ECRONICON OPEN ACCESS

EC EMERGENCY MEDICINE AND CRITICAL CARE

Research Article

Can the Adjunctive Therapy Increase the Efficacy of Streptokinase in ST Elevation Myocardial Infarction?

Souissi Sami*, Ben Turkia Hela, Ghazali Hanene, Chermiti Ines, Zaouche Khadija and Keskes Syrine

Emergency Department, Regional Hospital of Ben Arous, Faculty of Medicine of Tunis, University Tunis El Manar, Tunisia

***Corresponding Author:** Souissi Sami, Emergency Department, Regional Hospital of Ben Arous, Faculty of Medicine of Tunis, University Tunis El Manar, Tunisia.

Received: November 18, 2020; **Published:** December 10, 2020

Abstract

Introduction: In ST segment elevation acute myocardial infarction (STEMI), pharmaco-invasive therapy with thrombolytic regimens is the cornerstone of achieving reperfusion, when primary PCI can't be performed timely.

The combination of thrombolysis with modern adjunctive antithrombotic therapy (dual antiplatelets therapy and low molecular weight heparin) has been widely examined in large clinical studies with fibrin specific fibrinolytics. But its effects when streptokinase is used are not sufficiently known.

Can the modern antithrombotic adjunctive therapy increase the efficacy of streptokinase?

Aim of the Study: The aim of this study was to evaluate the efficiency and the safety of the use of the modern adjunctive therapy in patients treated with Streptokinase for STEMI.

Methods: A retroprospective analysis of prospective registry included patients with ST segment elevation acute myocardial infarction who were treated with Streptokinase. Two groups were distinguished: The examined group (EG) included patients treated with modern adjunctive antithrombotic therapy enrolled from January 2009 to March 2012 and the control group (CG) included patients treated with conventional adjunctive (aspirin and unfractionated heparin) therapy enrolled from February to December 2008. Comparative study between the two groups according to the coronary reperfusion defined by clinical criteria's and bleeding risk.

Results: Inclusion of 271 patients. Mean age = 58 ± 11 years old, 85% were male. Forty-six patients were included in the control group, 225 patients in the examined group. Mean age and sex-Ratio were comparable in the two groups with respectively 57 ± 11 versus (vs) 58 ± 12 years (p = 0.36) and 4.1 versus 6.1(p = 0.45). The comparative study of cardiovascular risk factors between the first versus the second group (%): Current smoking (72) vs (77) (p = 0.45); Diabetes (39) vs (26) (p = 0.07); Hypertension (35) vs (28) (p = 0.36); dyslipidemia (17) vs (11) (p = 0.21). The mean delay onset of chest pain- first medical contact was about 3 hours in the two groups. There is no significative difference between the two groups according the early complications (N): Cardiogenic shock (1) in the first group vs (14) (p = 0.14); acute heart failure (9) vs (22) (p = 0.15); hematemesis (1) vs (6) (p = 0.8); intracranial bleeding (0) vs (2) (p = 0.75).

Thrombolysis success was higher in the examined group 63.3% versus 41.3% in the control group (p = 0.001).

Conclusion: In the STEMI patients; the modern adjunctive antithrombotic therapy can improve the efficacy of pharmacological reperfusion with streptokinase without enhancing bleeding risk.

Keywords: *Myocardial Infarction; Streptokinase; Fibrinolysis Failure; Bleeding; Adjunctive Therapy*

Abbreviations

ECG: Electrocardiogram; ESC: European Society of Cardiology; FMC: First Medical Contact; LWMH: Low Weight Molecular Heparin; STEMI: ST Elevation Myocardial Infarction; PCI: Percutaneous Coronary Intervention; UFH: Unfractionated Heparin

Introduction

Although primary percutaneous coronary intervention (PCI) is the recommended method of reperfusion in patients presenting with ST-segment elevation myocardial infarction (STEMI), Thrombolysis remains a good alternative when timely primary PCI is not available. Thrombolytic therapy is limited by high rate of inadequate reperfusion of the infarct-related artery. Initial reperfusion fails to occur in approximately 20 percent of patients [1] and is associated with a doubling of mortality rates [2]. Because thrombolysis is known to activate platelets and promote thrombin activity, the concomitant administration of antiplatelet and anticoagulant therapies is needed to lower the risk of thrombolysis failure [3]. In the Second International Study of Infarct Survival (ISIS 2), including patients with STEMI, aspirin reduced the odds of death from vascular causes by 23 percent and the odds of reinfarction by 46 percent [4]. Clopidogrel has been shown to prevent death and ischemic complications in patients with symptomatic atherosclerotic disease, patients who have undergone percutaneous coronary intervention, and patients with unstable angina or myocardial infarction without ST-segment elevation [5]. However, the addition of adjunctive therapy may cause an increased risk of bleeding [6].

Aim of the Study

The aim of this study was to evaluate the efficiency and the Safety of the use of the modern adjunctive antithrombotic therapy in patients treated with Streptokinase for STEMI.

Materials and Methods

A retro prospective analysis of prospective registry conducted over 4 years from February 2008 to March 2012

Inclusion criteria

Patients admitted in the emergency department for STEMI and treated with Streptokinase as reperfusion strategy.

STEMI was identified by the onset of typical chest pain lasting more than 20 minutes, unrelieved by nitrate and associated with ST-segment elevation of at least 0.1 mV in at least two contiguous limb leads, ST-segment elevation of at least 0.2 mV in at least two contiguous precordial leads, or left bundle-branch block that was not known to be old on the standard 12 lead ECG.

Exclusion criteria

presence of contra indication to Streptokinase therapy.

Treatment with aspirin, clopidogrel or heparin within 7 days before the enrollment.

Study protocol

All patients received Streptokinase in the standard dose of 1.5 x 10^6 units over 60 minutes.

Two groups were studied depending on the adjunctive therapy received.

Adjunctive therapy was given depending on the study period (Clopidogrel and Low Weight Molecular Heparin were no available before 2009).

The control group (CG) in 2008: 250 mg of aspirin and an intravenous bolus of 50 mg unfractionated heparin.

The examined group (EG) since January 2009:

- *250 mg of aspirin
- *Clopidogrel:
    - Age < 75 years old: 300mg oral loading dose
    - Age ≥ 75 years old: 75 mg
- *Low Weight Molecular Heparin (enoxaparin)
    - Age < 75 years old: bolus intravenous (IV) of 30 mg followed by 1mg/kg Subcutaneous (S-C) every 12 hours.
    - Age ≥ 75 years old: no bolus IV. 0.75 mg/kg S-C.

We identified demographic, clinical and evolutive characteristics. Univariate analysis was performed to compare the two groups according to reperfusion success based on clinical criteria's (relieve of chest pain and complete resolution or > 50% reduction in ST elevation in the worst lead at 90 minutes after fibrinolytic therapy). hemorrhagic complications and early mortality.

Results

We included 271 patients with a mean age of 58 ± 11 years old. Eighty five percent of patients were male. Forty-six patients were included in the first period 225 patients in the second period. Mean age and sex-Ratio were comparable in the two periods with respectively 57 ± 11 versus 58 ± 12 years (p = 0.36) and 4.1 versus 6.1 (p = 0.45).

Cardiovascular risk factors were similar in the two groups (Figure 1).

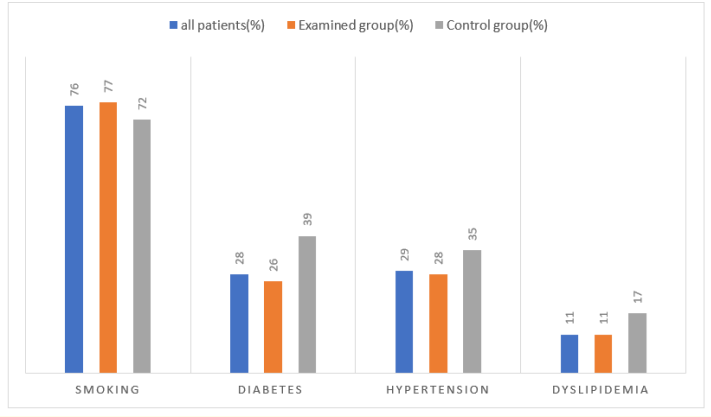

Figure 1: *Cardiovascular risk factors.*

The mean delay chest pain to first medical contact was comparable in the two groups 172 ± 162 minutes in the CG group versus 197 ± 174 minutes (p = 0.35).

No difference in neither hemodynamic nor hemorrhagic complications between the two groups (Table 1 and 2).

	CG (N = 46)	EG (N = 271)	p-value
Acute heart failure n (%)	9 (19)	60 (22)	0.15
Cardiogenic Shock n	1	14	0.14
Anaphylaxis n	0	0	

Table 1: *Hemodynamic complications.*

	CG (N = 46)	EG (N = 271)	p-value
Hematemesis n	1	6	0.8
Gingivorrhagia n	1	15	0.24
Intracranial bleeding n	0	2	0.75

Table 2: *Hemorrhagic complications.*

The mortality was similar in the two group respectively 2 in the examined group versus 0 in the control group.

Discussion

This study demonstrates the benefits of adjunctive therapy to fibrinolysis by enhancing the rate of successful thrombolysis by 22 % without increasing the risk of bleeding.

Thrombolytic therapy is known to promote thrombin activity and activate platelets [7]. Platelet activation after fibrinolytics administration reflect a direct mechanism mediated by plasmin or independent mechanisms by exposed subendothelial collagen at the site of the coronary lesion or by procoagulant systems on the clot surface [8]. The activation of the homeostatic system is considered to play an important role in preventing or impairing fibrinolysis-induced reperfusion and in producing early re-occlusion, that's why we need combining lytic therapy with adjunctive antithrombotic drugs.

Aspirin was the first antiplatelet molecule used and its benefits was studied since the ISIS 2 study, which demonstrate that the combination of streptokinase and aspirin was significantly better than either agent alone. Their separate effects were additive [4]. Aspirin has also been shown to reduce the rate of angiographic reocclusion by 22 percent, as compared with placebo [9].

Actually, the European Society of Cardiology (ESC) [10], recommends the early administration of Aspirin at the loading dose of 150 - 300 mg orally or 75 - 250 mg intra venously followed by maintenance dose of 75 - 100 mg daily.

The ESC recommends also to associate a P2Y12 inhibitors. In this Study we used the clopidogrel which is an adenosine diphosphate-receptor antagonist, that block the P2Y12 component of the adenosine diphosphate receptor and inhibit the activation and aggregation of platelets [11]. Clopidogrel is a potent antiplatelet agent with a synergistic antithrombotic effect with aspirin because platelet activation can still occur through thromboxane A2-independent pathways, despite the inhibition of cyclooxygenase by aspirin, leading to the aggregation of platelets and the formation of thrombin [12,13].

Evidence for the efficacy of clopidogrel over aspirin in patients receiving fibrinolytic therapy for STEMI arises from the Clopidogrel as Adjunctive Reperfusion Therapy - Thrombolysis in Myocardial Infarction 28 (CLARITY-TIMI 28) trial, a study of 3,491 patients who received a fibrinolytic agent, aspirin, and heparin dispensed according to body weight and were scheduled to undergo angiography [14]. However, Clopidogrel is limited by the variability in platelet inhibition, with low response in 5 - 40% of patients due to genetic, cellular, and clinical mechanisms [15]. Bonello., *et al*. found that the platelet function measurements during clopidogrel treatment demonstrated a variable and overall modest level of P2Y12 inhibition. High on-treatment platelet reactivity to adenosine diphosphate (ADP) was observed in selected patients [16].

In the present study the use of low weight molecular heparin associated to clopidogrel was associated to higher rate of successful thrombolysis without increasing bleeding risk. In our context we used Enoxaparin as recommended by the ESC.

Enoxaparin had multiple advantages over unfractionated heparin (UFH), including better bioavailability after subcutaneous injection, increased anti-factor X activity, and more efficient inhibition of thrombin generation [3].

The benefit and safety of enoxaparin are currently being tested in a large clinical trial [17].

The relative efficacy and safety of enoxaparin versus UFH has analyzed in the TRANSFER-AMI trial [18]. This analysis, enoxaparin and UFH were administered to 498 and 448 patients, respectively, the use of enoxaparin was associated with more access site-related (5.0 % vs 2.9 %, p = 0.04) and mild bleeding (12.1 % vs 7.8 %, p = 0.03). Notable, enoxaparin was associated with better outcomes compared with UFH when only one anticoagulant was used during the initial hospital stay, while mild bleedings were increased when transitioning from enoxaparin to UFH [18].

Conclusion

Compared to aspirin and UFH, the modern adjunctive antithrombotic therapy including Aspirin, clopidogrel and LWMH can improve the efficacy of reperfusion fibrinolysis by Streptokinase without increasing bleeding risk.

Conflict of Interest

We declare the absence of any conflict of interest.

Bibliography

1. TIMI Study Group. "The Thrombolysis in Myocardial Infarction (TIMI) Trial. Phase I Findings". *The New England Journal of Medicine* 312.14 (1985): 932-936.

2. Dalen JE., *et al.* "Six- and twelve-month follow-up of the phase I Thrombolysis in Myocardial Infarction (TIMI) trial". *The American Journal of Cardiology* 62.4 (1988): 179-185.

3. Capodanno D., *et al.* "Management of adjunctive antithrombotic therapy in STEMI patients treated with fibrinolysis undergoing rescue or delayed PCI". *Thrombosis and Haemostasis* 114.5 (2015): 945-957.

4. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group". *Lancet London England* 2.8607 (1988): 349-360.

5. CAPRIE Steering Committee. "A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE)". *Lancet* 348 (1996): 1329-1339.

6. Steg PG., *et al.* "ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation". *European Heart Journal* 33 (2012): 2569-2619.

7. Topol EJ. "Acute myocardial infarction: thrombolysis". *Heart* 83 (2000): 122.

8. Fitzgerald DJ., *et al.* "Marked platelet activation in vivo after intravenous streptokinase in patients with acute myocardial infarction". *Circulation* 77 (1988): 142-150.

9. Meijer A., *et al.* "Aspirin versus coumadin in the prevention of reocclusion and recurrent ischemia after successful thrombolysis: a prospective placebo controlled angiographic study: results of the APRICOT Study". *Circulation* 87 (1993): 152430.

10. Borja I., *et al.* "017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC).

11. Quinn MJ., *et al.* "Ticlopidine and clopidogrel". *Circulation* 100 (1999): 166772.

12. Patrono C., *et al.* "Platelet-active drugs: the relationships among dose, effectiveness, and side effects: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy". *Chest* 126 (2004): 234S-264S.

13. Herbert JM., *et al.* "The antiaggregating and antithrombotic activity of clopidogrel is potentiated by aspirin in several experimental models in the rabbit". *Thrombosis and Haemostasis* 80 (1998): 512-518.

14. Sabatine MS., *et al.* "Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation". *The New England Journal of Medicine* 352 (2005): 1179-1189.

15. Ferreiro JL., *et al.* "Clopidogrel response variability: current status and future directions". *Thrombosis and Haemostasis* 102 (2009): 7-14.

16. Bonello L., *et al.* "Consensus and future directions on the definition of high ontreatment platelet reactivity to adenosine diphosphate". *Journal of the American College of Cardiology* 56 (2010): 919-933.

17. Antman EM., *et al.* "Enoxaparin versus unfractionated heparin as antithrombin therapy in patients receiving fibrinolysis for ST elevation MI: design and rationale for the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment Thrombolysis in Myocardial Infarction–Study 25 (ExTRACT– TIMI 25)". *American Heart Journal* 149 (2005): 217-226.

18. Lavi S., *et al.* "Efficacy and safety of enoxaparin compared with unfractionated heparin in the pharmacoinvasive management of acute ST-segment elevation myocardial infarction: Insights from the TRANSFER-AMI trial". *American Heart Journal* 163 (2012): 176-181.

Volume 5 Issue 1 January 2021