ORIGINAL ARTICLE

Comparison of alteplase and heparin in maintaining the patency of paediatric central venous haemodialysis lines: a randomised controlled trial

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Objectives: To determine whether the tissue plasminogen activator, alteplase, is more effective than heparin in preventing blood clots developing in children's haemodialysis central lines between dialysis sessions.
Design: A prospective double-blind, within-patient multiperiod cross-over controlled trial of instilling a ''lock'' of either heparin 5000 U/ml or alteplase 1 mg/ml into the central lines of two children haemodialysed twice weekly, and seven dialysed thrice weekly, over 10 weeks.
Setting: A UK paediatric nephrology unit.
Main outcome measures: Weight of blood clot aspirated from the line at the start of the next dialysis session.
Results: The odds of a clot forming was 2.4 times greater with heparin than alteplase (95% CI 1.4 to 4.0; p = 0.001), and when present they were 1.9 times heavier (31 vs 15 mg; 95% CI 1.5 to 2.4; p<0.0005). There was no effect of inter-dialytic interval. One child required an alteplase infusion to clear a blocked line following a heparin lock. We subsequently changed our routine locks from heparin to alteplase. Comparing the year before and after that change, the incidence of blocked lines requiring an alteplase or urokinase infusion fell from 2.7 to 1.2 per child (p<0.03), and the need for surgical replacements from 0.7 to nil (p<0.02).
Conclusion: Alteplase is significantly more effective than heparin in preventing clot formation in central haemodialysis lines. This reduces morbidity and improves preservation of central venous access. It is more expensive, though relatively economic if packaged into syringes and stored frozen until needed, but reduces the costs of unblocking or replacing clotted lines.

Adequate haemodialysis depends on having vascular access with high flow rates. In children in the UK, this is usually provided through surgically inserted central venous lines, although arteriovenous fistulae are also frequently used. However, central lines may be complicated by infection and by obstruction with intraluminal blood clots.[1] Despite instilling heparin into the lumens between dialysis sessions, clots are commonly present when central lines are aspirated before their next use, frequently resulting in reduced or absent blood flow, and sometimes leading to extensive central venous thrombosis. These complications are shared by children who have central lines for other indications, such as administration of parenteral nutrition or chemotherapeutic agents.

Line obstructions due to clots frequently clear after the instillation or slow infusion of a fibrinolytic agent such as urokinase or streptokinase; otherwise line replacement may be needed, often with the loss of a vascular access site. The tissue plasminogen activator, alteplase, has recently been shown to be an effective alternative for restoring line patency,[2] and this is strongly supported by our own experience. After it had become our routine practice to instil it to clear obstructed lines, sometimes leaving it in overnight before a dialysis session, we wondered whether alteplase might act as an effective alternative inter-dialytic lock to heparin. We therefore undertook this within-patient, multiperiod double-blind crossover controlled trial to determine the relative efficacy of these two agents. We subsequently changed our clinical practice to locking with alteplase instead of heparin, and compared the frequency with which blocked lines required treatment with alteplase or urokinase infusions, or needed surgical replacement, during the year prior to and the year after the change.

METHOD

We compared the efficacy of instilling either alteplase or heparin into the central venous lines of patients being dialysed in our regional children's haemodialysis unit. Parents gave informed consent, and older patients their assent, using a protocol approved by the local Ethics Committee. Our main outcome measure was the weight of clot aspirated from each line on its next use. A volume of blood 0.5 ml greater than the volume of the line lumen was aspirated and expelled onto gauze, leaving clots easily visible on the surface to be collected into pre-weighed tubes and weighed to within 0.1 mg.

We routinely use single lumen central lines because of their greater efficiency,[3] and ones with multiple distal side holes to minimise obstruction against the vessel walls. We use 8FG lines for children under 10 kg, and 10FG lines for larger children. The lines were locked with heparin 5000 U/ml, or alteplase 1 mg/ml, using a volume approximately 0.2 ml larger than the lumen volumes (1.5 or 2.0 ml for these two lines). The alteplase was drawn up into 2 ml syringes and stored at −20°C for up to 2 weeks before use. On the day of use, the pharmacy department thawed them to 4°C and supplied them to the dialysis nurses labelled with the child's name, and the date to be used, but not the content of the syringe, and they also supplied heparin in an indistinguishable format at 4°C.

We used a specially designed double-blind, multiperiod cross-over experiment. This assumed that carryover was likely to be negligible, a reasonable supposition given that very little of each agent would be delivered systemically and would be metabolised long before the next dialysis session, and that the line would then be vigorously ''washed'' by many litres of blood before the next agent was instilled. Some children were dialysed twice weekly (M, F), and some thrice weekly (M, W, F); the experiment was designed assuming a model with no conventional period effect but with a term which allowed for different inter-dialytic intervals. Thus, in this study each patient received both types of line lock an equal number of times, and the order of these was allocated such that each lock was used equally often after that child's different

What is already know on this topic

- Central venous haemodialysis lines are usually locked with heparin, but frequently clot, requiring urokinase or alteplase infusions, or needing a change of line, often with loss of an access site.

What this study adds

- Alteplase locks reduce the weight of clots formed between dialysis sessions compared to heparin.
- Using alteplase locks routinely reduces the numbers of blocked lines, infusions, and line replacements that are necessary.

inter-dialytic intervals. Based on data from routine therapy we designed the study to last 10 weeks, as this would give 80% power to detect a difference in mean clot weight of 10 mg at the two-sided 5% level.

The data were very skew with some large clots but also many occasions on which no measurable clot was obtained. We therefore used a two-stage analysis. The first stage assessed the probability of a clot being present using logistic regression. The second stage assessed the weights of clots when they were present. These data were still very skew and the analysis used a gamma distribution and log link. The models included terms for treatment and different inter-dialytic periods and they accommodated the serial measurements on each patient by fitting using generalized estimating equations with exchangeable correlation structures.[4] The models were fitted using Stata version 7 (Stata, College Station TX).

RESULTS

We studied nine children for 10 weeks, except one child did not complete the study because she was transplanted during week 8. Thus, seven children dialysed thrice weekly were each tested an average of 29 times, and the two children dialysed twice weekly were each tested 20 times. One child required an alteplase infusion to clear a blocked line; on completion of the trial we learnt that this event had followed a heparin lock.

The odds of a clot forming following a heparin lock was 2.4 times greater than after alteplase (95% CI 1.4 to 4.0; $p = 0.001$), and when they did occur, their mean weight was 1.9 times heavier (95% CI 1.5 to 2.4; $p<0.0005$), with geometric means of 15 and 31 mg. There was no evidence that the differences in inter-dialytic periods affected the probability of a clot being present ($p = 0.63$), or its weight ($p = 0.31$).

After completing the study, we changed our clinical practice to using alteplase locks routinely instead of heparin. In the year before the study, seven children were each dialysed for a full year using heparin locks, and of these six developed blocked lines which needed urokinase or alteplase infusions on a total of 19 occasions. Five lines could not be unblocked, and had to be replaced surgically. Six children were each managed throughout the year after changing to routine alteplase locks, four of whom were among the seven previously studied, and three of these needed a total of seven infusions, and none required a line change. These annual rates per child were significantly lower, at 2.7 versus 1.2 infusions ($p<0.03$, Fisher's exact test), and 0.7 versus 0 line changes ($p<0.02$).

Table 1 Vial sizes and costs of alteplase, and the cost of using vials to make 2 ml syringes for storage at −20°C (at prices purchased by local NHS Trust)

	Cost, £	
Size of vial (mg)	Vial	2 ml syringe
10	135	27.00
20	180	18.00
50	205	8.20

DISCUSSION

It is clear that alteplase is superior to heparin in preventing clot formation in children's haemodialysis central lines. This study was not designed to determine whether the marked reduction we saw in frequency and weight of clots would translate into fewer episodes of line occlusion, and consequently into a reduction in the number of urokinase or alteplase infusions, and of line replacements required, or whether it would lead to fewer central venous thrombotic episodes, and greater preservation of central access for the future. However, it seemed intuitively very likely that this might be the case, and since completing the study we have changed our routine practice from using heparin to using alteplase only, and have confirmed that these complications are now considerably less common. We have seen no side-effects from this treatment. Because only minimal quantities of alteplase enter the systemic circulation when it used as a line lock, we have continued to use it immediately after major surgical events, and have not encountered any problems with peri-operative bleeding.

Because alteplase is most commonly used to treat adults with acute myocardial infarction, pulmonary embolus, and acute ischaemic stroke, it is packaged in relatively large ampoules containing from 10 to 50 mg. Its pricing structure therefore tends to result in a great deal of waste if it is used for locking central lines in only one child, or a small number of children, which makes it an expensive option (table 1). However, alteplase has been shown to be stable when stored at −20°C for up to 6 months.[5 6] In clinical practice, our pharmacy department make up a batch of 2 mg syringes every 3 months which reduces our line lock costs to £8.20. Although this is more expensive than heparin (5 ml ampoule of 5000 U/ml, £0.92), we anticipate that it will prove cost-effective by reducing the rate of expensive complications.

The preservation of central venous access is vitally important in children with end-stage renal failure. Some children die because of loss of access whilst they are still young,[7] and others who do well early on could yet face a lifetime during which they may require further treatment with haemodialysis. We suggest that the routine use of alteplase has an important role in preserving vascular access, and therefore the quality of life for patients requiring renal replacement therapy.

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Competing interests: None.

Statements of contributions and conflicts of interest: I, Nicola S Gittins, declare that I participated in the study entitled ''Comparison of alteplase and heparin in maintaining the patency of paediatric central venous haemodialysis lines: a randomised controlled trial'', and that I have seen and approved the final version. I shared in designing the study, collecting specimens, analysing the results and writing the manuscript. I have no conflicts of interest.

I, Yan L Hunter-Blair, declare that I participated in the study entitled ''Comparison of alteplase and heparin in maintaining the patency of

paediatric central venous haemodialysis lines: a randomised controlled trial'', and that I have seen and approved the final version. I shared in designing the study, and writing the manuscript. I have no conflicts of interest.

I, John NS Matthews, declare that I participated in the study entitled ''Comparison of alteplase and heparin in maintaining the patency of paediatric central venous haemodialysis lines: a randomised controlled trial'', and that I have seen and approved the final version. I shared in designing the study, analysing the results and writing the manuscript. I have no conflicts of interest.

I, Malcolm G Coulthard, declare that I participated in the study entitled ''Comparison of alteplase and heparin in maintaining the patency of paediatric central venous haemodialysis lines: a randomised controlled trial'', and that I have seen and approved the final version. I shared in designing the study, analysing the results and writing the manuscript. I have no conflicts of interest.

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IMAGES IN PAEDIATRICS

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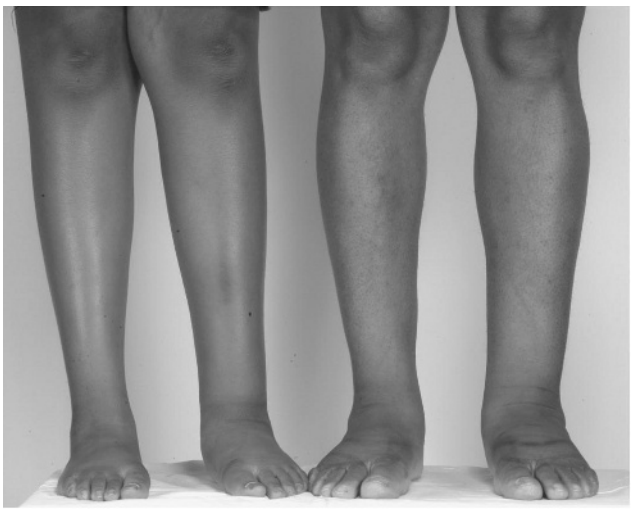
A case of familial unilateral tight shoe

An apparently healthy 13 year old girl noted progressive swelling of the left leg as her shoe was becoming increasingly tight. A general examination was unremarkable apart from non-pitting oedema of the left leg without any signs of inflammation. Further questioning revealed that her mother also had a similar ''shoe problem'' and was thoroughly investigated in 1980s without any specific diagnosis (fig 1). Her maternal grandmother who lives abroad was reported to be on diuretics for leg swelling.

Primary lymphoedema (praecox subtype) was confirmed by lymphoscintigraphy which showed markedly reduced lymphatic drainage from the left leg (fig 2).

Lymphoedema praecox is the most common type of primary lymphoedema and usually affects females. Although by definition it can present up to 30 years of age, it mostly manifests during puberty. About 70% cases are unilateral, with left lower extremity predominance.[1] In these patients lymphatic transport capacity is reduced due to hypoplastic lymphatic channels. This can be confirmed by lymphoscintigraphy which has become the investigation of choice.[2]

Management is usually conservative with weight loss, good hygiene and avoidance of local trauma/tight garments being most useful. Diuretics have not been found to be of much benefit. In severe cases surgery may be helpful.



Index case Mother

Figure 1 Legs of the patient and her mother. Parental/guardian informed consent was obtained for publication of this figure.

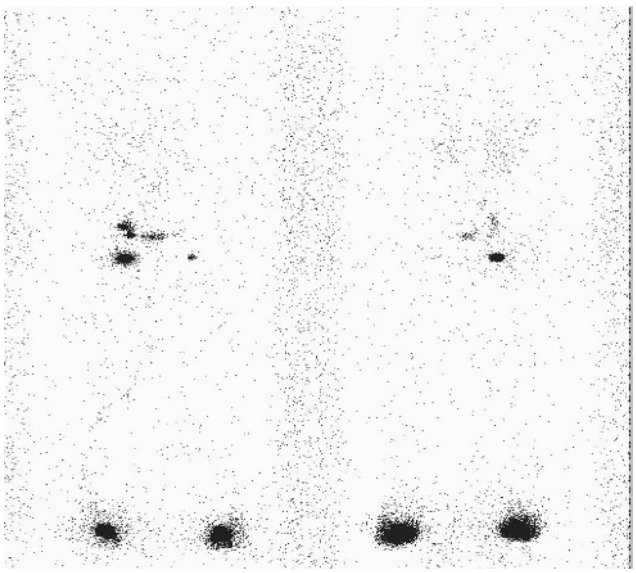


Figure 2 Lower limbs lymphoscintigraphy of the patient showing absence of lymphatic channels on the left leg.

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Competing interests: None.

Parental/guardian informed consent was obtained for publication of the person's details in this report.

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