Clinical predictors of successful thrombolysis with Streptokinase and possible circadian periodicity.

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Abstract:

Hypothesis: Predictive strength of each predictor of successful thrombolysis is different. There is diurnal variation in the efficacy of streptokinase thrombolysis.

Methodology: Retrospective study. 34 consecutive patients treated with streptokinase ed retrospectively; success or failure of thrombolysis was determined according to accepted clinical and ECG criteria.

Results: The mean age of the group with successful thrombolysis is quite younger than the group who failed. Inferior wall MI with or without posterior wall, smoker (current or ex-) and hypertensive patients had significant thrombolysis success rate than their counterparts. A definite time peak for successful thrombolysis could be detected at the afternoon and early evening hours (12.00-2100 h); 72% of all successful cases were observed in this time interval compared with 33.3% of all failed cases, while between 21.00– 24.00 h, the percentage of successes was 8% compared with 22.2 % of all failures.

Conclusions: Dose adjustment for the time of day may be required, with higher doses during morning hours, or preference for primary coronary angioplasty in order to avoid the increase in bleeding complications related to higher doses of thrombolytic agents.

Keywords: Clinical predictors; Circadian periodicity; Thrombolysis; Streptokinase

Introduction:

Acute myocardial infarction (AMI) remains one of the major healthcare problems worldwide and as our population ages; the incidence of myocardial infarction will remain high and is, in fact, expected to increase in women. 1 Diabetes mellitus is one of the six primary risk factors identified for myocardial infarction, others are dyslipidemia, hypertension, smoking, male gender, and family history of atherosclerotic arterial disease. Modern therapy for AMI involves rapid and effective reperfusion. Numerous studies have demonstrated that muscle necrosis is a time-dependent process, with brief periods of ischemia causing cell dysfunction, stunning (loss of function but preserved viability), and eventually death. 2
Coronary angiography is the gold standard to determine coronary artery patency after reperfusion therapy but it is expensive, invasive and not always available early. Therefore, bedside noninvasive markers are more attractive options. Among these, electrocardiogram (ECG) has good predictive value and sensitivity. It is also easily available and cheap. Sutton et al showed that less than 50% resolution of ST segment elevation in the worst infarct lead had a sensitivity of 81%, specificity of 88% and positive predictive value of 87% to predict less than Thrombolysis In Myocardial Infarct (TIMI) grade 3 flow. Clinical variables that determine the efficacy of thrombolytic therapy, however, have been poorly described. This study aims to determine the successful revascularization rate following thrombolyis with streptokinase in AMI using ECG criteria and its association between various independent variables and outcome parameters.

Besides, circadian periodicity has been described for the time of onset of acute myocardial infarction. The early morning peak seen in transmural infarction, non-Q wave infarction and variant angina parallels the onset of other related phenomena, including sudden cardiac death, thrombotic stroke, transient myocardial ischaemia, silent ischaemia and ST-T changes in mitral valve prolapse. Morning hypercoagulability and hypofibrinolysis with circadian variations in circulating activated factor VII, prothrombin fragment F1+2, plasminogen activator inhibitor-1 and plasmin-plasmin inhibitor complex have been described, as well as other haemostatic and physiological factors, all of which might predispose towards enhanced clotting during morning hours. This is probably the reason for the relative resistance to thrombolysis in the early morning that has been shown for both tissue plasminogen activator (t-PA) and urokinase. This study is also designed to assess possible diurnal fluctuations in the efficacy of thrombolysis with streptokinase and to see whether they follow the circadian periodicity which has already been described for the abovementioned haemostatic, physiological and ischaemic phenomena.

Methods

This retrospective cohort study involved patients who were admitted to the Intensive Care Unit of Manipal Teaching Hospital, Phoolbari, Nepal with AMI (World Health Organisation criteria). Cohorts were selected from the admission registry of ICU from the year 2006 March to 2008 February. Data was extracted from the patient records using a data extraction form. Exclusion criteria included bundle branch block AMI, non-ST elevation myocardial infarction (NSTEMI), patients who were not given streptokinase due to contraindications to the therapy, previous streptokinase use, streptokinase given in other hospitals, symptom-to-needle time of more than 12 hours.

Streptokinase infusion was given as per protocol at the standard dose of 1.5 MU over 60 min. Infusion was stopped if there was a drop of blood pressure below systolic blood pressure of 90mmHg or if asthmatic attacks developed. The first ECG was recorded prior to starting streptokinase, and the second and third ECG was then recorded immediately after completion of streptokinase infusion and after 2 hours of completion of thrombolysis respectively.
Vertical height of ST segment elevation in the lead with the maximum ST segment elevation (worst infarct lead), before and after streptokinase was measured using a standard ruler in mm. The ST segment was measured 80 ms from J point, which corresponded to the peak of ST elevation. J point was defined as the first turning point in the ST segment on ECG. Successful thrombolysis with streptokinase was defined ≥ 50% reduction in ST segment elevation after 120 min in the worst infarct lead, and complete relief of chest pain and evidence of reperfusion arrhythmias.

Baseline characteristics between groups were compared with the use of the two-sample t-test. A multivariate regression analysis that included clinical descriptors was performed to determine which factors correlated with success or failure in the various time periods and to evaluate the impact of the time of streptokinase administration parameters on success rate. Statistical data are expressed as Median (range) or Mean (± Standard deviation) for continuous variables or as rates (percentage) for categorical variables. The data was entered and analyzed using the SPSS Version 11.

**Results:**

246 patients diagnosed as acute coronary syndromes were admitted in ICU from the year 2006 March to 2008 February, and 122 (49.6%) patients were diagnosed as ST elevation myocardial infarction. Only 36 patients underwent thrombolysis with streptokinase, were taken as the study subjects. Among them, 2 were excluded (due to new onset left bundle branch block, and un-interpretable ECG as per criteria of successful thrombolysis).

The age distribution of the all the study population is given in Table 1. The most of the patients (13, 38.2%) of age group 61-70 underwent thrombolysis.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Thrombolysis successful (25)</th>
<th>Thrombolysis unsuccessful (9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>&lt;40</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>41-50</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>51-60</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>61-70</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>&gt;71</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>12</td>
</tr>
</tbody>
</table>

Thrombolysis was determined to have been successful in 25 patients (73.5%), failed in 9 patients (26.5%). The success rate in male (13) and females patients (12) was not significantly different (52% Vs 48%), while the failure rate in male (7) was significantly higher than females (2) patients (77.7% Vs 22.3%). The mean age of the group with successful thrombolysis was 60.28 ± 9.41 years which is quite younger than the group who failed (65.44±10.44 years). The detailed clinical data of study population according to thrombolysis results are given in Table 2.
Table. 2 The clinical data of study population according to thrombolysis results

<table>
<thead>
<tr>
<th></th>
<th>Thrombolysis successful (n=25)</th>
<th>Thrombolysis unsuccessful (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.28±9.41</td>
<td>65.44±10.44</td>
</tr>
<tr>
<td>Male</td>
<td>13 (52.0%)</td>
<td>7 (77.8%)</td>
</tr>
<tr>
<td>History of Hypertension</td>
<td>13 (52.0%)</td>
<td>3 (33.3%)</td>
</tr>
<tr>
<td>Current/ex- smokers</td>
<td>16 (64.0%)</td>
<td>7 (77.8%)</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>5 (20.0%)</td>
<td>2 (22.2%)</td>
</tr>
<tr>
<td>DM</td>
<td>3 (12.0%)</td>
<td>2 (22.2%)</td>
</tr>
<tr>
<td>Past CAD history</td>
<td>1 (4.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Average Hospital Stay days</td>
<td>9.35±4.75</td>
<td>7.78±4.11</td>
</tr>
<tr>
<td>Mortality</td>
<td>3 (12.0%)</td>
<td>2 (22.2%)</td>
</tr>
<tr>
<td>Anterior wall MI</td>
<td>9 (36.0%)</td>
<td>6 (66.6%)</td>
</tr>
<tr>
<td>Inferior ± posterior wall MI</td>
<td>16 (64.0%)</td>
<td>2 (22.2%)</td>
</tr>
<tr>
<td>Other location MI</td>
<td>0 (0.0%)</td>
<td>1 (11.1%)</td>
</tr>
</tbody>
</table>

Patients of inferior wall MI with or without posterior wall have significant success rate than of anterior wall MI (64% Vs 36%). Similarly smoker (current or ex-) had significant higher thrombolysis success rate than the non-smoker (64% Vs 36%) and hypertensive patients also had significant success than normotensive patients.

Success and failure of thrombolysis were assessed in either eight intervals of 3 hours or six intervals of 4 hours, starting from midnight, in order to find out whether there are circadian fluctuations in the thrombolytic potency and efficacy of streptokinase. A definite time peak for successful thrombolysis could be detected at the afternoon and early evening hours. When the 24-h day was divided into eight 3-hour intervals from midnight, a peak of success was observed between 12.00–21.00 h; 72% of all successful cases (18 out of 25) were observed in this time interval compared with 33.3% of all failed cases (3 out of 9), while between 21.00– 24.00 h, the percentage of successes was 8% compared with 22.2 % of all failures (Figure 1). When the 24-h day was divided into six 4-hour intervals the results were similar; in the 12.00–20.00 h time interval 60.0% of all successful cases of thrombolysis were observed (Table 3).
These findings were even more pronounced when success/failure rates were determined separately for patients treated in each time interval (Figure 2). Among 21 patients treated in the 12.00–21.00 h time interval, successful thrombolysis was determined in 18 patients (85.7%) with 3 failures (14.3%).
In order to find out whether these findings could have been influenced by the most powerful determinant of thrombolysis success, the time elapsed from pain onset to streptokinase administration, this time interval was checked for each 3- and 4-hour time segment of the 12-hour period no significant difference was found between the various time intervals of “pain to needle time”.

**Table 4. Thrombolysis results in each 3 – and 4 - hour time periods**

<table>
<thead>
<tr>
<th>Pain to needle time</th>
<th>Successful</th>
<th>unsuccessful</th>
</tr>
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<tbody>
<tr>
<td>00–03</td>
<td>14 (93.3%)</td>
<td>1 (6.7%)</td>
</tr>
<tr>
<td>03–06</td>
<td>7 (53.8%)</td>
<td>6 (46.2%)</td>
</tr>
<tr>
<td>06–09</td>
<td>3 (75.0%)</td>
<td>1 (25.0%)</td>
</tr>
<tr>
<td>09–12</td>
<td>1 (50.0%)</td>
<td>1 (50.0%)</td>
</tr>
<tr>
<td>00–04</td>
<td>15 (93.8%)</td>
<td>1 (6.2%)</td>
</tr>
<tr>
<td>00–08</td>
<td>8 (57.1%)</td>
<td>6 (42.9%)</td>
</tr>
<tr>
<td>08–12</td>
<td>2 (50.0%)</td>
<td>2 (50.0%)</td>
</tr>
</tbody>
</table>

The percentage of male patients during the time interval of peak success rate (12.00–21.00h) does not differ with the percentage of males in the entire study group (55.56% Vs 52.00%), and it also did not differ from the relative male/female percentages during other time intervals.

**Discussion:**

Landmark studies, including Global Utilisation of Streptokinase and T-PA for Occluded coronary arteries-1 (GUSTO-1) 17 and Second International Study of Infarct (ISIS-2) 18 have shown the convincing benefits of thrombolysis and provided the groundwork for current therapeutic practice. A review by fibrinolytic therapy trialists’ (FTT) group has shown that thrombolysis prevents 20–30 deaths per 1,000 patients with 25% reduction in
mortality. However, 90 minutes arterial patency rate after streptokinase was only achieved in 50%–60%, and TIMI grade 3 flow from angiographical study was only achieved in 30% of the patients. Mortality reduction in acute myocardial infarction is dependent upon the efficacy of thrombolytic regimens with regard to reestablishing normal infarct-related artery flow. Successful reperfusion of initially occluded infarct-related coronary arteries is the result of a complex interplay among clinical, hemodynamic, mechanical and biochemical factors. While thrombolysis clearly is effective, it has a number of serious limitations like thrombolysis is ineffective in 20% to 30% of patients with ST-segment elevation.

Thrombolysis was determined to have been successful in 25 patients (73.5%), failed in 9 patients (26.5%) which also agree with lots of studies. The success rate in male and females patients was not significantly different (52% Vs 48%), while the failure rate in male was significantly higher than females (77.7% Vs 22.3%). The mean age of the group with successful thrombolysis was quite younger than the group who failed. Patients of inferior wall MI with or without posterior wall have significant success rate than of anterior wall MI (64% Vs 36%). Similarly smoker (current or ex-) had significant higher thrombolysis success rate than the non-smoker (64% Vs 36%) and hypertensive patients also had significant success than normotensive patients.

There are conflicting reports concerning the effect of infarct related artery location on early patency in response to thrombolytic therapy. The TIMI I investigators reported a greater reperfusion rate (TIMI 2 + TIMI 3) in the left anterior descending coronary artery compared to either the right or circumflex coronaries in patients who received double chain t-PA. GUSTO-I trial, with angiographic insights database represents the largest single trial patient population with complete demographic and angiographic data sets thus far utilized to detail important predictors of early infarct-related artery patency. It appears by multivariable analysis that the likelihood of achieving TIMI 3 flow 90-min postthrombolytic therapy in the right or left circumflex coronary artery is approximately 1.3 to 2.1 fold greater than the likelihood of achieving normal reperfusion in the left anterior descending coronary vessel. The location of the infarct segment within the infarct-related artery, that is, proximal or distal, also appears to be of importance and retains significance following adjustment for multiple clinical variables. The reason for the greater likelihood of achieving early normal flow in the right or circumflex vessels and in more proximal infarct segments of these vessels is most likely multifactorial and related, for example, to thrombus burden, plaque burden and possibly collateral flow in the infarct region. But the investigators were unable to determine the effect of collateral flow on early postthrombolytic therapy infarct-related artery patency because our database does not include pretreatment assessment of collateral flow status. Anderson et al., reporting for the TEAM-2 Investigators, found a significantly greater reperfusion rate (TIMI 2 + TIMI 3) in the combined right and circumflex coronary arteries compared to the left anterior descending with anistreplase but no difference in vessel-specific patency rates with streptokinase. Pacouret et al. and Leizorovicz et al. failed to find any significance of infarct-related artery on patency (TIMI 2 + TIMI 3) rates with either anistreplase or streptokinase even after adjustment for clinical variables.
Smokers may have a more complete fibrinolytic response to thrombolysis, leading to improved vessel recanalization for the same degree of stenosis compared with non-smokers. A detailed analysis of the paradoxical beneficial effects of smoking with regard to mortality in patients receiving thrombolytic therapy for acute myocardial infarction has been reported using the GUSTO-I Angiographic Study database.\(^{28}\) A significant difference was noted in early (90-min) TIMI 3 patency rates between patients with a history of smoking and those who never smoked in favor of those with a smoking history (41% vs. 33%, \(p = 0.02\)). The TEAM-2 investigators also reported that current smokers have a significantly greater chance of achieving TIMI 3 flow in infarct related arteries 90–240 min following thrombolysis in patients treated with either streptokinase or anistreplase.\(^{29}\) The beneficial effect of smoking remained significant in that study after adjustment for baseline clinical and angiographic variables and was independent of the infarct-related artery.\(^{29}\) Based on a much larger data set, Barbash et al supports the TEAM-2 findings with regard to early patency and patient smoking status. The physiologic mechanism responsible for this phenomena remains to be explained but may be related to a greater initial thrombus burden and less plaque burden in smokers.\(^{29}\)

Success and failure of thrombolysis were assessed in either eight intervals of 3 hours or six intervals of 4 hours, starting from midnight, in order to find out whether there are circadian fluctuations in the thrombolytic potency and efficacy of streptokinase. Thrombolytic therapy with streptokinase has a definite circadian pattern of efficacy, as defined by the clinical criteria, peak creatine kinase levels, time elapsed from thrombolysis initiation to peak creatine kinase, Killip class, time to disappearance of pain, time to 50% recovery of ST segment shift, and presence of reperfusion arrhythmias, as well as TIMI flow grade III in coronary angiography. Efficacy was higher in the afternoon and early evening hours and during these hours it was not related to the time elapsed from pain onset to thrombolysis initiation, gender, individual risk factors, or infarct location. When the 24-h day was divided into eight 3-hour intervals from midnight, a peak of success was observed between 12.00–21.00 h; 72% of all successful cases were observed in this time interval compared with 33.3% of all failed cases, while between 21.00–24.00 h, the percentage of successes was 8% compared with 22.2% of all failures.

These findings are concordant with the relative resistance to thrombolysis with t-PA and urokinase during morning hours and higher success rate during late afternoon/early evening hours reported by Kono\(^{16}\) E. Goldhammer\(^ {30}\) and Kurnik\(^ {14}\) who used the same clinical and angiographic indices for evaluation of diurnal variations in thrombolysis efficacy. E. Goldhammer et. al found that the evidence for better efficacy in the late afternoon/early evening hours is two-fold; firstly, 30.23% of all successful thrombolytic treatments occurred in the 16.00–20.00 h period, and secondly, among patients who were treated during these hours, 86.4% had successful thrombolysis.\(^ {30}\) Thus, the circadian variations in thrombolysis efficacy and success rate which have been shown for the most frequently used thrombolytic agents are probably independent of the type of agent used.

Chronic use of low-dose aspirin may lead to a circadian shift of acute myocardial infarction incidence, with a greater reduction during the morning waking hours.\(^ {31}\) Acute
administration just prior to streptokinase administration in our study patients could have potentiated somewhat the overall success rate of streptokinase efficacy but certainly could not have an effect on the relative success/failure rates in each time segment.

The a priori hypothesis for this study defined streptokinase efficacy as the variable being analysed for a circadian pattern, and thus the time of initiation of treatment is the independent variable. These findings may have several clinical implications; dose adjustment of streptokinase according to the time of day may be required, with higher doses during morning hours, or a preference for primary angioplasty in order to avoid the increase in bleeding complications, particularly intracerebral hemorrhage, related to higher doses of thrombolytic agents.

**Conclusion:**

Successful revascularization rate following thrombolysis with streptokinase in AMI using ECG criteria clearly demonstrate that inferior wall MI with or without posterior wall, smoker (current or ex-) and hypertensive patients had significant thrombolysis success rate than their counterparts. A definite time peak for successful thrombolysis could be detected at the afternoon and early evening hours. These findings may have several clinical implications.

**References:**


