The impact of pre-hospital thrombolytic treatment on re-infarction rates:

analysis of the Myocardial Infarction National Audit Project (MINAP).

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Key words: Pre-hospital thrombolysis, ST-elevation myocardial infarction, re-infarction, acute myocardial infarction.
Word count: text 2970 words, abstract 250

ABSTRACT

Objective To examine the frequency and determinants of re-infarction after thrombolytic treatment of ST-elevation myocardial infarction (STEMI).

Design Observational study of national registry.

Setting Emergency ambulance services and admitting hospitals in England and Wales.

Patients 35356 cases of STEMI given thrombolytic treatment in 2005-6.

Main outcome measures Re-infarction during hospital admission

Results For 22391 (63.3%) the presence or absence of re-infarction was recorded, and 1460 (6.5%) had re-infarction. Re-infarction rates with in-hospital treatment were similar for reteplase (6.5%) and tenecteplase (6.4%). When the interval from pre-hospital treatment to hospital arrival was greater than 30 minutes re-infarction rates were 12.5% for reteplase, and 11.4% for tenecteplase. Overall, re-infarction rates were higher after pre-hospital treatment with tenecteplase than reteplase (9.6% vs. 6.6%, p = 0.005). After multivariate analysis independent predictors of re-infarction for tenecteplase were pre-hospital treatment, OR 1.44 (95% CI 1.21 to 1.71, p < 0.001) and weight in the highest quartile compared to the lowest, OR 1.66 (95% CI 1.19 to 2.31, p = 0.003). For reteplase neither factor predicted re-infarction.

Bleeding was less common with pre-hospital treatment - overall 1.8% against 3.1%; intra-cerebral bleeding 0.4% against 0.7%.

Conclusion Pre-hospital treatment with tenecteplase was associated with higher re-infarction rates. Longer intervals from pre-hospital treatment to arrival in hospital were associated with high re-infarction rates for both tenecteplase and reteplase. Differences in the use of adjunctive anti-thrombotic therapy in the two treatment environments may underlie the differences in re-infarction rates and bleeding complications observed between pre-hospital and in-hospital thrombolytic treatment. [250]

INTRODUCTION

Delivery of thrombolytic treatment in ST-elevation myocardial infarction (STEMI) before arrival at hospital allows earlier treatment and improves outcome. [1,2] Pre-hospital treatment accounted for 15% of all reperfusion treatment with thrombolytic drugs for this indication in England and Wales during 2006. [3] Re-infarction following re-occlusion of a recently reperfused artery, is a recognised complication of thrombolytic treatment, and comprises most of the difference in composite end-points seen in trials comparing thrombolytic therapy with primary angioplasty. [4]

Re-infarction rates between 1.8% and 6.3% have recently been reported. [5-10] The rate may vary with the type of adjunctive anti-thrombotic therapy used and the degree with which early treatment is provided. The use of pre-hospital treatment is increasing in England and Wales, and there have been anecdotal reports of higher rates of re-infarction after pre-hospital treatment. This led us to analyse the frequency and determinants of re-infarction reported following thrombolytic treatment using the Myocardial Infarction National Audit Project (MINAP) database.

METHODS

Details of MINAP have previously been published [11,12]. The project uses a dataset that allows examination of care of patients with acute coronary syndromes and is based on the technological platform developed by the Central Cardiac Audit Database group [13]. The primary purpose of the project is to provide hospitals and ambulance services with contemporary online analyses of their performance and comparisons with national aggregate data.

Data were collected on patients with STEMI including demographics, previous medical history, the times of onset of symptoms, call for help, arrival in hospital, and start of reperfusion treatment, and the place this was delivered, between January 2005 and September 2006. Data sources routinely include information provided by the patient, the ambulance service patient record form, and hospital records. Analysis of time intervals is dependant on the recording of accurate times. MINAP accepts these data, and is not able to perform independent cross-checks. Evidence of STEMI was based on reported electrocardiographic findings. Choice of thrombolytic agent was locally determined.

Re-infarction was defined as ischaemic pain or other symptoms consistent with acute cardiac ischaemia persisting until relieved by analgesia or nitrates, accompanied by new electrocardiographic changes (elevation or depression of the ST-segment or T wave changes) in the territory of the initial event. These features had to be accompanied by new elevation of creatine kinase or other marker of cardiac necrosis to more than the upper limit of normal or an increase to a value ? 50% greater than the previous value. Bleeding complications were defined as any bleeding within 24 hours of a therapeutic intervention.

Pre-hospital thrombolytic treatment

In England and Wales treatment is delivered by ambulance paramedics following protocols based upon guidelines from the Joint Royal Colleges Ambulance Liaison Committee [14] (see appendix). During 2005 treatment was restricted to those aged 75 yr or younger, and subsequently 80 years or less, within 6 hours of symptom-onset. Drugs used for pre-hospital treatment were reteplase and tenecteplase with an immediate intravenous bolus of unfractionated heparin. When reteplase was used a second bolus was given after 30 minutes (either in the ambulance or in hospital). An infusion of heparin was not started before arrival in hospital.

Statistical analyses.

Categorical data were expressed as percentages, and comparisons between groups used the X^2 test. The Wilcoxon rank sum test was used for continuous variables. Multivariate logistic regression analysis was used to derive odds ratios for potential predictors of re-infarction using variables previously selected with univariate analysis and having individual p values ? 0.05. Statistical analysis was performed using SPSS V14.

RESULTS

During the study period MINAP recorded 49017 episodes with a final diagnosis of STEMI, of which 35356 received thrombolytic treatment. For 22391 (63.3%) the presence or absence of re-infarction was recorded; 1460 (6.5%) had re-infarction during the index admission. Streptokinase was used in 4514 (20.2%) cases, alteplase in 835 (3.7%), reteplase in 5053 (22.6%) and tenecteplase in 10915 (48.7%). In 1074 (4.8%) cases the thrombolytic agent was not recorded.

Clinical characteristics and co-morbidity

Patient characteristics were similar in those for whom re-infarction status was recorded and those for whom it was not recorded or unknown. Where re-infarction status was recorded those having re-infarction were slightly older, median 66.7 against 65.2 years, p = 0.04, and were significantly heavier, median 80 against 78 kg, p = 0.017. They received treatment earlier than those who did not have re-infarction, for both in-hospital, p <0.001 and pre-hospital treatment, p = 0.017 (table 1). Previous myocardial infarction, previous angina, and chronic renal failure were more common in those having re-infarction. Those who had re-infarction were less likely to be smokers (table 2).

	No re-infarction		Re-infarction		
	n = 20931		n = 1460		p
Age, years	65.2	56.5, 76.5	66.7	56, 75	p = 0.04
Male gender %	71.6	14926/20859	71.2	1036/1456	NS
Systolic blood pressure, mm Hg	139	119, 158	137	119, 158	NS
Heart rate, min-1	74	62, 88	73	61, 87	NS
Weight, kg	78	69, 89	80	70, 90	p = 0.017
Onset to treatment - in-hospital, minutes	150	100, 254	135	90, 231	<0.001
Onset to treatment - pre-hospital, minutes	97	65, 163	85	60, 137	0.017

Table 1 Clinical characteristics of patients. Data are presented as medians and interquartile range (IQR) unless stated otherwise.

	No re-infarction		Re-infarction		
	n	%	n	%	
Onset - treatment delay	% treated		%		

In-hospital (a) | Pre-hospital (b) | b – a, p | In-hospital (a) | Pre-hospital (b) |

	%	n	%	n		%	n	%	n			
0-2 hours	6.8	86/1258	7.0	26/371	0.2, NS	7.4	208/2801	10.9	140/1287	3.5, p <0.001		
2-4 hours	6.0	78/1305	6.3	9/144	0.3, NS	5.8	139/2399	6.8	34/499	1.0, NS		
>4 hours	6.2	56/903	5.4	4/74	-0.8, NS	5.0	84/1682	8.9	21/237	3.9, p = 0.014		
Total	6.3	220/3466	6.6	39/589	0.3, NS	6.3	431/6882	9.6	195/2023	3.6, p < 0.001		

Table 4 Re-infarction rates for pre-hospital and in-hospital treatment in relation to interval from onset of

symptoms; b-a is the difference between pre-hospital and in-hospital treatment re-infarction rates. NS = not significant(p >0.05)

Pre-hospital treatment

Pre-hospital treatment was limiteded to reteplase and tenecteplase, and was given to 3138/22391 (14%) patients**.** Patients receiving pre-hospital treatment were younger than those having in-hospital treatment; 62 yr (IQR 53 to 70) vs. 66 yr (IQR 56 to 76), p <0.001, and a greater proportion were male; 2430/3130 (77.6%) vs. 13532/19185 (70.5%) p <0.001. For reteplase re-infarction rate after pre-hospital and in-hospital initiation was 6.6% and 6.3% respectively. For tenecteplase pre-hospital initiation was associated with an absolute excess re-infarction rate of 3% (9.6% vs. 6.3%, p < 0.001). Although re-infarction rates for in-hospital treatment did not differ between the two agents, there was a large difference in re-infarction rate when they were given out of hospital, tenecteplase 9.6% against reteplase 6.6%, p = 0.005. (table 4)

Treatment to arrival in hospital

The interval from thrombolytic treatment to arrival in hospital was recorded for 2839/2999 (95%) patients. When this was greater than 60 minutes 8/49 (16.3%) had re-infarction, between 30 and 59 minutes, 83/734 (11.3%) and for the majority (68%) who reached hospital within 30 minutes after lytic treatment, re-infarction occurred in 166/2051 (8.1%). For longer delays to hospital arrival a similar rate of re-infarction was seen with individual agents; for delay of greater than 30 minutes 72/631 (11.4%) having tenecteplase had re-infarction compared with 19/152 (12.5%) for reteplase. For delays of 30 minutes or less re-infarction was commoner following tenecteplase (145/1552 (9.3%) vs. 21/499 (4.2%), difference 5.1%, p = 0.001).

Predictors of re-infarction

A model was developed using multivariate logistic regression analysis to establish factors predictive of re-infarction. This was limited to treatment with reteplase and tenecteplase in order to examine differences between in-hospital and pre-hospital treatment. Variables having a p value < 0.05 on univariate analysis were included together with age and gender. The model included treatment within 2 hours of onset, chronic renal failure, previous angina, previous myocardial infarction, place where thrombolytic treatment given, patient weight (in quartiles) and current smoking habit. Variables examined and excluded from the model were prior clopidogrel treatment, prior aspirin treatment, pre-existing heart failure, diabetes, hypertension, peripheral vascular disease, and treated hyperlipidaemia.

Considering both lytic drugs together, the determinants of re-infarction were; weight in the highest quartile, OR 1.67 (95% CI 1.27 to 2.27, p < 0.001), previous myocardial infarction, OR 1.67 (95% CI 1.38 to 1.99, p <0.001), pre-hospital treatment, OR 1.36 (95% CI 1.17 to 1.58, p < 0.001), and treatment within two hours of onset of symptoms, OR 1.23 (95% CI 1.01 to 1.51, p = 0.039). Current smoking habit predicted a lower risk of re-infarction, OR 0.77 (95% CI 0.60 to 0.99, p = 0.041). Neither gender nor age predicted re-infarction.

For reteplase, only chronic renal failure, OR 2.60 (95% CI 1.14 to 4.8, p = 0.002) and previous myocardial infarction, OR 2.74 (95% CI 2.02 to 3.72, p < 0.001) predicted re-infarction. Neither the interval from onset to treatment, patient weight, nor place of treatment were predictive of re-infarction.

For tenecteplase, weight in the upper quartile compared with the lowest, OR 1.66 (95% CI 1.19 to 2.31, p = 0.003) and pre-hospital treatment, OR 1.44 (95% CI 1.21 to 1.71, p <0.001) were predictors of re-infarction. Previous myocardial infarction, OR 1.25 (95% CI 0.99 to 1.25, p = 0.06) was of borderline significance, and treatment within the first two hours was not predictive of re-infarction (p = 0.1). For tenecteplase, patient weight in the upper quartile predicted re-infarction both for in hospital treatment, OR 1.53 (95% CI 1.056 to 2.23, p = 0.024) and for pre-hospital treatment, OR 2.35 (95% CI 1.11 to 4.9, p = 0.025).

Bleeding risk

Information on bleeding events was available from 20720/22391 (92.5%) records. Bleeding occurred in 585/20720 (2.8%), of which 149 (0.7%) were intracranial. Bleeding was commoner following in-hospital

treatment compared with pre-hospital treatment; any bleeding in 371/12142 (3.1%) vs. 49/2722 (1.8%), p <0.001, and intracranial bleeding in 100/1214 (0.8%) vs. 11/2722 (0.4%).

Logistic regression analysis was used to determine factors that were predictive of bleeding. Variables included were the same as those used for re-infarction, but with the addition of re-infarction to the model. Factors that predicted bleeding were age, OR 1.04 (95% CI 1.03 to 1.05, p < 0.001), the occurrence of re-infarction, OR 1.58 (95%CI 1.14 to 1.8, p = 0.006) and previous myocardial infarction, OR 1.33 (95% CI 1.0 to 1.76, p 0.045). Pre-hospital treatment was associated with lower bleeding risk, OR 0.72 (95% CI 0.53 to 0.98, p = 0.04).

In-hospital mortality

In-hospital mortality data was available for 21677/22391 (97%); 198/1387(13.6%) of those experiencing re-infarction died against 1192/20290 (5.7%) of those without re-infarction.

DISCUSSION

In this study 6.5% of patients with STEMI having thrombolytic therapy had re-infarction during hospital admission and had unadjusted mortality rate more than twice that of those without re-infarction. This re-infarction rate is higher than reported in a number of randomised trials involving thrombolytic treatment. [5-10] Re-infarction rates for individual drugs in common use within hospital were similar, streptokinase 5.6%, reteplase 6.3%, and tenecteplase 6.3%. While there was no difference in re-infarction rates between reteplase and tenecteplase administered within hospital, pre-hospital treatment with tenecteplase was associated with more re-infarction than reteplase, 9.6% against 6.6%, p = 0.005. However re-infarction was particularly prevalent for both tenecteplase, 11.4% and reteplase, 12.5% when the interval from pre-hospital treatment to arrival in hospital was greater than 30 minutes.

Re-infarction and re-occlusion.

Re-infarction is the outward and visible manifestation of coronary re-occlusion. This is supported by the association of angiographically-proven infarct-related artery re-occlusion with symptomatic re-infarction [15]. Re-infarction can be difficult to diagnose, being observed less commonly than re-occlusion is observed angiographically. In the 1980's and 1990's, when the rate of re-occlusion following thrombolytic therapy was in the region of 16%, rates of reported re-infarction were much lower: 4.3% during hospitalisation (at a median 3.8 days) in the GUSTO trials of streptokinase, alteplase and reteplase and between 2.9% and 3.6% amongst 41299 patients in the ISIS-3 trial of streptokinase, alteplase and anistreplase [5,16,17].

Early treatment

This study shows that treatment with tenecteplase within two hours of onset of symptoms, when more than 40% patients had lytic treatment, was associated with higher re-infarction rates. There was no relation between earlier treatment and re-infarction for streptokinase, but there was a statistically non-significant trend towards more re-infarction with early treatment with alteplase and reteplase. It is recognised that earlier administration of thrombolytic therapy achieves higher reperfusion rates both in terms of patency of the epicardial vessel and myocardial perfusion, and this inevitably provides a greater opportunity for re-infarction. [18]

Pre-hospital treatment and the journey to hospital

The re-infarction rate for patients, 32% of all those having pre-hospital treatment, who had an interval longer than 30 minutes from pre-hospital treatment to arrival in hospital was high; reteplase 12.5%, tenecteplase 11.4%. For intervals shorter than 30 minutes the re-infarction rates were significantly greater for tenecteplase (9.3%) than reteplase (4.2%). These findings are unlikely to be due to intrinsic differences between tenecteplase and reteplase as treatment within hospital was associated with identical re-infarction rates. We speculate that high rates of re-infarction reflect variation in the precise method of administration of the lytic agents and associated anti-thrombotic treatment within the pre-hospital environment.

National guidelines for pre-hospital thrombolytic therapy then extant reflected a degree of caution about the risks of intra-cranial bleeding and the lack of a licence for the use of low-molecular-weight heparins. [14] In summary, the guidelines recommended a bolus dose of unfractionated heparin of 4000u for those under 67 kg, and 5000u for those of greater weight. No recommendation was made about the use of the heparin infusion - used as a routine within the hospital environment - and in practice this was not used in the pre-hospital environment (see appendix). Tenecteplase and reteplase, having plasma half lives less than 25 minutes, require effective immediate adjunctive anti-thrombotic support at a time of intense thrombotic and inflammatory activity at the site of the plaque. [19, 20] A combination of guidelines that may

have erred on the side of caution, and the use of heparin, an agent which has considerable practical limitations, may be relevant to the higher rates of re-infarction found with pre-hospital treatment. [8,21,22] In this study we also show that pre-hospital treatment was independently associated with a lower rate of bleeding complications, a factor that supports the view that anti-thrombotic treatment may have been less intense than that provided in hospital.

We consider that the high re-infarction rates noted with intervals from pre-hospital treatment to arrival at hospital of more than 30 minutes may be the result of delay from the first bolus dose of heparin to the start of the heparin infusion in hospital. It appears that maintenance of heparin levels by heparin infusion is critical at a time of intense thrombotic and inflammatory activity. The effect of the lack a heparin infusion was reduced for reteplase by the administration of the second dose of the lytic agent, but only where the interval from the initial to the second bolus dose of reteplase was within the recommended limit of 30 minutes. For tenecteplase a treatment to hospital arrival time of under 30 minutes was associated with a lower, albeit still very high, re-infarction rate of 9.3% indicating that even within this interval a heparin infusion is vital.

The ASSENT-3 PLUS trial, where the re-infarction rate was 5.8% after pre-hospital tenecteplase, offers support for the importance of heparin infusion. In the unfractionated heparin arm of the study only about 60% patients started a heparin infusion in the ambulance and this group had a small, but non-significantly lower rate of re-infarction, 4.0% vs. 5.9%, compared to those for whom it was started in hospital. [23]

The impact of patient weight

Multiple logistic regression analysis showed that for tenecteplase, but not for reteplase, patient weight in the highest quartile when compared with the lowest, was an independent predictor of re-infarction. This was apparent both for in-hospital treatment, OR 1.53, p = 0.024, and pre-hospital treatment where the association was stronger, OR 2.35, p = 0.025. The practical significance of this finding remains to be established.

Bleeding complications

Bleeding complications occurred less commonly following pre-hospital than in-hospital treatment. This may reflect a younger cohort having pre-hospital treatment. However the lower bleeding rate persisted after multivariate adjustment, and may be another manifestation of the different anti-thrombotic regimes. Bleeding was independently associated with re-infarction. Although the timing of these events was not recorded, a bleeding event in this study by definition occurred within 24 hours of therapeutic intervention. Others have reported a median interval of 3 days to re-infarction.[5] If this was the case here it would suggest an initial bleeding event, leading to withdrawal of anticoagulation, might be responsible for re-infarction.

Limitations

In this observational study re-infarction status was recorded in only 63% of cases. If re-infarction status was more often left blank in the absence of re-infarction this would lead to an overestimate of the true incidence of re-infarction. However, it seems unlikely that the completion of the re-infarction data item should be systematically influenced by the type of thrombolytic drug or by the location of treatment. We do not have information on the timings nor doses of adjunctive antiplatelet therapy nor on the frequency with which admitting hospitals administered low-molecular-weight heparin (off-licence). During the study hospitals did not routinely use either clopidogrel or fondaparinux in cases of STEMI – the use of which have been associated with lower rates of re-infarction. [7,24]

CONCLUSIONS

Pre-hospital thrombolytic treatment is independently associated with re-infarction. While re-infarction rates for reteplase and tenecteplase did not differ with in-hospital treatment, there were substantial differences when used outside hospital. We speculate that inadequate anticoagulation with unfractionated heparin in the period immediately following pre-hospital treatment may be responsible. These findings stress the critical importance of an effective anticoagulant regime in order to maximise the benefit associated with pre-hospital thrombolytic therapy.

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Acknowledgments

We acknowledge those who have entered data into the MINAP database, and encouragement from

members of both the MINAP Steering Committee and MINAP Academic Group.

Competing interests

Dr Weston, Dr Birkhead and Professor Quinn have at various times received honoraria for acting as advisors to Boehringer Ingelheim on the early management of acute myocardial infarction and for lecturing at meetings sponsored by Boehringer Ingelheim.

Funding

MINAP receives core funding from the Healthcare Commission and is housed within the National Institute for Clinical Outcomes Research, UCL, London. The research presented here is independent of any influence of the funders of MINAP.

Dr Birkhead is the guarantor of the study.

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Appendix: Recommended use of thrombolytic treatment outside hospital from JRCALC guidelines 2004 [14].

Reteplase was administered as a 10 U injection with a second 10 U injection after 30 minutes while tenecteplase was given as a single weight-adjusted bolus (<60 kg: 6,000 U; 60-69 kg: 7,000 U; 70-79 kg: 8,000 U; 80-89 kg: 9,000 U; ?90 kg: 10,000 U). The guidelines recommended that heparin treatment be deferred if such treatment could be delivered in hospital within 30 minutes of tenecteplase or 20 minutes of the first dose of reteplase. Otherwise, the recommended pre-hospital dose of heparin was 4,000 U when

used with tenecteplase and 5,000 U when used with reteplase.

Trials mentioned in text

ASSENT-3 PLUS – Assessment of the Safety and Efficacy of a New Thrombolytic regimen: Efficacy and safety of tenecteplase in combination with the low-molecular weight heparin enoxaparin or unfractionated heparin in the prehospital setting

ISIS-3 – Third International Study of Infarct Survival

GUSTO –Global Use of Strategies to Open Occluded Coronary Arteries