety and avoid the need of post lysis HDU admission, which in turn will help to decrease the cost of the procedure.

SIR [36] recommended the following measures to prevent bleeding complication such as complete bed rest with immobility of the catheter-bearing extremity, frequent contact with nursing staff, blood draws for hematocrit, platelet count, fibrinogen and aPTT at least every 12 hours, consider potential markers of impending bleeding like pericatheter oozing, minor sentinel bleeds (e.g., epistaxis), and elevated aPTT, and it should be confirmed that arterial punctures and intramuscular injections did not occur during thrombolysis.

Bækgaared et al. [50] is a retrospective analysis of Copenhagen experience (89 patients with 91 limbs) suggest that in addition to same recommendations by society of interventional radiology absolute bed rest with IPC and careful observation of vital signs and bleeding signs every eight hours by dedicated nurse (Table 1).

6) Timing of intervention

There is no formal definition of an acute or chronic DVT.

The speed of intervention in acute thrombotic events is of clinical relevance as there is an increase possibility to reverse the occlusion, relief of symptoms, and preservation of valve function, which helps to decrease the risk of post-thrombotic syndrome (Fig. 4).

It is known that acute thrombi respond better to thrombolysis compared to established DVTs (86% vs. 68%, significant grade II or III lysis; 34% vs. 19%, grade III lysis) due to thrombus organisation over time several studies and international guidelines recommended that CDT should be performed within 14 days of onset of symptoms [26,35].

Table 1. Ward based monitoring recommendations

1. Complete bed rest with immobility of the catheter-bearing extremity.
2. Blood draws for hematocrit, platelet count, fibrinogen and PTT at least every 12 hours.
3. Careful observation of vital signs and bleeding signs (pericatheter oozing, minor bleeds like epistaxis, hematuria or PR bleeding) every 8 hours by dedicated nurses.
4. Continue of contraceptive pills during treatment.

PTT, partial thromboplastin time; PR, per-rectal bleeding.

However, the quality of evidence supporting early thrombus removal strategies is very low (level 3 evidence) because of the methodological limitations of the relevant studies (lack of randomization, incomparability of study groups, loss to follow-up).

National Venous Registry suggested that patients with symptoms more than ten days in duration had significantly worse outcomes than those with a first episode of acute iliofemoral DVT of less than ten days in duration. However, the 10-day interval of symptoms was arbitrary as symptom duration among those symptomatic for 10 days varied from days to many months [13]. Cavent trial treated patients with symptoms less than 21 day [8].

Arnoldussen et al. [28]; a prospective study with a total of 53 cases of DVT to identify DVT characteristics with contrast-enhanced MRV (Fig. 4) comparing it with average duration of complaints and was able to classify DVT into acute 2-13 days, subacute 8-18 days, chronic 15-32 days.

Bækgaard et al. [29] has treated the 53 cases with thrombolysis and found that acute thrombus will lyse quickly, subacute thrombus will lyse within reasonable time and chronic will either lyse little or not at all, even in an extended time frame.

We recommend treating the iliofemoral DVT within 14 days of diagnosis. However, the earlier start of treatment the better as it helps to decrease total tPA dose needed to treat the DVT which in turn reflect on procedure safety and efficacy.

7) Intermittent pneumatic calf compression

During CDT, patient has to be immobilised during management to prevent moving of the catheter from thrombus site and avoid bleeding from puncture site. Immobilisation lead to static flow due to decrease venous return, which in turn may lead to further thrombosis despite adequate thrombolytic therapy.

IPCC can improve venous blood flow during continuous thrombolysis, which may help to improve CDT outcome and decrease amount of thrombolytic agent needed for thrombolysis.

Ogawa et al. [27] evaluated the effects and safety of CDT

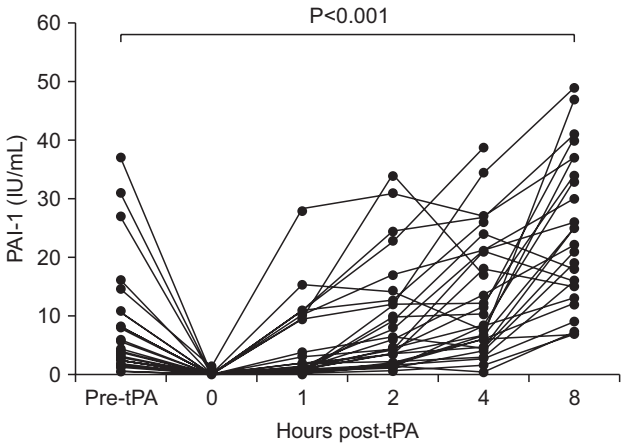

Fig. 4. The effect of single bolus tPA on PAI-1 level. tPA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor-1. Data from the article of Lozie et al. (Transl Res 2012;160:217-222) [26].

with IPC for acute proximal DVT compared with CDT alone revealed that adding IPC to CDT using low-dose urokinase for DVT treatment of the leg resulted in better early and late outcomes compared with CDT alone and was not associated with an increased risk of symptomatic PE. The overall effect of thrombolysis for CDT with IPC was better than for CDT alone (P=0.0037).

There are no other studies discuss the effect of IPC on CDT from safety and efficacy.

However, the principle of IPC to improve venous outflow and prevent stasis in immobile patient during thrombolysis may help to improve outcome and decrease total tPA dose needed for thrombolysis (level 3 evidence).

8) Thrombolysis imaging assessment

Clot lysis may be quantified and stratified according to the percentage of venous luminal patency restored.

The difference between the pre- and post-lysis thrombus scores divided by the pre-lysis score gave the grade of thrombolysis; grade I ≤50%; grade II=50%-90%, and grade III=complete thrombolysis [14].

Venography is the main assessment image for throm-

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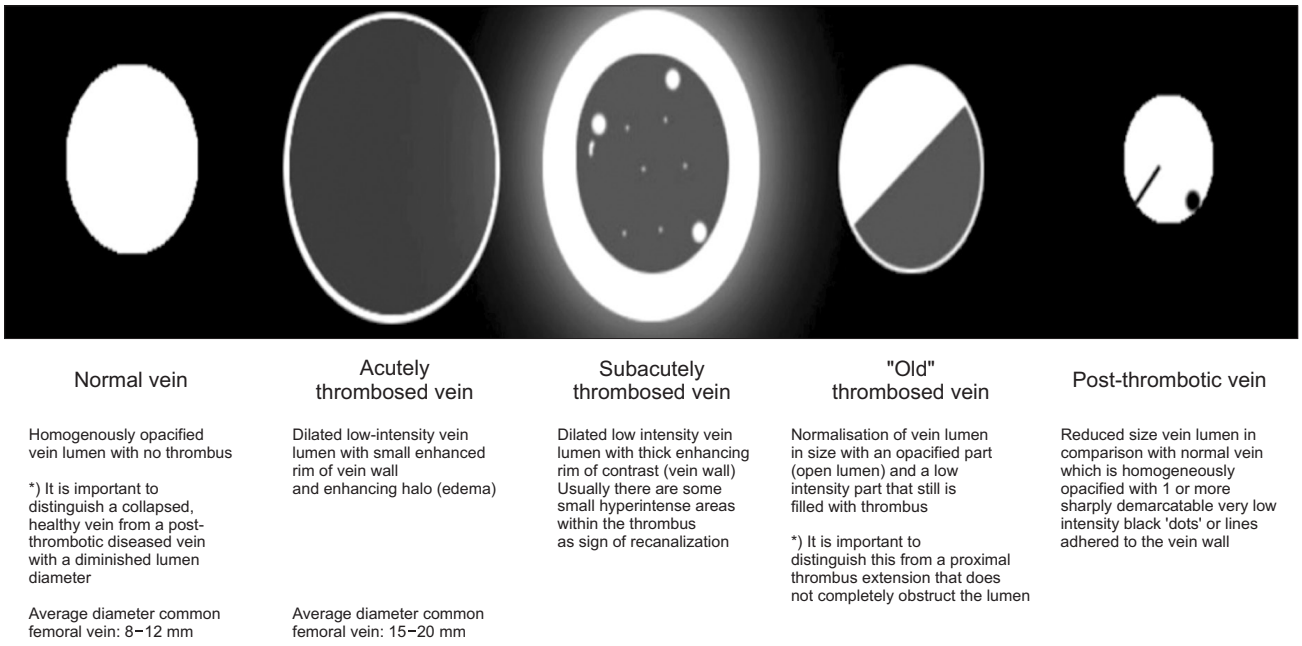

Fig. 5. Thrombus characteristic as identifiable with magnetic resonance venography. Data from the article of Arnoldussen et al. (Phlebology 2014;29(1 Suppl):119-124) [29].

Table 2. Recommendations to improve safety and efficacy of CDT (ward based protocol)

1. Patient selection: Careful selection of DVT patients with strict exclusion criteria helps to reduce bleeding complication.
2. Timing for intervention: We recommended early intervention within 14 days of DVT diagnosis. The earlier we start the treatment the better as it helps to decrease total tPA dose needed to treat the DVT that in turn reflect on procedure safety and efficacy (level 3 evidence).
3. Type of fibrinolytic drug: The high specificity of alteplase and tenecteplase to fibrin make them theoretically more safe and efficient than urokinase and streptokinase as we avoid systemic lytic effect.
4. Mode of fibrinolytic drug injection: CDT has better safety and efficacy that systemic thrombolysis. Large-scale studies needed to compare between both continuous and single bolus CDT.
5. Biochemical markers monitoring: D-dimer monitoring has role in predicting the outcome of CDT and potential bleeding complication. Fibrinogen monitoring has no role in safety or efficacy of CDT. PAI-1 levels monitoring might be useful to predict bleeding (level 2 evidence).
6. Intermittent pneumatic compression: It helps to improve the outcome of CDT and may lead to decrease total tPA dose needed for thrombolysis (level 3 evidence).
7. IVUS: It has many potential advantages than can help to provide more information before stenting such landing zone, residual thrombus and underlying cause of acute DVT (chronic lesion and compression site)
8. Ward based care: It should include complete bed rest with immobility of the catheter-bearing extremity, blood draws for hematocrit, platelet count, and aPTT at least every 12 hours, careful observation of vital signs and bleeding signs (pericatheter oozing, minor bleeds like epistaxis, hematuria or PR bleeding) every 8 hours by dedicated nurses and continue of contraceptive pills during treatment (level 3 evidence).

CDT, catheter direct thrombolysis; DVT, deep vein thrombosis; PAI-1, plasminogen activator inhibitor-1; tPA, tissue plasminogen activator; IVUS, intravascular ultrasound; aPTT, activated partial thromboplastin time; PR, per-rectal bleeding.

bolysis procedure to detect any stenotic or occlusive iliac lesions that need stenting.

It is known that IVUS in chronic patients is an excellent imaging modality to identify the extension of the intraluminal and mural lesions, which can be missed on a single-plane venography. However, it has not been recommended in any guidelines in the management of acute iliofemoral DVT, probably due to the lack of data on the use of IVUS in existing publications in patients with CDT.

Neglén and Raju [30] is a cohort study comparing between IVUS and standard, single-plane, transfemoral venography were performed in 304 consecutive limbs during

balloon dilation and stenting of an obstructed iliac venous segment and showed that venography had poor sensitivity (45%) and negative predictive value (49%) in the detection of a venous area stenosis of >70% when compared to IVUS as the standard, the actual stenotic area was more severe when measured directly with IVUS (P<0.001), probably as a result of the non-circular lumen geometry of the stenosis.

IVUS has many other potential advantages than can help to provide more information before stenting such landing zone for the distal part of the stent plus ensure the optimal lumen restoration.

Also it provides more adequate morphological information, which can help to identify post-thrombolysis residual thrombus and underlying cause of acute DVT, that can not be identified by single plan venography, like trabeculation, frozen valves, mural thickness, and outside compression.

This can help to identify the early need for stenting of this lesions to prevent recurrence and improve safety by avoid unnecessary thrombolytic drugs injection.

DISCUSSION

As CDT is relatively new treatment, it has to be safe and effective. In numerous studies, it has been tried to correlate between variable factors like (haemostatic parameters, timing of thrombolysis, mode of fibrinolytic drug administration and ward monitoring) and clinical events (bleeding risk and successful thrombolysis).

In our review we tried to identify factors that can improve safety and efficacy of CDT in clinical ward (Table 2).

We found that careful selection of patients with strict exclusion criteria helps to reduce bleeding complication.

There are no enough studies to compare between fibrinolytic agents from safety and efficacy point of view. However, the high specificity of alteplase and tenecteplase to fibrin make them theoretically more safe and efficient than urokinase and streptokinase as we avoid systemic lytic effect.

The longer half-life of tenecteplase and high resistant to inactivation by PAI-1 might increase its efficacy, in addition to that the less affinity to DD may lead to improve safety by avoiding systemic lytic effect. Theoretically, we can give it as a single bolus that will be more comfortable as the patient is not bed bound and can start mobilizing one after the end of thrombolysis.

CDT thrombolysis has better safety and efficacy that systemic thrombolysis. Single bolus CDT has a promising outcome with low total TPA dose comparing to continuous CDT that may lead to decrease cost and increase safety. However, large-scale studies needed to compare between both techniques.

Repeated analysis of Hb, platelet count, aPTT every twelve hours in clinical ward is recommended.

We analyze the biochemical markers and correlate it with safety and efficacy of CDT and found that no clear evidence to correlate between fibrinogen level and bleeding incidence or treatment success in management of iliofemoral DVT.

Failure to achieve the initial peak of DD level after thrombolysis level may indicate failing of thrombolysis therapy. However, venogram is required to confirm this finding.

Persistent high level or plateau of DD and FDPS during thrombolysis indicate resistant thrombus and the possibility of increase risk of bleeding as DD has affinity as potent as fibrin as a stimulator of plasminogen activation by alteplase.

PAI-1 level remains low through the treatment in continuous tPA infusion which according to Carmeliet et al. [49] can induce a mild hyperfibrinolytic state and a greater resistance to venous thrombosis but not to impair hemostasis.

Studies showed that if PAI-1 levels persistently decrease significantly (reach zero level), bleeding is likely to happen (level 2 evidence).

In single bolus altepase, the rebound increase in PAI-1 level either locoregionally or systemically to normal or three fold of normal level may lead to increase safety by opposing the active tPA but also may affect negatively the thrombolysis process. Monitoring and maintaining PAI-1 at low level (above zero level) can improve both safety and efficacy of CDT.

aPTT should be maintained at 1.2 to 1.7 times prolongation, that is, at 40s to 60s, during CDT, however, proper matching of the anticoagulation level to each patient according to bleeding risk should be considered.

CDT should be performed within 14 days of onset of symptoms prethrombolysis MRV help to identify the extent of the lesion, thrombus age and exclude pelvic tumors. The earlier the start of thrombolysis treatment, the better the outcome with less tPA dose needed (level 3 evidence).

The usage of intermittent pneumatic compression during thrombolysis help to improve the outcome of CDT and may lead to decrease total tPA dose needed for thrombolysis (level 3 evidence).

Ward based care should include complete bed rest with immobility of the catheter-bearing extremity, blood draws for hematocrit, platelet count, PAI-1 and aPTT at least every 12 hours, careful observation of vital signs and bleeding signs (pericatheter oozing, minor bleeds like epistaxis, hematuria or PR bleeding) every 8 hours by dedicated nurses and continue of contraceptive pills during treatment (level 3 evidence).

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IVUS has many potential advantages than can help to provide more information before stenting such landing zone for the distal part of the stent plus ensure the optimal lumen restoration. Also it provides more adequate morphological information, which can help to identify post-thrombolysis residual thrombus and underlying cause of acute DVT (chronic lesion and compression site), that can not be identified by single plan venography, like trabeculation, frozen valves, mural thickness, and outside compression.

This can help to identify the early need for stenting of this lesions to prevent recurrence and improve safety and efficacy by avoid unnecessary thrombolytic drugs injection and ensure adequate management of underlying stenotic lesions that can't be assessed by single plan venography.

Lack of randomized controlled trials and cohort trials that discuss the safety and efficacy issue of CDT in management of acute iliofemoral DVT was the main limitation of this review.

We have included studies that correlate between hemostatic parameters and bleeding incidence during thrombolysis management of acute myocardial infarction as it follows the same principle of DVT management such as same fibrinolytic drugs but in higher doses and same hemostatic parameters monitored during thrombolysis procedure.

CONCLUSION

The ward based protocol during CDT procedure including proper patient selection, biochemical markers monitoring and fibrinolytic drug choice, usage of IPC, usage of IVUS and ward monitoring is able to predict and prevent complications plus improve outcome.

Further robust research needed to assess the value of PAI-1, IVUS, single bolus thrmbolysis and tenecteplase in management of acute iliofemoral DVT.

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