REVIEW ARTICLE

Drip-and-ship for acute ST-segment myocardial infarction

The pharmacoinvasive strategy for patients treated with fibrinolytic therapy

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KEY WORDS

angioplasty, myocardial infarction, thrombolysis

ABSTRACT

Primary percutaneous coronary intervention (PCI) has been demonstrated to be superior to fibrinolytic therapy in reducing mortality in ST-segment elevation myocardial infarction (STEMI) when it can be performed rapidly. However, many STEMI patients present to hospitals without PCI capability and often cannot undergo PCI within the guideline-recommended timelines; instead, they receive fibrinolysis as the initial reperfusion therapy. Several studies have explored the potential of combining the best of both therapies by performing PCI soon after fibrinolysis, including TRANSFER-AMI (Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction). Patients (n = 1059) with anterior or high-risk inferior STEMI presenting to non-PCI centers within 12 h of symptom onset treated with tenecteplase and other standard antithrombotic therapies were randomized to either a pharmacoinvasive strategy (urgent transfer, angiography and PCI when appropriate within 6 h) or standard treatment (including rescue PCI, or angiography and PCI when appropriate beyond 24 h). The composite primary endpoint of 30-day death, reinfarction, recurrent ischemia, new or worsening heart failure, and cardiogenic shock occurred less frequently in the routine early PCI patients compared to the standard treatment patients (11.0% vs. 17.2%, $P = 0.004$). Based upon these findings, consistent with other studies, we believe that STEMI patients who cannot undergo timely primary PCI should receive prompt fibrinolysis followed by initiation of an immediate transfer to a PCI-capable hospital without waiting to see whether reperfusion is successful.

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Acute ST-segment elevation myocardial infarction (STEMI) is caused by disruption of coronary artery plaque with exposure of substances that promote platelet activation, adhesion, and aggregation, thrombin generation, and thrombus formation leading to an occluded epicardial infarct-related artery (IRA).[1] In addition to antiplatelet and anticoagulant therapy, patients presenting with persistent ST-segment elevation should also receive timely reperfusion therapy, either pharmacologic or catheter-based, in order to restore coronary flow, limit myocardial necrosis and salvage jeopardized myocardium, and improve clinical outcomes.[2-4] Primary percutaneous coronary intervention (PCI) is an extremely effective reperfusion treatment for STEMI and has been demonstrated to be superior to fibrinolytic therapy in reducing mortality when it can be performed rapidly.[5] This has led to the recommendation that primary PCI be the preferred reperfusion strategy employed whenever feasible,[3,4] reflected by a dramatic increase in the use of primary PCI coincident with a significant decrease in the use of fibrinolysis in STEMI patients over the past decade in many parts of the world.[6]

Nevertheless, many STEMI patients present to hospitals that do not have the capability of performing PCI and often cannot undergo PCI within

the timelines recommended in the guidelines; instead, they receive fibrinolysis as the initial reperfusion therapy. Several studies have explored the potential of combining the best of both therapies by performing PCI soon after fibrinolysis.[7] While initial studies[8,9] failed to demonstrate a clinical benefit with this strategy, more recent studies, performed in the era of coronary stenting and contemporary pharmacotherapy, have been more encouraging but have not been adequately powered to definitively establish the safety and efficacy of this approach.[10-14] Interestingly, a meta-analysis[15] in the coronary artery stenting era comparing an early invasive strategy after fibrynolysis to traditional, ischemia-guided strategy suggested an impressive reduction in mortality (4.7% vs. 8.1%; odds ratio [OR] 0.55; 95% confidence intervals [CI] 0.34–0.90) and reinfarction (4.5% vs. 8.1%; OR 0.53; 95% CI 0.33–0.86). These benefits were seen with numerically higher but not statistically significant differences in the rates of stroke (1.1% vs. 0.8%; OR 1.31; 95% CI 0.42–4.10) or major bleeding (4.6% vs. 2.8%; OR 1.41; 95% CI 0.74–2.69). However, less than 80 deaths were observed in all 5 trials combined and the total sample size was limited to 1235 patients.

It is important to distinguish the above mentioned early strategy of PCI following fibrinolysis with that of "facilitated" PCI – a planned, immediate PCI after an initial pharmacological regimen such as half- or full-dose fibrinolysis, glycoprotein (GP) IIb/IIIa inhibitor, or the combination.[3] Despite the theoretical appeal of facilitated PCI, clinical trials have not borne out an advantage of this approach when compared to primary PCI alone; in fact, there is evidence that this approach may be harmful.[16] It is also important to recognize that a routine early strategy of PCI differs from rescue PCI after unsuccessful fibrinolysis. Indeed, it is already well established that, in the setting of persistent ST-segment elevation (<50% when compared to the presenting electrocardiogram) and/or hemodynamic compromise 60 to 90 min postlysis, an emergent transfer to a PCI-capable hospital is the preferred approach.[17]

Thus, while the strategy of routine early PCI after fibrinolysis appeared promising, the advisability of transferring STEMI patients to a PCI center immediately after fibrinolysis for routine early PCI remained unclear in 2004 after we completed a small feasibility study[18] and then embarked upon a randomized trial to compare a pharmacoinvasive strategy of transfer and PCI within 6 h after fibrinolysis with a strategy of early transfer and PCI only for failed fibrinolysis.[19] TRANSFER-AMI (Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction) was undertaken with the understanding that the majority of Canadian STEMI patients present to hospitals that do not have the capability of performing PCI and therefore cannot undergo PCI within the timelines recommended in the guidelines; instead, they receive fibrinolysis as the initial reperfusion therapy.[19,20]

Between July 2004 and December 2007, we enrolled 1059 patients with STEMI presenting to 42 non-PCI centers within 12 h of symptom onset treated with tenecteplase, the most commonly employed fibrinolytic agent in Canada. Inclusion criteria included either ≥2 mm ST-segment elevation in 2 anterior leads or ≥1 mm ST-segment elevation in 2 inferior leads. Patients with inferior ST-segment elevation also required at least one of the following high-risk characteristics: systolic blood pressure <100 mmHg, heart rate >100 beats/min, Killip class II–III, ≥2 mm of ST-segment depression in the anterior leads, or ≥1 mm of ST elevation in right-sided lead V_4 (V_4R), indicative of right ventricular involvement. Key exclusion criteria included cardiogenic shock prior to randomization, PCI within the previous month, previous bypass surgery, or availability of primary PCI with an anticipated door-to-balloon time of less than 60 min.

In addition to tenecteplase (received at a median of 26 min from hospital presentation and a median of 114 min from symptom onset), all patients received acetylsalicylic acid and anticoagulant therapy (unfractionated heparin 60 U/kg bolus [maximum 4000 U] followed by 12 U/kg/h [1000 U/h maximum] adjusted to maintain an activated partial thromboplastin time of 1.5–2.0 times control or enoxaparin 30 mg intravenous bolus followed by 1 mg/kg subcutaneously every 12 h for age <75 years) in the emergency department. The protocol was amended in April 2005 to strongly recommend concomitant treatment with clopidogrel at the time of fibrinolysis (initial dose 300 mg for age ≤75 years, 75 mg for age >75 years). All other therapies were left to the discretion of the treating physician.

Patients randomized to the pharmacoinvasive strategy were then transferred urgently to a PCI center and underwent coronary angiography and PCI of the IRA within 6 h of fibrinolysis. PCI was performed for persistent occlusion or significant stenosis of the infarct-related artery (≥70% stenosis or 50–70% stenosis with thrombus, ulceration or spontaneous dissection). Patients randomized to standard treatment had a 12-lead electrocardiogram repeated 60 to 90 min after randomization; those with persistent ST elevation (<50% resolution of ST-segment elevation) and chest pain, or hemodynamic instability, were transferred for rescue PCI. All other standard treatment patients remained at their presenting hospital for at least 24 h, and cardiac catheterization was encouraged beyond 24 h.

Coronary angiography and PCI were performed in 99% (median of 2.8 h post-randomization) and 85% (median 3.2 h) of patients in the early PCI group. In contrast, 89% (median 32.5 h post-randomization) and 67% (median 21.9 h) of standard treatment patients underwent angiography and PCI; 35% of standard treatment patients required urgent angiography, most for

failed reperfusion postlysis or recurrent cardiac events (e.g., reinfarction, cardiogenic shock, recurrent ischemia). Over 98% of the patients who underwent PCI had coronary stents implanted and 83% received a GP IIb/IIIa inhibitor. Apart from a greater use of clopidogrel within the first 6 h (90% vs. 69%, P <0.001) and at discharge (90% vs. 81%, P <0.001) in the early PCI group, most likely due to a higher proportion of patients undergoing PCI with stenting, medical therapy was otherwise relatively similar.

The primary endpoint – a composite of 30-day death, reinfarction, recurrent ischemia, new or worsening heart failure, and cardiogenic shock – occurred in 11% of routine early PCI patients and in 17.2% of standard treatment patients (relative risk [RR] 0.64; 95% CI 0.47–0.87; P = 0.004). The study was not powered to evaluate the individual components of the primary endpoint; however, there were numerically lower rates of reinfarction (3.4% vs. 5.8%; RR 0.57; 95% CI 0.33–1.04; P = 0.06), and significantly lower rates of recurrent ischemia (0.2% vs. 2.1%; RR 0.09; 95% CI 0.01–0.68; P = 0.003) and new or worsening congestive heart failure (3.0% vs. 5.6%; RR 0.54; 95% CI 0.30–0.98; P = 0.04) with the routine early PCI strategy. Six-month rates of death and reinfarction did not differ between the 2 groups (8.9% vs. 10.6%; RR 0.83; 95% CI 0.55–1.25; P = 0.36). Mortality rates at 30 days (4.5% vs. 3.4%, P = 0.39) and 6 months (98.1% follow-up; 5.7% vs. 4.5%, P = 0.39) were not significantly different and the numeric excess in the early PCI group (6 at 30 days and 7 at 6 months) was likely due to an imbalance at randomization in patients in Killip class IV (despite the fact that cardiogenic shock was supposed to be an exclusion criterion) associated with 5 excess deaths in the early PCI group.

During transfer, only 2.4% of the early PCI and 3% of the standard patients had complications, most commonly hypotension. There were more mild GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) bleeding events with the pharmacoinvasive strategy (13% vs. 9%, P = 0.04) but there were no significant differences in the rates of TIMI (Thrombolysis in Myocardial Infarction) major or minor bleeding, GUSTO moderate or severe bleeding, transfusions or intracranial hemorrhage.

Thus, for high-risk STEMI patients receiving fibrinolysis at non-PCI centers, urgent transfer and PCI within 6 h was associated with significantly less ischemic complications and no excess in major bleeding. These results are consistent with those of previous trials,[10-14] and a more recently published study[21] of patients (n = 266) with acute STEMI living in rural areas with more than 90 min transfer delays to PCI treated with tenecteplase, aspirin, enoxaparin, and clopidogrel and randomized to immediate transfer for PCI or to standard management in the local hospitals with early transfer only if indicated for rescue or clinical deterioration.

The optimal time window for early angiography and PCI where appropriate after fibrinolysis is uncertain. The 7 trials examining this early strategy had time intervals from fibrinolysis to PCI ranging from 2 to 17 h.[10-14,20,21] The increased hemorrhagic and ischemic complications that were observed in the facilitated vs. primary PCI trials[16] suggest that PCI should not be performed very early (e.g., within the first 2 h after fibrinolysis) in hemodynamically stable patients with evidence of successful reperfusion after fibrinolysis. In contrast, the routine early PCI group in the TRANSFER-AMI trial underwent PCI a median of 3.9 h (interquartile range 3.1–4.9) after fibrinolysis and 98% of the PCI procedures were performed more than 2 h after fibrinolysis. Preliminary, unpublished data from our TRANSFER-AMI study[20] suggest that the benefit of the early PCI strategy was already realized within that 6 h window and consistent within the first 24 h. Fibrinolysis increases both the early bleeding risk but also platelet activation and aggregation. Thus, the appropriate timing of stent implantation with concomitant use of adequate antiplatelet and anticoagulant therapy is critical in order that the presumed benefit of PCI in mitigating the risk of reinfarction and recurrent ischemia is not outweighed by the potential early hazard for bleeding and stent thrombosis. Although a randomized trial actively comparing time intervals would be the only definitive way to address this important question, this is unlikely to be undertaken; perhaps the best insights will come from a patient-level analysis from of all the trials to date – stay tuned.

In summary, we believe that STEMI patients who cannot undergo timely primary PCI should receive prompt fibrinolysis followed by initiation of an immediate transfer to a PCI-capable hospital without waiting to see whether reperfusion is successful.

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ARTYKUŁ POGLĄDOWY

Metoda „*drip-and-ship*” w ostrym zawale serca z uniesieniem odcinka ST

Strategia farmakoinwazyjna dla chorych leczonych fibrynolitycznie

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SŁOWA KLUCZOWE

angioplastyka, tromboliza, zawał serca

STRESZCZENIE

Wykazano, że pierwotna przezskórna interwencja wieńcowa (*percutaneous coronary intervention* – PCI) w zawale serca z uniesieniem odcinka ST (*ST-segment elevation myocardial infarction* – STEMI) ma przewagę w zmniejszaniu śmiertelności nad leczeniem fibrynolitycznym, jeśli tylko można przeprowadzić zabieg odpowiednio szybko. Niemniej jednak wielu chorych ze STEMI trafia do szpitali niewykonujących PCI i często nie można u nich wykonać zabiegu w ramach czasowych zalecanych w wytycznych postępowania; chorzy ci otrzymują leczenie fibrynolityczne jako pierwsze leczenie reperfuzyjne. W kilku badaniach, na przykła ANSFER-AMI (Trial of Routine Angioplasty and Stenting after Fibrynolysis to Enhance Reperfusion in Acute Myocardial Infarction), analizowano możliwość optymalnego połączenia obu terapii poprzez wykonanie PCI tuż po fibrynolizie. Chorych (n = 1059) ze STEMI ściany przedniej lub ze STEMI ściany dolnej z cechami dużego ryzyka, przybywających w ciągu 12 godzin od wystąpienia objawów do ośrodków niewykonujących PCI i otrzymujących tenekteplazę oraz inne standardowe leki przeciwzakrzepowe, przydzielano losowo do strategii farmakoinwazyjnej (pilny transport, angiografia i w razie wskazań PCI w ciągu 6 godzin) lub leczenia standardowego (obejmującego PCI ratunkową lub angiografię i w razie wskazań PCI po upływie 24 godzin). Złożony punkt końcowy w ciągu 30 dni: zgon, ponowny zawał serca, nawracające niedokrwienie mięśnia sercowego, wystąpienie lub nasilenie niewydolności serca i wstrząs kardiogenny, wystąpił rzadziej u chorych z grupy rutynowej wczesnej PCI, w porównaniu do chorych leczonych standardowo (11% *vs* 17,2%, $P = 0{,}004$). W oparciu o te wyniki – zbieżne z innymi badaniami – wyrażamy przekonanie, że chorzy ze STEMI, u których nie można w wymaganym czasie wykonać pierwotnej PCI, powinni bezzwłocznie otrzymać leczenie fibrynolityczne, a następnie zostać bezpośrednio przekazani do ośrodka wykonującego PCI, bez oczekiwania na ocenę skuteczności reperfuzji.

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