Iliofemoral deep vein thrombosis treated by catheter directed thrombolysis - short term outcomes and associated radiation burden

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Aims and objectives

Direct venous thrombolysis offers an alternative in managing significant iliofemoral thrombosis. We utilise a protocol which selectively treats iliofemoral deep vein thrombosis (DVT) with catheter-directed thrombolysis (CDT) with the use of adjuvants such as stenting, venoplasty or mechanical thrombectomy (MT) as required. Initial work up and subsequent follow-up involves the use of conventional ultrasound, CT pulmonary angiography (CTPA), CT venogram (CTV) and intravascular ultrasound (IVUS).

We prospectively evaluated procedural and short term outcome along with the radiation burden associated with our protocol.
Methods and materials

Patient Population

We identified patients with iliofemoral DVT treated by CDT with or without adjuvants between May 2013 and July 2014.

Data Collection

Images and reports involved in initial work up, procedures and follow up such as ultrasound scan, IVUS, CTV, CTPA and venogram of all patients were retrieved from picture archiving and communication system (PACS), and electronic hospital records.

Associated radiation burden for each procedure and other relevant clinical information were also collated.

Identification of patients for treatment

Patients who present to A&E with symptoms suggestive of DVT, a Wells score >= 2 and raised D-Dimers are referred for an ultrasound to confirm the presence of a DVT. If iliofemoral DVT is suspected, the vascular registrar on call is contacted and a full lower limb venous duplex scan is performed by the vascular lab.

Patients with confirmed iliofemoral DVT who meet the inclusion criteria (Table 1) for the CDT are transferred to the care of the vascular team on a ward.

Patients who do not meet the criteria or meet the exclusion criteria (Table 2) are reviewed on an individual basis for CDT or MT, but if considered unsuitable, proceed to maximal medical therapy. Age is a relative criteria; 18-75 years is considered the optimal age, however age alone should not exclude patients from receiving CDT. All patients who are otherwise suitable should be discussed at a multidisciplinary meeting and CDT may be performed if risk / benefit analysis is in favour of treatment.

Further imaging
Patients who fulfill the criteria for intervention proceed to CTV and a CTPA in addition to a full vascular lab duplex scan.

**CTV protocol**

CTV is used to delineate the extent of thrombus extension with particular attention to the inferior vena cava (IVC). Any other factors that may be causing obstruction should also be identified.

The protocol for CT scanning is as follows:

- 120 mls bolus administration of iodinated contrast media into the antecubital fossa
- CTPA as per standard timing and protocol
- Venogram through the abdomen and pelvis at 120s post contrast.

CTPA is used to assess if there is any evidence of pulmonary embolus and/or right heart strain. If there is suggestion of right heart enlargement then a supplementary echocardiogram is performed. Catheter venogram is performed at the time of the interventional procedure.

**Anticoagulation**

All patients with a confirmed DVT are commenced on anticoagulation in the form of subcutaneous LMWH Dalteparin (Fragmin) until CDT / MT is commenced. LMWH is discontinued the night before / the morning of the treatment and an IV heparin infusion at a dose of 100 U/kg is started. LMWH is to be reintroduced in combination with warfarin or newer agents (with a target INR of 2.0 - 3.0) 1 hour after completion of the procedure. This is guided by the haematologists who manage the patients jointly with the vascular team.

Post procedure transition to oral anti-coagulants is covered throughout with LMWH to prevent re-thrombosis. Post procedure anti-coagulation is monitored through the thrombosis clinic and continued for a minimum of 3 months.

**IVC filter placement**

Selective use of IVC filters is indicated in the presence of:
1) Unstable IVC clot as detected on CTV

2) Symptomatic pulmonary embolus

3) Right heart strain

Patients with none of the above features proceed to CDT without IVC filter placement.

During the procedure for filter placement, passage through the thrombosed limb needs to be avoided. At placement, adequate space is needed for inflation of thrombectomy catheter balloons to prevent dislodging the filter (i.e. the filter should be placed as high as is practicable). Right femoral and right internal jugular venous approaches are the most suitable. All filters should be retrieved at the earliest possible opportunity once the period of risk has passed and on completion of successful treatment.

**Catheter Directed Thrombolysis**

**Venous Access**

An appropriate vein is selected for puncture under US guidance and local anaesthetic and a 5 or 6 Fr introducer sheath inserted. This is usually at the ipsilateral femoral or popliteal vein depending on the extent of thrombosis. Ideally, access is preferred below the level of the thrombus to facilitate venographic assessment of the progress of lysis. A venogram is then performed to determine the location and extent of the thrombus.

**Thrombolysis**

A multi-side-hole infusion catheter is then introduced over a guide wire and embedded within the main body of the thrombus. Alteplase is prepared (Table 3) and administered using a syringe driver, usually at a dose of 0.5 mg/hour. In general, a maximal dose of 20 mg/24 hours should not be exceeded.

**Continuation and Monitoring of the CDT**

When catheter-directed infusion of Alteplase and intravenous UFH are established, treatment continues on a ward. Blood pressure, pulse and the puncture site are assessed several times a day. The progress of thrombolysis can be graded by a scoring system (Table 4 & 5). If there is limited radiographic evidence or progress of CDT after 48 hours...
and a decision is made to continue CDT, this should not continue beyond a maximum of 96 hours.

During the interventional procedure, the concomitant use of other antithrombotic agents is avoided because of increased risk of bleeding.

**Indications for MT**

All patients who do not fulfill the criteria for CDT are considered for MT. MT is useful for isolated, segmental thrombus to either attempt complete treatment in one session or to reduce overall length of time that CDT is carried out. MT is preferentially performed at the start of the procedure rather than as an adjunct after failed CDT.

**Indications for Stenting**

Following completion of CDT and/or MT, balloon dilatation and stent placement is considered in patients in whom there is:

1. Residual stenosis
2. Residual chronic clot that has not lysed
3. Residual occlusion

**Stent Placement**

Stent procedures can be performed in the interventional suite under local anaesthetic and conscious sedation unless the dilatation is very painful in which case the patient may need to be scheduled for general anaesthesia.

Successful passage into the vena cava beyond the disease segment is confirmed by venogram and/or IVUS. Serial progressive dilations to 16 mm for the distal cava and common iliac veins, to 14 mm for the external iliac vein, and 12 mm for the common femoral vein are performed prior to stent placement. A stent of appropriate size to match the nominal diameter of the diseased venous segment is then used. Extension of the stent into the distal vena cava for 2 to 3 cm or even longer as well as distally below the inguinal ligament is considered in all cases to reduce the risk of delayed stenosis.

**Discharge and Follow up**
All patients are discharged with thigh length class 2 compression stockings. These may be changed to knee length stockings to aid compliance at 6 weeks follow up if clinically appropriate.

All patients who undergo CDT / MT or stent placement are followed up by haematology and additionally DVT clinic every other week. The anti-coagulation programme for each patient is guided by haematology input. Haematology investigations for any underlying cause for the development of DVT are conducted and used to guide the on-going management of anti-thrombotic therapy.

All patients with evidence of PE are referred to the pulmonary hypertension clinic for outpatient follow up. All patients are discussed on completion of CDT / MT at the venous MDT.

Patients who have successful lysis and who do not require additional stent have post procedure duplex assessment performed at 6 weeks, 3 months, 6 months and 12 months to monitor the treated segments.

All patients who undergo an additional stent procedure have a duplex performed at 2 weeks, 6 weeks, 3 months, 6 months, and 12 months to assess stent patency and evidence of restenosis. If there are any concerns regarding the stent and imaging is unclear then the patients may require CTV / MRV / venogram in addition to duplex assessment.

Patients in whom a stenosis / re-occlusion or suspicion of stenosis are identified undergo venogram and appropriate re-intervention (balloon dilatation or additional stent procedure) at the next available elective opportunity.
1. Onset of symptoms within 21 days
2. Objectively verified DVT (ultrasonography, venography, computed tomography, or magnetic resonance imaging) localized in the upper half of the thigh, the common iliac vein, or the combined iliofemoral segment
3. Written informed consent

**Table 1**: Inclusion criteria.

<table>
<thead>
<tr>
<th>Contraindications to thrombolytic therapy (e.g. bleeding diathesis)</th>
<th>Less than 14 d post surgery /post trauma (may be included after 14 d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indications for systemic thrombolytic therapy (e.g. plegmasia cerulea dolens/ isolated vena cava thrombosis / existing PE)</td>
<td>History of subarachnoid / intracerebral bleeding</td>
</tr>
<tr>
<td><strong>Severe anaemia</strong> (Hb less than 8 g/dL)</td>
<td>Disease with life expectancy less than 24m</td>
</tr>
<tr>
<td><strong>Thrombocytopenia</strong> (platelets 80 to 109/dL)</td>
<td>Drug abuse or mental disease that may interfere with the treatment and follow-up</td>
</tr>
<tr>
<td><strong>Severe renal failure</strong> (EGFR less than 30)</td>
<td>Previous ipsilateral proximal DVT</td>
</tr>
<tr>
<td><strong>Severe hypertension</strong> (&gt;=160 mm Hg or diastolic blood pressure above 100 mm Hg)</td>
<td>Malignant disease requiring chemotherapy</td>
</tr>
<tr>
<td><strong>Pregnancy and thrombosis =&lt; 7 d postpartum</strong></td>
<td>Any thrombolytic therapy within 7 d before presentation</td>
</tr>
</tbody>
</table>
Table 2: Exclusion criteria.

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<table>
<thead>
<tr>
<th>Dilution of Alteplase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alteplase is provided in a 1mg/ml concentration.</td>
</tr>
<tr>
<td>2.5ml (2.5mg) Alteplase is added to 47.5ml normal saline to make up a 50cc volume (0.5 mg Alteplase / 10ml saline). The infusion is run at 10 cc/hr to deliver 0.5mg tPA/hour.</td>
</tr>
</tbody>
</table>

Table 3: Dilution of alteplase.

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<table>
<thead>
<tr>
<th>Thrombus score</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
</tbody>
</table>

0  Vein is patent and completely free of thrombus.
1  Vein is partially occluded
2  Vein is completely occluded i.e. vein lumen totally filled with thrombotic material

A total thrombus score is calculated before, during, and at the completion of CDT by adding the scores for the following seven vein segments: inferior vena cava, common iliac vein, external iliac vein, common femoral vein, proximal and distal segments of femoral vein, and popliteal vein. Total score ranges from 0-14

Table 4: Dilution of alteplase.

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<table>
<thead>
<tr>
<th>Lysis Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade III</td>
<td>100% lysis with no residual clots</td>
</tr>
<tr>
<td>Grade II</td>
<td>50%-99% lysis</td>
</tr>
<tr>
<td>Grade I</td>
<td>Less than 50% lysis</td>
</tr>
</tbody>
</table>

Lysis grade is then calculated by dividing the **difference** of the total pre- and post lysis thrombus scores by the pre lysis score.

**Table 5:** Lysis grade.

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Fig. 1: Patient assessment. 25 year old male presenting with acute right lower limb pain and swelling. US duplex scan demonstrates extensive iliofemoral thrombosis extending into below-knee veins. Red arrow: no flow within the R CFV, which contains thrombus and is non-compressible. Green arrow: patent R CFA.

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Fig. 2: (a) CTPA demonstrates bilateral proximal pulmonary emboli. (b) CT venogram demonstrates extensive right-sided deep venous thrombosis extending from the lower aspect of the IVC. (c) From the right common iliac vein to the right femoral vein. (d) The left common iliac, external iliac and common femoral veins are patent with no evidence of thrombus. Patient did not have any contraindications for venous thrombolysis. Red arrow: bilateral pulmonary emboli. Green arrows: thrombus in IVC (image B), thrombus in IVC and right common iliac vein (image C), thrombus in right CFV (image D).

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Fig. 3: Management. Right lower limb venous thrombolysis. Ultrasound guided right popliteal vein puncture. 5-French sheath. Venograms demonstrate extensive thrombus from the right popliteal vein to the right common iliac vein and distal IVC. (a) Guidewire access to right common iliac vein origin. (b) Cragg-McNamara catheter (20 cm infusion length) placed from right CFV to common iliac vein (arrow). Actilyse 5 mg and 5000 units heparin bolus. Heparin and tPA infusion commenced via sheath and catheter respectively (2.5 mg Actilyse and 47.5 ml normal saline running at 5 ml/hour via each catheter. Heparin infusion (25,000 units 50 ml normal saline) running at 1 ml/hour in each leg via sheath side-arm).

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Fig. 4: (a) Right venogram 20 hours later shows significant reduction of clot burden and improved flow with patency of the SFV and CFV. (b) The EIV is also patent, but there is a 50-75% stenosis present. Right CIV is patent and with a normal caliber. Red arrow: residual stenosis in the right iliac vein. (c) A 14x 80mm EV3 stent was inserted from the CIV to the EIV and angioplastied to 12mm (arrow). (d) Final venography showed a successful angiographic result.

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Fig. 5: Management of recurrent intra-stent thrombus. Patient returned one month later. (a) Right venogram performed via 5F sheath placed in popliteal vein demonstrates a contrast filling defect in the proximal right EIV-CIV stent that is extending to the IVC. (b) This was treated via venoplasty with a 16 x 40mm high pressure balloon. (c) The final venogram showed improved appearances within the stent.

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Fig. 6: Follow up venogram performed 3 months later demonstrates widely patent right femoral, iliac and lower IVC.

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## Results

Twenty-eight patients were included (16 females) with a mean age of 39±17.6 years. Patient demographics are presented in Table 6.

Eight patients (28.6%) presented with a co-existing pulmonary embolus.

### Procedural Outcome

All patients underwent CDT (28/28) with technical success rate of 93% (26/28). One patient required insertion of an IVC Filter before thrombolysis. Most patients had stent insertion post thrombolysis (22/28), whilst 64.3% of patients (18/28) were followed by adjunctive procedures including venoplasty (14/28), and MT (8/28) (Fig. 7).

Patency was achieved in 60.9% of patients via CDT with or without stent insertion at 1-year follow-up (primary patency). With additional adjunctive procedures, 21.7% more patients acquired patency, resulting in the total of 82.6% of the patients with patent vessel (primary assisted patency). Re-intervention due to re-occlusion (secondary stent patency) added 21.7% to the overall patency at 1-year follow-up, resulting in cumulative patency of 100% (Fig. 8).

### Complications

Short-term complications such as bleeding (3.6%), neutropenia (3.6%), sepsis (3.6%) and AKI (7.1%) arose post-intervention during the admission. According to SIR criteria, the minor complication rate was 2/28 (7.1%) and major complication rate 4/28 (14.3%).

After the initial discharge, 21.4% of patients developed recurrence of thrombus, requiring further intervention. 29.2% of patients were found to have developed PTS at the vascular or haematology follow-up clinics (Table 7).

### Radiation Burden

#### Interventional Procedures

Associated DAP of 11.5 G y cm$^{-2}$ (median) with thrombolysis alone was deemed to have negligible radiation risk [0.1(MIN)-60.3(MAX) G y cm$^{-2}$] as per the SIR guideline (radiation injury >500 G y cm$^{-2}$).
Not one interventional procedure had higher than DAP of 500 Gy cm$^2$ at any point, suggesting radiation safety of the procedures. None of the patients suffered from radiation injury.

Cumulative radiation burden per patient from interventions including thrombolysis, venogram, venoplasty, stent insertion, MT, IVC Filter and IVUS was 87.4 Gy cm$^2$ (median) with a minimum of 11.6 Gy cm$^2$ and maximum of 1298.7 Gy cm$^2$. 2 out of 28 patients had cumulative DAP of all procedures higher than 500 Gy cm$^2$. There was no evidence of any radiation injury in these patients. The impact of cumulative radiation burden associated with these interventional procedures is unclear as there are no current guidelines available (Table 8).

**Imaging: CTV, CTPA**

The extent of thrombus was initially assessed with CTV in 82.1% of the patients (23/28). DLP of CTV was 528.9 mGycm per patient (median) with minimum and maximum values of 280 and 2893.4, respectively. Similarly, 71.4% of patients (20/28) had CTPA with median DLP of 411.5 mGycm with a minimum and maximum DLP of 173 and 1385.2, respectively.
Table 6: Patient demographics.

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Fig. 7: Adjunctive Interventional Procedures After CDT

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Fig. 8: Patency of the treated veins post-adjunctive CDT at 1-year follow-up

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<table>
<thead>
<tr>
<th>Post Thrombotic Syndrome</th>
<th>29.2 % (7/24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re-occlusion</td>
<td>21.4 % (6/28)</td>
</tr>
<tr>
<td>Complications</td>
<td>17.9 % (5/28)</td>
</tr>
<tr>
<td>Bleeding (ITU transfer)</td>
<td>3.6 % (1/28)</td>
</tr>
<tr>
<td>Neutropoenia</td>
<td>3.6 % (1/28)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>3.6 % (1/28)</td>
</tr>
<tr>
<td>AKI</td>
<td>7.1 % (2/28)</td>
</tr>
</tbody>
</table>

Table 7: Complications during the admission after CDT 4/28 Patients were lost to follow up, thus sample size for the data regarding PTS and re-occlusion is 24 patients instead of 28

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<table>
<thead>
<tr>
<th>Radiation Burden</th>
<th>Number of patients</th>
<th>Number of Procedures</th>
<th>Mean</th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Range</th>
<th>STDEV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombolysis</td>
<td>28</td>
<td>34</td>
<td>15.9</td>
<td>11.5</td>
<td>0.1</td>
<td>60.3</td>
<td>60.2</td>
<td>15.9</td>
</tr>
<tr>
<td>CTV</td>
<td>23</td>
<td>28</td>
<td>731.5</td>
<td>528.9</td>
<td>280.0</td>
<td>2893.4</td>
<td>2613.4</td>
<td>571.4</td>
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<tr>
<td>CTPA</td>
<td>20</td>
<td>23</td>
<td>584.5</td>
<td>411.5</td>
<td>173.0</td>
<td>1385.2</td>
<td>1212.2</td>
<td>367.7</td>
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<tr>
<td>Venogram</td>
<td>28</td>
<td>93</td>
<td>5.8</td>
<td>13.0</td>
<td>0.3</td>
<td>274</td>
<td>273.7</td>
<td>3.7</td>
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<tr>
<td>Stent Insertion</td>
<td>22</td>
<td>32</td>
<td>45.2</td>
<td>22.2</td>
<td>15.2</td>
<td>274</td>
<td>273.8</td>
<td>66.1</td>
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<tr>
<td>Venoplasty</td>
<td>14</td>
<td>20</td>
<td>40.4</td>
<td>15.6</td>
<td>0.3</td>
<td>263.8</td>
<td>263.5</td>
<td>64.3</td>
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<tr>
<td>Mechanical Thrombectomy</td>
<td>8</td>
<td>10</td>
<td>49.5</td>
<td>24.5</td>
<td>4.7</td>
<td>263.8</td>
<td>259.2</td>
<td>81.8</td>
</tr>
<tr>
<td>IVC Filter</td>
<td>1</td>
<td>1</td>
<td>7.8</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<td>IVUS</td>
<td>2</td>
<td>2</td>
<td>21.8</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Cumulative Radiation Burden per person</td>
<td>NA</td>
<td>NA</td>
<td>219.3</td>
<td>87.4</td>
<td>11.6</td>
<td>1298.7</td>
<td>1287.1</td>
<td>298.1</td>
</tr>
</tbody>
</table>

**Table 8:** Radiation burden associated with each interventional and imaging procedure. DAP is measured in Gy cm2 for Thrombolysis, Venogram, Stent Insertion, Venoplasty, Mechanical Thrombectomy, IVC Filter and IVUS. DLP is measured in mGy cm for CTV and CTPA.

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Conclusion

In our initial experience with CDT, we have found it to be safe and effective in the management of acute iliofemoral DVT. Despite the requirement for stent insertion and repeat procedures to maintain patency, radiation burden has been shown to be low. The immediate effect of achieving patency is reflected in symptomatic improvement in the majority of patients. Although symptomatic improvement was not formally recorded, a relatively low rate of post thrombotic syndrome was noted at follow up.

Further studies with longer term follow up and continuing vigilance of the radiation exposure incurred must be carried out to further define the role of CDT in the management of these patients.
Personal information

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References


