

PERSONAL VIEW

Is prehospital thrombolysis for acute myocardial infarction warranted in the urban setting? The case against

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This paper forms the second part of the debate on prehospital thrombolysis (PHT). It is argued that large scale studies have failed to show a benefit for PHT, even when the time saved over conventional treatment was considerably greater than would be the case in the UK urban setting. In practice, a relatively small proportion of the total population receiving thrombolysis would receive PHT. Other strategies to reduce time to thrombolysis can benefit all patients and are likely to be more cost effective and safer.

up to 3000 lives per year by saving 11 days of life per minute saved. A reference is not given, but the survival statistic is in line with an analysis of data from The Grampian Early Anistreplase Trial (GREAT).⁵ As will be discussed, there are many reasons for believing that this level of benefit will not apply to patients treated in an urban setting.

EARLIER IS BETTER—BUT HOW MUCH? THE THEORETICAL BASIS FOR PHT

Two models for the relation between time to thrombolysis and its benefit have been proposed (fig 1)—a linear decline of benefit with time,³ and a non-linear, exponential decline.⁴ There remains controversy as to which model is more accurate.⁶ If the linear model holds, with 1.6 lives saved per 1000 patients treated per hour of time saved, a typical ambulance service might have to provide PHT for several years before one life was saved. The non-linear model shows much higher levels of benefit for earlier treatment and has given rise to the concept of a “golden hour”,⁴ which is probably a little more than an hour in practice. If this is the correct model, and thrombolysis can be given within the first few hours from symptom onset, then the urgency of treatment is confirmed. This would undoubtedly have implications for the delivery of thrombolysis, but would not in itself warrant PHT for reasons described below.

THE TRIALS OF PHT

A recent meta-analysis of the randomised controlled trials of PHT identified six trials meeting their quality criteria for inclusion.⁸ The three largest and highest quality trials were The European Myocardial Infarction Project Group (EMIP, n=5469),⁹ The Myocardial Infarction Triage and Intervention Trial (MITI, n=360),¹⁰ and GREAT (n=311).¹¹ The remaining three trials added a further 294 patients, making a total of 6434. None of these trials showed a significant reduction in mortality at one month, although all showed a trend in this direction. The largest trial (EMIP) showed the smallest risk reduction with an odds ratio (OR) of 0.86 (95% CI 0.72 to 1.03), although it should be mentioned that it was terminated prematurely because of funding and recruitment problems. Only GREAT showed a benefit for PHT at one and five year follow up, with mortality of 25% in the PHT group and 36%

There is ample evidence for the benefit of thrombolysis in acute myocardial infarction (AMI).^{1,2} Furthermore, there is little doubt that the earlier thrombolysis is given, the greater the benefits, although the magnitude of the advantage of earlier treatment remains controversial.³⁻⁶ As delivering thrombolysis in the prehospital setting would be expected to ensure that it is given earlier, many have concluded that it would therefore be justified to introduce it as routine in all areas.

The NHS plan states that prehospital thrombolysis (PHT) will be introduced over the next three years, resulting in patients receiving thrombolysis an hour earlier on average compared with in-hospital treatment.⁷ This, it is stated, will save

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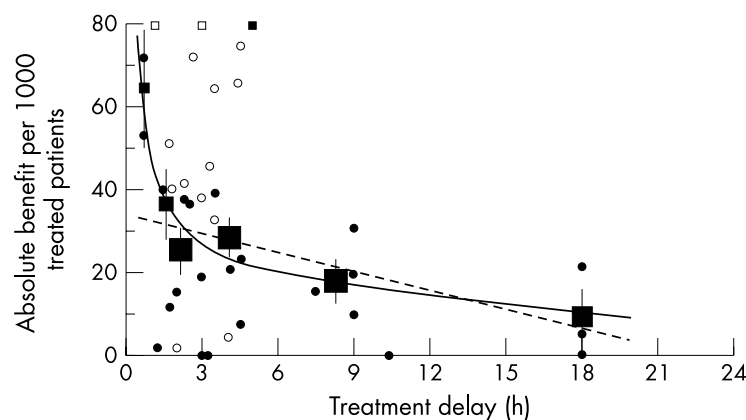


Figure 1 Linear and non-linear models of treatment delay compared with benefit for PHT. Small closed dots: information from trials included in FTT analysis; open dots: information from additional trials. Outcome is 35 day mortality. The hatched line shows the linear regression curve and the solid line shows the non-linear regression curve. The black squares show average effect in six time to treatment groups, the areas of the squares inversely proportional to variance of absolute benefit. Reproduced with permission from Boermsa, Maas, Deckers, *et al* (1996).⁴

Abbreviations: AMI, acute myocardial infarction; PHT, prehospital thrombolysis

Table 1 Summary of characteristics of selected major trials of PHT

| Study (n) | Provider | Thrombolytic agent | Time saving of PHT | Odds ratio (all cause hospital mortality) |
|-------------|---------------------------------|--------------------|--------------------|---|
| EMIP (5469) | Intensivist | Anistreplase | 55 min | 0.86 (0.72 to 1.03) |
| MITI (360) | Paramedic (with online support) | Alteplase | 33 min | 0.69 (0.30 to 1.57) |
| GREAT (311) | GP | Anistreplase | 130 min | 0.56 (0.25 to 1.23) |

in the inhospital thrombolysis (IHT) group ($p < 0.025$) at five years. By pooling the data from all six trials, an OR of 0.83 was found (95% CI 0.70 to 0.98), with an average time saving of 58 mins. By excluding GREAT, the time saving was reduced to 45 minutes; unfortunately the overall effect of excluding GREAT on the OR was not calculated.

These data form the evidence base supporting PHT, yet there are powerful reasons for doubting its applicability to the UK urban setting. Only one of the trials involved paramedics as compared with doctors giving thrombolysis, and in this one trial (MITI), the paramedics had online support. At present it is unclear whether online support would be provided for UK paramedics giving PHT. If it were provided, there are considerable cost and logistic implications for the supporting hospitals, particularly small district general hospitals.

The best evidence for PHT, from GREAT, is also the least applicable. The study only recruited patients who were at least 30 minutes from hospital, far longer than in any typical urban setting. The symptom to call time of 45 minutes was relatively low, while patients with pain for more than four hours were excluded, thus selecting a group of patients who were more likely to benefit from earlier treatment than the general AMI population. The inhospital door to needle time of 87 minutes was relatively long, thus inflating the time saving for PHT to 130 minutes, a figure vastly greater than would be possible in any urban setting (table 1).

POSSIBLE TIME SAVINGS IN A UK URBAN SETTING

The benefit of PHT is determined largely by the possible time saving that this would allow compared with standard inhospital treatment, when any risks have been allowed for. How great would this time saving be in a typical UK urban setting where inhospital treatment had been optimised? Current median values for ambulance response to category A chest pain calls in the South Yorkshire region have been used to illustrate the possible time saving if PHT were introduced (fig 2). The current door to needle time of 27 minutes is relatively fast, but in line with the targets set by the National Service Framework for Coronary Heart Disease (NSF for CHD,¹² see below), as is the eight minute call to response time. The projected PHT arrival to needle time has been arbitrarily set at 30 minutes. This is an improvement on MITI (35 min) and GREAT (43 min) although these times involved contacting either an emergency physician

or the trial coordinator before starting. In reality, outside a clinical trial, it would be impressive if paramedics could come so close to the inhospital time considering the increased practical difficulties in the field.

The projected time saving of 21 minutes shown in figure 2 does not provide a powerful argument for introducing PHT, when studies such as EMIP have failed to show a significant benefit for PHT even with a mean time saving approximately three times as great.

Box 1 PHT—applying the evidence locally

- EMIP (largest trial of PHT, n= 5469) showed time saving of 55 minutes for PHT, but no significant benefit.
- Benefit of PHT is dependent on time saving.
- Projected time saving in South Yorkshire is only 21 minutes, therefore benefit likely to be marginal at best

RISKS OF PHT

In the urban setting, with its short time savings compared with the previously described trials, any potential benefit is likely to be marginal at best. In this setting, the risks of PHT should be considered very carefully.

The principal risks of thrombolysis in any setting are CVA and non-cerebral bleeding. CVA occurs in an excess of 4/1000 patients treated with thrombolysis compared with controls, and is fatal in approximately half of these cases.³ Non-cerebral bleeding requiring transfusion occurs in an excess of 7/1000. In a study including 118 patients given thrombolysis for suspected AMI who were subsequently found to have no evidence of AMI,¹³ four (3%) developed serious complications and one (0.8%) died.¹⁴

Of the trials of PHT discussed above, all involved doctors giving thrombolysis, except MITI and here the paramedic contacted an emergency physician for review of the clinical information as well as the transmitted ECG. The performance of paramedics in delivering PHT without backup is not known.

By increasing the total number of people providing thrombolysis, the experience and expertise of the individual provider is reduced. SHOs working in accident and emergency find the decision to thrombolys difficult and frequently need to

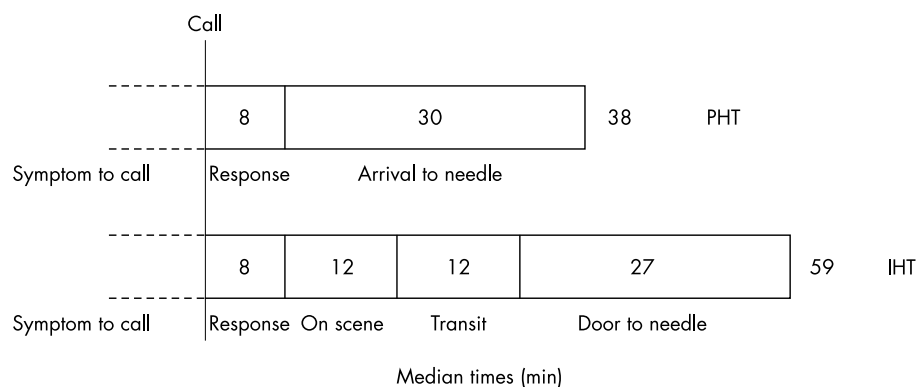


Figure 2 Projected time saving of PHT compared with inhospital thrombolysis in South Yorkshire.

Box 2 PHT may delay treatment of patients who do not receive it

- AMI patients form only around 5% of the total chest pain population.
- The proportion of thrombolysable AMI patients who are suitable for PHT is likely to be relatively low; the proportion of those suitable who actually receive it lower still.
- Assessment for PHT takes time in all patients considered. Ambulance response times may increase as a result.
- Implementing PHT may delay the treatment of more patients than it expedites.

recourse to senior advice. Considering local audit data in South Yorkshire, the average paramedic would be likely to see only approximately two thrombolysable infarcts per year. As paramedics are less familiar with ECGs and clinical decision making than SHOs, they are likely to have even greater difficulties. Although this can be partly circumvented by online support, the problems of providing this have already been described, and the senior support is likely to be less confident in advising thrombolysis than if they could assess the patient face to face.

As AMI patients form a small subset of the total chest pain population, around 5%,¹⁰⁻¹⁴ there is plenty of opportunity for giving thrombolysis inappropriately unless paramedic assessment is 100% specific. The benefit achieved by a 21 minute time saving could easily be reversed by inappropriate administration of thrombolysis.

COSTS OF PHT

The cost of providing PHT is likely to be substantial in the context of a health service where resources are strictly limited. Ambulances will need to be supplied with ECG facilities and stocked with up to date supplies of the (very expensive) thrombolytic agents. Although funding is now being provided for 12 lead ECG provision in ambulances, it is by no means clear that this is the most rational or cost effective way of improving AMI treatment. Paramedics will require training that must be ongoing given the infrequent exposure to AMI cases. The time spent on each case will increase, not just for the few patients who receive thrombolysis, but for all who are considered for it. The result of this could be an increase in response times to the detriment of all patients.

In practice, the number of patients treated would be relatively small. In a recent audit of a one year period at the Northern General Hospital, Sheffield (a large teaching hospital), 185 patients were thrombolysed in accident and emergency, of which only 107 were suitable for thrombolysis on arrival (57.8%). The number suitable for PHT would inevitably be lower than this. A proportion of paramedics are likely to be reluctant to give PHT, especially when the hospital is only a few minutes away, so for this and other reasons, the number who would actually receive PHT is likely to be yet lower. Therefore there is a real risk that the prehospital assessment would delay the thrombolysis of more patients than it expedites.

Furthermore, the resources put into PHT cannot benefit patients self presenting with AMI (10% of the total thrombolysed in accident and emergency in a recent Northern General Hospital audit). As the proportion of AMI patients who will benefit from PHT is relatively low, it is essential to consider whether resources would be better spent on alternative strategies for accelerating time to thrombolysis, which would benefit all AMI patients.

ALTERNATIVE STRATEGIES FOR DECREASING TIME TO THROMBOLYSIS

Much of the time saved by PHT, especially when transit times are short, is the result of delays between arrival in hospital and

Box 3 Alternative strategies for decreasing time to thrombolysis

- There are a number of strategies for expediting in-hospital thrombolysis.
- Education may reduce the delay from onset of pain to calling for help—usually the largest component of delay to thrombolysis.
- These strategies have the advantage of applying to all AMI patients who receive thrombolysis and are likely to be more cost effective than PHT.

starting thrombolysis for conventional treatment. The NSF for CHD has set the targets of 75% of patients being treated within 30 minutes of arrival in hospital by April 2002 and 20 minutes by April 2003. If this second target had been achieved at the time of the GREAT trial, the time saved by PHT would have been cut from 130 to 60 minutes.

There are several strategies that may be more cost effective for reducing delays to thrombolysis and are likely to apply to a greater range of patients than PHT (see box 3).

1 Thrombolysis in accident and emergency compared with coronary care unit

The common practice of transferring patients from A&E to coronary care unit before starting treatment results in unnecessary delay in starting thrombolysis. Time savings of 15 minutes or more are possible by starting thrombolysis before transfer.¹⁵ The NSF for coronary heart disease has set the target of 75% of A&E departments to be able to provide thrombolysis by April 2001.

2 Pre-alerting hospital of the imminent arrival of a patient likely to require thrombolysis

This could be done on clinical grounds, alerting the hospital to the need of ECG on arrival and possible thrombolysis thereafter. There would be negligible costs in implementing this strategy, and no increase in prehospital time. The paramedics could be made responsible for performing the ECG immediately the patient arrives in hospital in these cases, reducing the potential for delay in diagnosis.

3 Extended nursing roles

Nurse initiated thrombolysis has been shown to reduce door to needle times significantly on the coronary care unit.¹⁶ Specialist chest pain nurses in A&E can perform a number of functions in the triage and management of these patients. It is probable that thrombolysis can be expedited, even if the final responsibility for initiating thrombolysis remains with the doctor.

4 Reduction of delays in calling for help

The largest component of the time from symptom onset to thrombolysis is frequently the time between onset of symptoms and calling for help. A review of seven studies on this factor found a range of median delays of one to four hours, more than half of the studies being greater than two hours.¹⁷ The distribution of these times tends to be positively skewed with 20.6% presenting after six hours in one study.¹⁸ Therefore however efficient systems for delivering thrombolysis become, unless this variable can be changed, the steepest part of the curve (the golden "hour") has already passed, assuming a non-linear model. This greatly reduces the possible impact of improvements in call to needle time. The possibility of reducing this time with public and patient education has been considered in several studies.¹⁷ So far the results have been mixed. A concurrent increase in the number of patients attending with non-cardiac chest pain has frequently been noted, although this tends to be mainly at the

beginning of the campaign. However, this is definitely an area for future work to find the most effective strategy.

CONCLUSION

PHT has not shown significant benefit over in-hospital thrombolysis in any single, randomised, non-rural study. In the one study showing a significant benefit, in a rural population, it has been argued that several factors unrepresentative of urban practice favoured the finding of a benefit for PHT. The possibility that PHT may benefit selected AMI patients is not enough to justify the allocation of substantial resources and reorganisation of emergency care. The NHS is buckling under the strain of funding initiatives based on hope and hype rather than evidence. We cannot afford to fund wholesale changes in practice just because they *might* be effective; we should first collect data to show that they *are* effective and that they *are* cost effective.

Therefore PHT in the UK urban setting should be a high priority for research into feasibility and cost effectiveness compared with an efficient mode of delivering in-hospital thrombolysis. The proportion of the total thrombolysable AMI population who actually receive PHT should be determined, as should the cost of saving lives with PHT to permit comparison with other strategies that are simpler and can benefit the whole AMI population.

In the meantime, an audit programme should be used to identify the distribution of delay within a given locality, and a strategy for reducing all delays to giving thrombolysis in hospital should be tailored to the local situation with its geographical and healthcare peculiarities. The advantage, if any, of applying PHT to an urban setting where this has been done should then be evaluated.

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COMMENTARY

Stephenson and colleagues have written a clear and well referenced article, taking the view that urban prehospital thrombolysis is unlikely to be either clinically or cost effective.¹ Some of their arguments in support of this assertion, such as the idea that urban prehospital times are very short or that complications are a significant concern, I have already addressed. We both agree that one of the main problems in this field is a lack of research, and until adequately powered studies of paramedic administered urban prehospital thrombolysis are published we must rely upon educated guesswork and extrapolation. Such studies will also allow us to address the issue of cost effectiveness. I have already emphasised the potential benefits of investment in prehospital, rather than in-hospital, interventions, and while there is some evidence of cost effectiveness for the prehospital ECG,² this has yet to be investigated for prehospital thrombolysis.

There are two aspects of the article by Stephenson *et al* that I feel particularly compelled to respond to. The first concerns the relation between clinical benefit and the "pain to needle" time. As Stephenson and colleagues acknowledge, there is disagreement as to whether this relation is linear or exponential,³ but if exponential then the arguments for urban prehospital thrombolysis are considerably strengthened. In fact, there is good evidence that thrombolysis within about 90 minutes of infarction can have a dramatic, and disproportionate, effect on outcome.^{4,5} There are many clinical examples of the principle that early reversal of tissue ischaemia, before irrevocable damage occurs, can be followed by excellent recovery. Indeed, nobody suggests that the relation between skeletal muscle death and surgical tourniquet time is linear: why then should it be so for the heart? Our efforts therefore need to be directed towards the attainment of very short pain to needle times, and these will only be achieved by intervention in the prehospital phase of care.

Secondly, Stephenson and colleagues state that the most likely model for prehospital thrombolysis in the UK is administration by paramedics without online support. I disagree. As outlined in my article, most paramedics do not yet feel ready to administer prehospital thrombolysis without support, and in regions where this new technique is currently being adopted transmission of the ECG to hospital for physician authorisation and guidance is the norm. While this may change in years to come, remote physician support is a common, and relatively well researched, model at present.

Stephenson *et al* rightly draw attention to the importance of addressing the delay between symptom onset and calling for

help, and invoke the exponential model of thrombolysis benefit to support this. However, the other measures that they propose, which are designed to reduce the in-hospital "door to needle time", are all inferior to effective prehospital thrombolysis.

Regardless of medical opinion, there is now a clear government commitment to introduce prehospital thrombolysis throughout the UK.⁶ I hope that this also provides an opportunity for properly conducted research and evaluation, to govern policy and more fully inform this interesting and important debate.

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