Prospective Randomised Comparative Study of Pulse Spray and Conventional Local Thrombolysis*

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Objectives: To compare the time required to achieve lysis with the pulse spray technique and the conventional slow continuous infusion technique.
Design: Prospective randomised open Study.
Methods: Eighteen patients suitable for intra-arterial thrombolytic therapy with conventional and pulse spray technique were randomised 1:1 to receive either pulse spray thrombolysis with 0.33 mg/ml rt-PA injected as a bolus of 0.2 ml or conventional thrombolysis with 0.05 mg/ml rt-PA infused at a rate of 10 ml/h.
Results: The age, duration of symptoms, length of occlusion and prethrombolysis'ankle brachial pressure index were comparable in the two groups. The median duration of thrombolytic therapy in the pulse spray group was 195 min (range 90-1260) compared to 1390 min (range 300 – 2400) in the Conventional group. The difference between the two groups was significant, p < 0.002 (Mann-Whitney test).
Conclusions: Significantly shorter time is required to achieve local thrombolysis with pulse spray compared to the conventional infusion method.

Introduction

There is a consensus that percutaneous transluminal angioplasty (PTA) is the treatment of choice for symptomatic stenoses in the iliac, femoral and popliteal segments.1 In situ thrombosis, however, can supervene resulting in acute deterioration in the condition of the limb, and is now recognised as the commonest cause of acute lower limb ischaemia.2 Local thrombolytic therapy offers the opportunity of dissolving the thrombus and unmasking the underlying stenosis or stenoses which can then be subjected to PTA. A primary failure of thrombolysis or reclosure at a later date does not usually preclude subsequent surgical intervention. Similarly in grafts that occlude beyond the first 30 days of the operation, local thrombolytic therapy allows clearance of the graft and unmasking of the underlying problem which can then be dealt with either by a percutaneous catheter-directed intervention or limited surgery.3-4 The main drawback of the conventional intra-arterial infusion thrombolytic therapy has been the length of time required to restore circulation to the ischaemic leg rendering it unsuitable for severe limb threatening ischaemia with sensory deficit.5 Because of this thrombolytic therapy is not regularly used in many vascular surgical units. In a pilot study we have shown that rapid thrombolysis can be achieved with the pulse spray technique (PST) within 2 h as opposed to 25 h with our previous experience with conventional low dose infusion technique (CT).6 In the present study pulse spray thrombolysis was compared with the conventional infusion method in a prospective randomised trial.

Patients and Methods

The study was conducted with the approval of the Hospital Ethics Committee. Informed consent was obtained from each patient. The sample size of the study was estimated from the findings of the open studies with PST with rt-PA and conventional thrombolysis with rt-PA carried out previously in our unit7 as follows:

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$m = \text{sample size of group 1} = 120$

$n = \text{sample size of group 2} = 38$

$SD_1 = \text{standard deviation of group 1} = 17.3 \text{ h}$

$SD_2 = \text{standard deviation of group 2} = 3.3 \text{ h}$

$$\text{Standardised estimated difference (}\sigma\text{)} = \sqrt{\frac{(m-1) \cdot SD_1^2 + (n-1) \cdot SD_2^2}{m + n - 2}}$$

Sample size for difference between two means with a significance level of 0.05, i.e. $\beta = 1.96$ and a power of 90%, i.e. $\alpha = 1.28$ can be estimated by the following formula:

$$n = \frac{2 \left( \frac{Z_\alpha + Z_\beta}{d} \right)^2}{\sigma^2}$$

Mean duration of thrombolysis with

CT ($m_1$) = 31.7 h

Mean duration of thrombolysis with

PST ($m_2$) = 3.4 h

Difference between the two means

$(d) m_1 - m_2 = 28.3 \text{ h}$

$$\text{Standardised estimated difference (}\sigma\text{)} = 15.1$$

$$n = 2 \left( \frac{1.28 + 1.96}{28.3} \right)^2$$

$$n = 6$$

Therefore six patients were required in each group to have a 90% power to detect true difference of the magnitude observed in the open studies at a 5% level of significance. We decided to study 18 patients which was 50% more than the estimated sample size.

Eighteen patients suitable for local thrombolysis were randomised 1:1 to receive pulse spray or conventional thrombolysis. Randomisation was carried out after the arteriogram had been performed and the occlusion traversed with a guide wire. The exclusion criteria for the study were: (i) active internal haemorrhage; (ii) cerebrovascular accident within the preceding 2 months; (iii) major surgery within 2 weeks; (iv) infected bypass grafts; (v) pregnancy; (vi) inability to provide consent; (vii) infective endocarditis; (viii) inability to traverse the occlusion with a guidewire; (ix) inability to withstand further ischaemia up to 24 h (total ischaemia with rapidly progressing sensory and motor deficit); (x) presence of irreversible ischaemic injury.

The end point for the cessation of thrombolytic therapy were: (i) complete radiological lysis; (ii) no radiological and clinical improvement on two assessments over a period of 12 h; (iii) onset of irreversible ischaemic injury during the course of therapy; (iv) occurrence of major haemorrhagic complication.

The pulse spray catheters (E-Ze-M Ltd High Road London) used in this study were 5 F in size and measured 90 or 135 cm in length. The spray generating segments spanned 10, 20 or 30 cm at the distal end of the catheter. The catheters were selected according to the length of the occlusion and portal of catheter entry. When the occlusion was greater than 30 cm in length the proximal part of the occlusion was treated first. Lacing or preliminary treatment of the entire occlusion was not performed to avoid destabilisation of the thrombus and distal embolisation. Recombinant human tissue type plasminogen activator (Actilyse®), Boehringer Ingleheim, Bracknell Berkshire, U.K.) was used in a concentration of 0.33 mg/ml which was prepared by dissolving 20 mg rt-PA in 20 ml of water and diluting in another 40 ml of 0.9% NaCl. A purpose-built pulse spray injector (Angiodynamics Ltd., Glenfalls, New York, U.S.A.) was programmed to deliver a bolus of 0.2 ml every 15 s for the first 15 min and every 30 s thereafter. Following the arteriogram a pulse spray catheter of appropriate length was positioned and the patient was transferred to the recovery area in the angiography suite for the administration of the thrombolytic therapy. Haemodynamic and femoral puncture site monitoring was performed by observations every 15 min by the Vascular Surgical Research Fellow assisted by a nurse. Radiological progress of lysis was monitored with angiograms at variable intervals ranging from 30–120 min guided by the clinical state and depending on access to the angiography table. Percutaneous transluminal balloon dilatation of any underlying stenosis was performed at the same session and if there was any residual thrombus at this stage then the catheter was left for slow infusion of rt-PA via the end hole at a rate of 1 mg/h.

For conventional lysis a 4 or 5 F end hole straight catheter was used. With the tip of the catheter embedded into the distal end of the occlusion the rt-PA was infused at a rate of 0.5 mg/h with the aid of
MS 2000 Syringe Pump (Graseby Medical Ltd., Colonoal Way, Watford, Herts, U.K.). Radiological monitoring was performed with 'portable arteriogram' at intervals of 3–8 h depending upon the clinical condition and rate of lysis observed on the preceding arteriogram. The arteriogram was performed with a mobile X-ray machine (GEC Ltd.) and a large format (35 × 43 cm) film. Single radiographs were exposed during rapid injection of 10 ml undiluted Niopam 300 (Merck Ltd.). The position of the end of the catheter was withdrawn to maintain intrathrombic infusion according to the findings of the arteriogram. When lysis was completed, the patient was transferred to the angiography suite for angioplasty of any underlying stenosis and to enable a thorough radiological examination to exclude any residual problem.

The age, duration of symptoms, length of occlusion and severity of ischaemia in the two groups are shown in Table 1. The clinical categories outlined by the Ad Hoc Committee on Reporting Standards, Society for Vascular Surgery / North American Chapter, International Society for Cardiovascular surgery was used for describing the severity of ischaemia.9 The site of occlusion in the two groups is shown in Table 2. The criteria used for defining successful thrombolysis was in accordance with the standard previously recommended by our unit10 as shown in Table 3.

Statistical analysis was carried out using non parametric tests, Mann-Whitney U-test for comparing the two groups and Wilcoxon matched pair signed rank test for changes within the same group. The χ2 test was used with Yates’ correction for the categorical variables.

### Results

The total median duration of therapy was 195 min (range 90–1260) with the pulse spray and 1350 min (range -2400) with conventional thrombolysis (Fig. 1). There was a highly significant difference between the duration in the two groups, p < 0.002 (Mann-Whitney test). The changes in the ankle brachial index (ABI) after thrombolysis and angioplasty where performed in both the groups are shown in Figs 2, 3. In the conventional group the ABI increased from a pre-lysis median value of 0 to 0.5 (p < 0.02, Wilcoxon paired test). In the pulse spray group the ABI increased from a pre-lysis median value of 0 to a post-lysis value of 0.9 (p < 0.0001, Wilcoxon paired test). Thrombolysis was successful in 8/9 (88.8%) of the patients in the pulse spray group and 5/9 (55.5%) in the conventional group. One patient in the pulse spray group required adjunctive surgical intervention in the form of an extension graft due to an abnormality at the distal anastomosis, which was unmasked by thrombolysis. Therefore, successful clinical outcome was achieved in all patients who received pulse spray thrombolysis. The difference in the success rate between the two groups did not reach statistical significance probably because of the small numbers, (p < 0.9, chi-square with Yates’ correction). Minor groin haematoma were encountered in both groups. No major complication occurred in the PST group. One patient died and another two patients required an above- and a below-knee amputation within 30 days in the conventional group.

### Discussion

Despite encouraging reports on the results of intra-arterial thrombolysis (IAT) over the last decade11–13 a survey carried out in 1990 showed that the majority of vascular surgeons had never or only sporadically used IAT for the management of peripheral ischaemia.14 The poor response rate of 58% in this survey may also
Table 3. Criteria for successful thrombolysis

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<th>Criteria</th>
<th>Successful Thrombolysis</th>
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<tr>
<td>Radiological evidence of lysis with arterial recanalisation at least as far as the next major collateral</td>
<td>Must be achieved</td>
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<tr>
<td>An increase in the ABI ≥ 0.2</td>
<td>Must be achieved</td>
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<tr>
<td>Limb salvage at 30 days without recourse to reconstructive surgery at the level at which lysis was performed</td>
<td>Must be achieved</td>
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<tr>
<td>No clinical evidence or rethrombosis within the first 30 days (i.e. preservation of the increase in the ABI)</td>
<td>Must be achieved</td>
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reflect indifference towards thrombolytic therapy. The main reasons stated by the responders for not using IAT were doubts regarding its efficacy and lack of radiological support. Both these reasons are rooted in experience of conventional thrombolysis which is time consuming and imposes considerable strain on resources. During conventional thrombolysis patients require careful clinical monitoring in an intensive care or high dependency area. Radiological monitoring frequently requires out of hours angiography and some radiology departments may not be able to provide such a service. The slow action of CT means that cases where there is a doubt about the ability of the limb to withstand further ischaemia for 24 h or more cannot be treated. Even in experienced centres the success rate in a well-selected group of patients is of the order of 60%. The issue is further confounded by the paucity of controlled trials and lack of uniformity in the reporting standards used in the literature on intra-arterial thrombolytic therapy.

In our pilot study PST was successful in 75% of the cases including those with sensory and motor deficit and the median duration of thrombolysis was 137.5 minutes. This was a highly significant reduction compared to our previous experience with conventional thrombolysis. In the present study, a significant difference in the time required to achieve lysis was maintained with a median duration of 195 min with PST compared to 1350 min with conventional thrombolysis when the two techniques were compared in a randomised trial (p < 0.002).

The term pulsed spray thrombolysis was first coined by Bookstein, who reported rapid thrombolysis in occluded dialysis grafts, peripheral bypass grafts and native arteries with a technique of spraying urokinase into the occlusion. In a retrospective review of this technique, Valji and Bookstein reported complete or near complete lysis in 23/23 cases of native arterial occlusion and 24/25 cases of bypass graft occlusions, with a mean lysis time of 65 min for native arteries and 93 min for bypass grafts. However, clinical success without surgical intervention was achieved in only 15/23 native arteries and 14/25 bypass grafts. The duration of lysis was documented in only first 15 cases of arterial occlusion and first 18 cases of graft occlusion. The retrospective nature of this study with incomplete documentation detracts from the significance of this important observation on a technique of accelerated local thrombolysis.
More recently Kandarpa et al. have reported a randomised trial of forced periodic infusion and slow continuous infusion method. Although they used a similar catheter system as we have done in the present study, their results are very different. The mean duration of thrombolysis in the forced periodic infusion group was 20 ± 14 h and 28 ± 26 h in the conventional slow infusion group. Interestingly, in the conventional slow infusion group, they used pulse spray (E-Ze-M) catheters initially to deliver 25,000 units of urokinase every 10 cm of the occlusion prior to commencement of slow infusion. The explanation offered for inability to achieve rapid lysis with the pulse spray catheter is that once the flow is restored through the occluded segment, the clot penetrating ability of the spray is lost due to change in the direction of spray due brisk antegrade blood flow. However, this is merely a conjecture and certainly did not occur in our experience. The major difference was in the choice of agent and regime, which could largely account for our different results.

While the rate of administration with the pulse spray regime was nearly 20 times greater than the conventional infusion group, it seems unlikely that the highly significant difference in lysis time observed is mainly due to more rapid administration of rt-PA. In other studies where high dose rt-PA has been used at a much faster rate in the form of boluses the rate of lysis is much slower than observed in our study. One of the earlier reports on bolus administration of 15 mg of rt-PA over 30 min showed accelerated lysis. However, the majority of patients in this study had bypass graft occlusion (60%) and in such cases, it is the practice of the authors of this particular study to employ clot aspiration following rt-PA administration. The rapid clearance of thrombus therefore cannot be attributed to high dose of rt-PA alone. Moreover, in a subsequent study by Ward et al., a mean lysis time of 14.4 hours and a success rate of 48% was achieved following administration of 21 mg rt-PA during the first hour. Similar results have been reported by Braithwaite et al. who administered 18.5 mg rt-PA over the first hour and achieved a mean lysis time of 11 h. These studies clearly support the hypothesis that it is the technique of intrathrombic injection of rt-PA and not merely the rate of administration which is responsible for rapid thrombolysis with the pulse spray technique.

Multi-level infusion catheters are available for infusion thrombolysis, and their use can eliminate the need for repositioning the catheter in short occlusions. However, their use has not been reported to reduce the duration of thrombolysis and most centres in the U.K. still use an end-hole catheter for conventional infusion thrombolysis. We, therefore, used an end-hole catheter for conventional thrombolysis in the present study.

The success rate in the present study with pulse spray lysis is 8/9 (88.8%) compared to 5/9 (55.5%) with the conventional lysis, but due to the small numbers in each group this difference is not statistically significant. It is desirable and important to evaluate the difference in outcome in terms of success rate between pulse spray and conventional lysis in a prospective randomised trial but the large sample size required in each group for such a study is beyond the scope of any single centre. If we estimate the sample size for such a study using data from our previous experience with pulse spray and conventional lysis then 426 will be required in each group to have the statistical power to detect a true difference in the success rate. At the current rate of recruitment it would take more than 15 years to complete such a study or nearly eight years if the power of the study is reduced and a greater difference in success rate is expected. Large-scale multicentre trials like the STILE can address broad issues and provide valuable data but it would be difficult to organise such a study for specific techniques of thrombolysis.

The rapid rate of lysis with pulse spray means that where resources are available to institute pulse spray thrombolysis without delay, patients with rapidly progressing sensory and motor deficit who could not withstand a prolonged trial of conventional thrombolysis can be safely treated with thrombolytic therapy. Apart from clear cases of embolic occlusion with normal pulses in the contralateral limb, where balloon embolectomy with an on-table completion arteriogram may be considered acceptable, a preliminary arteriogram is usually obtained in patients with acute limb ischaemia prior to surgical intervention. Under these circumstances a catheter can be positioned with minimum delay for local thrombolytic therapy. Due to the rapid rate of lysis with pulse spray, it is easy to assess the response to therapy. If there is minimal or no radiological improvement after 1 h of pulse spray thrombolysis then alternative surgical intervention can be carried out without loss of valuable time even in the most urgent cases. The short duration of therapy eliminates the need for prolonged intensive monitoring and limits the out of hours demand on the radiology department. With close co-operation between the vascular surgeons and radiologists, PST can be effectively used for treating most cases of acute limb ischaemia, irrespective of the severity of ischaemia.
References


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