NICE guidance

Ultrasound-enhanced, catheter-directed thrombolysis for pulmonary embolism

Interventional procedures guidance
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www.nice.org.uk/guidance/ipg524

1 Recommendations

1.1 The evidence on ultrasound-enhanced, catheter-directed thrombolysis for pulmonary embolism 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 pulmonary embolism (PE) should take the following actions.

- Inform the clinical governance leads in their NHS trusts.

- 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 PE (see section 7.1).

1.3 NICE encourages further research into ultrasound-enhanced, catheter-directed thrombolysis for pulmonary embolism. Ideally this should include comparative studies against catheter-directed thrombolysis alone. Patient selection should be documented. 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 Pulmonary embolism (PE) is a condition in which a thrombus, most commonly from a deep vein thrombosis (DVT) in the legs or pelvis, obstructs the pulmonary arterial system. Symptoms of PE depend on the extent of obstruction to the pulmonary arteries: they include chest pain, dyspnoea and haemoptysis. In severe cases PE can result in reduced cardiac output, cardiogenic shock and sudden death. Risk factors for PE include surgery, immobility, trauma, malignancy, acquired or inherited hypercoagulable states, use of oral contraceptives or hormone replacement therapy, pregnancy and dehydration.

2.2 A PE without haemodynamic instability is normally treated with low molecular weight heparin (LMWH) or fondaparinux, followed by oral anticoagulants (typically warfarin). The newer factor X inhibitors may be used without preliminary heparin. PEs with haemodynamic instability are sometimes treated with systemic thrombolysis or, occasionally, with endovascular interventions such as catheter-directed thrombolysis and percutaneous mechanical thrombectomy. Thrombolysis is associated with a risk of haemorrhagic complications including stroke. Surgical thrombectomy may occasionally be performed for patients with a

life-threatening PE.

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 usually 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, an angiographic catheter is inserted from the femoral vein into the main pulmonary artery. The position of the pulmonary embolic occlusion is identified using angiography. A guide wire is passed into the embolus and the angiographic catheter is removed. A multi-lumen infusion catheter is passed over the guide wire into the embolus and the guide wire is replaced with an ultrasound wire. This wire has multiple small transducers that deliver ultrasound waves along the entire treatment zone. A thrombolytic drug is infused directly into the embolus through holes in the side of the catheter, using an infusion pump, along with a flow of saline to serve as a coolant while the ultrasound wire is activated. An electronic device controls the ultrasound power output. The patient is continuously monitored from the start of treatment. Treatment typically lasts for 12–24 hours.

3.4 Follow-up angiographic and echocardiographic assessment is performed at regular intervals after the start of the procedure. Once the embolus has cleared, or there is no further progress, the treatment is stopped and the patient starts standard anticoagulation 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 retrospective comparative case series of 25 patients with acute massive pulmonary embolism (PE) compared ultrasound-enhanced, catheter-directed thrombolysis (UE-CDT; n=11) against catheter-directed thrombolysis alone (CDT; n=14). It reported a significant difference between the 2 groups in the rate of complete thrombolysis (>90% removal) at angiography assessment performed 12–48 hours after the start of treatment (UE-CDT 100% [11/11] and CDT 50% [7/14]; p=0.01). The study also reported that there was a significant difference in the mean overall infusion time between the 2 treatment groups (UE-CDT group 17.4±5.23 hours, CDT group 26.7±8.64 hours; p=0.03).

4.2 In a systematic review of 7 studies (n=197), 3 studies assessed the right-to-left ventricular dimension (RV/LV) ratio using a chest CT scan or echocardiography, before and after UE-CDT. The pooled mean RV/LV ratio decreased from 1.36 to 1.03 (no significance test was reported).

4.3 In the systematic review of 7 studies, 3 studies reported mean pulmonary artery pressure before and after UE-CDT. The pooled mean pulmonary artery pressure decreased from 31.3±9.0 mmHg before treatment to 22.7±6.9 mmHg after treatment (no significance test was reported).

4.4 In the systematic review of 7 studies, 2 studies reported cardiac index before and after UE-CDT. The pooled mean cardiac index increased from 2.2±0.7 l/min/m^2 before treatment to 3.1±1.3 l/min/m^2 after treatment (no significance test was reported).

4.5 In the systematic review of 7 studies, 4 studies assessed pulmonary thrombus load before and after UE-CDT using various angiographic scores (Miller index, modified Miller score, and Mastora score). The pooled mean relative reduction in the pulmonary occlusion score was 41% (scores ranged from 32% to 69%; no significance test was reported).

4.6 In the systematic review of 7 studies, 2 studies reported recurrence of PE in 2 patients at follow-up. A suspected recurrent PE 1 day after UE-CDT was reported in a case series of 24 patients. This was treated with rescue thrombolysis (100 mg rtPA) given intravenously over 2 hours. A recurrent PE 4 months after thrombolysis, from non-compliance with anticoagulant treatment, was reported in a case series of 10 patients. This patient died of severe right ventricular failure.

4.7 A retrospective case series of 22 patients with a sub-massive or massive PE who had UE-CDT reported that 86% (19/22) of patients were alive at 180 day follow-up.

4.8 The specialist advisers listed additional efficacy outcomes as long-term reduction in pulmonary hypertension and right ventricle dysfunction, reduction in right ventricle strain, shortened recovery time and hospital stay, symptom relief and vessel patency.

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 Overall mortality at 3 month follow-up was 4% (7/197) in a pooled analysis of ultrasound-enhanced, catheter-directed thrombolysis (UE-CDT), in a systematic review of 7 studies with 197 patients. Deaths were mainly in patients with a massive pulmonary embolism (PE) and were caused by multi-organ failure (n=1), discontinued treatment (n=1), acute abdominal haemorrhage with hypovolaemic shock 6 days after treatment (n=1), ovarian cancer and multiple factors (n=1), cardiogenic shock (n=1) and recurrent PE (n=1). Reasons for the other death were not given.

5.2 Mortality was 9% (1/11) in the UE-CDT group and 14% (2/14) in the catheter-directed thrombolysis (CDT) alone group in a retrospective comparative case series of 25 patients. One patient in the UE-CDT group who had a massive PE died of multi-organ failure 7 hours after treatment. One patient in the CDT group died of cardiac arrest and acidosis 2 hours

after treatment, and 1 had severe heart failure and died 13 hours after treatment.

5.3 Acute kidney injury and cardiac arrest were reported in 1 patient (in whom a retracted infusion catheter was replaced and thrombolysis was extended) in a case series of 60 patients, in the systematic review of 7 studies. The patient was successfully resuscitated and recovered after lengthy hospitalisation.

5.4 Major bleeding complications were reported in 4% (7/197) of the patients in a pooled analysis of UE-CDT, in the systematic review of 7 studies. These included: bleeding from the access site that needed a blood transfusion (n=4), intra-abdominal haemorrhage (n=1), intra-thoracic bleeding after cardiopulmonary resuscitation that needed a blood transfusion (n=1) and intrapulmonary bleeding that needed a lobectomy (n=1).

5.5 Minor bleeding complications were reported in 11% (21/197) of the patients in a pooled analysis of UE-CDT, in the systematic review of 7 studies. These included: puncture site haematomas that needed no intervention (n=6) and non-fatal haemoptysis (n=3). Details of the other 11 patients were not available.

5.6 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: distal embolisation, pulmonary artery perforation, extracranial haemorrhage, cerebrovascular accident, cardiac dysrhythmias and right ventricle failure.

6 Committee comments

6.1 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 supported the recommendation for

comparative research.

6.2 In considering the risks and benefits of this procedure, the Committee noted that patients with major pulmonary embolism may die without thrombolytic treatment. It also noted the substantial risks of systemic thrombolysis. The Committee noted that NICE's guideline on management of venous thromboembolic diseases recommends that systemic thrombolytic therapy for pulmonary embolism should be considered for patients who have haemodynamic instability but should not be offered to patients who are haemodynamically stable.

7 Further information

7.1 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).

7.2 For related NICE guidance, see the NICE website.

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