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Prehospital Administration of Unfractionated Heparin in ST-Segment Elevation Myocardial Infarction Is Associated With Improved Long-Term Survival

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Objective: Administration of unfractionated heparin to STEMI patients by the ambulance service is an established practice in Scotland, but the efficacy is unknown. We studied the effects of unfractionated heparin in STEMI patients treated by primary percutaneous coronary intervention, on infarct artery patency and mortality.

Methods and Results: Consecutive patients (n = 1000) admitted to Ninewells Hospital, Dundee, from 2010 to 2014 for primary percutaneous coronary intervention were allocated to 2 groups: 437 (44%) prehospital heparin (PHH) administered by paramedics, and 563 (56%) in-hospital heparin. A trained medical student assessed coronary flow at presentation and collected the data. Mortality status was ascertained at 30 days and 5 years. Cox proportional hazards regression models were generated. The patient groups were similar, although PHH had shorter symptom onset-treatment time (187 vs. 251 minutes, $P < 0.001$) and less cardiogenic shock (3.9% vs. 8.0%, $P = 0.008$). Initial coronary flow was not different between the groups. Thirty day mortality in PHH was 2.5% versus 8.3%, $P < 0.001$. Independent predictors of 30-day mortality were age (odds ratio 1.07, 95% CI 1.04–1.09), cardiogenic shock (5.97, 3.33–10.69), radial access (0.53, 0.28–0.98), and PHH (0.33, 0.17–0.66). Five-year mortality in PHH was 13.0% versus 21.6%, $P < 0.001$. Significant predictors of long-term mortality were age (1.07, 1.06–1.09), cardiogenic shock (3.40, 2.23–5.17), and PHH (0.68, 0.49–0.96).

Conclusions: PHH was associated with reduced short- and long-term mortality after adjusting for important potential confounders.

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The authors report no conflicts of interest.

C. McGinley, J. Irving performed retrospective analysis of coronary flow and designed the study. P. Kell provided Scottish Ambulance Data. All authors analyzed and commented on the data. C. McGinley, J. Irving wrote the manuscript with input from all authors.

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INTRODUCTION

ST-segment elevation myocardial infarction (STEMI) is caused by a thrombotic occlusion of a coronary artery superimposed on a ruptured atherosclerotic plaque. Immediate primary percutaneous coronary intervention (PPCI) is well established as the optimal treatment for STEMI because it delivers effective and sustained reperfusion of the infarcted territory.[1–3] Treatment efficacy is greatest when delivered rapidly.[4] Not all patients presenting with STEMI have sustained and complete occlusion of the culprit coronary artery; when residual coronary flow is present at angiography, it is associated with better long-term outcomes.[5,6] Enhancing coronary flow before PPCI with prehospital thrombolysis, a strategy of facilitated PCI, was tested extensively, but was found to increase bleeding and stroke.[7]

In the absence of randomized trial data, it is perhaps surprising that prehospital administration of unfractionated heparin (UFH) is recommended in many STEMI protocols. A few retrospective studies have indicated a possible benefit.[8–12] The reasoning is pragmatic: anticoagulation and antiplatelet therapy are essential for safe PCI, early administration may lead to improved flow at initial angiography, and thus benefit. The risk of harmful bleeding is significantly less than with thrombolysis. Heparin is well established as the ideal antithrombotic for PPCI, with the randomized HEAT-PPCI trial demonstrating reduced major adverse ischemic events, expense, and similar bleeding rates to bivalirduin.[13]

The aim of this study was to investigate the effects of prehospital heparin (PHH) on infarct artery patency in STEMI patients before PPCI. We hypothesized that early administration of UFH by the Scottish Ambulance Service may improve IRA patency before PCI. This in turn would be associated with improved short-term and long-term survival.

METHODS

Population

This retrospective observational study examined consecutive patients presenting with STEMI, treated with

TABLE 1. Baseline Characteristics

	Prehospital Heparin Group (PHH), n = 437	IHH Group, n = 563	*P*
Male sex, n (%)	304 (69.6)	390 (69.3)	0.92
Age, yr	63.7	63.7	0.99
Smoking, n (%)	173 (39.6)	232 (41.2)	0.60
Hypertension, n (%)	132 (30.2)	168 (29.8)	0.89
Diabetes, n (%)	38 (8.7)	53 (9.4)	0.70
Dyslipidaemia, n (%)	90 (20.6)	99 (17.6)	0.22
Family history CAD, n (%)	100 (22.9)	114 (20.2)	0.31
Previous CVA/TIA, n (%)	24 (5.5)	26 (4.6)	0.66
Peripheral vascular disease, n (%)	9 (2.1)	15 (2.7)	0.54
Chronic lung disease, n (%)	26 (5.9)	19 (3.4)	0.05
LVEF < 45, n (%)	71 (16.2)	81 (14.4)	0.42
LVEF (%)	50.74	51.44	0.24
Previous PCI, n (%)	19 (4.3)	42 (7.5)	0.04
Previous CABG, n (%)	7 (1.6)	13 (2.3)	0.43
Radial access, n (%)	397 (90.8)	487 (86.5)	0.03
Duke jeopardy score	3.18	3.43	0.03

Differences between categorical variables were assessed with χ^2 test. Differences in continuous variables were assessed with the Student's t-test if normally distributed.
CABG, coronary artery bypass graft; CAD, coronary artery disease; CVA, cerebrovascular accident; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

PPCI at Ninewells Hospital, Dundee, United Kingdom between February 2010 and October 2014. The Ninewells PPCI service covers approximately 500,000 patients from Tayside, Fife, and Angus. The study was approved by the local ethics committee.

The indication for PPCI was established in patients with chest pain and an electrocardiogram showing ST-segment elevation in 2 or more contiguous leads, with a minimum of 0.1 mV in frontal leads and 0.2 mV in precordial leads or new left bundle branch block that evolved within 12 hours. ECG telemetry to the Coronary Care Unit in Ninewells Hospital assisted prehospital diagnosis.

Patients diagnosed prehospital by the Scottish Ambulance Service paramedics were treated according to the national protocol with oral aspirin 300 mg, clopidogrel 300 mg, and 5000 units of UFH administered intravenously by a paramedic as per standard protocol in Scotland.

A total of 1000 patients were used in this study. Data were retrospectively collected from routine databases. All-cause mortality was ascertained at 30 days and 5 years post-PPCI from a local patient administration database (TOPAZ).

Heparin Pretreatment

Patients were classified into the following groups relative to PHH administration:

1. PHH group: UFH administered before arrival at PCI center
2. In-hospital heparin (IHH) group: UFH administered immediately before PCI.

Thrombolysis in Myocardial Infarction (TIMI) Flow

A trained medical student assessed coronary artery flow before PCI. Flow was retrospectively determined using the TIMI study group grade flow. Patients were classified in 2 groups: TIMI flow 0–1 (coronary artery occluded) and TIMI flow 2–3 (coronary artery patent). Interobserver and intraobserver variability was measured after data collection to determine the reliability of this assessment.

TABLE 2. Temporal Delays and Hemodynamic Status

	Prehospital Heparin Group (PHH), n = 437	IHH Group, n = 563	*P*
Mechanical ventilation, n (%)	9 (2.1)	18 (3.2)	0.27
Circulatory support, n (%)	13 (3.0)	41 (7.3)	0.003
Cardiogenic shock, n (%)	17 (3.9)	45 (8.0)	0.008
Temporal intervals			
Call time—PPCI time, min	99	127	<0.001
Symptom onset—PPCI time, min	187	251	<0.001

Differences between categorical variables were assessed with χ^2 test. Differences in continuous variables were assessed with the Student's t-test if normally distributed. Use of intra-aortic balloon pump (IABP) defined circulatory support in this study.

TABLE 3. Coronary Flow Assessment Variability

	Interobserver Variability	Intraobserver Variability
IRA TIMI flow	Kappa 0.59	Kappa 0.64
IRA (0/1) or (2/3) TIMI flow	Kappa 0.87	Kappa 0.85

Cohen's kappa coefficient was used to measure interobserver agreement.

Primary Endpoint

The primary end point was defined as infarct artery patency according to PHH administration. Secondary endpoints were 30-day mortality and 5-year mortality.

Statistical Analysis

Statistical analysis was performed using SPSS 22.0 (SPSS Inc, Chicago, IL). Categorical variables are shown as proportions (percentage), and were analyzed using Pearson's χ^2 test. Quantitative variables are expressed as means ± SD. A two-sided *P*-value of 0.05 was considered statistically significant. To determine independent predictors of initial IRA TIMI 2–3 flow, multiple regression analysis using logistic regression model was performed. The model included age, sex, cardiogenic shock, radial access, call for help—PPCI time, symptom onset—PPCI time, previous CABG, Duke score, and PHH administration. Multiple regression models were also used to determine independent predictors of 30-day mortality and 5-year mortality. Graphs and diagrams were plotted on GraphPad Prism version 6 (GraphPad Software).

RESULTS

In total, 1000 patients were included in this study with none lost to follow-up. Baseline characteristics for the PHH group (n = 437) and IHH group (n = 563) (Table 1).

Patients in both groups had similar baseline characteristics except PHH group were more likely to suffer chronic lung disease, have a lower Duke Jeopardy score and have radial access PCI, and less likely to have had previous PCI treatment. Duke Jeopardy scoring quantifies the amount of myocardium at risk dependent on coronary artery anatomy.[14]

Procedural characteristics for the heparin groups are displayed in Table 2. PHH group had a significantly lower incidence of circulatory support and cardiogenic shock. Temporal intervals were significantly increased in IHH (Table 2).

Interobserver and intraobserver variation of coronary flow was assessed. A trained medical student assessed TIMI scoring for the purposes of this study. Intraobserver variability was calculated in retrospect, after collating data, and this showed substantial agreement (kappa $>$ 0.81). Interobserver variability between a medical student and consultant cardiologist demonstrated moderate agreement on a continuous scale of TIMI 0–3 and substantial agreement when TIMI scoring was grouped (0/1) and (2/3) (Table 3).

Primary and secondary end point analyses are displayed in Table 4. IRA flow was not significantly different between the 2 groups. In addition, in-lab and in-hospital event rates were comparable. Preheparin treatment was associated with improved 30-day mortality (2.5% PHH vs. 8.3% IHH) and 5-year mortality (13.0% vs. 21.5%) (Table 4).

Figure 1 shows an unadjusted Kaplan–Meier graph of survival between PHH group and IHH group (P = 0.0032) (Fig. 1).

Cox proportional hazard analysis showed PHH is an independent predictor of lower 30-day, with OR 0.332 (CI 95% 0.168–0.858, P = 0.002) (Table 5), and 5-year mortality with OR 0.684 (CI 95% 0.489–0.925, P = 0.07) (Table 6).

DISCUSSION

In this retrospective observational study, prehospital treatment with heparin was associated with significantly improved long-term survival, after adjustment for important confounders. However, we did not support our hypothesis that early administration of heparin would improve early coronary patency, limiting the extent of myocardial infarction, and hence improve survival. Although improved flow at

TABLE 4. Primary and Secondary End Point Analysis

	Prehospital Heparin Group (PHH), n = 437	IHH Group, n = 563	*P*
IRA patency			
TIMI flow 0–1, n (%)	326 (74.6)	427 (75.8)	0.65
TIMI flow 2–3, n (%)	111 (25.4)	136 (24.2)	0.65
In-lab complications, n (%)	25 (5.7)	33 (5.9)	0.92
In-hospital complications, n (%)	67 (15.3)	81 (14.4)	0.68
Haemorrhagic complications, n (%)	6 (1.4)	5 (0.9)	0.91
Mortality			
30-d mortality, n (%)	11 (2.5)	47 (8.3)	<0.001
5-yr mortality, n (%)	57 (13.0)	121 (21.5)	<0.001

Differences between variables were assessed with χ^2 test.
IRA, infarct artery patency.

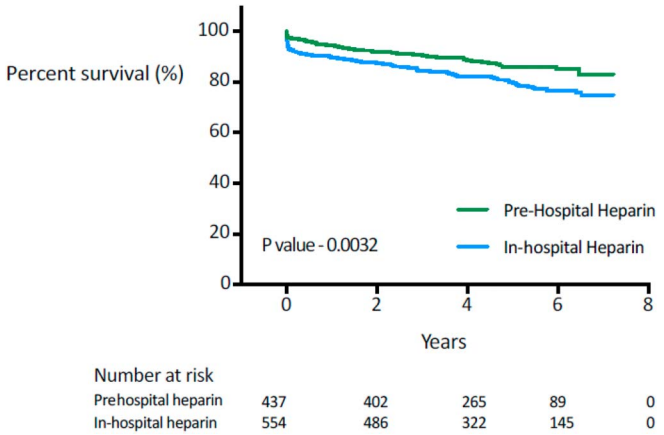

FIGURE 1. Kaplan–Meier survival curve shows survival differences between the 2 groups. Numbers remaining at different time intervals are shown for both treatment groups.

presentation tended to predict improved survival, there was no observable difference in coronary flow depending on heparin status. It is uncertain how much of the observed association can be attributed to a therapeutic effect from heparin, one that is not apparent in our assessment of coronary flow, and how much to unmeasured confounding.

Early reperfusion is well established as the most important goal in the treatment of STEMI patients. Myocardial damage during STEMI is a time-dependent process therefore early infarct-related artery patency (defined as TIMI grade 3) is associated with better clinical outcomes including survival.[15,16] A combination of patient delay, transportation delay, and time needed to establish reperfusion in the catheter laboratory contribute to total ischemic time for patients.[17] Therefore, any efforts made to promote coronary reperfusion before PPCI will theoretically decrease myocardial injury and potentially improve patient outcomes.

Previous studies of heparin on vessel patency have given inconsistent results. There was no benefit seen from high bolus IV heparin versus low-dose heparin in the HEAP study.[18] In contrast, Zjilstra and colleagues showed improved vessel patency and improved survival at 30 days in patients treated with PHH.[9] The largest study to date was an analysis of outcomes in 7000 patients in the TASTE study from Sweden. This paper described decreased visible thrombus and increased vessel patency in patients receiving PHH. There was no association with 30-day survival.[19]

In these studies coronary flow was assessed by experienced interventional cardiologists, which may be more accurate than our results using a trained medical student, notwithstanding the good accuracy we have shown. Giralt et al[20] showed that vessel patency at presentation is sensitive to timing of heparin administration relative to symptom onset; it may be that ischemic preconditioning, preceding aspirin prescription, and other factors that are difficult to fully account for in analysis influence the apparent effect on coronary flow from heparin.

It is open to question how much effect could be expected from the dose of heparin that is currently used.

TABLE 5. Cox Regression Analysis of Mortality at 30-D

	Odds Ratio	CI 95%	*P*
Age	1.07	1.04–1.09	<0.001
Male	1.06	0.74–1.40	0.93
Cardiogenic shock	1.79	3.33–10.7	<0.001
IRA patency	0.82	0.61–1.09	0.42
Radial access	0.53	0.28–0.98	0.04
Pre-hospital heparin	0.33	0.17–0.66	0.02
Call time - PPCI time	0.56	0.01–447.5	0.87
Symptom onset - PPCI time	0.14	0.01–2.34	0.18

Cox regression model used to determine independent predictors of 30-d mortality post-PPCI. Age, cardiogenic shock, radial access and prehospital heparin administration were independent predictors in this model.

The Scottish Ambulance Service administers a standard dose of 5000 international units of IV heparin.[21] In a study of 1553 consecutive cases in the Netherlands, this dose was assessed by activated clotting time measured on arrival in the catheter laboratory. The ACT was subtherapeutic 82% of all cases, and subtherapeutic in 92.3% of cases not pretreated with tirofiban, (which may also prolong the ACT).[22] A low ACT was predicted by increasing weight, and published obesity prevalence statistics (Scotland 29% vs. Netherlands 19%)[23,24] suggests that the Tayside population is not likely to have a high proportion of patients with a sustained therapeutic effect from 5000 units of IV heparin.[25]

Our study benefits from long follow-up. The association between PHH and survival is apparent at 30 days and at 5 years. It is implausible that a single dose of heparin that is likely to have a significant therapeutic effect for a short time, in a minority of patients, can be responsible for such a large observed difference in mortality. The baseline characteristics and comorbidities (Fig. 1) were strikingly similar given the difference in survival. Nevertheless, patients who received PHH had shorter intervals between symptom onset and treatment, and lower incidence of cardiogenic shock. The IHH patient group was clearly more ill, and probably had more advanced coronary disease as shown by a higher Duke Jeopardy score.

TABLE 6. Cox-Regression Analysis of Mortality at 5-Years

	Odds Ratio	CI 95%	*P*
Age	1.07	1.06–1.09	<0.001
Male	1.06	0.74–1.40	0.93
Cardiogenic shock	3.40	2.23–5.17	<0.001
IRA patency	0.94	0.82–1.09	0.43
Radial access	0.77	0.50–1.17	0.22
Previous CABG	1.29	0.57–2.96	0.54
Prehospital heparin	0.68	0.49–0.96	0.03
Call time–PPCI time	4.30	0.16–116.5	0.39
Symptom onset–PPCI time	2.21	0.79–6.22	0.13

Cox regression model used to determine independent predictors of 5-year mortality post-PPCI. Age, cardiogenic shock, and prehospital heparin administration were independent predictors in this model.

It may be that the patients who contact the emergency services earlier in the clinical course of their MI illustrate a tendency to interact more favorably with medical services throughout their lives. We can speculate that they may be more health literate, more concordant with prescribed therapy, more likely to stop smoking, and better engaged with cardiac rehabilitation services. Further investigation of the differences between the groups regarding decision-making processes when confronted with the symptoms of myocardial infarction, may be more effective further investigation of the observed association than a randomized trial of PHH.

In conclusion, PHH treatment has been associated with improved survival in this, and other observational studies. We take the view that it is not likely to be a direct effect of heparin, but that the differences between patient groups are worthy of further investigation.

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