Multicentre randomized trial comparing transport to primary angioplasty vs immediate thrombolysis vs combined strategy for patients with acute myocardial infarction presenting to a community hospital without a catheterization laboratory

The PRAGUE Study

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Background Primary coronary angioplasty is an effective reperfusion strategy in acute myocardial infarction. However, its availability is limited, and transporting patients to an angioplasty centre in the acute phase of myocardial infarction has not yet been proved safe.

Methods The PRAGUE study (PRimary Angioplasty in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis) compared three reperfusion strategies in patients with acute myocardial infarction, presenting within 6 h of symptom onset at community hospitals without a catheterization laboratory: group A — thrombolytic therapy in community hospitals (n=99), group B — thrombolytic therapy during transportation to angioplasty (n=100), group C — immediate transportation for primary angioplasty without pre-treatment with thrombolysis (n=101).

Results No complications occurred during transportation in group C. Two ventricular fibrillations occurred during transportation in group B. Median admission–reperfusion time in transported patients (group B 106 min, group C 96 min) compared favourably with the anticipated >90 min in group A. The combined primary end-point (death/reinfarction/stroke at 30 days) was less frequent in group C (8%) compared to groups B (15%) and A (23%, P<0·02). The incidence of reinfarction was markedly reduced by transport to primary angioplasty (1% in group C vs 7% in group B vs 10% in group A, P<0·03).

Conclusions Transferring patients from community hospitals to a tertiary angioplasty centre in the acute phase of myocardial infarction is feasible and safe. This strategy is associated with a significant reduction in the incidence of reinfarction and the combined clinical end-point of death/reinfarction/stroke at 30 days when compared to standard thrombolytic therapy at the community hospital.

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Key Words: acute myocardial infarction, reperfusion, thrombolysis, transport, primary coronary angioplasty.

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Introduction

In-hospital mortality from acute myocardial infarction has decreased dramatically during the last 30 years as a result of several major achievements: organization of
**Table 1  Treatment arms (reperfusion strategies)**

<table>
<thead>
<tr>
<th>Group A (Thrombolysis)</th>
<th>Group B (Thrombolysis+PTCA)</th>
<th>Group C (PTCA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient stays in the primary hospital</td>
<td>Transport to PTCA centre immediately after beginning of thrombolysis</td>
<td>Transport to PTCA centre immediately after randomization</td>
</tr>
<tr>
<td>Lysin salicylate 900 mg i.v.</td>
<td>Lysin salicylate 900 mg i.v.</td>
<td>Lysin salicylate 900 mg i.v.</td>
</tr>
<tr>
<td>Streptokinase 1.5 ml U⁻¹ i.v. 45–60 min</td>
<td>Streptokinase idem+PTCA/stent if significant obstruction persists</td>
<td>Heparin 10 000 U i.v.</td>
</tr>
<tr>
<td>Ticlopidin 500 mg for 1 month</td>
<td>Ticlopidin 500 mg for 1 month</td>
<td>PTCA/stent+additional</td>
</tr>
<tr>
<td>Fraxiparin 0.8 ml s⁻¹ for 3 days</td>
<td>Fraxiparin 0.8 ml s⁻¹ for 3 days</td>
<td>Heparin (5000 U)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ticlopidin 500 mg for 1 month</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fraxiparin 0.8 ml s⁻¹ for 3 days</td>
</tr>
</tbody>
</table>

The coordinating site was at the Cardiocenter, University Hospital Vinohrady, Prague, which was also one of the four participating angioplasty centres. Since 1995–96 all four angioplasty centres have routinely used primary coronary angioplasty in all patients attending the centres from their respective primary care region. Seventeen community hospitals without catheterization facilities were the primary sites; here patients were enrolled into the study immediately after the initial electrocardiogram and after obtaining informed consent.

**Randomization and the treatment arms**

Patients were randomized by telephone into one of the three arms (Table 1).

**Patients**

During the study period (1 June 1997–23 March 1999) a total of 1588 patients with acute myocardial infarction and ST elevations or bundle branch block presented to the emergency departments of 17 participating community hospitals, which did not have catheterization laboratories. Three hundred of these patients were patients with acute myocardial infarction presenting initially to regional hospitals without catheterization laboratories in the Czech Republic. This is the first randomized study of transport to an angioplasty centre in comparison to receiving thrombolysis. The aim was to compare three reperfusion strategies: ‘classical’ treatment routinely used in this country (intravenous streptokinase) vs transport to primary coronary angioplasty vs a combined approach (thrombolysis during the transport to immediate coronary angioplasty).
finally randomized into the study. The reasons for not randomizing the remaining 1288 patients are listed in Table 2. During the same period, 773 other patients presented directly to the four participating angioplasty centres. They were not randomized, were treated routinely with primary angioplasty and are not part of this study. The routine workload of the angioplasty centres are briefly described in Table 3. The inclusion criteria were: acute myocardial infarction (ST elevations >1 mm in at least two leads or a new bundle branch block on the initial electrocardiogram), less than 6 h after onset of symptoms; time to angioplasty centre <60 min (it was <75 km in all participating hospitals), feasibility to begin the transport to the centre within 30 min of randomization, signed written informed consent. Exclusion criteria were: contraindication to thrombolysis and absence of bilateral femoral artery pulsations. Between 2 June 1997 and 23 March 1999 300 patients were randomized (Table 4).

**Coronary interventional procedure**

Coronary angiography in groups B and C was performed via the femoral artery. The procedure was begun by visualization of the ‘non-infarct’ coronary artery, using a diagnostic 5–6 F catheter and immediately thereafter the guiding catheter, 6–8 F, was used to visualize the ‘infarct’ artery followed by angioplasty/stent. According to the protocol, angioplasty was performed in all patients with TIMI flow 0–2 in the ‘infarct’ artery. In case of TIMI flow 3, the decision to perform acute angioplasty was left to the discretion of the operator. Stenting was performed whenever anatomically suitable (>2.5 mm in diameter, no extreme tortuosity), or when there was a suboptimal result (as assessed by the operator) after balloon angioplasty.

**Examinations and follow-up**

Complete clinical examination with electrocardiogram was performed on days 1, 2, 3, at discharge and on day 30. Echocardiography was performed on day 30.

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**Table 2** Reasons for excluding patients with acute myocardial infarction from the study

<table>
<thead>
<tr>
<th>Reason for not randomizing patients presenting to the 17 participating community hospitals (n=1288, mean age 67 years)</th>
<th>No of patients</th>
<th>In-hospital mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;6 h from the onset of symptoms</td>
<td>810</td>
<td>17</td>
</tr>
<tr>
<td>Patient did not agree to participate</td>
<td>125</td>
<td>6</td>
</tr>
<tr>
<td>Terminal phase of cardiogenic shock</td>
<td>83</td>
<td>67</td>
</tr>
<tr>
<td>Contraindication to thrombolysis</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Problems with transport (emergency ambulance not immediately available, etc.)</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Absence of femoral artery pulses</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>252</td>
<td>16</td>
</tr>
<tr>
<td>Total all not randomized patients with Q infarctions</td>
<td>1288</td>
<td>19</td>
</tr>
<tr>
<td>Randomized patients</td>
<td>300</td>
<td>11</td>
</tr>
</tbody>
</table>

**Table 3** Routine primary PTCA results in the participating PTCA centres during the study period (primary admissions, non-transported patients, are NOT part of the study population)

<table>
<thead>
<tr>
<th>1 June 1997–23 March 1999</th>
<th>Primary/rescue PTCA for AMI (n=)</th>
<th>Morphologic success rate (%)</th>
<th>In-hospital mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centre no. 1</td>
<td>288</td>
<td>93</td>
<td>5.5</td>
</tr>
<tr>
<td>Centre no. 2</td>
<td>158</td>
<td>91</td>
<td>7.7</td>
</tr>
<tr>
<td>Centre no. 3</td>
<td>220</td>
<td>98</td>
<td>2.7</td>
</tr>
<tr>
<td>Centre no. 4</td>
<td>107</td>
<td>93</td>
<td>7.4</td>
</tr>
<tr>
<td>Total</td>
<td>773</td>
<td>94</td>
<td>5.4</td>
</tr>
</tbody>
</table>

**Table 4** Patients baseline characteristics

<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of randomized patients</td>
<td>99</td>
<td>100</td>
</tr>
<tr>
<td>Males (%)</td>
<td>68</td>
<td>73</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>61 ± 10</td>
<td>62 ± 11</td>
</tr>
<tr>
<td>Anterior infarction (%)</td>
<td>43</td>
<td>54</td>
</tr>
<tr>
<td>Previous infarction (%)</td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td>Heart failure (Killip II–IV) at initial presentation (%)</td>
<td>21</td>
<td>20</td>
</tr>
</tbody>
</table>
Coronary angiography was performed immediately after arrival in the angioplasty centre in groups B and C. In group A (as well as any repeat angiography in groups B and C) it was performed according to routine clinical indications: post-infarction unstable angina pectoris, reinfarction, rescue angioplasty after failed thrombolysis. Further follow-up (1 year) is under way, but not yet completed and is not the subject of this paper.

Study end-points and definitions

**Death**
Death was defined as death from any cause within 30 days of randomization.

**Reinfarction**
Recurrent myocardial infarction was defined as recurrent symptoms of myocardial infarction with a more than double increase in the level of creatine kinase MB and/or new electrocardiographic changes.

**Stroke** was defined as any new neurological deficit lasting >24 h.

**Procedural success** was defined as TIMI-3 flow and <50% stenosis after the intervention.

**Procedural complications** were defined as procedure-related death within 24 h, need for an additional intervention (e.g. bypass surgery, pericardiocentesis or vascular surgery) and need for transfusion.

**Statistic assessment**
Patients were analysed on the intention-to-treat principle. Statistical comparisons between groups were performed using the chi-square statistics for categorical variables.

**Results**

**Transport: complications and time delays**
All 201 patients in groups B and C were transported immediately after randomization. The distances between primary hospitals and angioplasty centres varied between 5–74 km. There was no death and only two ventricular fibrillations (successfully treated with defibrillation in the emergency ambulance car) during the transport or within 30 min after transport. In two patients, Killip class worsened during transport from class II to pre-angioplasty class IV. One had a left main coronary artery occlusion and the other an ostial left anterior descending occlusion. The transport times are shown in Fig. 1.
Results and complications of coronary angiography, angioplasty and thrombolysis

TIMI flow at the initial angiogram (pre-angioplasty) and immediately after angioplasty is shown in Fig. 2. Angioplasty was performed acutely in 82 group B patients and in 91 group C patients. Two group B and two group C patients had <50% stenosis in all three coronary arteries (two had definite myocardial infarction by biochemical and electrocardiographic criteria, another two had a false diagnosis of infarction). Twenty-four patients from both groups had TIMI-3 flow after medication and anatomy not suitable for angioplasty (most had three-vessel disease and were scheduled for elective bypass surgery later). The overall technical success rate of the interventions was 91% in group B and 92% in group C. Stents were implanted in 79% of all acute interventions in each group. Significant procedure-related complications occurred in one patient in group A (rescue angioplasty), in two patients in group B and in two patients in group C. Intracranial bleeding occurred in one patient (group B).

Clinical outcome at 30 days

Table 5 shows the mortality, reinfarction and stroke at 30 days. The reduction in the combined primary endpoint (death/reinfarction/stroke) by using the transport strategy is shown in Fig. 3. Stent thrombosis occurred in five group B patients (incidence 8.1% among 62 stented patients) compared to only one group C patient (incidence 1.4% among 70 stented patients). Three of the five group B patients died due to the reinfarction caused by this stent thrombosis. Fatal bleeding complications and/or fatal cardiac tamponade relating to the treatment used is shown in Fig. 4. Additional revascularization procedures (not those prescribed by the protocol) during the initial 30 days are shown in Table 6. All these procedures were performed because of ongoing infarction (rescue angioplasty in group A), reinfarction or unstable angina pectoris.

Discussion

Feasibility and safety of transport in the acute phase of myocardial infarction

Several non-randomized observational reports[18–21] have confirmed the feasibility and safety of transporting patients to the catheterization laboratory for primary PTCA and percutaneous transluminal coronary angioplasty (PTCA) if they are in a state of shock or coma. In the PRAGUE Study, the transport strategy was used to achieve a higher rate of IMI-3 flow immediately after PTCA in group B compared to group C. The mortality, reinfarction and stroke at 30 days are shown in Table 5. The reduction in the combined primary endpoint (death/reinfarction/stroke) by using the transport strategy is shown in Fig. 3. Stent thrombosis occurred in five group B patients (incidence 8.1% among 62 stented patients) compared to only one group C patient (incidence 1.4% among 70 stented patients). Three of the five group B patients died due to the reinfarction caused by this stent thrombosis. Fatal bleeding complications and/or fatal cardiac tamponade relating to the treatment used is shown in Fig. 4. Additional revascularization procedures (not those prescribed by the protocol) during the initial 30 days are shown in Table 6. All these procedures were performed because of ongoing infarction (rescue angioplasty in group A), reinfarction or unstable angina pectoris.

Table 5 Mortality, reinfarction and stroke at 30 days

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>14%</td>
<td>12%</td>
<td>7%</td>
</tr>
<tr>
<td>Reinfarction</td>
<td>10%</td>
<td>7%</td>
<td>1%*</td>
</tr>
<tr>
<td>Stroke</td>
<td>1%</td>
<td>3%</td>
<td>0</td>
</tr>
</tbody>
</table>

*P<0.03.
patients with acute myocardial infarction to tertiary centres for primary (or rescue) coronary angioplasty. However, this is the first randomized trial, proving clinical benefit from transport for primary angioplasty over ‘classical’ treatment, i.e. intravenous thrombolysis in the community hospital. Transporting a patient to a distant angioplasty centre probably carries less risk than thrombolysis (the risk of major bleeding complications after thrombolysis seems to be higher than the risk of transport complications).

Potential reperfusion delay caused by transport

The published data are controversial in this respect. Evidence has accumulated, that ischaemic time is related to infarct size and to clinical outcome[16,22–25]. It has been shown that delayed thrombolysis is associated with decreased clinical benefit[25]. However, primary angioplasty performed later (i.e. between 6–12 h of the onset of symptoms) has a similar success rate and a similar clinical outcome to that of patients presenting between 2–6 h[17,26–28].

Mortality analysis

The slightly higher mortality in this study compared to other studies can be explained mainly by the

<table>
<thead>
<tr>
<th>Additional revascularization procedures within 30 days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group A</strong></td>
</tr>
<tr>
<td>Angioplasty</td>
</tr>
<tr>
<td>(incl. 7 rescue)</td>
</tr>
<tr>
<td>Bypass surgery</td>
</tr>
</tbody>
</table>
characteristics of the patients on admission. Our population was older (there was no age limit in this study), had more anterior infarctions and there were more heart failure patients (Killip class II–IV on admission). These factors have been shown previously to have a major impact on prognosis[90]. Transportation strategy decreased the mortality from 14% (group A) to 7% (group C); however, due to the small sample size this difference was not significant. Mortality of non-randomized registry patients was 19% (Table 2).

Role of centre/operator experience

There were differences between the participating angioplasty centres: the two most experienced centres had a mortality of 0% for group C and 4–7% for group B patients, while in the other two angioplasty centres this was 9–12% in group C and 16–22% in group B. The success rate of primary angioplasty varied between the four participating centres from 71% (in a centre, which had performed only 17 interventions) to 98%. The numbers are too small for subgroup analysis. However, two risk factors may have contributed to the low success rate: the low total number of primary angioplasties per year (the centre with the 71% success rate performs around 80 acute procedures yearly, while another three centres with a success rate of 86–98% performed c. 150 primary angioplasties per year) and inexperienced operators (the best enrolling centre started the study with three of four interventionalists having limited experience: the success rate in this centre during the first year was 82% and rose to 95% in the second year, corresponding to the improved experience of these operators). This is in accordance with the ACC/AHA guidelines for the treatment of acute myocardial infarction[90] as follows: Class I indication for primary angioplasty is fulfilled when it can be performed by experienced personnel within 90 min of diagnosis.

The use of stents

The relatively high use of stents in this study was based on the protocol (see the Method section). Only small or markedly tortuous vessels were not stented. The interesting observation is the higher frequency of stent thrombosis after streptokinase compared to primary angioplasty without previous thrombolysis. Whether this is due to rebound platelet hyperactivity remains to be established.

Combination of thrombolysis with immediate transport for angioplasty

Another limitation of this study is that the thrombolytic arm was represented by streptokinase rather than more potent thrombolytic agents. Streptokinase is used routinely in the treatment of myocardial infarction in the Czech Republic. However, the use of a more potent thrombolytic would probably not substantially affect the main results of the study (the difference between tPA and streptokinase could be hardly expected in the population of 100 patients in group A). The use of heparin in the catheterization laboratory in conjunction with thrombolysis contributed to two haemorrhagic complications: one patient in group B died 5 h after angioplasty from intracranial bleeding and another patient in group C received streptokinase after unsuccessful angioplasty on top of 15,000 units of heparin and died from haemopericardium.

Although the benefits of primary angioplasty have clearly been demonstrated, the use of thrombolysis during immediate transport for angioplasty (group B) remains controversial. The aim was to reassess this combination 10 years after the negative results of larger studies[31–34] — in the era of stents, better balloons, and with the belief that angioplasty will be performed much earlier in the course of infarction (due to the protocol: transport directly to a cath lab during the infusion of streptokinase) than in previous trials. However, the results of the combined strategy (group B) were disappointing. Although angioplasty was performed c. 1 h after the beginning of the streptokinase infusion and opened more than twice as many vessels than with the streptokinase infusion, this did not result in better patient outcome. Clinical outcomes in group B did not differ significantly from group A. The explanation is difficult and complex — resulting from a combination of several negative factors: more bleeding complications when streptokinase is combined with heparin given in the cath lab (see the two cases described above and see also Fig. 4), and more reinfarctions (including stent thrombosis) and strokes. The delay caused by preparing and starting the streptokinase infusion before transport was relatively short and was unlikely to have influenced these results. The comparison of infarct vessel patency with the initial coronary angiogram (before angioplasty) in groups B and C is interesting. Streptokinase opened only 20% more vessels compared to intravenous aspirin and heparin (47% vs 27% TIMI-flow 2–3 in groups B vs C). Thus, this study confirmed the results of previous studies: even in the era of stents and sophisticated balloon technology and despite the fastest possible strategy the combination of thrombolysis and angioplasty is not beneficial for every patient. The value of rescue angioplasty cannot be assessed from this study due to the small number of such patients in group A.

Future reperfusion strategies

The data favouring primary angioplasty as the best reperfusion strategy for patients with acute myocardial infarction are accumulating. It is true to say, that primary angioplasty is the treatment of choice for all patients with ST elevations or new bundle branch block, whenever it can be performed by an experienced team.

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within a reasonable time. How to define an ‘experienced team’ and a ‘reasonable time delay’ remains to be established. Based on our data, we can confirm that a reasonable time delay is at least 90 min from the diagnosis, as recommended by ACC/AHA[29]. An intervention team may be considered as ‘experienced’ for this purpose after 1 year of non-stop service performing primary angioplasties if more than 100 primary angioplasties are carried out in this 1 year (with >30 primary angioplasty cases done by each operator per year). In future, primary angioplasty should be carried out in high volume angioplasty centres, with thrombolysis reserved for regions with very difficult and untimely access to the nearest angioplasty centre. It is very likely that approximately 50% of all patients suitable for any type of reperfusion will be treated by primary angioplasty in the near future, depending on the economic conditions in each country. Future studies will also elucidate whether intravenous GP IIb/IIIa inhibitors given before/during the transport with or without reduced dose thrombolytics can further improve the outcome of primary angioplasty patients in this setting. This may be the case for longer transport distances.

The authors express thanks to the physicians, nurses and technicians of participating catheterization laboratories, coronary care units and regional emergency medical services.

References


Appendix

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