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Benefit of the early use of tissue plasminogen activator (Alteplase) in the management of acute myocardial infarction

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Abstract
Background: ST segment elevation myocardial infarction (STEMI) result from complete occlusion of coronary artery following atherosclerotic plaque rupture and subsequent thrombosis. Pharmacological thrombolysis by tissue plasminogen activator (t-PA) Alteplase, which is the first generation recombinant t-PA convert plasminogen to plasmin and mimicking endogenous t- pA and thereby precipitating thrombolysis and induce patency in the infarction related vessel (IRV).
Objective: This study aims to assess the benefit of early use of tissue plasminogen activator (Alteplase) in the management of acute myocardial infarction (AMI).
Material and Method: 20 patient 4 femals and 16 males were enrolled, 13 of them within first 6 hrs of severe chest pain consistent with acute MI, and 7 of them within 2nd 6 hrs of the symptoms, accompanied by an ECG ST- elevation where randomly assigned to weght adjusted, accelerated infusion of 100mg. of Alteplase. The rate of success is assessed by 2 parameter: ECG and by biochemical cardiac markers CK MB isoenzyme before and 90 minutes after Alteplase infusion, which is regarded by my study as equivalent to assessment of restoration of the blood flow 9 (reperfusion) by angiography by GUSTO1 trial.
Result: Complete reperfusion was achieved in about 45% of patient assessed by EC Gand in about 40%of patient as assessed by biochemical cardiac markers CK-MB. High prevalence of positive (53-84%) was achieved among patient within first six hrs of symptoms of total patient benefit from treatment.
Conclusion: As compared with GUSTO1 trial accelerated infusion of alteplase over period of 90 mint. Considered an excellent method for myocardial l reperfusion and appears to induce re-canalization if used within 12 hrs. Dramatic response occur during first 6 hrs after symptoms of acute MI with high rate of patency in infarction related vessels. (IRV).

Keywords: infarction, myocardial, treatment

Introduction

Acute myocardial infarction occur when atherosclerotic plaque – rupture or ulcerate so that a mural thrombus form at the site of rupture and lead to coronary artery occlusion. If complete coronary artery occlusion occur, ST elevation MI will result (1, 4). Certain protein called cardiac marker are released in to the blood in large quantities from necrotic heart muscle after MI (1). The American College of Cardiology and European Society of Cardiology have redefined MI as a typical rise in cardiac enzyme:- criatine kinase (CK-MB), Troponin T or Troponin I above 99th. Centile of normal with at least one of the following:- Ischemic symptoms, development of pathological Q- wave on the ECG, ECG changes (ST segment elevation or depression) or coronary artery intervention (3).Detection of elevated concentration in plasma macromolecules released from irreversibly injured myocardium has been the definitive diagnostic criterion of MI (biochemical marker of AMI). Characteristic sequential changes of plasma CK-MB include elevation above normal within 4 hrs, a 2 to 10 fold peak in 16 – 24 hrs. and a return ti baseline within 3-4 days. Analysis of sub form (isoform) of individual isoenzyme CK-MB provides accurate estimation of the time of accurrence of re-canalization. It can be used to determine re-infarction as levels drop back to normal after 36-72 hrs.The myocardial form of CK-MB (CK-MB2) carboxylated by carboxypeptidase enzyme to produce CK-MB1 with different electrophoretic mobility. CK-MB2:CK-MB2 ratio mor than 1.5 is highly sensitive for the diagnosis of AMI, particularly 4-6 hrs. after onset of coronary occlusion (1, 2, 5).Reperfusion either pharmacologically (by thrmbolysis) or mechanically (angioplasty and /or stenting) accelerate the process of opening of occluded infarction –related artery in those patients in whom spontaneous thrmbolysis ultimately would have occluded and also greatly increase the number of patients in whom restoration of flow in the infarction related vessel (IRV) is accomplished (1, !9). Prompt and complete restoration of coronary flow is the principle mechanism by which perfusion therapy improve survival in patients with STEMI (10). Pharmacological thrmbolysis can induce patency in infracted related vessel (IRV) about 50 – 60 %. The high re-occlusion rates (6-20%) seen in patient given recombinant tissue plasminogen activator (rt-PA) is reduced by concomitant use of full dose of heparin for at least 24 hrs and also to decrease growth of clot (2, 12, 22). The long term outcome is similar to those achieved with catheter based approach- percutaneous transluminal coronary angiography (PTCA) but with slightly higher

residual stenosis, recurrent ischemia, high risk of re-occlusion and intracerebral bleeding (ICB) (0.5%). percutaneous transluminal coronary angiography (PTCA) is associated with better clinical outcome over 5 years especially with coronary stent plus Abciximab (glycoprotien11b/111a inhibitor) which is antagonist of binding fibrinogen to the platelet surface (2,10,11,24). Intravenous (IV) thrombolytic therapy is the standard of care for patient with AMI because of its wide spread availability and its ability to reduce mortality. Thrombolysis achieved either by non- fibrin specific agent such as streptokinase (which is antigenic and induce hypotension), or by fibrin specific agent rt-PA such as (Alteplase, Retaplase, and recently discovered Tencteplase) (1, 16, 17, 18).

Alteplase (Actylase)

It is the first generation recumbent form of t-PA that operate in the presence of fibrin. It is mimicking endogenous t-PA a Serine protease converting plasminogen to plasmine which subsequently lyses fibrin thrombi (8, 22).

Retaplase (Retavase)

Can be administrated as a bouls dose (2 bolus doses, each 10 u. over 2 minut, 30 mint. Apart). The ease of administration of this dosage regimen is conducive to prehospital initiation of) thrombolytic treatment in patient with STEMI.

Although Reteplase was superior to Alteplase for coronary artery patency, there was no significant difference between the 2 agents for mortality rate and incidence of intracranial bleeding. (8).

Tencteplase (TNK-t-PA)

A bioengineered variant of tissue type - plasminogen activator appears to induce re-canalization mor rapidly than Alteplase, and thrombolysis (initiated early after the onset of symptom) is associated with remarkably low mortality than Alteplase (30 days mortality rate) (7).

The use of recumbent DNA technology to produce rt-PA thrombus specific agent which dissolve the clot rapidly so that the blood flow resumed to the organ involved and dose not Effect the other clotting factor in the circulation, so thy are less prone to produce hemorrhage, are effective in inducing re-canalization within 90 mint. And decrease mortality especially early after MI, reflecting improve collateral blood flow, and improve ventricular function (2, 5, 16, 17, 18).

GUSTO1 Trial

(Global Utilization of Streptokinase and tissue plasminogen activator for Occluded Coronary Arteries): which an Angiographic studies comparing thrombolytic regimen with 4 drugs. Have demonstrated that restoration of blood flow in the culprit artery is faster and more complete with tissue plasminogen activator (Alteplase, Retaplase, and Tencteplase) than streptokinase (4, 12, 13, 14).

GUSTO11b Trial

(Global Use of Strategies to open Occluded coronary artery in Acute Coronary Syndrom (which is clinical trial comparing primary angioplasty with tissue plasminogen activator for management of AMI) (10).

Materials and Methods

This is a prospective randomized clinical trials was carried out over 20 patients, 16 males and 4 females admitted at coronary care unit (CCU) of AL-Ramadi Teaching Hospital conducted between March 2006 and September 2006. Patients eligible for this study were those of any age who present within 12 hrs. after the onset of the symptoms of Sever chest pain for at least 20 minutes (chest pain consistent with acute MI) (4) and who had on the basis of 12 lead ECG, ST segment elevation of at Lest 1mm in2 or mor limb leads or at least 2mm in 2 or mor continuous precordial leads or a newly developing left bundle branch block (LBBB were considered eligible (5). The following were reason for exclusion: active bleeding or bleeding diathesis, a history of stroke or structural damage of the central nervous system, major surgery or trauma within preceding 6 months, uncontrolled hypertension (systolic blood pressure of more than 180 mmHg or diastolic blood pressure greater than 110 mmHg) or concomitant use of oral anticoagulant therapy with international normalization ratio (INR) greater than 2. All patient received 300mg of oral aspirin and subcutaneous low molecular weight heparin (LMWH) 1mg/kg twice daily. (2, 12). Other medications include B-blocker and nitrate were given at the time of treatment at the emergency room. Patient who randomly assigned to be given accelerated infusion of Alteplase (15) received a bolus dose 15 mg (Actylase) Boehringer ingelheim Germany30mint. Followed by 90mint.infusion in which 0.75mg/kg of body weight (max. dose 50mg) was given over period of 30 mint, followed by 0.5 mg/kg(max. dose 35mg)over a period of 60 mint. A bedside monitor was used for continuous ECG monitoring to allow identification and early treatment of malignant arrhythmias. ECG was done pre and post infusion. For the assessment of the infracted size and the time of re-canalization, plasma were assayed for Creatine Kinase-MB iso – enzyme in samples acquired at baseline(before initiation of infusion)and 90 mints after complete infusion of t-PA. The sample had been drawn then centrifugation was initiated less than 30 mints after acquisition of each sample and performed for 2 mints in micro-centrifugation to separate plasma and isolate serum for study of enzyme and then fast frozen (deep freezing) and transmitted on dry ice to the lab. Dept. of AL-Anbar Medical College. The end point of this study were: resolution of ST elevation in electrocardiography (ECG), Biochemical cardiac marker and intra-hospital Complication. Detection of re-canalization is readily accomplished as reflected by a sudden elevation in the rate of increase of concentration of creatine kinase-MB iso form

in the blood because of cardiac washout. (3, 7) Reperfusion is regard to occur if 50% resolution of ST segment elevation within 90 mint. After thrombolytic therapy.(5), or development of idioventricular tachycardia (accelerate idioventricular rhythem), which is a slow ventricular tachycardia with rate of 60- 100 beat/mint occur transiently during thrombolytic therapy at the time of reperfusion Statistical analysis of this result was done using Excel program MS2003. Chi square (X) test for normal data were used to compare between the result of this study. P value of less than 0.05 where considered to be statistically significant of difference. P value of less than 0.01 where considered to be statistically highly significant of difference.

AIM OF STUDY, to asses the benefit of the early use of tissue plasminogen activator (Alteplase) in the management of acute myocardial infarction.

Results

Table 1: ECG changes 90 mint after treatment with Alteplase *+ve result = ≥50% resolusion of ST segment elevation, return to normal

ECG changes	1st.6 hr symptoms		2nd. 6 hrs of symptoms	
	NO.	Percentage	NO.	Percentage
No changes	5	38.46	3	42.85
Significant Qwave (established MI)	0	0	1	14.28
<50% resolution of ST elevation	1	7.69	1	14028
*≥50%resolusion of ST elevation	5	38.48	2	28.57
*Return to normal	1	7.69	0	0
*Idioventricular Tachycardia	1	7.69	0	0
Total	13	100.00	7	100-00

oridioventricular tachycardia (5+1+1=7)

Table 2: Serum biochemical cardiac marker (Creatine Kinase MB isoform) 90 mint after treatment with Alteplase.

Enzyme study (CKMB)	1st.6hrs symptoms		2nd.6 hrs of symptoms	
	NO	Percentage	NO	percentage
NO changes	1	7.69	1	14.28
*Markedly ↑	6	46.15	2	28.57
Moderately ↑	2	15.38	1	14.28
Slightly ↑	1	7.69	1	14.28
Markedly ↓	1	7.69	0	0
Moderately ↓	1	7.69	1	14.28
Slightly ↓	1	7.69	1	14.28
Total	13	100.00	7	100.00

*+ ve result = markedly increase enzyme (CK-MB)

Table 3: The difference of positive result between 2 group of patient as assessed by2 parameter (ECG changes and Enzyme study)

Parameters	1st.6hrs of symptoms		2nd. 6hrs of symptoms		P value
	Total NO	+ve result	Total NO	+ve result	
ECG changes	13	7 (53.84%)	7	2 (28.57%)	0.048 (>0.05) significant
Enzyme study	13	6 (46.15%)	7	2 (28.57%)	0.06(>0.05) Not significant

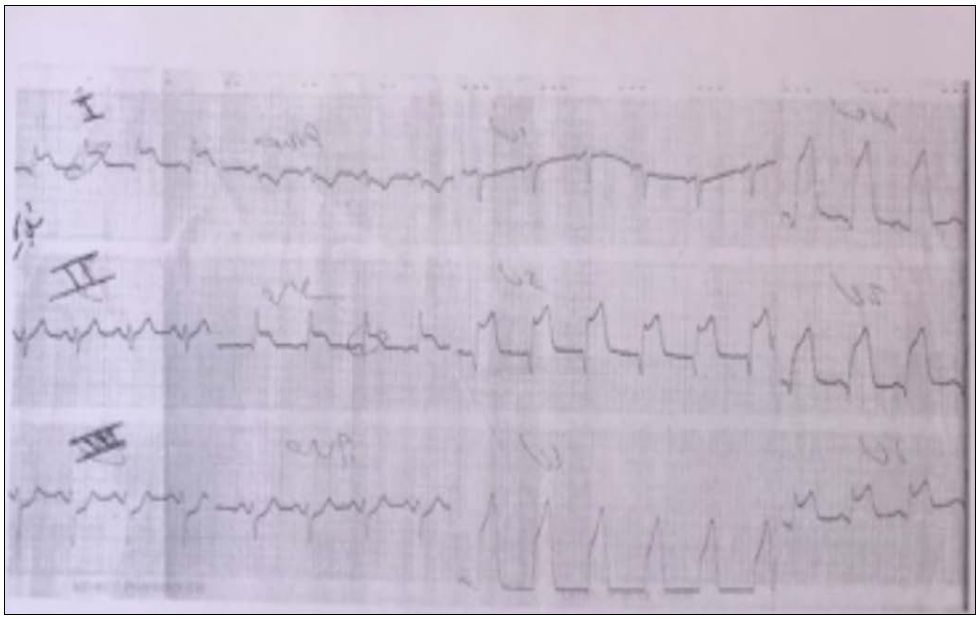

Fig 1: ECG was recorded from 57 years old male, who had developed sever chest pain during 2 hrs earlier. Ther is ST- segment elevation in lead 1, aVL, V1,-V6 (extensive anterior MI). Before initiation of treatment with Alteplase

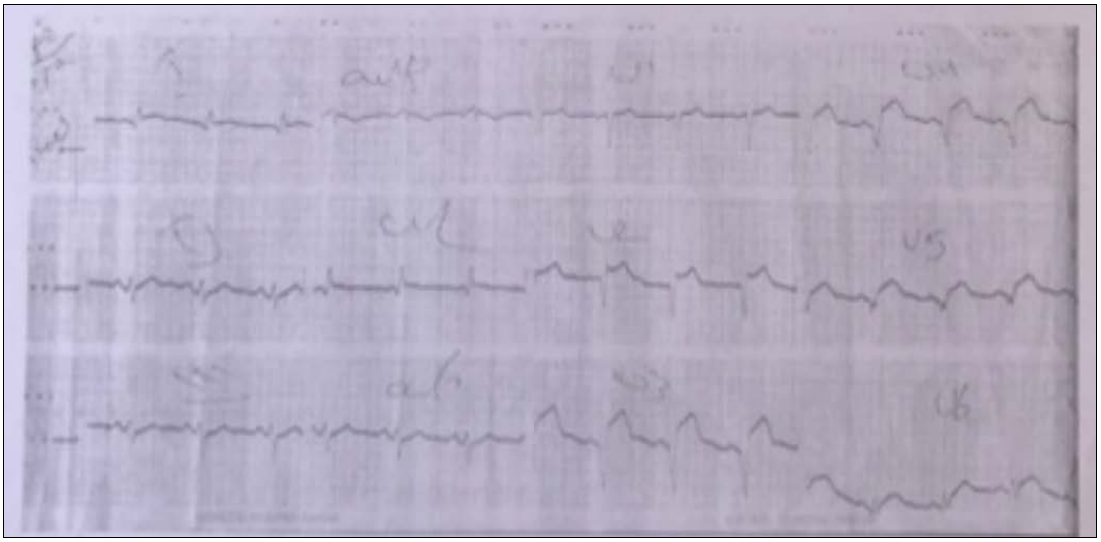

Fig 2: ECG changes of the same patient 90 mint after treatment with thrombolytic therapy (Alteplase)

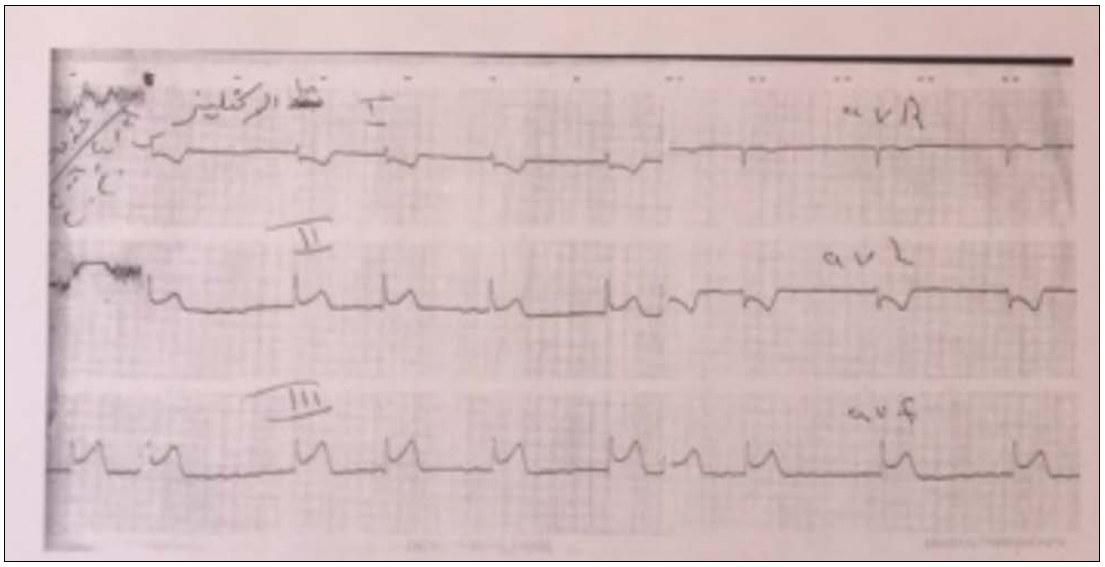

Fig 3: ECG changes of inferior MI (ST-segment elevation of leads 11.111.aVf) middle aged female with history of chest pain consistent with acute MI during 1st.6hrs.of symptoms (befor treatment with Alteplase)

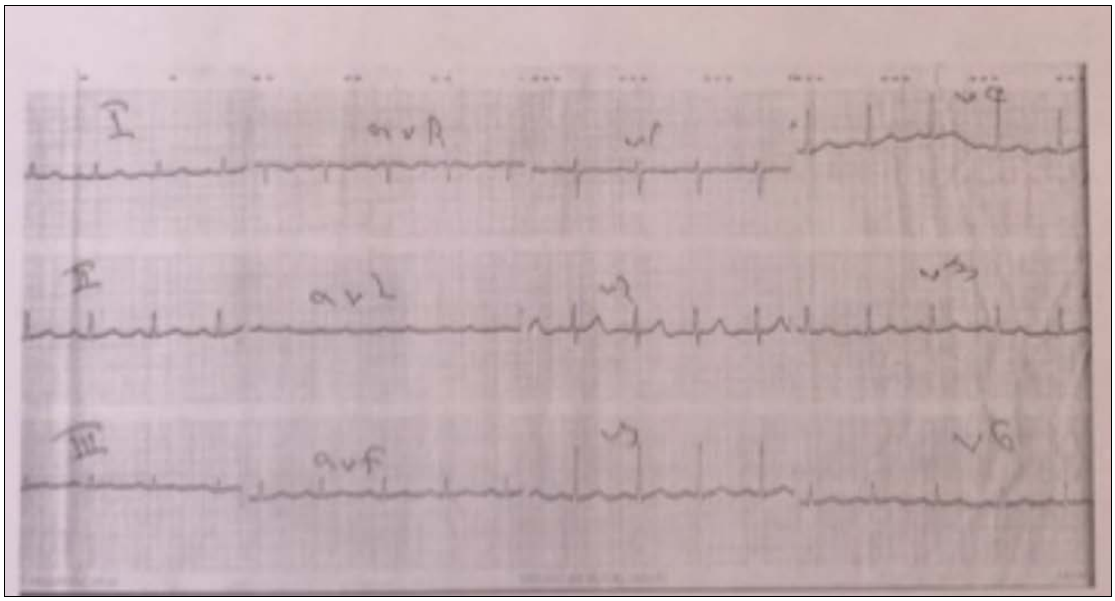

Fig 4: ECG changes of the same patient (of Fig.3) 90mint after thrombolytic therapy (Alteplase). Dramatic response seen as assessed by diminished ST- segment elevation.

Discussion

This study was designed to evaluate the effectivity of the tissue plasminigen activator (t-PA) with respect to the rapidly of re- canalization IN this study. We assessed the re –perfusion of the infarction –related vessels by 2 parameters: ECG, Creatine Kinase- MB isoenzyme befor and after Alteplase infusion as equivalent to angiographic study in GUSTO1 trial. Nine patients from total 20 patient (45%) had complete patency as determined by ECG, 90 mint after thrombolytic therapy (accelerated t-PA infusion). 7 of them during first 6 hrs.of symptoms (53.84%) and other two patient during 2nd 6 hrs. (28.57%). Eight patient from total 20 patient (40%) with patency(re-canalization)as determined by biochemical cardiac marker CK-MB after 90 mint of Alteplase therapy. 6 of them during 1st.6hrs of symptoms (46.15%), and other 2 patients during 2nd. 6hrs (28.57%). The percentage of positive result identified throughout ECGand enzyme study will be relatively lower as compared with that found by GUSTO1 trial and GUSTO11b trial, which was (54%,60% respectively) (9). And markedly less than Binbrek AS,NS, Neimane D,*et al*, study, when the rapidly of ercanalization is judged by analysis of serial changes in blood concentration of Creatine Kinase- MM isoform. (7)

This difference with the above studies related to:

1. The enrollment of population at high risk (mor elderly patients with anterior myocardial infarction).
2. The long delay between the onset of symptoms and the initiation of therapy.
3. The end point of study in GUSTO1 trials was by angiographic study, which more accurate than ECG and biochemical marker that used in our study to assess reperfusion.

The P value is less than 0.05 were considered statistically significant of difference between 2 groups, asjudged by electrocardiogram (ECG).

The P value is more than 0.05 were considered statically not significant of difference between 2 groups, as judged by analysis of creatine kinase (CK-MB) iso form and this because enrollment of small number of patient.

In this current study, my data indicate a high prevalence of positive Resued

Among patient assigned to accelerate t-PA infusion during first 6 hrs of symptoms (as assessed by ECG and the biochemical cardiac marker CK-MB)

The result of the present study suggest that the use of rt-PA in the thrombolysis is regarded as an excellent strategy of reperfusion and restoration of myocardial fuction.

These results also demonstrate that when thrombolysis is initiated under condition in which the interval from onset of symptoms to onset of administration of thrombolytic drug is shot, outcomes are remarkably favorable.

Recommendation

1. The drugs must be given as early as possible especially in the 1st. 6 hrs after the onset of symptoms of acute MI, because dramatic effect on the coronary re-perfusion occur in this period,
2. We must use heparine 500 IU,IV infusion of unfractionated type(standerd heparin) at the same time of accelerated infusion of Alteplase,because t-PA have short half-life and thus have only small systemic fibrinolytic effect and high re-occlusion rate and also for decrease of clot growth.(2,12,22).
3. We must use Aspirin 300 mg and platelet inhibiter as concomitant therapy to reduce cardiovascular event in acute MI by 25% (22).
4. The promotion of embolization by fibrinolytic therapy has recently been underscored as major problem in the treatment of AMI. This problem can largely be surmounted by adjunctive blocked of glycoprotein 11b /111a receptor, because Abciximab facilitate the rate and extent of thrombolysis result in MI (TIMI)14 trial(25,26)
5. The patien must be put under observation by close cardiac monitoring for any ECG changes, during and after accelerated infusion of t-PA because transient idioventricular tachycardia may be developed (re-perfusion arrhythmia).
6. Infusion must be stopped if any active bleeding from anywhere except at site of vascular access (IV (IV canula).

Conclusion

Successful early re-perfusion occur when coronary patency were achieved which define as the restoration of normal blood flow in the infracted –related vessel and preserve myocardial tissue, result in improve survival. ECG and enzymatic study confirm the benefit of early use of Alteplase in about 42.5% of 20 patients presented with 12 hrs of symptoms of acute MI after inclusion and exclusion criteria were checked.High percentage of benefit was noted in those who received thrombolytic therapy within first 6 hrs of symptoms.

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