Participation in thrombolytic trials delays reperfusion therapy in acute myocardial infarction

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Abstract

Background: Shortening the time delay at the beginning of treatment in ST-segment elevation myocardial infarction (STEMI) has proven to be clinically essential. Invasive vs. thrombolytic treatment strategy is currently under investigation, particularly in terms of the time from the onset of symptoms to treatment initiation. It is likely that enrolment to trials in STEMI may paradoxically prolong the time delay to treatment if randomisation procedures are too complex.

Aim: To evaluate time to the onset of reperfusion therapy (door-to-thrombolysis time — DtT) in patients randomised to trials (TT) or treated routinely with thrombolytics (Thrx).

Methods: We evaluated DtT in a group of 189 consecutive STEMI patients (TT: n = 96; Thrx: n = 93). The inclusion criteria for the analysis were identical in both groups: 1. STEMI diagnosis was given on admission. 2. Patients had no signs of heart failure. 3. Patients did not require any additional therapy prior to thrombolysis (no need for electrical cardioversion or blood pressure lowering). 4. There were no contraindications for immediate reperfusion therapy. The comparison of DtT between evaluated groups was performed. To find out the independent predictors of DtT prolongation, the impact of patients’ age, gender, admission time, pre-hospital delay and trial participation has been evaluated in multivariate analysis.

Results: Highly statistically longer mean value of DtT was measured in the entire TT group than in Thrx (41 ± 18 vs. 22 ± 8 min; p < 0.001). The difference was also significant for patients who constituted the subgroup of TT who were proposed and refused to participate in trials (37 ± 13 vs. 22 ± 8 min; p < 0.01). No differences in DtT were found between groups of patients enrolled to various trials. The participation in TT was found to be the strongest predictor of DtT prolongation over 30 min (OR 13.2; 95% CI 6.1–28.5; p < 0.001). The risk of over 30 min DtT prolongation was five times higher if patients were admitted in an early phase of the trial.

Conclusions: 1. Participating in trials delays the beginning of reperfusion therapy. 2. This delay may be clinically important, particularly in patients hospitalised in a very early phase of STEMI. 3. The call for reappraisal of informed consent issues and randomisation procedures in the context of simplicity seems to be justified.

Key words: myocardial infarction, thrombolysis, delay
tality reduction in the treatment of STEMI [1–4]. It has been extensively proved that the effectiveness of reperfusion strategies, thrombolytic therapy and primary percutaneous coronary intervention is reversibly correlated with the time-delay: “time is muscle” and “every minute counts” [1–7].

According to the ESC and ACC/AHA guidelines, both strategies are equally effective in the management of patients with STEMI admitted within the first 2 h of the onset of symptoms [8]. It may be anticipated that this recommendation will trigger the initiation of further trials investigating optimal reperfusion strategies, particularly in terms of time from the onset of symptoms to the beginning of treatment [9–11]. The value of clinical studies in the development of strategies to reduce mortality and morbidity from cardiovascular disease is beyond dispute. However, it is likely that the enrolment of patients with STEMI to such trials may paradoxically prolong the time delay to treatment if the enrolment procedure (including informed consent), randomisation and drug preparation process is too complex. Numerous studies have focused on avoidable components of the time delay [12–18]. The pre-hospital patient-dependent phase has been mainly emphasised as a factor. However, the in-hospital component of the delay in the initiation of reperfusion therapy after hospital arrival is less studied, especially in the setting of randomised trials [19, 20].

The aim of this study was to evaluate the in-hospital time delay of the onset of reperfusion therapy in patients taking part in multicentre, randomised, thrombolytic trials performed in our institution and patients treated routinely with thrombolytics.

**METHODS**

**Patient population**

A group of 198 consecutive patients comprised our study population. The characteristics of the study group are presented in Table 1. The exclusion and inclusion criteria for the selection of patients suitable for this analysis were identical for patients treated routinely with thrombolytic therapy and for patients treated according to the protocols of the studies. The patients were available for analysis if STEMI was undisputedly diagnosed in the emergency department. The study group consisted of patients who presented within 12 h of the onset of symptoms with no contraindications for immediate thrombolysis. Patients with shock or any signs of heart failure (Killip > 1), arrhythmia or high blood pressure requiring treatment prior to reperfusion therapy and prolonging the time to the beginning of thrombolysis, were excluded. The thrombolytic therapy was initiated in the cardiac care unit (CCU) following immediate transfer from the emergency department. The study population consisted of two subgroups: 102 patients were randomised to three thrombolytic trials (TT). This subgroup included also nine patients who were proposed to participate in the trials but finally refused (analysis of intention to treat); 96 patients had not received the proposal to participate in the study and were treated routinely with thrombolytic therapy at the time when no study was conducted in our institution (Thrx).

**Time variables**

Based on the computed database and on data retrieved from medical charts, we retrospectively analysed the time elapsed from hospital admission to the beginning of thrombolytic therapy — the door-to-thrombolysis time (DtT). We compared the percentage of patients treated with DtT for longer than a median time delay as well as the mean values of DtT in both evaluated groups (TT and Thrx). DtT was also analysed separately in younger and older subgroups of patients (≤ 60 and > 60 years of age) and separately for patients admitted and treated at different times of day. To depict the independent predictors of DtT prolongation, the impact of patient’s age and gender, admission time (i.e. times of single-physician duty and night-time admissions), pre-hospital delay, and trial participation had all been evaluated in multivariate analysis.

**Statistical analysis**

The comparison of nonparametric data was performed by Mann-Whitney test and χ² test. The parametric parameters of both evaluated groups were compared by t-Student’s test. The influence of chosen covariates on odds of late treatment administration was examined by the multivariate logistic regression model. Backward selection procedure with 0.1 level for staying in the model was applied to choose significant

<table>
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<th>Table 1. Baseline characteristics of the study group</th>
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<td><strong>Characteristics</strong></td>
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<td>Total patients</td>
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<tr>
<td>Age:</td>
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<tr>
<td>Mean ± SD [years]</td>
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<td>Gender [males]</td>
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<td>Admission time:</td>
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<td>Mode of treatment:</td>
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<tr>
<td>Thrx</td>
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<td>Trial A</td>
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<td>Trial C</td>
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<td>Refused trial participation</td>
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Thrx — routine thrombolytic treatment
covariates at 5% level of significance. Model’s goodness-of-fit was checked by Hosmer-Lemeshow statistics. Calculations were done in Stata v. 8.2

**RESULTS**

**Univariate analyses**

The median time (25%, 75%) in the entire study group was 30 (20, 40) minutes, ranging from 10 (minimum) to 120 (maximum) minutes. The percentage of patients with DtT longer than median time delay was 11% (n = 11) in Thrx and 60% (n = 60) in TT (p < 0.001). Conversely, if a very short DtT (below 20 min) was analysed, the percentage of patients in Thrx was 56% (n = 54) and 9% (n = 9) in TT (p < 0.001). There was no difference in the mean value of DtT between three evaluated trials (trial A: 40 ± 11; trial B: 41 ± 16; trial C: 41 ± 22; NS). Highly statistically longer mean value of DtT was measured in the entire TT group than in Thrx. The difference was also significant for patients who constituted the subgroup of TT who were proposed and refused to participate in trials (Fig. 1).

The unfavourable for TT difference in the mean value of DtT was found in a whole spectrum of day-time and night-time admissions. In subgroups of younger as well as older patients, the mean value of DtT was also significantly longer in TT (Table 2).

**Multivariate analyses**

Among six factors possibly influencing the delay to treatment, the participation in TT was found to be the strongest predictor of DtT prolongation over 30 min (OR 13.2; 95% CI 6.1–28.5; p < 0.001). The median time (25%, 75%) of trial duration in our department was 124 (59, 171) days. To study the impact of trial duration on the risk of treatment delay lengthening, the TT group was divided into two subgroups of patients admitted early or late during the trial (before or after the median time of the trial duration). The risk of over 30 min DtT prolongation was five times higher if patients were admitted in an early phase of our department’s participation in the trial (Table 3). In the evaluated study group, 81% of patients were admitted to hospital when only one CCU physician was on duty (afternoon and night shifts between 2pm and 8am, holidays and weekends). Single physician duty was found to be a second, independent predictor of DtT prolongation, although with a ten times lower risk of delay than early participation in a trial (Table 3).

**DISCUSSION**

**The treatment delay**

The lifesaving potential of reperfusion therapy in STEMI is limited by the failure to initiate treatment early. Unfortunately, patients fail to react appropriately to symptoms, pre-hospital electrocardiograms are not widely used, and time to treatment after hospital arrival is too long [13, 14]. The GISSI study showed nicely that if the patient is treated within the first hour, the
mortality reduction reaches 47%, while if the treatment is delivered within 3 h, the mortality reduction is 23%. Further delay decreases the mortality reduction to 17% [21]. This result was confirmed by Boersma et al. [3]. The benefit of fibrinolytic therapy was 65, 37, 26 and 29 lives saved per 1,000 patients treated in the 0–1, 1–2, 2–3 and 3–6 h intervals [3]. According to the results of the GREAT study, every additional hour of delay in patients presenting 2 h after symptom onset leads to the loss of 21 lives per 1,000 within 30 days and 69 lives per 1,000 within 30 months [22]. This is true not only for thrombolytic therapy, but also for primary angioplasty. De Luca et al. [6] showed clearly that the risk of one-year mortality increases by 7.5% for each 30-min delay. These results bring the conclusion that “thrombolytic therapy in STEMI should be accorded the same degree of urgency as the treatment of cardiac arrest” [22]. Numerous studies have aimed to establish the independent factors leading to extension of the time delay to proper treatment initiation [12–18]. As a consequence, effective, educational programmes for the lay public have been implemented to speed up the pre-hospital phase. Furthermore, monitoring of medical staff performance led to various strategies simplifying and improving the in-hospital procedures to avoid unacceptable in-hospital delays. These have been widely implemented and have resulted in shortening of in-hospital time delay to about 20 min [23, 24]. On the other hand, however, the protocols of randomised trials made the in-hospital phase more complicated, putting into question the effects of previous strategies.

In our study, we showed a doubled mean in-hospital delay time in patients randomised to TT. The question as to whether participation of patients with STEMI in a trial influences outcome has surprisingly not been widely studied. The study by Vist et al. [19] was aimed at comparing the outcomes of participants in randomised trials to those in comparable non-participants who received the same or similar treatment. The comparisons of those trials in which patients were given the option of participating or not, provided limited information because of the small sample, and the question remained open.

In the study by McKendall et al. [20], the authors did not find a difference in time delay to treatment initiation between the routinely treated group and patients recruited into the trials. However, the groups were not comparable according to inclusion and exclusion criteria. The routinely treated group consisted of consecutive patients, including also individuals with shock, pulmonary oedema, arrhythmia requiring electrical therapy, or highly elevated blood pressure; these are cases where a decision regarding immediate fibrinolysis is usually difficult and delay is clinically justified. On the other hand, according to the trials’ protocols, patients with the abovementioned complications could not be included into the trials due to the exclusion criteria. In our study, this bias was avoided by the implementation of identical inclusion and exclusion criteria for both groups.

Clinical importance

The proportion of patients with a short pre-hospital delay recruited into the trials is usually high. Fifty per cent of our study population was hospitalised within 2 h of the onset of chest pain. The use of newly developed and potentially more effective drugs obviously raises the question of the risk/benefit ratio of individual trial participants, but certainly does not refer to patients randomised to the standard therapy arm, where this risk cannot be counterbalanced.

Avoidable factors influencing time delay

Based on results of the regression analysis, early participation in the trial carries the highest risk of treatment delay. This risk is five times lower if the randomisation takes place later on, when the CCU staff have become used to the study protocol procedures, indicating the importance of proper training with randomisation procedures and drug preparation.

This brings us back to the question of a need for simplicity in times when easily accessible old-fashioned books with randomising numbers are replaced by time-consuming long-distance calls to randomisation machines. It also gives rise to another unpopular suggestion for fewer centres and a longer series of patients at a centre, things that unfortunately might lead to the prolongation of a trial and increased costs. However, the consistency of results in subgroups analyses in our study, showing the power of this potentially modifiable factor (independent of age, gender, time of admission or pre-hospital delay), strengthens its importance.

Informed consent

The significantly longer time delay to reperfusion therapy in the subgroup of patients who were proposed and finally refused to participate in trials highlights the issue of informed consent. There is a general opinion among researchers that the involvement of a patient in a consent process in an emergency situation is an empty ritual [25].

The question as to whether a patient in an acute situation is actually able to give his or her valid informed consent has been raised in numerous studies. Based on the population of patients randomised to the OASIS-2 and PARAGON trials, Kucia et al. [26] showed that the level of protocol understanding reaches only 52%, with far greater impairment of knowledge of risk than of benefit. Similar results were reported in the HERO-2 consent substudy. The authors concluded that most patients with acute coronary syndromes recruited to randomised trials may be incapable of giving informed consent [27]. Regulation 21CFR50.24 of the Food and Drug Administration states that: “obtaining informed consent is not feasible when the subjects are not able to give their informed consent as a result of their medical condition”. Our data opens the discussion as to whether research without consent could be legally performed in patients hospitalised for acute coronary syndromes.
We showed that this theoretically low-risk procedure of achieving a written form of patient agreement may in fact lead to an increased risk of delay in receiving the reperfusion therapy, with all the consequences this entails. Current practice, which forces the patient to read pages of informed consent at a time of heavy chest pain, is legally justified, but it appears to be illogical and, based on our results, potentially harmful.

CONCLUSIONS

Randomised, multicentre, placebo-controlled trials are currently commonly used as a principal tool for proving the effectiveness of newly developed drugs or treatment techniques. Their value in terms of judging medical treatments is indisputable. Their positive results bring new treatment modalities to the medical world, which help people to live longer.

However, the results of our study show that participating in trials in the acute phase of STEMI carries the risk of receiving reperfusion therapy with a longer delay. Our study is small, and not powered for definite conclusions with regards to the major adverse cardiac events this delay could lead to.

However, well known relations between the time delay of reperfusion therapy and mortality reduction lead us to suspect that lengthening of the delay due to participation in randomised trials may be clinically important, especially in a very early phase of STEMI. The call for reappraisal of informed consent issues and randomisation procedures seems to be justified.

Conflict of interest: none declared

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Udział w badaniach klinicznych opóźnia leczenie reperfuzjne w ostrym zawale serca

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Streszczenie

Wstęp: Skrócenie czasu opóźnienia leczenia reperfuzjnego w zawale serca z przetwórnym uniesieniem odcinka ST (STEMI) ma podstawowe znaczenie dla skuteczności terapii. Nadal trwają badania porównujące różne strategie leczenia reperfuzjnego, przede wszystkim w kontekście czasu upływającego od początku wystąpienia dolegliwości do rozpoczęcia reperfuzji. Prawdopodobnie udział w badaniach klinicznych w STEMI może prowadzić, w przypadku gdy procedura randomizacyjna jest zbyt skomplikowana, do zwiększenia opóźnienia reperfuzji.

Cel: Celem badania było porównanie czasu od przybycia do szpitala do rozpoczęcia wlewu leku fibrynolitycznego (DtT) u chorych objętych badaniami klinicznymi (TT) i u pacjentów leczonych rutynowo fibrynolitycznie (Thrx).

Metody: Badaniami objęto 189 kolejnych chorych z STEMI (grupa TT: n = 96; grupa Thrx: n = 93). Kryteria włączenia do badania były jednakowe w obu grupach: rozpoznanie STEMI przy przyjęciu do szpitala; brak objawów niewydolności serca; brak konieczności zastosowania dodatkowej terapii przed podaniem leku fibrynolitycznego (w tym brak wskazań do kardiowersji lub leczenia hipotensyjnego); brak przeciwwskazań do natychmiastowej terapii reperfuzjnej. Porównano DtT w obu grupach. Za pomocą analizy wieloczynnikowej określono wpływ wieku chorych, płci, czasu przyjęcia, opóźnienia przedszpitalnego i udziału w badaniach klinicznych na DtT.

Wyniki: W całej grupie TT stwierdzono statystycznie istotnie dłuższy DtT niż w grupie Thrx (odpowiednio: 41 ± 18 v. 22 ± 8 min; p < 0,001). Również w grupie chorych, którym proponowano udział w badaniach klinicznych, ale nie wyrazili na to zgody, DtT był statystycznie istotnie dłuższy niż w grupie Thrx (37 ± 13 v. 22 ± 8 min; p < 0,01). Rodzaj badania klinicznego nie wpływał istotnie na DtT. Udział w badaniu klinicznym był najistotniejszym predyktorem wyników w kontekście opóźnienia DtT o ponad 30 min (OR 13.2; 95% CI 6,1–28,5; p < 0,001). Ryzyko wydłużenia DtT o ponad 30 min było 5-krotnie większe w początkowym okresie badań klinicznych.

Wnioski: 1. Udział w badaniach klinicznych opóźnia rozpoczęcie terapii reperfuzjnej. 2. Opóźnienie to może być szczególnie istotne u chorych hospitalizowanych we wcześniejszej fazie zawalu serca. 3. Wskazana jest weryfikacja stosowanych procedur randomizacyjnych i uzyskiwania świadomej zgody chorego w kierunku ich uproszczenia.

Słowa kluczowe: zawal serca, leczenie fibrynolityczne, opóźnienie

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