Institution: Newcastle University

Unit of Assessment: 10 Mathematical Sciences

Title of case study: Preventing Blood Clots in Children undergoing Kidney Dialysis

1. Summary of the impact

Following research carried out at Newcastle, a new anticoagulant is used in 12 of the 14 paediatric kidney units in the UK and Ireland. Substantial distress and delay to therapy can be caused to children undergoing haemodialysis when the central venous lines (CVLs), by which their treatment is delivered, are blocked by blood clots. Our research has shown that preventative use of a new anti-coagulant, alteplase (also known as Rt-PA), is much more successful than the traditional agent, heparin, in preventing blockages. The clinical trial which established the superiority of alteplase required a novel form of optimal crossover design. In one hospital, the annual probability of CVL replacement due to thrombosis was 0.7 prior to our work. During the reporting period, no lines have had to be replaced because of thrombosis. This represents a remarkable reduction in the levels of distress to children and allows haemodialysis.

2. Underpinning research

Matthews, a member of staff at Newcastle University (from 1987 to the present), devised and applied the statistical methodology for a study to help improve a treatment for children with renal failure by comparing different anticoagulants used to maintain patency in central venous lines used for haemodialysis.

Peritoneal dialysis is the preferred treatment for children with renal failure but when this is not suitable, or has failed, haemodialysis is the only other option. Haemodialysis requires attendance at the dialysis unit two or three times weekly, where the patient's blood is dialysed externally. Access to the circulation is usually through an in-dwelling venous central line and it is paramount that this line is kept free from clots between treatments.

The assessment of any aspect of paediatric haemodialysis is likely to be constrained by the limited number of patients available for study. However, as they are obliged to attend often, the shortage of patients is partly compensated by observing each patient many times. As such the application is ideal for a crossover design [P1]. However, fewer than 10 patients, but who can be studied on tens of occasions, is an extreme case even for a crossover trial. Designs using more than six periods are unusual, and there are very few in the literature for more than 12 periods [P2]. Consequently this study required a specially tailored 30-period design to be derived using optimal design theory [P3].

The bespoke crossover clinical trial compared the standard anticoagulant (heparin) with alteplase in haemodialysis patients at the Children's Kidney Unit in the *Royal Victoria Infirmary* (RVI) in Newcastle in 2005 [P4]. The aim was to reduce the weight of clot removed from the line prior to the next treatment. The model for the data assumed that the mean response allowed for the possibility of (i) systematic differences between patients and (ii) the treatment allocated. The modeling of the period effect, a topic discussed in references [P1] & [P2] below, required a special formulation which took account of the point in the dialysis cycle when the observation was made. The information matrix for the treatment effect depends on the design matrices for treatment, dialysis cycle and patient, respectively. The information in the reduced model, where patient terms are omitted, exceeds that in the full model, unless a form of orthogonality applies to the components of the design matrix. The research thereby identified designs which maximised the information from the full model. These designs required equal replication of the treatments on each patient and

equal replication on each day of the dialysis cycle. Further details can be found in [P3].

The trial found [P4] that a clot was 2.4 times more likely to form when the line was treated with heparin than alteplase and, if a clot did form, it was 1.9 times heavier when heparin had been used.

The trial was conducted by Dr M.G.Coulthard (Consultant Paediatric Nephrologist), Dr N.S.Gittins (Research Specialist Registrar) and Mr Y.L.Hunter-Blair (Senior Pharmacist) all of Newcastle Hospitals NHS Trust and Professor J.N.S.Matthews (Professor of Medical Statistics, School of Mathematics and Statistics, Newcastle University).

3. References to the research

[P1] Matthews, J. N. S. (1994). Modelling and optimality in the design of crossover studies for medical applications. Journal of Statistical Planning and Inference, 42(1), 89-108. (Google scholar: 29 citations) (Impact Factor: 0.713) [*Key reference]

[P2] Matthews, J. N. S. (1994). Multi-period crossover trials. Statistical Methods in Medical Research, 3(4), 383-405. (Google scholar: 18 citations) (Impact Factor:2.364) [*Key reference]

[P3] Matthews, J. N. S. (2013) An optimal multi-period crossover design for an application in paediatric nephrology. Statistics in Medicine, doi:10.1002/sim.5981. (Impact Factor: 2.044) [*Key reference]

[P4] Gittins, N. S., Hunter-Blair, Y. L., Matthews, J. N., & Coulthard, M. G. (2007). Comparison of alteplase and heparin in maintaining the patency of paediatric central venous haemodialysis lines: a randomised controlled trial. Archives of Disease in Childhood, 92(6), 499-501. doi: 10.1136/adc.2006.100065 (Google scholar: 19 citations) (Impact Factor: 3.051)

4. Details of the impact

Following the trial, the Children's Kidney Unit at the *Royal Victoria Hospital* (RVI), Newcastle changed its policy, so that alteplase was used in place of heparin as the routine 'lock' (i.e. preventative dose of anticoagulant) for venous central lines. In the intervening period, most of the paediatric kidney units in the UK and Ireland have followed the practice at Newcastle and switched to using alteplase. A blocked central line is traumatic, causes delays in treatment and incurs costs for the NHS through taking up the time of medical and nursing staff. The line is used repeatedly and, without anticoagulation, the lumen would become occluded by blood clots between treatments. Repeated blockage of central lines requires re-siting, a traumatic procedure that cannot be repeated indefinitely. If haemodialysis (HD) becomes impossible, the consequences for the child are dire.

Impact in significant reduction of re-siting

Prior to the Newcastle trial, any child with a central line in for a year would need to have it re-sited for thrombosis with probability 0.7. This failure rate is consistent with rates found elsewhere [E1]. After our research, from 2008 to 2012, similar numbers of children were treated at Newcastle, but *none* of the lines has been replaced for thrombosis. There are about 10 HD patients at any one time at the unit and each patient needs about 50-150 doses of alteplase per annum, usually until a renal transplant becomes available. Some indication of the financial cost is given by Canadian figures, where one dose costs around $50 whilst the cost of one catheter replacement is estimated to be around $1200, but may incur a further $6000 for hospital treatment costs if there are complications (caused by bacterial infections in a few percent of clotting events) [E1]. The high cost of the drug is therefore partially offset by savings in treatment regimen.

Impact on practice in other units

Following the research, information was obtained from all 14 paediatric kidney units in the UK and Ireland [E2]. This revealed that 12 have changed to using alteplase. Five centres (Newcastle, Cardiff, Guy's, Glasgow, Manchester) use it as their routine treatment, three times weekly: a further five centres (Nottingham, Belfast, Great Ormond Street, Birmingham, Liverpool) use it three times weekly in some patients and in others use it once per week with heparin on the other two occasions to minimise the expense. The two centres, Dublin and Bristol, use heparin initially, but move to using alteplase three times weekly if they encounter any problems, which is quite common (for example, alteplase is used for eight of the ten children currently treated in Dublin (June, 2012)). Typically, at any given time, the total number of children being haemodialysed in these units is around 100.

Supply of alteplase

The letter [E2] provides evidence, in the form of an e-mail survey, of the effect of the research on this usage of alteplase across the UK and Ireland.

Confirmation that the preventative use of alteplase spread from the RVI is provided by the distribution of alteplase from the RVI to other hospitals. At the time of the research, alteplase was marketed as a treatment for pulmonary emboli in adults and was supplied in much larger quantities than required for paediatric HD. Since 2009, the RVI pharmacy has been breaking 300mg ampoules down into 2mg doses suitable for locking dialysis lines and these have been supplied to other NHS trusts. The table below shows the number of alteplase units repackaged and issued by the RVI to other NHS trusts [E3]. The numbers have increased substantially in Newcastle for various reasons including some longer term HD patients. In the other trusts, the numbers are reducing because small doses are now available in a commercial product. This approach means that the drug costs in Newcastle are substantially lower than the Canadian figure quoted above.

	Newcastle Hospitals	Other Trusts
Alteplase issued by the RVI 04/2010-03/2011	*1692 UNITS*	*5350 UNITS*
Alteplase issued by the RVI 04/2011-03/2012	*2470 UNITS*	*3491 UNITS*

Prevention of harm

Further reinforcement of the importance of changing to alteplase is given in [E4] which notes that "*Clots form easily in relatively large central lines, such as those used for haemodialysis, presumably because blood enters the distal lumen*", and that "*Owing to the risk of pulmonary embolus, it is routine practice for children's dialysis lines to be aspirated before every use - it is apparent that small subclinical clots must be occurring, as evidenced by cardiac and post-mortem studies in children with lines for at least 3 months".*

The significance of the problem is also indicated in the article: *"Cumulatively, these small clots may cause morbidity. A child having a clot weighing about 14mg dislodged on 60% of days would have 3g of thrombus showered into their lungs annually.....If cumulative small thrombi did cause the gradual development of pulmonary damage, this might be difficult to detect, or even suspect clinically, especially in children whose other serious disorders had necessitated the use of a long-term central line*".

Use of alteplase for locking dialysis lines is beginning to spread to other countries. For example, a US review article from 2012 on tunnelled catheters (TC) [E5], cites Newcastle research in

concluding that "*Since the introduction of TCs in the late 1980s, heparin catheter lock has been the standard prophylactic regimen for the prevention of TC dysfunction. More recently, alternative catheter locking agents have emerged, and in some cases have shown to be superior to heparin lock with respect to improving TC patency and reducing TC-associated infections*."

5. Sources to corroborate the impact

[E1] Brenda R. Hemmelgarn, M.D., Ph.D., Louise M. Moist, M.D., Charmaine E. Lok, M.D., Marcello Tonelli, M.D., S.M., Braden J. Manns, M.D., Rachel M. Holden, M.D., Martine LeBlanc, M.D., Peter Faris, Ph.D., Paul Barre, M.D., Jianguo Zhang, M.Sc., and Nairne Scott-Douglas, M.D., Ph.D., (2011), "*Prevention of Dialysis Catheter Malfunction with Recombinant Tissue Plasminogen Activator*", New England Journal of Medicine. 364, 303-312.

[E2] Corroboration from Honorary consultant paediatric nephrologist, NHS.

[E3] Corroboration from Pharmacist, Newcastle Hospitals NHS Trust.

[E4] Short Report. Malcolm G Coulthard and Roderick Skinner, (2007) "*Should paediatric central lines be aspirated before use?*", Archives of Disease in Childhood, 92(6): 517–518. doi: 10.1136/adc.2006.100073

[E5] Review Article. Timmy Lee, Charmaine Lok, Miguel Vazquez, Louise Moist, Ivan Maya, and Michele Mokrzycki, (2012), "*Minimizing Hemodialysis Catheter Dysfunction: An Ounce of Prevention".* International Journal of Nephrology. Article ID 170857, doi:10.1155/2012/170857