CASE REPORT

Successful use of Alteplase during cardiopulmonary resuscitation following massive PE in a patient presenting with ischaemic stroke and haemorrhagic transformation

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SUMMARY

The management of patients with acute stroke regarding treatment of thromboembolism is supported by a limited evidence base. We present the case of a 55-year-old female patient who initially presented with an ischaemic cerebral infarct with haemorrhagic transformation. Her clinical recovery was complicated by cardiac arrest secondary to massive pulmonary embolism. This was successfully treated with cardiopulmonary resuscitation and thrombolysis using Alteplase, which led to a full recovery to the pre-arrest state with no evidence of haemorrhagic complication. The patient was successfully discharged to a specialist centre for on-going stroke rehabilitation with no additional neurological impact. Despite the limited evidence base we believe this case highlights that thrombolysis can be used in select patients with haemorrhagic transformation of stroke and serious thromboembolic complications to achieve a positive outcome.

BACKGROUND

Current National Institute for Health and Care Excellence (NICE) guidelines recommend that patients who have suffered an acute ischaemic stroke should not be offered antiembolism stockings, and those with evidence of haemorrhage should not receive pharmacological venous thromboembolism (VTE) prophylaxis. The only recommended options are mechanical, such as intermittent compression devices, with little in the way of strong supporting evidence.¹ This leaves patients with acute haemorrhagic stroke or haemorrhagic transformation of an ischaemic infarct at significant risk of VTE due to often significantly reduced mobility and other comorbidities with little in the way of prophylaxis. In those who suffer VTE there are limited treatment options; the benefit of treating active VTE having to be weighed against the risk of further haemorrhage. There is a limited evidence base in such situations, particularly in the case we describe with a massive life-threatening pulmonary embolism (PE) causing cardiac arrest in a patient who presented initially with an ischaemic infarct and secondary haemorrhagic transformation. We believe this case could be used to illustrate the successful use of thrombolysis without measurable negative effects in a patient with a risk of further haemorrhage.

CASE PRESENTATION

A 55-year-old woman presented to the accident and emergency department of a district general hospital after having been found on the floor at home unable to move or communicate and incontinent of urine. On admission, the patient's vital signs were normal, with clinical examination demonstrating an expressive aphasia, right-sided hemiplegia and evidence of prolonged time on the floor with erythematous pressure areas. The patient was able to understand and communicate through nodding her head and blinking her eyes. There was very little history available from the patient due to her difficulty communicating. Collateral history revealed risk factors for VTE in the form of hormone replacement therapy and considerable alcohol and tobacco use. There was no known personal or family history of cardiac or cerebrovascular disease. A clinical diagnosis of left partial anterior circulation stroke was made and the patient was admitted for further investigation, treatment and post-stroke rehabilitation.

On day 9 the patient was found to be acutely agitated and poorly responsive. On arrival of the medical team the patient was unconscious with a clear airway, good respiratory effort and clear chest, but cold and clammy peripheries with only carotid and femoral pulses palpable, and an unrecordable blood pressure. Over the following 10 min the patient deteriorated despite fluid resuscitation and oxygen therapy, developing evidence of cyanosis and skin mottling, decreasing oxygen saturations and increased respiratory rate before falling into a pulseless electrical activity (PEA) cardiac arrest. Cardiopulmonary resuscitation (CPR) was initiated according to Advanced Life Support (ALS) guidelines.² A diagnosis of massive PE was made given the rapid onset, significant risk factors for VTE and lack of evidence for other causes. The patient received CPR and was treated with an epinephrine infusion and intravenous Alteplase on the ward. After the return of spontaneous circulation (ROSC) the patient was transferred to the critical care unit (CCU) for an additional Alteplase infusion and postcardiac arrest care.

The patient made an excellent recovery, with her functional level returning to her pre-arrest state within 24 h of admission to CCU. On day 12 the patient was medically fit for transfer back to the stroke ward for further rehabilitation, and for

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discharge to a specialist rehabilitation centre by day 14. The patient indicated she had no recollection of events surrounding her cardiac arrest, and demonstrated no negative neurological sequelae beyond those of her admitting stroke.

INVESTIGATIONS

CT of the head on admission demonstrated a subacute basal ganglia infarct with haemorrhagic transformation ([figure 1](#)). Admission ECG revealed normal sinus rhythm and the chest radiograph demonstrated mild left lower lobe atelectasis. Blood tests on admission were unremarkable.

Investigations during and postcardiac arrest were as follows:

ECG demonstrated a new right bundle branch block and evidence of right ventricular strain during the course of the arrest event.

Arterial blood gas on 15 L oxygen via non-rebreathing mask demonstrated severe metabolic derangement, with pH 6.97, pO₂ 15.3, pCO₂ 5.46, lactate 9.9, HCO₃ 8.7.

Beside echocardiography demonstrated good left ventricular function and no evidence of cardiac tamponade, but revealed a dilated right ventricle and flattened interventricular septum. More specifically, the echocardiogram demonstrated akinesia of the mid-free wall and normal apical motion (McConnell's sign—77% sensitivity/94% specificity for acute PE).³ Right ventricular systolic pressures were not measurable due to difficult windows.

CT imaging was obtained 5 h postcardiac arrest. Head CT demonstrated the original stroke with resolution of the previously haemorrhagic area and no further bleeding. Imaging did show the original infarct had extended into the posterior aspect of the left frontal lobe with mass effect effacing the right ventricle. It is possible that this represents conversion of the original penumbra area to true tissue infarct but, unfortunately, MRI was not available to investigate this ([figure 2](#)).

CT pulmonary angiogram demonstrated moderately large bilateral pulmonary emboli, with some patchy atelectasis of both lungs ([figure 3](#)).

CT of the abdomen and pelvis showed no evidence of haemorrhage.

Figure 2 Head CT following thrombolysis demonstrates original infarct, albeit slightly increased in size (arrow). The area of infarction is now of uniform density, with resolution of the previously demonstrated haemorrhagic transformation. Mild mass effects remain. There is no evidence of any new intracranial bleeding.

DIFFERENTIAL DIAGNOSIS

In cardiac arrest in a patient suitable for resuscitation the priorities are support of airway, breathing and circulation, followed by identification and treatment of any reversible causes. ALS guidelines classically divide these causes into the four H's (hypoxia, hypovolaemia, hypothermia, hyperkalaemia/metabolic) and the four T's (thrombosis, tamponade, toxins, tension pneumothorax).

The most likely diagnosis in this case was that of thrombosis, specifically a massive PE. The history was consistent, with an elevated risk due to a profound hemiparesis, pre-existing risk factors and a lack of VTE prophylaxis (based on a risk/benefit analysis of thrombosis vs further bleeding), and sudden onset in

Figure 1 Contrast CT head scan on admission demonstrating an area of low attenuation in the left frontoparietal lobe (arrow), with an area of increased attenuation within this (*). There is mild mass effect with effacement of the left lateral ventricle and a 4 mm midline shift to the right. Appearances are typical of a subacute basal ganglia infarct with haemorrhagic transformation, usually caused by transient occlusion of the M1 branch of the middle cerebral artery.

Figure 3 CT pulmonary angiography 5 h following thrombolysis demonstrating bilateral pulmonary emboli (arrows). (A) ascending aorta, (B) descending aorta, (C) superior vena cava, (D) pulmonary trunk, (E) left pulmonary artery branch, (F) right pulmonary artery, (G) left bronchus, (H) right bronchus, (I) left upper pulmonary vein and (J) small wedge infarct.

an otherwise relatively well patient. Clinically, the weak pulses, raised jugular venous pressure, worsening hypoxia, skin mottling and unrecordable blood pressure indicated a failure in oxygenation and cardiac output. Bedside echocardiogram demonstrated a dilated right ventricle, flattened interventricular septum with good left ventricular function and no tamponade/effusion. Together these portray a picture of the right ventricle being exposed to an acute rise in pulmonary pressures, consistent with a massive PE. Based on this thrombolytic therapy was initiated at the bedside, with clinical improvement as described.

In patients experiencing left-sided and right-sided embolic events one should consider the possibility of paradoxical embolism. In these events a right-sided thrombosis develops, with subsequent embolisation and entry into the left-sided circulation via a patent foramen ovale (PFO) or atrial septal defect (ASD), and distal impaction. Structural abnormalities such as these have been shown to be more common in those suffering cryptogenic stroke, for example, a prospective case-control study of 503 patients demonstrated an independent association of PFO with cryptogenic stroke in young (<55 years, OR 3.7, $p=0.008$) as well as old (≥ 55 years, OR 3.0, $p<0.001$).⁴ However, prospective population-based cohort studies (SPARC study, NOMAS study) have called this association into question, failing to demonstrate PFO to be an independent risk factor for ischaemic stroke.^{5 6} Investigation for PFO/ASD using bubble echocardiography was not performed in this patient as she has been placed on long-term warfarin therapy given her now significant immobility and PE, and so closure of such a defect would not be indicated.

TREATMENT

Treatment following acute stroke with evidence of haemorrhage as per NICE stroke guidelines. No heparin for VTE prophylaxis, no antiembolism stockings, no mechanical deep vein thrombosis (DVT) prophylaxis applied.

Management of cardiac arrest

- ▶ Three cycles of CPR according to ALS guidelines with ROSC between each cycle. Total time from first PEA arrest to final ROSC without further arrest was 25 min.
- ▶ 50 mg intravenous Alteplase bolus administered on diagnosis of life-threatening PE, 17 min after initial arrest, followed by an intravenous infusion of 50 mg Alteplase over 60 min.
- ▶ Epinephrine infusion started following third cycle to maintain cardiac output.
- ▶ 8.4% HCO₃ given following third cycle because of profound metabolic acidosis.

Following transfer to CCU the patient was started on treatment dose dalteparin (15 000 units subcutaneously, once daily) under advice from the haematology service. Warfarinisation was started on day 14 following the acute stroke, with dalteparin stopped once the international normalised ratio (INR) reached therapeutic levels (with a reduced target INR of 2).

OUTCOME AND FOLLOW-UP

The patient responded well to the management of her life-threatening PE. She made a full recovery to her pre-arrest functional level within 24 h following the cardiac arrest. There was no evidence of haemorrhagic stroke extension or other haemorrhagic complication and her neurological status was unchanged compared to pre-arrest. The patient was discharged from hospital to a specialist rehabilitation centre for on-going care.

DISCUSSION

Haemorrhagic transformation after an ischaemic stroke is not uncommon. It occurs in about 9% of patients.⁷ Several risk factors

have been identified, including an older patient age, a cardioembolic stroke subtype (most often on a background of atrial fibrillation), hypertension, large size of the ischaemic territory involved and treatment with thrombolytic agents within 3–6 h post-stroke.^{8–14} Overall, our patient was of a younger age, with no history of atrial fibrillation or hypertension, and had not undergone thrombolysis at initial presentation. The clinical outcome in cases of haemorrhagic transformation postischaemic infarction depends strongly on the extent of the haemorrhage.¹⁵ The current classification of haemorrhagic transformation distinguishes between haemorrhagic infarction (types 1 and 2) and parenchymal haematoma (types 1 and 2) on the basis of CT scan characteristics: isolated petechial staining of infarcted tissue and confluent petechiae without mass effect (haemorrhagic transformation types 1 and 2) and homogenous haematoma in $\leq 30\%$ of the infarcted area with some slight mass effect (parenchymal haematoma type 1) or dense haematoma in $>30\%$ of the infarcted area with significant mass effect, as well as any haemorrhage outside the infarcted area (parenchymal haematoma type 2).¹⁶ Only the type 2 parenchymal haematoma is associated with a significant clinical deterioration and a poor neurological outcome over 3 months.¹⁷ In our case the initial CT of the head was in keeping with parenchymal haematoma type 1.

It is well recognised that following acute ischaemic stroke patients are at increased risk of medical complications, as demonstrated in the Randomized Trial of Tirilazad Mesylate in Acute Stroke (RANTTAS) with serious medical complications in 24% and any medical complication in 95%. Overall medical complications account for approximately 50% of deaths after a cerebrovascular accident.^{18 19}

Complications following acute stroke demonstrate characteristic time courses. In the first week most mortality is directly related to the stroke. In the second to fourth weeks, PE is the predominant cause of death, while bronchopneumonia predominates in the second and third months. After the third month, cardiac disease is the major cause of death.²⁰ The significance of an in-hospital complication following a stroke is profound—such patients have demonstrably higher mortality up to 4 years after the event.²¹

DVT and PE are significant complications post-stroke. In screening studies of untreated patients with hemiplegic stroke the incidence of DVT within 2 weeks of the acute stroke reach 50%—most are asymptomatic, affect the hemiparetic leg and are below the knee. The peak for DVT development is approximately day 7—but can be as short as 2 days. Those with more pronounced hemiparesis and pre-existing risk factors for VTE are at increased vulnerability.²² Patients with acute stroke similarly are at increased risk of PE, although with a wide range in reported incidence.²³ Patients who develop a PE appear to have a higher mortality relative to PE in other clinical conditions, at least in more elderly patients.²⁴

Current NICE clinical guideline 92 (CG92) specifically addresses VTE prophylaxis in those with acute stroke.¹ At no point are thromboembolic deterrent stockings indicated given their non-significant protective effects, but significant complications (CLOTS1 trial).²⁵ The evidence for mechanical methods of VTE prophylaxis in acute stroke is of generally low quality, and the recommendation is largely based on trials of devices in postoperative patients. However, the findings of the randomised CLOTS3 trial have recently been published, strengthening the case for intermittent pneumatic compression stockings (IPC) in VTE prophylaxis.²⁶

CG92 goes on to distinguish between those with haemorrhagic stroke/further risk of bleeding versus those without. The

recommendation is for those without to be placed on standard low-molecular-weight heparin (LMWH) treatment following a risk/benefit analysis. A number of trials have demonstrated reduced DVT/PE incidence in treated groups of patients with acute ischaemic stroke, but at the risk of bleeding events (particularly intracranial). A 2007 systematic review of randomised controlled trials assessed the available evidence and recommended low-dose (≤ 6000 units daily) LMWH, with numbers needed to treat as 7 for DVT and 38 for PE.²⁷ This was supported by a later meta-analysis of LMWH and unfractionated heparin for VTE prophylaxis in acute ischaemic stroke.²⁸

The guidance in those with haemorrhagic stroke/risk of bleeding is less clear, with 'consideration' of mechanical methods of VTE prophylaxis (impulse or intermittent mechanical compression) and LMWH therapy when risk is low. There is less evidence to guide clinical decisions regarding LMWH therapy in those with haemorrhagic stroke compared to ischaemic stroke. The American Heart Association/American Stroke Association Stroke Council 2007 Guidelines on the Management of Spontaneous Intracerebral Hemorrhage in Adults suggest LMWH for VTE prophylaxis after 3–4 days of the stroke if there is no evidence of further bleeding (class IIb, level of evidence B).²⁹ A 2011 meta-analysis assessing safety and efficacy of pharmacological VTE prevention in those with acute cerebral haemorrhage demonstrated a significant reduction in PE. There was, however, a non-significant reduction in mortality and a non-significant enlargement of haematoma. The authors caution against using this as evidence for generalised early LMWH VTE prophylaxis, but instead advocate well-designed clinical trials.³⁰

There are no randomised placebo-controlled trials supporting a treatment for life-threatening VTE in patients with acute stroke and a haemorrhagic component.

Clearly the dilemma is deciding when a patient with a haemorrhagic element to their stroke can be considered 'low risk' and suitable for LMWH VTE prophylaxis. In the case presented the risk level was not felt to be low enough, and unfortunately a life-threatening PE resulted. The optimum management of this complication is unclear, with very little published evidence or expert consensus. There are limited case reports on predominantly young patients who presented with haemodynamically relevant PEs concomitant with or postischaemic stroke.^{31–33} Thrombolytic agents used in these cases included streptokinase and Alteplase. In these cases thrombolysis led to haemodynamic stabilisation and clinical improvement. No subsequent intracerebral haemorrhage was reported.

It should be noted that physical removal of the pulmonary embolus is now a possibility using catheter embolectomy or surgical embolectomy. The proposed benefits of such techniques are that they can be used in patients not suitable for thrombolysis, or where thrombolysis has failed. However, such techniques require the equipment as well as expertise to be available at short notice. To date there are no high-power trials to support one intervention over the other, and thrombolysis remains first line in clinical practice.

Clinical screening strategies to identify patients with DVT post-stroke have been suggested, including the use of Doppler ultrasound as well as D-dimer measurement and MRI venous imaging.³⁴ Alongside this is the need for high-quality evidence-based methods for VTE prophylaxis and treatment of VTE, specifically in patients with acute stroke and with a haemorrhagic component. The ideal, however, is effective prophylaxis for VTE, rather than relying on active treatment and its associated risks (prevention being better than cure). To this end, we would recommend IPC devices as supported by the CLOTS3 trial and

regular patient review to consider the safety of introducing LMWH as additional VTE prophylaxis.

Learning points

- ▶ Consider acute thrombolysis in patients with previous stroke and secondary intracerebral haemorrhage if life-threatening pulmonary embolism/venous thromboembolism (PE/VTE) is suspected.
- ▶ Decisions on VTE prophylaxis require a careful assessment of the risk of further haemorrhagic events in patients with known haemorrhagic or ischaemic with haemorrhagic change acute stroke.
- ▶ The evidence for intermittent pneumatic compression stockings for VTE is in favour of their use.
- ▶ Treatment of VTE in patients with haemorrhagic transformation of acute stroke may be safely achieved using treatment dose low-molecular-weight heparin in selected patients where the risk of further haemorrhage is low, but further research is needed to determine when the risk is 'low enough'.
- ▶ A positive outcome is possible in cardiac arrest patients given a reversible cause is promptly identified and treated, and resuscitation is long enough (25 min in this case),³⁵ even in the face of grossly abnormal clinical signs, haematological and biochemical parameters.

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