NICE guidance

Ultrasound-enhanced, catheter-directed thrombolysis for deep vein thrombosis

Interventional procedures guidance
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www.nice.org.uk/guidance/ipg523

1 Recommendations

1.1 The evidence on ultrasound-enhanced, catheter-directed thrombolysis for deep vein thrombosis raises no major safety concerns over those of catheter-directed thrombolysis (CDT) alone. With regard to efficacy, evidence of any enhancement of thrombolysis over CDT alone is inadequate in quality and quantity. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research.

1.2 Clinicians wishing to do ultrasound-enhanced, catheter-directed thrombolysis (UE-CDT) for deep vein thrombosis (DVT) should:

- Inform the clinical governance leads in their NHS trust.

- Ensure that patients understand the uncertainty about the procedure's efficacy and provide them with clear written information. In addition, the use of NICE's information for the public is recommended.
- Audit and review clinical outcomes of all patients having UE-CDT for DVT (see section 7.2).

1.3 NICE encourages further research comparing ultrasound-enhanced, catheter-directed thrombolysis for deep vein thrombosis against catheter-directed thrombolysis alone. Patient selection should be documented, including the duration and extent of thrombosis. The dose of thrombolytic agent used and the duration of thrombolysis should be reported, together with all complications. Outcome measures should include the success of thrombolysis (complete, partial or failed) and long-term sequelae. NICE may update the guidance on publication of further evidence.

2 Indications and current treatments

2.1 Deep vein thrombosis (DVT) occurs most commonly in the deep veins of the legs. Signs and symptoms include pain, swelling, tenderness and colour change, but some DVTs cause no symptoms. Risk factors for DVT include surgery, immobility (caused by acute illness such as stroke), malignancy, acquired or inherited hypercoagulable states, pregnancy and dehydration.

2.2 DVT is associated with the risk of potentially life-threatening pulmonary embolism (PE) and in the longer term with post-thrombotic syndrome caused by chronic venous insufficiency, which is associated with pain, swelling, and sometimes chronic leg ulcers.

2.3 A DVT is normally treated with unfractionated or low molecular weight heparin, followed by oral anticoagulants (typically warfarin). The newer factor X inhibitors may be used without preliminary heparin. Extensive DVT is sometimes treated by systemic thrombolysis or by endovascular interventions such as catheter-directed thrombolysis and percutaneous mechanical thrombectomy. Thrombolysis is associated with a risk of haemorrhagic complications including stroke. Surgical thrombectomy is

an option in patients with DVT that is refractory to thrombolytic therapy, or for whom thrombolysis is contraindicated, but it is rarely used.

3 The procedure

3.1 Ultrasound-enhanced, catheter-directed thrombolysis is an endovascular technique that uses high-frequency, low-energy ultrasound waves in combination with infusion of a thrombolytic drug, with the aim of accelerating plasmin-mediated thrombolysis. It aims to reduce treatment time, the dose of thrombolytic drug delivered and thrombolysis-related complications, compared with catheter-directed thrombolysis alone.

3.2 The procedure is done using local anaesthesia, with imaging guidance by fluoroscopy. Therapeutic doses of heparin are administered through a peripheral catheter before and during the procedure.

3.3 With the patient in the supine position, a diagnostic catheter is inserted into the area of the thrombosis via the femoral, jugular or popliteal vein and a venogram is done. A guide wire is passed through the thrombosed segment of vein under X-ray guidance and the diagnostic catheter is removed. A multi-lumen infusion catheter is passed over the guide wire into the thrombosed venous segment and the guide wire is replaced with an ultrasound core wire. This wire has multiple small ultrasound transducers that deliver ultrasound waves along the entire treatment zone. A thrombolytic drug is infused directly into the thrombus through holes in the side of the catheter, using an infusion pump, along with a flow of saline to act as a coolant while the ultrasound is activated. An electronic device controls the ultrasound power output. The patient is continuously monitored from the start of the treatment. Treatment typically lasts for 12–24 hours.

3.4 Follow-up venographic and echocardiographic assessment is performed at regular intervals after the start of the procedure. Once the thrombus has cleared, or there is no further progress, the treatment is stopped and the patient starts standard anticoagulant therapy.

4 Efficacy

This section describes efficacy outcomes from the published literature that the Committee considered as part of the evidence about this procedure. For more detailed information on the evidence, see the interventional procedure overview.

4.1 A randomised controlled trial (RCT) of 48 patients with acute iliofemoral deep vein thrombosis (DVT) comparing ultrasound-enhanced catheter-directed thrombolysis (UE-CDT; n=24) against catheter-directed thrombolysis (CDT; n=24), with a fixed dose thrombolysis regimen in all patients, reported that there was no significant difference in the percentage of thrombus load reduction from baseline to 15 hours after treatment (according to Length-Adjusted Thrombus score, obtained from venograms) between the 2 treatment groups (UE-CDT 55±27% and standard CDT 54±27%; p=0.91).

4.2 A retrospective comparative case series of 83 patients with DVT comparing UE-CDT (n=64) against CDT alone (n=19) reported no significant difference between the 2 groups in the rate of substantial thrombolysis (>50% removal) at the last angiography assessment at a median follow-up of 26 hours (UE-CDT 89.1% [57/64] and CDT 89.5% [17/19]; p=0.96). The study also reported that there was no significant difference in overall infusion time between the 2 treatment groups (UE-CDT 27 hours [range 21–27], CDT 25 hours [range 22–39]; p=0.39).

4.3 A retrospective comparative case series of 178 patients with DVT comparing UE-CDT (n=46) against pharmacomechanical thrombectomy (PMT) (n=84) and against PMT plus UE-CDT (n=27) reported that in patients with chronic DVT (n=62), the combined intervention achieved complete treatment success (defined as complete thrombus removal based on angiographic evidence) more frequently (74% [20/27]) than either UE-CDT or PMT alone (64% [9/14] and 33% [7/21] respectively; p values not reported). Complete treatment success was similar in patients with acute DVT (n=116) who had UE-CDT or PMT alone (88% [28/32] and 82% [69/84] respectively).

4.4 A retrospective comparative case series of 47 patients with 53 occlusive DVTs comparing UE-CDT against historical controls who had CDT alone

(n=82) reported that median total dose of each thrombolytic drug was lower in UE-CDT compared with CDT alone (respectively, urokinase 2.0×10^{o}units and 4.4×10^{o}units; tissue plasminogen activator 14 mg and 21.6 mg; recombinant plasminogen activator 6.9 units and 21.4 units).

4.5 The retrospective comparative case series of 178 patients with acute and chronic DVT comparing UE-CDT against PMT alone and combined UE-CDT plus PMT reported that in patients with chronic DVT (n=62) immediate clinical improvement occurred more often in the UE-CDT and combined intervention group (64% [9/14] and 63% [17/27] respectively) compared against PMT alone (28% [6/21], p values not reported).

4.6 A case series of 12 patients who underwent UE-CDT reported that recurrent DVT needing treatment occurred in 46% (6/13) of occlusions at a mean follow-up of 7 months.

4.7 The RCT of 48 patients with acute iliofemoral DVT comparing UE-CDT against standard CDT reported no significant difference in the severity of post-thrombotic syndrome, measured by mean Villalta score, between the 2 treatment groups (UE-CDT 3.0±3.9 and standard CDT1.9±1.9; p=0.21), at 3-month follow-up. A case series of 26 patients who underwent UE-CDT reported mild post-thrombotic syndrome in 11.5% (3/26) of patients: this mainly manifested as pain, heaviness and oedema of the affected limbs after activity. The median post-thrombotic syndrome score in these patients was 2 (range 0–7).

4.8 The specialist advisers listed efficacy outcomes as duration of thrombolysis ('enhanced' thrombolysis over a shorter period of time), dose of thrombolytic drug, recanalisation of deep veins ('resolution of thrombus'), DVT symptom relief, prevention of long term sequelae of DVT (that is, freedom from post-thrombotic syndrome), recurrent DVT, long-term vessel patency and quality of life.

5 Safety

This section describes safety outcomes from the published literature that the Committee considered as part of the evidence about this procedure. For more detailed information on the evidence, see the interventional procedure overview.

5.1 Major bleeding (retroperitoneal hematoma needing 4 units of blood) was reported in 1 patient in the ultrasound-enhanced, catheter-directed thrombolysis (UE-CDT) group (n=24) in the randomised controlled trial of 48 patients. Minor bleeding at the site of catheter insertion (resolved by elevation of the limb or compressive banding) was reported in 12% (3/26) of patients in a case series of 26 patients.

5.2 Haematoma at the access site was reported in 1 patient in the UE-CDT group (n=24) and 2 patients in the standard catheter-directed thrombolysis group (n=24) in the RCT of 48 patients.

5.3 Pulmonary embolism (34 days after UE-CDT) was reported in 1 patient in the case series of 87 patients (no further details available).

5.4 Haematuria (25 hours after minor bleeding during thrombolysis) was reported in 1 patient in the case series of 26 patients (further details were not reported).

5.5 Fever with positive cultures for staphylococcus aureus was reported in 6% (2/37) of patients in the case series of 37 patients. Both patients recovered after treatment with antibiotics for 6 weeks.

5.6 Transient foot drop was reported in 1 patient who had an access-related popliteal haematoma in the case series of 87 patients (further details were not reported).

5.7 In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never done so). For this procedure, specialist advisers considered that the following were theoretical adverse events: thermal damage to surrounding structures, septic thrombophlebitis, vessel perforation and death.

6 Committee comments

6.1 The Committee noted that most of the published evidence on ultrasound-enhanced, catheter-directed thrombolysis for deep vein

thrombosis (DVT) was about patients with acute DVT, but there was some evidence of its use for subacute and chronic DVT. It noted that NICE's clinical guidance on management of venous thromboembolic diseases recommends that catheter-directed thrombolysis should be considered for patients with symptomatic iliofemoral DVT who have symptoms of less than 14 days' duration, good functional status, a life expectancy of 1 year or more and a low risk of bleeding.

6.2 The Committee noted that ultrasound-enhanced, catheter-directed thrombolysis has been claimed to reduce the dose of thrombolytic agent and the duration of thrombolysis compared with catheter-directed thrombolysis alone and this underpinned the recommendation for comparative research. It noted that a number of studies are currently in progress.

7 Further information

7.1 For related NICE guidance, see the NICE website.

7.2 This guidance requires that clinicians doing the procedure make special arrangements for audit. NICE has identified relevant audit criteria and has developed an audit tool (which is for use at local discretion).

Information for patients

NICE has produced information on this procedure for patients and carers (information for the public). It explains the nature of the procedure and the guidance issued by NICE, and has been written with patient consent in mind.

About this guidance

NICE interventional procedures guidance makes recommendations on the safety and efficacy of the procedure. It does not cover whether or not the NHS should fund a procedure. Funding decisions are taken by local NHS bodies after considering the clinical effectiveness of the procedure and whether it represents value for money for the NHS.

This guidance was developed using the NICE interventional procedures guidance process.

We have produced information for the public explaining this guidance. Tools to help you put the guidance into practice and information about the evidence it is based on are also available.

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Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the available evidence. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. This guidance does not, however, override the individual responsibility of healthcare professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

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Endorsing organisation

This guidance has been endorsed by Healthcare Improvement Scotland.

Accreditation

NICE accredited

www.nice.org.uk/accreditation