NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Interventional procedure consultation document

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

A blood clot (thrombus) in a vein is usually treated with anticoagulant drugs. This stops further clotting but does not dissolve the thrombus. For severe deep vein thrombosis (DVT) thrombolysis is sometimes used: a catheter (tube) is inserted into a vein (usually in the leg) and used to deliver clot-busting drugs to dissolve the clot (thrombolysis). In this procedure ultrasound energy is also used, with the aim of making thrombolysis work better and faster.

The National Institute for Health and Care Excellence (NICE) is examining ultrasound enhanced, catheter-directed, thrombolysis for deep vein thrombosis and will publish guidance on its safety and efficacy to the NHS. NICE's Interventional Procedures Advisory Committee has considered the available evidence and the views of specialist advisers, who are consultants with knowledge of the procedure. The Advisory Committee has made provisional recommendations about ultrasound enhanced, catheter-directed, thrombolysis for deep vein thrombosis.

This document summarises the procedure and sets out the provisional recommendations made by the Advisory Committee. It has been prepared for public consultation. The Advisory Committee particularly welcomes:

- comments on the provisional recommendations
- the identification of factual inaccuracies
- additional relevant evidence, with bibliographic references where possible.

Note that this document is not NICE's formal guidance on this procedure. The recommendations are provisional and may change after consultation.

The process that NICE will follow after the consultation period ends is as follows.

- The Advisory Committee will meet again to consider the original evidence and its provisional recommendations in the light of the comments received during consultation.
- The Advisory Committee will then prepare draft guidance which will be the basis for NICE's guidance on the use of the procedure in the NHS.

For further details, see the Interventional Procedures Programme process guide, which is available from the NICE website.

Through its guidance NICE is committed to promoting race and disability equality, equality between men and women, and to eliminating all forms of discrimination. One of the ways we do this is by trying to involve as wide a range of people and interest groups as possible in the development of our interventional procedures guidance. In particular, we aim to encourage people and organisations from groups who might not normally comment on our guidance to do so.

In order to help us promote equality through our guidance, we should be grateful if you would consider the following question:

Are there any issues that require special attention in light of NICE's duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations between people with a characteristic protected by the equalities legislation and others?

Please note that NICE reserves the right to summarise and edit comments received during consultations or not to publish them at all where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would otherwise be inappropriate.

Closing date for comments: 5 February 2015

Target date for publication of guidance: March 2015

1 Provisional 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 undertake ultrasound-enhanced, catheter-directed thrombolysis (UE-CDT) for deep vein thrombosis (DVT) should take the following actions:

- Inform the clinical governance leads in their NHS trust.
- Ensure that patients understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. In addition, the use of NICE's information for the public *[[URL to be added at publication]]* is recommended.
- Audit *[URL to audit tool to be added at publication]* and review clinical outcomes of all patients having UE-CDT for DVT (see section 7.1).

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 explicitly 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 (due to 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 due to chronic venous insufficiency causing 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 side-holes in 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 ***[add URL]***.

4.1 A retrospective comparative case series of 83 patients with deep vein thrombosis (DVT) comparing ultrasound-enhanced, catheter-directed thrombolysis (UE-CDT; n=64) against catheter-directed thrombolysis alone (CDT; 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). There was also no significant difference in the percentage resolution of thrombus load between the two groups (UE-CDT 82%, [interquartile range 55-92%], CDT 89% [interquartile range 70-90%]; p=0.56). 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).

4.2 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 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).

4.3 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 2.0x 10^{o}units and 4.4x10^{o}units; tissue plasminogen activator 14 mg and 21.6 mg; recombinant plasminogen activator 6.9 units and 21.4 units).

4.4 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).

4.5 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.

4.6 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).

4.7 The specialist advisers listed key 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 (i.e. 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 ***[add URL]***.

5.1 Major bleeding was reported in 4% (2/37) of patients in a case series of 37 patients (further details were not reported). 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 surgical site was reported in 4% (2/47) of patients who underwent surgery for bleeding complications in a case series of 47 patients. This was treated by surgical removal and blood transfusion and resolved with no sequelae.

5.3 Pulmonary embolism (34 days after ultrasound-enhanced, catheter-directed thrombolysis) 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 Transient asymptomatic haemoglobinuria was reported in 2 patients in a case series of 87 patients (further details were not reported).

5.6 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.

5.7 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).

5.8 The specialist advisers listed additional theoretical adverse events as 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 the potential 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 undertaking the procedure make special arrangements for audit. NICE has identified relevant audit criteria and is developing an audit tool (which is for use at local discretion), which will be available when the guidance is published.

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