Chest pain with nondiagnostic electrocardiogram in the emergency department: a randomized controlled trial of two cardiac marker regimens

Research

Recherche

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Abstract

Background: Early detection of acute myocardial infarction (AMI) may save lives. In the emergency setting, it is unclear whether the early use of certain cardiac markers (myoglobin and cardiac troponin I [cTnI]) assists in making appropriate decisions whether to admit or discharge patients with chest pain of possible ischemic cause who have nondiagnostic electrocardiograms (ECGs). We performed a study to determine whether the addition of new cardiac markers in the emergency department results in improved clinical decisions.

Methods: A single-blind randomized controlled trial was conducted between June 1997 and June 1998 in a tertiary care emergency department in Kingston, Ont. Of 296 patients aged 30 years or more who presented to the emergency department with chest pain and nondiagnostic ECGs, 146 were randomly assigned to the intervention group (determination of baseline creatine kinase [CK] level, CK MB fraction and cTnI level, and myoglobin level at baseline and at 2 hours) and 150 to the control group (determination of baseline CK level and CK MB fraction). Outcome measures included the rate of admission to the inpatient cardiology service and length of stay in the emergency department.

Results: Of the 296 patients, 34 (11.5%) received a diagnosis of AMI in the emergency department, and 92 (31.1%) had chest pain of noncardiac cause. Patients in the intervention group were less likely than those in the control group to be admitted to the cardiology service (67 [45.9%] v. 81 [54.0%]). The absolute difference in the proportion (8.1% [95% confidence interval –3.3 to 19.5]), although potentially important clinically, was not statistically significant. The length of stay in the emergency department was essentially the same in the 2 study groups. At 30 days, the proportions of patients with a diagnosis of recurrent angina (58.2% in the intervention group and 58.0% in the control group) and AMI (12.3% and 14.7%) were also similar.

Interpretation: The optimal cardiac marker panel to be used in the emergency department remains unknown. The addition of serial testing of myoglobin with cTnI confirmation to the standard panel did not substantially change the clinical management or outcomes of patients presenting with chest pain and nondiagnostic ECGs.

Acute myocardial infarction (AMI) is the leading cause of cardiovascular death.[1] Early diagnosis is of paramount importance. Despite clear-cut diagnostic criteria,[2] identification of AMI can be challenging: one-third of affected patients do not have typical anginal chest pain, and the initial electrocardiogram (ECG) is nondiagnostic in 40%.[3–7] In 70% of cases, hospital admissions to "rule out" AMI have a noncardiac discharge diagnosis.[8–12] About 1% to 4% of patients discharged from the emergency department experience AMI.[8,11,13] Delays in clinical decision-making may reduce the opportunity to deploy available strategies to salvage myocardium.[4,5,13–16] For patients presenting with chest pain but at low risk for AMI or ischemia, hospital admission is an expensive option.[17–19]

In patients with chest pain and nondiagnostic ECGs, the diagnosis of AMI de-

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pends on the selected use of cardiac markers. Our institution and others[20] have relied on serial testing of the serum level of creatine kinase (CK) and its MB isoenzyme fraction (CK MB fraction) after hospital admission. Myoglobin and cardiac troponins I (cTnI) and T (cTnT) are new tests with diagnostic and prognostic potential. The time profile of cTnI parallels that of the CK MB fraction. It has an added benefit of late detection of AMI, its level remaining elevated for 5 to 7 days after myocardial injury. Unlike the CK MB fraction, cTnI is cardiospecific and is elevated only in patients with myocardial injury.[21–25] Algorithms have been proposed to identify patients at low risk, and strategies have been developed to shorten the hospital stay.[26–33] "Observation and chest pain units" are purported to avoid unnecessary hospital admissions.[12]

In the emergency setting, there is a lack of consensus about which cardiac markers effectively exclude the necessity of inpatient or observation unit monitoring of patients with nondiagnostic ECGs. Certain combinations of cardiac markers demonstrate high sensitivity for the identification of patients with AMI, but this evidence comes mainly from retrospective analysis of inpatients. Few studies have focused on patients without ECG evidence of injury or ischemia on presentation.[34–37]

We conducted a single-blind randomized controlled trial in the emergency department to evaluate the efficacy of 2 different cardiac marker regimens in making decisions about the disposition of patients with chest pain whose ECGs are nondiagnostic. Our study hypothesis was that, compared with baseline CK level and CK MB fraction alone, the addition of baseline myoglobin and cTnI levels and 2-hour myoglobin level would improve decisions regarding admission or discharge. End points included reduction in the proportion of patients admitted to the cardiology service, in the proportion of admitted patients who were discharged with an identifiable noncardiac cause for the presenting chest pain, and in the rate of adverse cardiac outcomes at 48 hours and 30 days among both admitted and discharged patients.

Methods

The study was conducted in the Emergency Department of Kingston General Hospital, Kingston, Ont., a tertiary care centre serving a population of 250 000. The study population consisted of patients who presented to the emergency department with chest pain of possible cardiac cause. The inclusion criteria were age 30 years or more, chest pain at rest for 30 minutes or longer, occurring within 12 hours of presentation to the emergency department, and inability to rule out an ischemic cause. Patients were excluded if they had a definitive diagnosis of AMI or acute coronary ischemia based on ECG findings of ST segment elevation or depression, had chest pain of proven cause (musculoskeletal, gastrointestinal or pulmonary), had previously documented abnormalities in CK level or CK MB fraction, had renal failure or had participated in another research trial within the previous 3 months. The study was conducted from June 1, 1997, to June 30, 1998.

The Queen's University Research Ethics Board approved the study design. Patients provided written consent to be randomly assigned to 1 of 2 study groups and to provide blood samples for laboratory tests, for their medical records to be used for research purposes, and to be contacted and interviewed following their initial treatment. Baseline testing included determination of the CK level and CK MB fraction, and measurement of myoglobin and cTnI levels for all patients. An additional sample for myoglobin testing was obtained 2 hours later.

Randomization was performed as follows. Before the study, a list of 300 random allocations (150 intervention and 150 control) was created, and each code was inserted into a sealed opaque envelope. The envelopes were ordered randomly and were filed in a box. Randomization was completed on an individual basis by having research staff select an envelope. The contents of the envelope included the order made to the hospital laboratory, and this indicated which regimen of cardiac marker results would be made available to attending emergency department staff.

The patients assigned to the control group received the standard panel of cardiac marker tests (baseline CK level and CK MB fraction). The patients assigned to the intervention group received an expanded panel of cardiac marker tests (CK level and CK MB fraction and cTnI level at baseline, and myoglobin level at baseline and at 2 hours).

Clinical follow-up occurred 48 hours and 30 days after the emergency department visit. The evaluated outcome measures were as follows:

Primary	Proportion of patients admitted to cardiology service
Secondary	Noncardiac hospital admission
	Length of stay (in hours) in emergency department
	Acute myocardial infarction in discharged patient
Clinical*	Recurrent angina
	Acute myocardial infarction
	Congestive heart failure
	Sustained arrhythmia
Other*	Return to emergency department
	Return to family doctor
	Follow-up hospital admission
	Hospital readmission
	Angioplasty
	Bypass surgery
	Death

*Assessed at 48 hours and 30 days.

Laboratory methods

The CK MB fraction, cTnI level and myoglobin level were measured by means of 2-site monoclonal antibody sandwich methods. Myoglobin and cTnI were measured on the ACCESS Immunoassay System (Sanofi Diagnostics Pasteur S.A., Mamesla-Coquette, France). The CK MB fraction was measured on the Technicon Immuno 1 (Bayer Corporation, Tarrytown, NY). The CK level (Beckman Instruments Inc., Brea, Calif.) and the CK MB fraction were always measured on receipt of the sample. The myoglobin and cTnI levels were measured immediately if the patient had been assigned to the intervention group, or frozen at

–70°C and measured in batches within the next month for the control group.

The reference range for CK was 55 to 197 U/L for men and 35 to 155 U/L for women. Testing for the CK MB fraction was negative if the absolute mass was less than 8 μg/L; it was positive if the absolute mass was greater than 8 μg/L with a relative index ([CK MB × 100]/CK) greater than 3%. The borderline range (absolute mass of 8 μg/L or greater with a relative index of 3% or less) was considered positive in this study. Testing for myoglobin was positive if either sample was greater than 90 μg/L or if the second sample was more than double the first and greater than 50 μg/L. The reference range for cTnI was validated in our laboratory by clinical correlation with values for a series of coronary care unit patients with unequivocal AMI; samples from 30 healthy subjects were analysed to validate the reference interval. The cTnI result was positive if the result was greater than 0.15 μg/L.

Statistical analysis

The study had an 80% power to detect an absolute difference of 15% in admission rates to the cardiology service, assuming a baseline rate of admission of 54% and a 5% chance of a type I error. The data were analysed on an intent-to-treat basis. Statistical significance was defined a priori at a p level of less than 0.05 (2-sided). We compared primary and secondary study outcomes between groups using differences in proportion as the measure of association, and calculated 95% confidence intervals (CIs) according to methods described by Fleiss.[38]

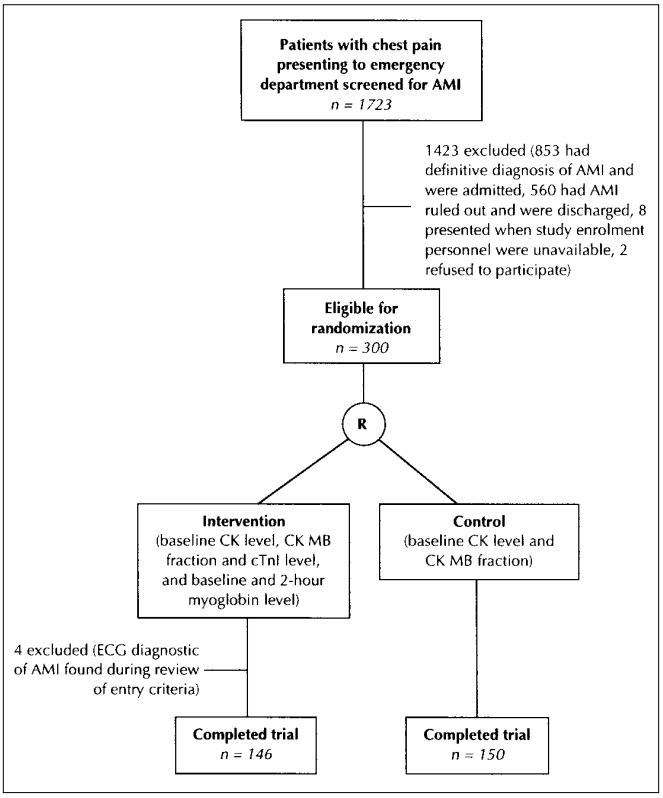

Fig. 1: Flow of study participants through screening and intervention protocols. AMI = acute myocardial infarction, CK = creatine kinase, cTnI = cardiac troponin I, R = randomization.

Results

Over the study period 1723 patients presented to the emergency department with chest pain (Fig. 1). After initial assessment (radiography, electrocardiography and laboratory analysis) 853 patients were admitted and 560 were discharged with certain evidence for or against AMI respectively. The remaining 310 patients without ECG evidence of ischemia formed the group available for study inclusion. Of the 310, 8 were not assigned to a study group because study enrolment personnel were unavailable, and 2 refused to participate in the study. Of the 300 remaining patients,

Table 1: Characteristics of patients presenting to emergency department with chest pain and nondiagnostic electrocardiograms who received 2 different cardiac marker regimens*

Characteristic	Group; no. (and %) of patients: Intervention *n = 146*	Control *n = 150*
Age, yr		
30–40	12 (8.2)	11 (7.3)
40–49	23 (15.8)	25 (16.7)
50–59	36 (24.7)	32 (21.3)
60–69	34 (23.3)	35 (23.3)
≥ 70	41 (28.1)	47 (31.3)
Sex		
Male	85 (58.2)	85 (56.7)
Female	61 (41.8)	65 (43.3)
Race		
White	143 (97.9)	148 (98.7)
Other	3 (2.0)	2 (1.3)
Duration of chest pain, h		
< 2	47 (32.2)	38 (25.3)
2 to < 6	59 (40.4)	50 (33.3)
6 to < 12	23 (15.8)	33 (22.0)
12 to < 24	13 (8.9)	14 (9.3)
≥ 24	3 (2.0)	5 (3.3)
Missing/unknown	1 (0.7)	10 (6.7)
Diagnosis from emergency department		
Angina	90 (61.6)	80 (53.3)
Acute myocardial infarction	15 (10.3)	19 (12.7)
Chest pain, undiagnosed	41 (28.1)	51 (34.0)
Risk factors for coronary artery disease†		
Hypertension	54 (37.0)	67 (45.0)
Diabetes mellitus	31 (21.4)	24 (16.1)
Smoking	88 (61.5)	84 (56.8)
Elevated lipid levels	33 (30.6)	42 (33.3)
Family history of coronary artery disease	85 (63.0)	87 (63.5)
≥ 1 risk factor	128 (87.7)	139 (92.7)

*Intervention group: baseline creatine kinase (CK) level and its MB fraction (CK MB fraction), baseline cardiac troponin I and myoglobin levels, and myoglobin level at 2 hours; control group: baseline CK level and CK MB fraction.
†Missing data for some patients.

150 were assigned to the intervention group and 150 to the control group. Four patients assigned to the intervention group were later ruled to be ineligible on retrospective review of entry criteria following enrolment, leaving a sample of 146 patients in this study arm.

Information on the primary outcome (admission to cardiology service) was collected for all patients. Information on length of stay in the emergency department was available for 142 patients in the intervention group and 148 patients in the control group. Complete assessment of cardiac events was done at 48 hours for 131 patients and 137 patients in the intervention and control groups respectively. The corresponding numbers at 30 days were 135 and 137. Of the 24 patients with incomplete assessments at 30 days, 11 had died, and 13 were lost to follow-up.

The 2 groups were well balanced in terms of baseline demographic characteristics, presenting symptoms and risk factors for coronary artery disease (Table 1). The study population had a median age of 61 years (interquartile range 50–71 years), and men accounted for 57.4%. The duration of chest pain before presentation to the emergency department varied (median interval 2–6 hours) and was greater than 12 hours for 11.8% (35/296) of the patients. The hospital admission rate was 50%. Test regimens did not affect the timing of the discharge decision. At baseline AMI was confirmed in 34 patients (11.5%), unstable angina was diagnosed in 170 (57.4%), and 92 patients (31.1%) had a final diagnosis of chest pain of noncoronary cause (Table 1). Of the 148 patients admitted to hospital, 26 (17.6%) had a discharge diagnosis of chest pain without identified cardiac cause (Table 2).

Patients in the intervention group were less likely than those in the control group to be admitted to the cardiology service (45.9% v. 54.0%) (Table 2). The absolute difference of 8.1% (95% CI –3.3% to 19.5%), although potentially important clinically, was not statistically significant. Length of stay in the emergency department was similar in the 2 groups. This was true overall and when the groups were stratified by admission status (Table 2). Among patients admitted to the cardiology service, the risk of having a noncardiac diagnosis was lower by 4.9 percentage points (95% CI –9.0% to 13.5%) in the intervention group than in the control group (14.9% v. 19.8%).

At 30 days the proportions of patients with a diagnosis of recurrent angina (58.2% in the intervention group v. 58.0% in the control group) and AMI (12.3% v. 14.7%) were also similar (Table 3).

A total of 40 AMIs occurred during the study, 35 within 48 hours, and 5 between day 3 and day 30. The overall death rate was 3.7%. The rate of return to the emergency department was 13.8%, resulting in 27 further admissions to hospital for cardiac causes.

Interpretation

We found a modest and nonsignificant difference in the rate of admission to the cardiology service between patients who received the standard cardiac marker tests (baseline CK level and CK MB fraction) and those who received an expanded panel of tests (baseline CK level, CK MB fraction, cTnI level and myoglobin level, and myoglobin level at 2 hours). The confidence limits do not exclude the possibility of clinically important differences in disposition of patients attributable to the availability of cTnI and serial myoglobin testing as cardiac markers in the emergency department.

The rate of AMI observed in our study, 12%, is comparable to findings from other investigations.[35–37,39] The rate of missed diagnosis of AMI was 0.34% (1/296) for the total population and 0.68% (1/148) for patients discharged from the emergency department. The latter proportion could have been 0% if the available values for myoglobin and CK MB fraction had been used in the decision whether to admit. A rate of 4% is the typical rate of missed AMI among patients presenting with chest pain to the emergency department.[8,11,13] Among admitted patients in our study, the proportion discharged with a noncardiac diagno-

Table 2: Outcomes of the emergency department encounter

Outcome	Group; no. (and %) of patients		
	Intervention	Control	Difference (and 95% CI)
Primary outcome			
Admitted to cardiology service	67 (45.9)	81 (54.0)	8.1 (–3.3 to 19.5)
Secondary outcomes			
Admitted patients			
Length of stay in emergency department, h			
> 3	63 (94.0)	72 (88.9)	5.1 (–1.2 to 11.4)
> 6	34 (50.7)	42 (51.8)	1.1 (–10.3 to 12.5)
> 12	2 (3.0)	3 (3.7)	0.7 (–3.4 to 4.8)
Missing/unknown	2 (3.0)	2 (2.5)	–
Noncardiac discharge diagnosis	10 (14.9)	16 (19.8)	4.9 (–3.7 to 13.5)
Discharged patients	*n = 79*	*n = 69*	
Length of stay in emergency department, h			
> 3	68 (86.1)	60 (87.0)	0.9 (–6.9 to 8.7)
> 6	17 (21.5)	16 (23.2)	1.7 (–8.8 to 11.1)
> 12	2 (2.5)	0	–
Missing/unknown	2 (2.5)	0	–
Acute myocardial infarction	1 (1.3)	0	–

Note: CI = confidence interval.

sis was low compared with that reported in other studies.[8–12]

At 30 days adverse outcomes in patients with nondiagnostic ECGs were common and of critical importance. A total of 58.1% reported recurrent chest pain. The overall death rate was 3.7%. The 30-day total of 175 admissions demonstrates the need for early accurate identification and risk stratification within this patient population.

One limitation of our study is that the attending physicians and other emergency department staff were not blinded to the randomization allocations. Although it is unlikely that chart documentation of study outcomes was biased, this situation may have influenced, in a differential manner, the extent of clinical investigation and degree of caution exercised in case management in the 2 study groups. The modest, yet clinically important, effect attributed to the additional cardiac markers themselves may be inflated owing to this detection bias. In addition, although our trial involved 296 participants, the sample was still too small to achieve the statistical power necessary to confirm the observed absolute difference of 8.1% in the rate of admission to the cardiology service. Finally, caution must be exercised in the generalization of the results beyond the study population of interest.

Table 3: Outcomes among discharged patients at 48 hours, admitted patients during the hospital stay, and at 30 days for all patients

	Group; no. (and %) of patients	
Admission status; outcome	Intervention	Control
Discharged patients: 48 hours	*n = 79*	*n = 69*
Recurrent angina	19 (24.0)	14 (20.3)
Acute myocardial infarction	1 (1.3)	0
Hospital admission	4 (5.1)	0
Return to emergency department	5 (6.3)	4 (5.8)
Death	1 (1.3)	0
Admitted patients: inhospital	*n = 67*	*n = 81*
Recurrent angina	24 (35.8)	32 (39.5)
Acute myocardial infarction	15 (22.4)	20 (24.7)
Congestive heart failure	7 (10.4)	13 (16.0)
Sustained arrhythmia	6 (9.0)	8 (9.9)
Angioplasty	4 (6.0)	8 (9.9)
Bypass surgery	3 (4.5)	5 (6.2)
Death	1 (1.5)	4 (4.9)
All patients: 30 days	*n = 146*	*n = 150*
Recurrent angina	85 (58.2)	87 (58.0)
Acute myocardial infarction	18 (12.3)	22 (14.7)
Direct hospital admission	67 (45.9)	81 (54.0)
Return to emergency department	23 (15.8)	18 (12.0)
Return to family doctor	80 (54.8)	70 (46.7)
Hospital admission following initial discharge	5 (3.4)	4 (2.7)
Hospital readmission	10 (6.8)	8 (5.3)
Death	5 (3.4)	6 (4.0)

Conclusion

The optimal testing regimen for patients presenting to the emergency department with nondiagnostic ECGs remains unknown. Although clinically significant improvements in decisions to admit or discharge cannot be ruled out, the additional cardiac markers (baseline and 2-hour myoglobin level and baseline cTnI level) did not substantially change the clinical management or outcomes of the patients in our study. Improvements in decisions to admit or discharge were substantially lower than would be expected from studies involving patients admitted to hospital.[34–37]

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