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Thrombolytic therapy in ST-elevation myocardial infarction

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Abstract

Aim

Early myocardial reperfusion after ST segment elevation myocardial infarction (STEMI) has been shown to reduce morbidity and mortality. Chemical thrombolysis is the preferred reperfusion mechanism if timely primary percutaneous coronary intervention (PPCI) cannot be achieved. Our aim was to evaluate the efficacy and safety of thrombolytic therapy in a cohort of patients who were predicted to have a delayed time to PPCI and who were subsequently thrombolysed, versus those who were not.

Methods

We conducted a retrospective case control study of 21 thrombolysis and 42 PPCI control patients, who had a confirmed STEMI and were admitted to St. James' Hospital (SJH) between 30/6/17 and 30/6/20 (1161 total patients). TIMI flow grades and total ischemic time were assessed along with impact of demographics, procedural factors and 30-day mortality.

Results

Using TIMI flow as an indicator of reperfusion, successful reperfusion (TIMI 2/3) was seen in 15/21 (71.4%) patients in the thrombolysed group versus only 15/42 (35.7%) patients in the control group ($P<0.008$). In relation to the potential complications of thrombolysis analysed, 0/27 had a clinically significant haemorrhagic event.

Discussion

Chemical thrombolysis is a safe and effective means of achieving early myocardial reperfusion in cases where there is a predicted delay to PPCI. This can potentially lead to benefit in terms of patient mortality and overall clinical outcomes. There is currently an underutilisation of thrombolysis in STEMI care in Ireland.

Introduction

ST elevation myocardial infarction (STEMI) is a cardiac emergency which causes high rates of morbidity and mortality. Prompt intervention resulting in early cardiac reperfusion and restoration of blood flow to the infarcted myocardium is of vital importance. Multiple studies

have shown that a shorter time to reperfusion is associated with increased survival in STEMI patients [1,2,3]. Primary percutaneous coronary intervention (PPCI) performed in timely fashion, has become the international gold standard for achieving reperfusion and treating a STEMI [4]. This is because PPCI is safer and more effective than thrombolysis when both are available[5]. However, when the delay from ECG diagnosis to PPCI wire cross time is expected to be greater than 120 minutes (or ECG to arrival at catheterisation laboratory is expected to be greater than 90 minutes), the major international guidelines instead recommend using thrombolytic therapy to achieve prompt revascularisation [6].

Chemical thrombolysis involves the administration of parenteral fibrinolytic agents, with subsequent transfer to a primary PCI centre for rescue PCI if required. The potential benefit gained from early reperfusion with these agents when PPCI is not available can be great. Boersma et al analysed 22 papers and in excess of 50,000 STEMI patients who received thrombolysis. They suggested that administering thrombolytic therapy within one hour of symptom onset could save an estimated 65 lives per 1000 treated patients. This number fell to 18 lives per 1000 when the time interval was 6-12 hours after symptom onset [7]. It has also been shown that thrombolytic therapy is capable of re-establishing blood flow and coronary perfusion in up to 75% of patients when administered within 30 minutes of presentation [8]. Thrombolysis can however be associated with clinically significant bleeding events such as intracranial haemorrhage. The largest trial of thrombolytic therapy, GUSTO-I, found a 1.8 percent incidence of severe bleeding events in patients who received thrombolysis [9]. The severity of these potential side effect may cause hesitance in medical professionals to administer thrombolysis.

TIMI Coronary Flow Grade, established in the TIMI 1 trial, was designed to assess epicardial perfusion at angiography. It is scored from 0 to 3, with TIMI Flow Grade 0 representing a total occlusion and TIMI Flow Grade 3 representing normal epicardial perfusion. The TIMI Flow Grade post PCI is a powerful predictor of clinical outcome and has been validated in many clinical trials. However pre-PCI TIMI flow has also now been shown to predict positive clinical outcomes as demonstrated in a recent study by Kim et al [10].

Due to improvements in the availability of PPCI in high-income countries, rates of thrombolysis administration have reduced in the last few decades [11]. However, even in these countries with better access to PPCI, meeting the goals set out in the international guidelines in terms of time from diagnostic ECG to balloon time can prove challenging. This was demonstrated in a previous study published by our department, where we showed that over a 3-year period, only 65.3% of STEMI patients had a time from ECG to reperfusion of less than 120 minutes. Furthermore, in the patients who were technically eligible for thrombolysis

administration based on a transfer time to PPCI centre of greater than 90 minutes, only 8.7% of patients received thrombolytic therapy [12].

Our primary aim was to evaluate the efficacy of thrombolytic therapy, in terms of the pre-PCI TIMI flow grades, in a cohort of patients who were predicted to have a delayed time to PPCI and who were subsequently thrombolysed, versus those who also had a delayed time to PPCI, but were transferred directly to the PPCI facility without receiving thrombolysis. Our goal was to illustrate the efficacy of thrombolysis in achieving reperfusion with the aim of improving the numbers of STEMI patients who receive thrombolysis in line with international guidelines. Secondly, we aimed to evaluate the safety of thrombolytic therapy in the cohort of patients studied.

Methods

Patients were identified from the St. James's hospital PPCI database, derived from the National
Heartbeat Portal. This database records over 60 mandatory data points, encompassing patient characteristics, the date and time of chest pain onset, initial medical contact, reperfusion timing, and in-hospital clinical outcomes. All STEMI patients treated at an Irish hospital have this information documented on a paper pro-forma. Subsequently, this data is transferred to the electronic national database, which is managed by the National Office of Clinical Audit (NOCA). The collection of individual patient data is carried out by the clinical cardiology team and rigorously validated by a specialized cardiology nurse. The accuracy of the data was further confirmed by the study team through a robust review of the electronic and paper clinical records.

The study design was observational, and no clinical interventions were performed. Therefore, according to the local policies, approval of the local ethics committee was waived. Permission to carry out the study was obtained from St. James's hospital Research and Innovation department.

We conducted a retrospective case control study of 21 thrombolysis and 42 PPCI control patients. These patients were identified from the group of patients who had acute STEMI confirmed on admittance to St. James's Hospital from 30/6/17 to 30/6/20. The total group consisted of 1161 patients, with 29 of those having received thrombolysis. 21 thrombolysis patients were selected because their angiogram was performed directly after arrival to the PPCI centre. Each thrombolysis patient was matched by time (+/- 5% total time) from first ECG to arrival at the PPCI centre, with two control patients who had not received thrombolysis. The eligibility criteria for these patients included reporting a time from diagnostic ECG to PCI

of at least 120 minutes, implying that had this delay been foreseen and no contraindications to thrombolysis were present, they would have been candidates for thrombolytic therapy administration. An exclusion criterion for the patients in the control group was the presence of a contraindication to thrombolysis documented in their medical notes.

TIMI flow grades and total ischemic time were assessed along with impact of demographics, laboratory and procedural factors, medications and 30 day mortality. Table 2 illustrates a comparison of the baseline characteristics of the two groups.

The success of thrombolysis in achieving reperfusion in this study was assessed angiographically, using TIMI flow. We used a grading system previously validated in the TIMI trial [13]. This designated perfusion grades 0 (occluded) and 1 (minimal flow) as representative of treatment failure, versus grades 2 (partial occlusion) and 3 (complete perfusion) as representative of treatment success [13]. The individual angiograms were analysed by a consultant reviewer.

The statistical analysis was performed using SPSS 27 software. Quantitative variables were presented as mean ± standard deviation (SD) and assessed using an independent samples t-test. Categorical variables were conveyed as absolute or relative frequencies and analysed through chi-square analyses. Values of p less than 0.05 were considered statistically significant. An independent samples T test was used to assess for a statistical difference in the TIMI flow grades between the thrombolysed and control group (Table 1).

Patients were not involved in the design and conduct of this research.

Results

In the group that received thrombolysis (N=21), 6/21 (28.6%) were deemed to have had failed reperfusion, compared to 27/42 (64.3%) of the non thrombolysed group (P=<0.006). Successful reperfusion (TIMI 2/3), on the other hand was seen in 15/21 (71.4%) patients in the thrombolysed group versus only 15/42 (35.7%) patients in the control group (P<0.008). These results are illustrated below (Table 1 / Image 1).

Using TIMI flow as an indicator of reperfusion, successful reperfusion (TIMI 2/3) was seen in 15/21 (71.4%) patients in the thrombolysed group versus only 15/42 (35.7%) patients in the control group (P<0.008).

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TIMI flow before PCI	Thrombolysed, n=21	PPCI, n= 42	P value-
TIMI 0-1 flow	28.6% (6)	64.3% (27)	0.006
TIMI 2-3 flow	71.4% (15)	35.7% (15)	0.008

*Table 1: TIMI flow on initial angiography. (*P values calculated using independent samples T test to assess for statistical differences between means for independent variables).

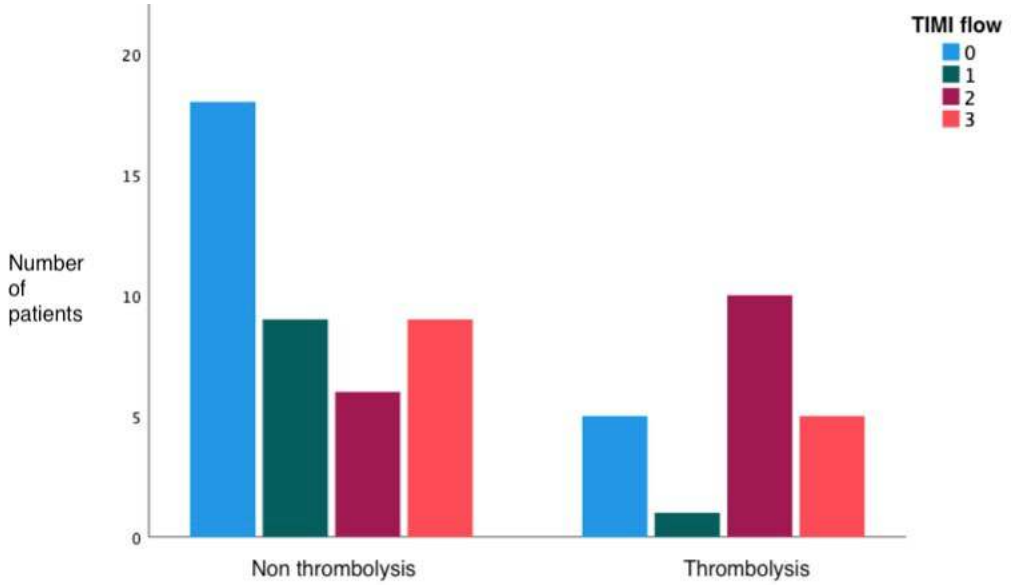

Image 1: Bar count of TIMI flow in thrombolysis vs non-thrombolysis

The baseline characteristics of this case control group are shown in image 2, including age, gender, smoking status, the prevalence of hypertension, diabetes and hypercholesterolaemia, the administration of GPIIbIIIa 1and the 30 day mortality of each group.

Characteristic	**Thrombolysed (n=21)**	**Non Thrombolysed (n=42)**	**P value**
Median time – ECG to procedure start (hr:min) [IQR]	3:38 [1:42]	3:35 [1:27]	
Age (mean)[+/-SD]	61.6 [+/-9.4]	63.7 [+/-14.0]	0.539

Male gender	85.7% (18)	71.4% (30)	0.209
Smoking (current)	23.8% (5)	28.6% (12)	0.743
Diabetes	19% (4)	21% (9)	0.271
Hypertension	23.8% (5)	33.3% (14)	0.123
Hypercholesterolaemia	33.3% (7)	45.2% (19)	0.366
GP IIbIIIa inhibitor	9.5% (2)	29% (12)	0.086
30 day mortality	10.5% (2)	9.5% (2)	0.571

Table 2: Baseline characteristics of Thrombolysed group. A Chi-square test was used to analyse.

The potential major complications of thrombolysis such as the potential for major intracranial bleeds were also analysed in this cohort. Among the 21 patients, 0 had a clinically significant haemorrhagic event.

Discussion

The time to reperfusion and completeness of reperfusion are the key determinants to the patient's clinical outcome in the treatment of STEMI. While PPCI has become the international mainstay of treatment for STEMI, the administration of chemical thrombolysis can be a crucial treatment option in achieving timely reperfusion and thus saving valuable myocardium, in those patients that have a STEMI diagnosed in a hospital situated greater than 90 minutes from a PPCI centre.

The results of this analysis suggest that thrombolysis does in fact result in reperfusion angiographically, in most patients. The clinical correlate of achieving this earlier reperfusion is likely that it will improve clinical outcomes, as it has been extensively shown the literature that delays in achieving reperfusion can result in increased mortality and morbidity [1,2,3].

While the efficacy of fibrinolysis and that of PPCI have been extensively studied in the literature, there have been few studies comparing the outcomes of patients who had a time period from first ECG to PCI of greater than 120 minutes, and were thrombolysed, with subsequent angiography on arrival to PPCI centre and those who just went directly to PPCI without thrombolytic therapy. Furthermore, we could find no previous studies that were able to illustrate the difference in perfusion through the culprit vessel, angiographically. Despite

the small sample size of the study, we believe to have shown that thrombolysis is an efficacious and convenient treatment option in patients who are outside the recommended window for PPCI. There are undoubted bleeding risks that need to be considered with the administration of thrombolysis, but the earlier reperfusion it provides and the resultant improvement in clinical outcomes for STEMI patients, mean that this is still an important tool in the emergency management of STEMI, as is reflected in the international guidelines.

There was a disparity demonstrated between the groups in relation to GP IIb3IIIa inhibitor administration. In the thrombolysed group, 2/21 (9.5%) received one of these agents versus 12/42 (29%) in the non thrombolysed group. This disparity between the groups may indicate that clinicians are hesitant to administer these drugs together because of the potential increased bleeding risk. However, there is no current contraindication between the two therapies and some research has found a beneficial effect on 30-day event-free survival rates, without a significant increase in bleeding complications [14].

Despite the small sample size in our thrombolysis group, there were no incidences of bleeding documented. This is in keeping with the rate of bleeding complications seen in the literature of around 1-2% [9].

A decline in thrombolysis administration rates has been observed across developed nations due to the improved availability and accessibility of PPCI centres [15]. We posited, that some of the potential reasons for hesitance in administering thrombolysis, even when it is indicated in the guidelines, were; the severity of potential side effects, an increasing unfamiliarity with their use given the low rates of thrombolysis and an underestimation of the time that it will take to organise and execute the transfer of the patient to the PPCI centre. It is vital that clinicians in rural centres are provided with sufficient training to provide them with the confidence and the experience to administer thrombolysis once a diagnosis of STEMI is made.

The most recent national guidelines outlined in the Optimal Reperfusion Service (ORS) protocol are aligned with the international guidelines (ESC guidelines[16]), in suggesting that patients who are have a predicted time period from first positive ECG to arrival at PPCI centre, of over 90 minutes should receive thrombolysis prior to transfer. However, as mentioned previously, analysis of data from our own tertiary PPCI centre [12] and research published from other centres in high income countries indicate that the rates of thrombolysis administration have been falling over the past few decades [15]. The results from our own 3-year service audit indicated that there is a vast underutilisation of thrombolysis in acute STEMI care in Ireland.

The limitations of this study include the small sample size studied, which was limited by the small numbers of patients who were administered thrombolysis over the 3-year period.

Secondly there were 8 other patients who were also thrombolysed in the study time period who could not be included in the analysis because they did not proceed to angiography directly after arrival to the PPCI centre. The likely reason they didn't progress to immediate angiography is because they may have had ECG or clinical evidence indicating resolution of STEMI and success of thrombolysis. This would likely have been represented on angiography as a TIMI score of II/III indicating successful reperfusion. As such we may be still underestimating the efficacy of thrombolysis.

The results of this review will be disseminated to relevant parties involved in STEMI management in Ireland, with a view to informing people of the potential benefits of thrombolytic therapy and to hopefully improve the rates of thrombolysis administration and consequently clinical outcomes for STEMI patients.

Declaration of Conflicts of Interest:
None declared.

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