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Effects of streptokinase in patients presenting within 6 hours of prolonged chest pain with ST segment depression

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Abstract

***Background*—The effects of streptokinase on the occurrence of a combined clinical outcome in patients presenting with recent chest pain and ST depression were investigated in view of the role of thrombus in the pathogenesis of acute ischaemic syndromes.**

***Methods*—112 patients aged ⩽75 years presenting within 6 h of the last episode of ischaemic chest pain of least 20 min duration with ⩾1 mm ST depression were randomised in a double blind manner to receive either streptokinase 1·5 million units over 30 min (n = 57) or placebo (n = 55). The primary end point was the combination of death, frequency of myocardial infarction (defined as peak creatine kinase >600 U/ml), need for angiography because of uncontrollable ischaemia, and an exercise test within 35 days showing ⩾1 mm ST depression at ⩽6 min. The secondary end points were safety, frequency of chest pain, readmission with myocardial infarction or unstable angina, or need for revascularisation between 35 days and 1 year. The severity of ST depression on presentation was analysed with respect to clinical outcome.**

***Results*—The frequency of the combined hierarchical end point of death, myocardial infarction, early angiography, and a positive exercise test was 82% (47 of 57 patients) with streptokinase and 75% (41 of 55 patients) with placebo. There were four deaths, two in each group. 27 patients (47%) receiving streptokinase and 22 (40%) receiving placebo developed myocardial infarction. 11 patients (eight streptokinase and three placebo) required coronary arteriography and subsequent revascularisation because of angina uncontrolled by medical treatment. 44 patients (22 in each group) had a positive exercise test. There were three further cardiac deaths (one streptokinase, two placebo), and three non-cardiac deaths within 1 year. A conservative approach to intervention was adopted and over a period of 1 year 29 patients (26%) (13 streptokinase and 16 placebo) underwent revascularisation procedures. Three patients (two streptokinase and one placebo) required transfusion. ST depression ⩾3 mm had 90% specificity but only 60% positive predictive value for myocardial infarction at presentation (P = 0·008, stepwise logistic regression). ST depression ⩾2 mm was predictive of death, late development of myocardial infarction, or a need for angiography (P = 0·02).**

***Conclusion*—Patients presenting with ischaemic chest pain and ST depression frequently develop myocardial infarction. Severe ST depression is predictive of an adverse outcome. The 35 day (3·6% cardiac and total) and 1 year mortality (8·9% total, 6·3% cardiac) are low with conservative management and expeditious revascularisation. Streptokinase treatment within 6 h of the last episode of pain does not seem to be beneficial.**

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Keywords: unstable angina; thrombolytic treatment; ST depression

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Angiography and angioscopy have identified intracoronary thrombus in many patients presenting with recent chest pain and ST depression.[1–4] Traditional treatment has used antianginal medication such as β blockers, nitrates, and calcium channel blockers, but these agents do not have a significant effect on intracoronary thrombus and have not been shown to reduce the incidence of myocardial infarction or death. Antiplatelet and antithrombin treatments that are particularly directed at thrombus, however, have been shown to be beneficial in patients with unstable angina.[5–8]

Thrombolytic treatment decreases the amount of intracoronary thrombus,[2 9] but the effects of such treatment on clinical end points have been variable, with some studies suggesting benefit while others have not.[10–17] The second international study of infarct survival (ISIS-2) and gruppo italiano per lo studio della streptochinasi nell'infarto miocardico (GISSI-1) studies showed that thrombolytic treatment with streptokinase in patients with ST depression was associated with no evidence of benefit and a 1 month mortality of 19–20%.[18 19] The results reflect in part the clinical heterogeneity of the patients included in the studies.

We hypothesised that if thrombolytic treatment could lyse intracoronary thrombus and allow healing and stabilisation of the disrupted plaque, subsequent management

could be based on the amount of inducible ischaemia and not mandated by the presenting clinical features and coronary arteriographic findings. We therefore examined the effect of streptokinase in patients whom we considered to have a high likelihood of intracoronary thrombus and a high risk of developing myocardial infarction. Patients presenting within 6 h of an episode of chest pain at rest of at least 20 min duration and with $\geqslant 1$ mm ST depression were randomised to receive either streptokinase (1·5 million units over 30 minutes) or placebo in a double blind manner.

Patients and methods

PATIENT POPULATION

Consecutive patients aged $\leqslant 75$ years presenting to three coronary care units in Auckland within 6 h of an episode of chest pain at rest of at least 20 min duration and with $\geqslant 1$ mm ST depression (0·04 mm after the J point) in any electrocardiogram lead were entered in the trial from 1 November 1989 to 31 January 1992. The exclusion criteria were recent trauma including prolonged cardiac massage, a history of stroke, gastric or genitourinary bleeding during the previous 2 months, concurrent life threatening disease, sustained systolic blood pressure >200 mm Hg, and previous streptokinase treatment. Patients without contraindications received antiplatelet agents. Concurrent medication was given according to the physician's practice. It was recommended, however, that β blockers, oral nitrates, calcium channel blockers, intravenous glyceryl trinitrate, and heparin be used in that order and incrementally according to symptoms.

END POINTS

The primary end point within 35 days of initial presentation was a composite of death, development of myocardial infarction, need for angiography because of continuing ischaemic pain uncontrolled by medication, or a positive exercise test defined as >1 mm ST depression within 6 min of the Bruce protocol associated with dyspnoea or chest pain. Secondary end points were safety, readmission with myocardial infarction or unstable angina, need for revascularisation after 35 days, and the number of episodes of chest pain recorded by patient diaries during the first 35 days. A conservative policy was adopted towards cardiac catheterisation, the indication being recurrent angina uncontrolled by medication or associated with electrocardiographic changes at rest or during exercise testing before 6 min of the Bruce protocol. Revascularisation was performed for left main coronary artery stenosis or for symptoms unable to be controlled by medical treatment. Patients were followed for 1 year.

Myocardial infarction was defined as chest pain associated with a peak creatine kinase of twice normal for our laboratory (>600 U/ml) in conjunction with the development of Q waves, or evolutionary ST or T wave changes. Serum creatine kinase was measured on admission and at 12, 24, 48, and 72 h. Patients with creatine kinase greater than twice normal within 12 h were considered to have myocardial infarction on presentation. The severity of ST depression was examined as a predictor of myocardial infarction at presentation and for a composite outcome of death, late myocardial infarction (>12 h after admission), or need for urgent angiography.

STATISTICAL ANALYSIS

To show a reduction (power 80%; $P < 0·05$) from 80% to 55% in the end points of death, myocardial infarction, need for angiography or a positive exercise test, 54 patients in each group would be required. Results for continuous variables are expressed as mean (SD) and differences between means are compared by one way analysis of variance. All p values are two tailed. Categoric variables are compared by the χ^2 test with Yates' correction for continuity in 2 × 2 tables; $P < 0·05$ was regarded as significant. Stepwise logistic regression was performed entering all baseline variables into the model.

Table 1 Baseline characteristics

	Streptokinase (n = 57)	*Placebo (n = 55)*
Age (years)	63 (11)	63 (9)
Male	38 (67)	42 (76)
Previous angina	36 (63)	33 (60)
Previous myocardial infarction	20 (35)	18 (33)
Previous CABG	6 (11)	9 (16)
Hypertension	27 (47)	17 (31)
Diabetes mellitus*	9 (16)	2 (4)
Current smoking	12 (21)	17 (31)
Cholesterol (mmol/l)	6·5 (1·4)	6·4 (1·3)
Triglycerides (mmol/l)	2·2 (1·5)	1·7 (1·6)
HDL cholesterol (mmol/l)	1·1 (0·4)	1·0 (0·7)
LDL cholesterol (mmol/l)	4·6 (1·3)	4·4 (1·1)

Values in parentheses are percentages except for age and lipid concentrations (mean (SD)). *There were no differences in baseline characteristics between the groups except for diabetes ($P = 0·04$). CABG, coronary artery bypass grafting; HDL, high density lipoprotein; LDL, low density lipoprotein.

Results

112 consecutive patients presenting within 6 h of ischaemic chest pain at rest and with $\geqslant 1$ mm ST depression on the presentation electrocardiogram were randomised in a double blind manner to receive either streptokinase 1·5 million u (n = 57) or placebo (n = 55). One year follow up was completed in 99·1%, with one patient moving overseas. The baseline characteristics of the patient groups were similar (table 1). Antiplatelet treatment was administered to 97% of patients: 70 received aspirin and 39 the thromboxane A_2 receptor antagonist GR32191. Of the three patients who did not receive antiplatelet agents, two were taking non-steroidal anti-inflammatory drugs and one had thrombocytopenia. Other concurrent medication during the first 48 h was according to the preference of the physician (table 2).

EFFECTS OF STREPTOKINASE

The frequency of the combined hierarchical

end point of death, myocardial infarction, early angiography, or a positive exercise test was 82% (47 of 57 patients) with streptokinase and 75% (41 of 55 patients) with placebo (table 3). Two patients in each group died in hospital (two of shock in the streptokinase group, one of shock and one of rupture in the placebo group). Twenty seven patients (47%) in the streptokinase group and 22 (40%) in the placebo suffered a myocardial infarction. An initial increase in creatine kinase >600 U/ml occurred more than 12 h after admission in 16 patients (eight streptokinase and eight placebo). Fourteen patients (six streptokinase and eight placebo) had a Q wave and 35 (21 streptokinase, 14 placebo) a non-Q wave myocardial infarction.

Eleven patients required cardiac catheterisation because of angina uncontrolled by medical treatment, nine of whom had ⩾2 mm ST depression associated with chest pain. Of the remaining 101 patients, 90 underwent exercise testing within 5 weeks of presentation. Of the 11 patients who did not undergo exercise testing, four had died, five were precluded by other serious medical conditions, and in two cases the physician declined. Forty four patients had ⩾1 mm ST depression within 6 min of exercise associated with chest pain or dyspnoea (22 each in the streptokinase and placebo groups); 10 stopped within 6 min because of fatigue, leg pain, or either angina or dyspnoea without ST changes.

There was no difference in the secondary end point of recorded episodes of chest pain. Eighty three patients (42 streptokinase, 41 placebo) had recurrent chest pain over 35 days with 604 episodes in the streptokinase group and 508 in the placebo (table 3). Nor was there any difference in the number of episodes of chest pain in hospital (206 streptokinase *v* 190 placebo). There were no differences in the recorded episodes of chest pain in the first 24 h (11 streptokinase *v* 15 placebo) or 48 h (27 streptokinase *v* 38 placebo).

Revascularisation was performed in 10 patients in the streptokinase group and 10 in the placebo for severe symptoms or left main stenosis (two streptokinase, one placebo). There was no haemorrhagic stroke. Three patients (two streptokinase, one placebo) had ischaemic stroke. Three patients (two streptokinase, one placebo) required transfusion for bleeding.

Table 2 Concurrent treatment (0–48 hours)

	Streptokinase (n = 57)	*Placebo (n = 55)*
Aspirin	36 (63)	34 (62)
Other antiplatelet agent	20 (35)	19 (35)
No antiplatelet agent	1 (2)	2 (4)
β blocker	22 (39)	28 (51)
Oral nitrates	18 (32)	19 (35)
Intravenous nitrates	2 (4)	9 (16)
Calcium antagonists	17 (30)	21 (38)
Heparin (intravenous)	7 (12)	10 (18)

Values in parenthesis are percentages.

Table 3 Patient outcomes at 35 days

	Streptokinase (n = 57)	*Placebo (n = 55)*
Primary end points		
Death	2	2
Myocardial infarction	27 (24)	22 (21)
Early angiogram	8 (3)	3 (1)
Positive exercise test*	22 (14)	22 (14)
Freedom from the above	10	14
Secondary end points		
Episodes of chest pain	604 [42]	508 [41]
Chest pain in hospital	206 (36)	190 [41]
Readmission	5	5
CABG	10	8
Angioplasty	0	2

Values in parentheses are the ranking of end points in the hierachial order death, myocardial infarction, early angiogram, and ⩾1 mm ST depression at 6 min on exercise testing (χ^2 4 × 2 = 0·80, $p > 0·5$). Values in square brackets are the number of patients with recurrent pain. *Defined as ⩾1 mm ST depression associated with either chest pain or breathlessness within 6 min of the Bruce protocol. CABG, coronary artery bypass grafting.

Table 4 Severity of ST depression and development of myocardial infarction

	At presentation		*During admission*	
	⩾2	⩾3	⩾2	⩾3
Sensitivity (%)	50	35	40	29
Specificity (%)	63	90	63	90
Positive predictive value (%)	37	60	49	70

*Table 5 Multivariate analysis of risk of a composite of adverse outcomes**

Variable	*Parameter estimate*	*Standard error*	χ^2	*Probability* $>\chi^2$	*Standardised estimate*	*Odds ratio*
Intercept	1·1748	0·7221	2·6470	0·1037		3·238
Age ⩾70 years	–0·0606	0·5168	0·0137	0·9067	–0·015986	0·941
Male	0·4035	0·5329	0·5734	0·4489	0·100948	1·497
Previous infarction	–0·5119	0·5096	1·0094	0·3150	–0·134238	0·599
Hypertension	0·5737	0·5300	1·1717	0·2790	0·155172	1·775
Diabetes	0·5636	0·8153	0·4779	0·4894	0·092895	1·757
Previous CABG	–0·4482	0·6636	0·4561	0·4994	–0·084532	0·639
ST depression ⩾2 mm†	–1·1472	0·4917	5·4434	0·0196	–0·312556	0·318
Smoking	0·7517	0·6570	1·3091	0·2526	0·182362	2·121
Cholesterol	0·2790	0·5183	0·2897	0·5904	0·074806	1·322

*Death, development of late myocardial infarction, or the need for urgent angiography. †P < 0·01, stepwise logistic regression. CABG, coronary artery bypass grafting.

ST SEGMENT DEPRESSION AND OUTCOME

While ST depression ⩾3 mm was 90% specific for myocardial infarction at either presentation or any stage during admission (table 4), the sensitivity was low (35% and 29% respectively). ST depression of ⩾3 mm was the only baseline characteristic predictive of myocardial infarction at presentation (P = 0·008, stepwise logistic regression). On multivariate analysis of all baseline characteristics (table 5) ST depression ⩾2 mm was the only predictor of a composite end point of death, development of myocardial infarction, or the need for urgent angiography (P = 0·02), but it was not predictive of a combined end point which also included the presence of a positive exercise test (P = 0·2). The effect of streptokinase on outcome was similar to that of placebo regardless of the degree of ST depression on admission (table 6).

OUTCOME AT 1 YEAR

During the year after initial presentation there were no significant differences in outcome between the streptokinase and placebo groups (table 7). There were three further cardiac and three non-cardiac deaths. Two patients

Table 6 Outcome according to amount of ST depression and treatment

	<2 mm		⩾2 mm	
	Streptokinase (n = 31)	*Placebo (n = 35)*	*Streptokinase (n = 26)*	*Placebo (n = 20)*
Death	0	0	2	2
Myocardial infarction	14	12	13	10
Urgent angiography	1	1	7	2
Positive exercise test	12	14	10	8
Freedom from the above	7	11	3	3
Episodes of chest pain	332 [21]	280 [24]	272 [21]	228 [17]
Readmission	3	3	0	4
CABG	4	2	6	6
Angioplasty	0	2	0	0

Values in square brackets are the number of patients with recurrent pain. CABG, coronary artery bypass grafting.

Table 7 Total events from day 0 to 1 year

	Streptokinase (n = 57)	*Placebo (n = 55)*
Death	5 (9)	5 (9)
Non-fatal MI	27 (47)	22 (40)
Reinfaction	2 (4)	1 (2)
CABG	11 (19)	14 (25)
Angioplasty	2 (4)	2 (4)
Freedom from the above	17 (30)	19 (35)

Values in parentheses are percentages. CABG, coronary artery bypass grafting.

receiving placebo died of heart failure and one patient receiving streptokinase died suddenly. Two non-cardiac deaths were caused by chronic renal failure (both streptokinase) and one by chronic obstructive pulmonary disease (placebo). There were 17 readmissions for unstable angina (10 streptokinase and seven placebo) and revascularisation was required in nine patients (three streptokinase and six placebo). The total mortality at 1 year was 8·9% (cardiac 6·3%).

Discussion

This study shows that thrombolytic treatment with streptokinase has no effect on a combined end point of death, myocardial infarction, need for angiography for ischaemia not controlled by medical therapy, or inducible ischaemia within 6 min of exercise on the Bruce protocol. Patients presenting within 6 h of chest pain of at least 20 min duration associated with continuing ST depression were enrolled. We considered that this group of patients would be most likely to have intracoronary thrombus.

Thrombolytic treatment has been shown to reduce mortality[18–21] and preserve left ventricular function[22] in patients with ST elevation. For patients with ST depression the data are limited by a lack of statistical power and no benefit has been demonstrated.[18 19 23 24] In many patients with ST depression the ischaemia producing coronary artery is patient, although usually containing thrombus,[2] and it is therefore unlikely that thrombolytic treatment would improve perfusion in this group. These patients may therefore derive no benefit but be exposed to the bleeding risks of thrombolytic treatment. Our results may also in part be the result of the fact that thrombolytic treatment is procoagulant, as there is significant *in vivo* activation of platelets when streptokinase is used in acute myocardial infarction.[25] Thrombolysis also exposes clot bound thrombin which is a potent stimulus for platelet aggregation.[26] The thrombus may be, or may become, platelet rich[3] or extensively cross-linked with fibrin and resistant to thrombolysis. These procoagulant effects could result in conversion of a subocclusive to an occlusive thrombus and an increased incidence of infarction.[10 27]

This study, like previous ones,[18 19 23] was not large enough to determine differences in mortality. The previous ISIS-2,[18] third international study of infarct survival (ISIS-3),[28] GISSI-1,[19] and late assessment of thrombolytic efficacy (LATE)[29] trials included a total of 3563 patients with ST depression. The mortality of the control patients was 13·8% and of the thrombolytic treated patients 15·2%[23]; the confidence intervals in these trials were wide. In the present study the 1 year cardiac mortality was 6·3%, considerably lower than in these trials and in the report by Lee *et al*[30] from Aberdeen of 26%. In the retrospective observational study from Aberdeen the time from pain onset was not reported and the patients may have had more comorbidity. Furthermore, 54% had had a previous infarction compared with 34% in our study.

The thrombolysis in myocardial infarction (TIMI IIIB) study compared tissue plasminogen activator therapy with placebo in patients presenting within 24 h with unstable angina or non-Q wave myocardial infarction and found no difference in outcome.[24] This study was performed in the United States and Canada and reported a mortality of 2·4% at 6 weeks. ST depression was present in 32% and 41% had a history of prior myocardial infarction. A combined end point of mortality or myocardial infarction was 11·5% at 1 year.[31] The mean age of patients in the TIMI IIIB study (59 years) was younger than in those reported here (63 years) and almost a decade younger than those reported by Lee *et al*[30] (68 years). Age is an important determinant of outcome in patients with ST depression and it is likely that the differences in outcome at 1 year are in part a reflection of age differences.[23] The better outcome in the TIMI IIIB trial may also relate to exclusion of patients with comorbidity.

Differences in outcome may also be the result of differences in revascularisation rates. Although the TIMI IIIB trial[24] showed no differences in outcome at 6 weeks or 1 year for patients with unstable angina randomised to either a conservative strategy or invasive strategy, the revascularisation rates at 6 weeks were 49% in the conservative strategy group and 61% in the invasive strategy group. At 1 year the revascularisation rates were 58% in the conservative strategy group and 64% in the invasive strategy group.[31] Had the rate of revascularisation in the conservative strategy group been significantly less, differences in outcome might have been shown. Revascularisation rates were not reported in the Aberdeen study. A strategy of selective expeditious revascularisation in patients with

marked ST depression on the admission electrocardiogram or recurrent pain, especially if associated with recurrent ST depression, could result in a better outcome than a more conservative approach with revascularisation only for uncontrollable symptoms. In our study revascularisation was performed in 18% of patients within 35 days and 26% within 1 year.

Patients with ST depression and recent chest pain represent a heterogenous group at high and low risk in whom the coronary artery anatomy is not well defined.[32] Patients with thrombotic occlusion of a circumflex artery may well be a group in whom thrombolytic treatment may be beneficial. These patients cannot be readily identified, however, by standard 12 lead electrocardiographic criteria.[33] Also severe ST depression of $\geqslant 3$ mm is 90% specific for myocardial infarction on presentation, but which of these patients may benefit from thrombolytic treatment remains to be addressed.

Some patients who have single vessel disease present with a posterior or lateral myocardial infarction pattern on their electrocardiogram are at low risk. Patients at high risk include those with severe three vessel disease and those with a history of previous infarction and impaired left ventricular function. Assessment of left ventricular function and coronary angiography are important in identifying these patients as coronary artery bypass surgery may improve their long-term survival.[34] In our study, patients with $\geqslant 2$ mm ST depression were more likely to have a combined adverse outcome of death, late development of infarction, or need for urgent angiography. Whether some of these patients would benefit from an aggressive reperfusion protocol or revascularisation strategy, or both, remains to be determined.

Patients with ST depression and recent, prolonged chest pain frequently have infarction on admission. Administration of streptokinase does not reduce the incidence of infarction, death, need for angiography, or the number of positive exercise tests. The hospital and 1 year mortality are low in these selected patients when a strategy of medical treatment and selective expeditious revascularisation is used. Whether newer antithrombin agents such as hirudin[35] or hirulog,[36] or antiplatelet agents such as inhibitors of the IIb-IIIa receptors[37] or their combinations, will improve clinical outcome of patients presenting with ST depression remains to be shown by ongoing trials.

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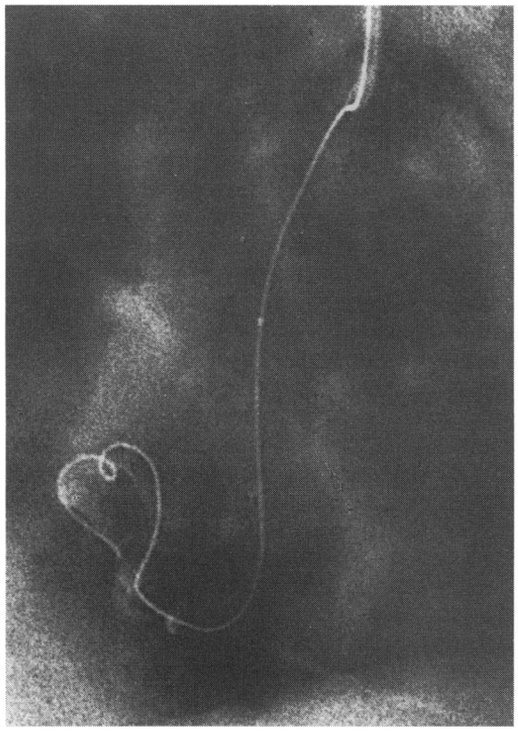
IMAGES IN CARDIOLOGY

Guide wire graffito



For cardiologists, coronary angioplasty has become a commonplace since its controversial beginnings in 1977. One operator (Professor Bernhard Meier of Bern) was reminded of the emotional dimensions of this high tech procedure when the guide wire graffito, shown opposite, appeared during a procedure.