Reducing call-to-needle times: the critical role of pre-hospital thrombolysis

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Summary

Background: Current guidelines recommend that patients with acute myocardial infarction should receive thrombolysis within 60 min of seeking professional help.

Aim: To compare current rates of pre-hospital thrombolysis in Grampian with historical data, and assess the effect of pre-hospital thrombolysis on the proportion of patients achieving ‘call-to-needle’ times within national guidelines.

Design: Prospective audit.

Methods: Data were collected on all patients (n = 535) admitted to the coronary care unit and thrombolysed, either in hospital or in the community from July 2000 to June 2002, using standardized forms.

Results: One hundred and thirty-three patients (25%) received pre-hospital thrombolysis and 402 (75%) received in-hospital thrombolysis. This compares with a 19% (195/1046) pre-hospital thrombolysis rate in the mid-1990s (p = 0.005). Median ‘call-to-needle’ times were 45 min for pre-hospital thrombolysis and 105 min for patients who received in-hospital thrombolysis (p < 0.001). Only 24% (96/396) of patients receiving in-hospital thrombolysis were treated within the recommended guideline, vs. 79% (88/111) of pre-hospital thrombolysis patients (p < 0.001).

Discussion: Pre-hospital thrombolysis rates in Grampian are increasing. Administration of thrombolysis in the community greatly increases the proportion of patients achieving a ‘call-to-needle’ time of 60 min, with a median time saving of ~1 h.

Introduction

Approximately 50% of patients suffering an acute myocardial infarction will die within the next 28 days, and around 50% of these deaths occur within the first 2 h of symptom onset.1 Furthermore, approximately two-thirds of deaths occur before the patient can reach hospital. Thus, although recent advances in treatment of acute myocardial infarction have resulted in a fall in the death rate of those treated in hospital, they have had limited effect on total mortality.1

Thrombolytic therapy for acute myocardial infarction is of proven benefit.2 A meta-analysis of nine large randomized trials of patients with acute myocardial infarction, in which fibrinolytic was compared to placebo, demonstrated an absolute mortality benefit of 3% for patients randomized within 6 h of symptom onset, and 2% for those randomized between 7–12 h.2 The benefit/time gradient is non-linear, with the maximal benefits obtained within the initial 2 h,3 and it is estimated that in the early stages of infarction, 23 lives can be saved per 1000 patients treated per hour.3,5 It is clear, therefore, that thrombolysis must be given as soon as possible. Ideally this should
be at first contact with medical or paramedical staff. North-East Scotland has a long tradition of pre-hospital thrombolysis dating back to the Grampian Region Early Anistreplase Trial. In rural patients, this found a median time saving of 130 min with domiciliary thrombolysis, resulting in a halving of mortality at 1 year. Similarly, a meta-analysis of six randomized trials of pre-hospital vs. in-hospital thrombolysis confirmed that the former strategy resulted in a significant reduction in all-cause hospital mortality (OR 0.83, 95% CI 0.70–0.98).

The Department of Health National Service Framework recommends that patients suffering from acute myocardial infarction should receive thrombolytic therapy within 60 min of calling for professional help. It is also recommended that, if local circumstances make it impossible to reduce ‘call-to-door’ times below 30 min, other models of care (such as pre-hospital thrombolysis), should be considered. In communities such as ours where a large proportion of patients live in rural areas, up to 60 miles from hospital, pre-hospital thrombolysis may be the only mechanism to meet such guidelines.

The primary aims of the current study were (i) to compare current rates of pre-hospital thrombolysis in Grampian with historical data and (ii) to assess the effect of pre-hospital thrombolysis on the proportion of patients achieving ‘call-to-needle’ times within national guidelines (both in urban and rural populations). The secondary aim was to determine whether pre-hospital thrombolysis was associated with an increased incidence of ‘inappropriate’ therapy.

Methods
Design, setting and patients
We prospectively studied all patients admitted to the coronary care unit of Aberdeen Royal Infirmary who received thrombolysis for presumed acute myocardial infarction between July 2000 and June 2002. No patients fulfilling these criteria were excluded.

Data collection
Time of symptom onset, time when professional help was sought (call time), time of arrival in hospital and time and place of thrombolysis were documented, along with demographic and clinical data. These were collected prospectively using a standardized general practitioner referral letter and a standard form that was completed by medical and/or nursing staff at the time of admission. Forms were collated and entered onto a database by a full-time audit nurse, who also confirmed that data were complete and accurate. To ensure accuracy, data were routinely checked with the treating clinicians, the patients and source documentation such as ambulance records and timed ECG recordings.

Definitions
Patients were classed as ‘rural’ if they lived >10 miles from Aberdeen Royal Infirmary or ‘city’ if they lived within this distance. This cut-off was chosen as being the limit at which a ‘call-to-door’ time of <30 min could reasonably be expected (and, assuming a ‘door-to-needle’ time of under 30 min, the target of <1 h ‘call-to-needle’ time achieved), and is comparable to similar studies. Patients who were thrombolysed within the coronary care unit, other wards in Aberdeen Royal Infirmary or the Accident and Emergency Department were classed as having in-hospital thrombolysis. Patients receiving thrombolysis by their general practitioner at home, or at a community hospital prior to transfer were classed as having pre-hospital thrombolysis.

Thrombolysis was deemed ‘appropriate’ where the patient had an ST-elevation myocardial infarction based on standard criteria. If this was not the case, two consultant cardiologists independently analysed the presenting electrocardiograms, blinded to all other clinical data. If the patient presented with symptoms of chest pain and the electrocardiogram on which the decision to administer thrombolysis was based (performed either in the community or on arrival to hospital) demonstrated ST-elevation (≥1 mm in two contiguous limb leads or ≥2 mm in two contiguous pre-cordial leads), or left bundle branch block, thrombolysis was considered appropriate. Disagreements were resolved by consensus, obtained while remaining blinded to other clinical data.

The hospital Patient Administration System was analysed to establish mortality at 30 days after admission. This system collates 30-day survival data based upon linkage to the Scottish Registrar General’s death records, and thus takes account of any deaths occurring after discharge from hospital.

Statistics
Categorical data are presented as absolute values (%) and analysed using Fisher’s exact test, with odds ratios (OR) and 95% CIs. Continuous data are presented as median and interquartile range (IQR) and compared using the Mann-Whitney U test. These analyses used SPSS software. Statistical
significance was set at a two-tailed $p$ value <0.05. The median differences for call-to-needle time, with 95%CI, were derived using CIA 2.0.0 software (University of Southampton), based on the method described by Altman et al.\textsuperscript{14}

**Results**

The study cohort consisted of 535 consecutive patients who had been thrombolysed for suspected acute myocardial infarction. Four hundred and two (75%) received in-hospital thrombolysis and 133 (25%) pre-hospital thrombolysis. There were no significant differences between the baseline clinical characteristics and demographics of the two groups (Table 1). Pre-hospital thrombolysis was, however, much more commonly administered to rural patients (OR 24.6, 95%CI 11.7–51.8, $p < 0.0001$), predominantly (125/133, 94%) by general practitioners.

The current data demonstrate a significant increase in the proportion of patients receiving pre-hospital thrombolysis since this was last audited in Grampian in the mid-1990s:\textsuperscript{15} 133/535 (25%), for July 2000–June 2002 vs. 195/1046 (19%) for May 1994–November 1997 (OR 1.44, 95%CI 1.12–1.86, $p = 0.005$). This is apparent both in patients from rural communities (44% in 2000–2002 vs. 35% in 1994–1997, OR 1.43, 95%CI 1.07–1.92, $p = 0.02$), and in patients from within the city, (3% in 2000–2002 vs. none in 1994–1997, OR 34.66, 95%CI 1.99–603.29, $p = 0.0002$). In the 1990s cohort, however, the definition of ‘rural’ was patients registered with general practices >25 miles from Aberdeen.\textsuperscript{15}

**‘Call-to-needle’ times**

Data regarding ‘call-to-needle’ time were incomplete in 22/133 (17%) of pre-hospital thrombolysed patients and 6/402 (1%) patients thrombolysed in hospital. Median ‘call-to-needle’ times were 45 min (IQR 30–60) for patients receiving pre-hospital thrombolysis and 105 min (IQR 65–156) for recipients of thrombolysis in hospital (median difference 55 min, 95%CI 45–65, $p < 0.001$, Figure 1). Patients living rurally who received pre-hospital thrombolysis had a median ‘call-to-needle’ time of 43 min (IQR 30–60), vs. 130 min (IQR 90–180) when thrombolysis was deferred until hospital (median difference 80 min, 95%CI 70–95, $p < 0.001$). Patients from the city had a median pre-hospital thrombolysis ‘call-to-needle’ time of 53 min (IQR 43–57), vs. 85 min (IQR 60–135) for thrombolysis in hospital (median difference 35 min, 95%CI 15–75, $p = 0.001$).

The median ‘door-to-needle’ time for hospital-thrombolysed patients was 30 min (IQR 15–50), suggesting that the time saving for patients receiving pre-hospital thrombolysis is not due to unacceptable delay in-hospital. Among patients who had an accurate ‘call-to-needle’ time recorded, only 24% (96/396) who had treatment deferred to hospital received thrombolysis within 60 min. In comparison, 79% (88/111) of patients who were given pre-hospital thrombolysis met this target (OR 12.0, 95%CI 7.1–20.0, $p < 0.0001$). Only 31% (78/246) of patients living within 10 miles of Aberdeen Royal Infirmary received thrombolysis within 60 min of seeking professional help.

**Appropriateness of thrombolysis**

The final diagnoses of the patients thrombolysed before and after admission to hospital are shown in Table 2. Three hundred and eighty patients who were thrombolysed in hospital had a ST-elevation myocardial infarction. In addition, a further four met electrocardiographic criteria for thrombolysis, but had no rise in cardiac troponin I. Thus, in total, 384 (96%) patients were considered to have received ‘appropriate’ thrombolysis in hospital. Of the patients who were thrombolysed in the community, 104 (78%) patients had a confirmed ST-elevation myocardial infarction, and five

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**Table 1** Comparison of patients receiving pre- and in-hospital thrombolysis

<table>
<thead>
<tr>
<th></th>
<th>Thrombolysis in Pre-hospital $p$</th>
<th>Thrombolysis in Hospital $p$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hospital ($n = 402$)</td>
<td>Thrombolysis ($n = 133$)</td>
</tr>
<tr>
<td>Age</td>
<td>69 (58–79)</td>
<td>69 (59–78)</td>
</tr>
<tr>
<td>Male</td>
<td>258 (64%)</td>
<td>94 (71%)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>118 (46%)</td>
<td>43 (32%)</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>35 (9%)</td>
<td>8 (6%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>143 (36%)</td>
<td>41 (31%)</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>74 (18%)</td>
<td>28 (21%)</td>
</tr>
<tr>
<td>Known CHD$^*$</td>
<td>99 (25%)</td>
<td>35 (26%)</td>
</tr>
<tr>
<td>Rural$^*$ patient</td>
<td>156 (39%)</td>
<td>125 (94%)</td>
</tr>
<tr>
<td>City$^*$ patient</td>
<td>246 (61%)</td>
<td>8 (6%)</td>
</tr>
<tr>
<td>Pain-to-needle time (min)</td>
<td>210 (135–360)</td>
<td>145 (75–285)</td>
</tr>
<tr>
<td>Call-to-needle time (min)</td>
<td>105 (65–156)</td>
<td>45 (30–60)</td>
</tr>
</tbody>
</table>

Figures are medians (IQR) or numbers (%). CHD, coronary heart disease. $^*$History of angina, myocardial revascularization or prior myocardial infarction $^*$Residence >10 miles from Aberdeen Royal Infirmary $^*$Residence ≤10 miles from Aberdeen Royal Infirmary.
additional patients met our pre-defined ECG criteria but cardiac troponin I levels were subsequently normal. In total, therefore, 109 patients (82%) received ‘appropriate’ pre-hospital thrombolysis (OR 0.21, 95%CI 0.11–0.41, \(p < 0.0001\) vs. in-hospital thrombolysis).

Of the 42 patients who received ‘inappropriate’ thrombolysis, no patient suffered any neurological complications or major bleeding requiring transfusion, but one patient died. This patient was thrombolysed in hospital, and the documented cause of death was ischaemic heart disease and cholecystitis. No post mortem was performed. All-cause mortality at 30 days was 4.7% (6/133) in the pre-hospital thrombolysis group vs. 9.5% (35/402) in the in-hospital thrombolysis patients (OR 0.50, 95%CI 0.20–1.21, \(p = 0.1\)).

### Discussion

The current study confirms that pre-hospital thrombolysis results in a significant fall in ‘call-to-needle’ times, not just in the rural population but also in patients residing <10 miles from hospital. Encouragingly, it also demonstrates a significant increase in pre-hospital thrombolysis rates.

Data from Grampian have previously demonstrated the time saving associated with pre-hospital thrombolysis in patients who live in rural communities.\(^{15,16}\) In addition, Pedley and colleagues have recently shown that among patients living >15 km from Ninewells Hospital in Dundee, the median ‘call-to-needle’ time for patients receiving pre-hospital thrombolysis (\(n = 28\)) was 52 min, compared to 125 min in patients whose thrombolysis was administered in hospital (\(n = 43\)).\(^{11}\) In this study, 64% of patients receiving pre-hospital thrombolysis did so within 60 min of seeking professional help, in comparison with a minimum of 66% in our larger cohort.

In our cohort, almost all pre-hospital thrombolytic therapy was administered by a general practitioner. In the Tayside study\(^{11}\) all pre-hospital thrombolysis was administered by paramedics in liaison with the local Accident and Emergency Department.
This appears to have introduced some delay, with a median of 30 min of the ‘call-to-needle’ time attributable to patient assessment. However, it does seem to improve the accuracy of diagnosis, with 89% of patients administered thrombolysis by paramedics in Tayside ultimately confirmed as having ST-elevation myocardial infarction, compared to 78% of those treated by general practitioners in Grampian. This is in keeping with other recent data showing that paramedics are more specific but less sensitive than doctors at detecting ST-elevation myocardial infarction on a 12-lead ECG. It also suggests that the use of a rigorous protocol, including checklists and telemedicine facilities, although it may introduce a slight delay, is associated with more appropriate use of thrombolytic therapy.

In the Grampian Region Early Anistreplase Trial median ‘call-to-needle’ times were 55 and 185 min for pre-hospital and hospital groups. Time reductions in both groups were demonstrated in the mid-1990s with median ‘call-to-needle’ times of 45 and 150 min, respectively. These two studies included patients registered with general practitioner practices located ≥25 km from Aberdeen. In the current study, patients living more than 10 miles (16 km) from Aberdeen Royal Infirmary had ‘call-to-needle’ times of 43 and 130 min, respectively. It is difficult to draw any direct comparisons because of the differing catchment areas, and it is likely that at least some of the improvement in the in-hospital ‘call-to-needle’ time reflects the potential for shorter transit times in the current study.

There is an ongoing program for training general practitioners in Grampian about the use of pre-hospital thrombolysis. It seems likely that this, at least in part, explains the observed increase in the use of this strategy. Wider availability of a single bolus thrombolytic agent is another potential factor. Interestingly, this is apparent both in patients from rural communities and in patients from within the city, where 3% (8/254) of patients in the current cohort received pre-hospital thrombolysis, compared to none in historical cohorts.

There are few data regarding pre-hospital thrombolysis in urban populations. In this setting a ‘scoop-and-run’ policy is often regarded as most appropriate. However, even in patients living relatively close to hospital, the administration of thrombolysis in the community is associated with a considerable median time saving (almost equivalent to the nationally recommended ‘call-to-door’ and ‘door-to-needle’ times). Similarly, very few patients achieve the 1 hour ‘call-to-needle’ target unless pre-hospital lysis is used. Thus, many more patients may benefit from pre-hospital thrombolysis than might have been previously perceived. This would have major logistical implications and necessitate adequate training of paramedics and clinicians. Nevertheless, it is an area worthy of further investigation.

The appropriateness of thrombolysis is difficult to establish retrospectively, but the criteria used were common to both groups and observers blinded to other clinical data interpreted the electrocardiograms. The finding that only 78% of patients thrombolysed in the community had an eventual diagnosis of ST-elevation acute myocardial infarction is somewhat better than previous audits of pre-hospital thrombolysis, where only 65% of patients thrombolysed in the community had an eventual discharge diagnosis of ‘definite’ acute myocardial infarction (ST or non-ST-elevation), with a further 14% and 8% diagnosed as ‘probable’ and ‘possible’ acute myocardial infarction respectively. There is little doubt, therefore, that pre-hospital thrombolysis initiated independently by general practitioners is associated with an increased risk of inappropriate therapy. This is, perhaps, to be expected, as electrocardiographic changes are likely to be more subtle in the very early stages of infarction, general practitioners may have less experience in interpreting electrocardiograms, and in the pre-hospital setting, prior records may not be available. Similarly, clinicians administering pre-hospital thrombolysis seldom have the opportunity to discuss equivocal cases with colleagues or use supplementary diagnostic tools to help confirm acute myocardial infarction or identify another potential cause for the patient’s symptoms.

The increased rate of inappropriate thrombolysis when administered in the community is concerning. Although no adverse events associated with inappropriate therapy were demonstrated in the current study, this most likely relates to chance. Thrombolysis with bolus tenecteplase (the agent primarily used in the community) is associated with a 0.9% incidence of intra-cranial haemorrhage and a 3% risk of an alternate major bleed. Therefore, on the basis of the current data, for every 140 patients treated with pre-hospital thrombolysis, one patient treated inappropriately would be expected to suffer one of these adverse outcomes. Likewise, for every 185 individuals thus treated, one extra patient (additional to that expected if thrombolysis were given in hospital) who was given thrombolysis inappropriately would be adversely affected. This must, however, be balanced against the benefits of earlier thrombolysis. This has recently been estimated to be one life saved at 35 days for every 61 patients treated, assuming a 45 min reduction in the time to treatment. This delay is less than
we have demonstrated, but is the median time reduction obtained in a meta-analysis of studies, excluding the Grampian Region Early Anistreplase Trial. It may, therefore, be a more generally applicable figure. Thus, if a 45 min median time saving is assumed, pre-hospital thrombolysis of 185 patients would be expected to save three additional lives at 35 days, but at the cost of one additional major bleed or intra-cranial haemorrhage in an inappropriately treated patient. It is possible that, as suggested by the Tayside study, increased use of telemedicine equipment may reduce the risk of inappropriate thrombolysis. This is being introduced in Grampian. In addition, we are using examples of inappropriate therapy identified in the current study to better educate general practitioners. Hopefully, with these changes the full benefits of pre-hospital therapy can be realised, with a lesser incidence inappropriate therapy.

The relative benefits of pre-hospital thrombolysis and primary percutaneous intervention remain controversial. Meta-analysis suggests that primary percutaneous coronary intervention reduces early mortality, re-infarction and stroke when compared to ‘conventional’ thrombolysis. In addition, the recently reported Danish Multicenter Randomized Study on Fibrinolytic Therapy versus Acute Coronary Angioplasty in Acute Myocardial Infarction (DANAMI) 2 study suggests that this superiority (at least in terms of reduced re-infarction) is maintained even when patients require transport to an interventional centre. However, in this study, like its predecessors, thrombolysis was administered in hospital. The single study to date which has directly compared pre-hospital thrombolysis with primary angioplasty failed to demonstrate any significant difference in terms of death, non-fatal re-infarction and non-fatal disabling stroke at 30 days. The study was, however, stopped prematurely due to lack of funding and, therefore, had limited statistical power. Until this issue is fully resolved, and perhaps more importantly until the necessary infrastructure is in place, it is unlikely that primary percutaneous intervention will be the preferred treatment in most cases of acute myocardial infarction, at least in the UK. Thus, for the foreseeable future, an impetus to administer earlier, but appropriate, thrombolysis must persist.

Limitations

The primary source of data relating to the timing of events was from standardized forms completed by treating clinicians and coronary care unit nursing staff. This prospective method of data collection is essential if attempting to document accurate times. It does, however, make blinding of the location of thrombolysis impossible, and also introduces the potential for delays to be underestimated. This would, however, be common to both the pre- and in-hospital groups. In addition, a full-time audit nurse ensured that all data were as accurate as possible.

Although we recorded who administered thrombolysis, we did not record the mechanism whereby patients were admitted to hospital: e.g. whether they called an ambulance directly or contacted their general practitioner. This may have had implications for the way in which they were treated. Almost all pre-hospital thrombolysis at the time of the study was administered by general practitioners. Therefore, patients who called directly for an ambulance would be less likely to receive such therapy.

The final limitation of this study is that it reflects practice in one specific region with distinct geography. Nevertheless, similar results in terms of time to thrombolysis have been documented by several other groups in a variety of countries, suggesting that the findings are generalizable to many other settings.

Conclusions

The current data suggest that, in the north-east of Scotland, ‘call-to-needle’ times are declining and rates of pre-hospital thrombolysis are rising. Administration of thrombolysis in the community is associated with a much higher proportion of patients achieving the 60 min ‘call-to-needle’ time recommended in national guidelines. Indeed, the only way in which patients with acute myocardial infarction living in rural communities will meet this target is through continued and increased use of such therapy. Our data suggest that patients living relatively close to hospital might also benefit from increased use of community thrombolysis. Additional efforts are required to ensure that general practitioners and paramedics have the education, support and resources necessary to increase the provision of pre-hospital thrombolysis in appropriate patients, and to reduce the incidence of inappropriate therapy.

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