CARDIOVASCULAR MEDICINE

Headache response to glyceryl trinitrate in patients with and without obstructive coronary artery disease

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Objectives: To examine the hypothesis that glyceryl trinitrate (GTN) may cause headache in patients with normal coronary arteries more often than in patients with obstructive coronary artery disease (CAD). This simple assessment may aid clinicians in the initial evaluation of chest pain syndrome and possible CAD.

Patients and methods: 118 patients (66 men and 52 women) with new onset of chest pain were enrolled in this study. Patients were excluded from the study if they had a history of chronic headache, long term nitrates use, or any coronary artery procedures. Mean age of the patients was 62.5 years. Coronary angiography was performed within one month of GTN administration with the usual clinical indications such as recurrent chest pain, abnormal ECG, or abnormal results of stress tests. Thirty patients had normal coronary arteries or minimal or non-obstructive CAD. Eighty eight patients had obstructive CAD defined as luminal narrowing greater than 50% in any one or more of the left or right coronary arteries or their major branches. All the patients had a varying degree of relief of chest pain with GTN administration within 10 minutes. 36% of patients reported significant headache after GTN administration.

Results: In patients with normal coronary arteries or minimal CAD, 73% had significant headache caused by sublingual GTN. In patients with obstructive CAD, only 23% had significant headache after GTN use ($p < 0.001$). There were no differences in patients' sex and vascular risk factors concerning the frequency of headache in patients with or without obstructive CAD.

Conclusions: GTN causes significantly more frequent headache episodes in patients with normal coronary arteries or minimal CAD than in patients with obstructive CAD. This unique finding may provide clinicians with an additional tool for the differential diagnosis of patients with chest pain syndrome.

It is often difficult to determine whether chest pain is from obstructive coronary artery disease (CAD) or is of non-cardiac origin. Glyceryl trinitrate (GTN) (nitroglycerine) is used extensively by patients with chest pain syndrome and response to GTN assists in differential diagnosis. GTN is highly effective in coronary vasodilatation and in relieving angina in patients with obstructive CAD. However, many patients often have headache after sublingual administration of GTN. In some patients the headache can be severe enough to interfere with their hospitalisation and rest. Many patients were given GTN paste for an extended time despite their initial response of significant headache after sublingual use of GTN.

Sublingual GTN has been extensively used by patients with chest pain for more than a century.¹ It is a safe and highly effective treatment for patients with CAD and chest pain or angina pectoris. Physicians often give GTN to patients with chest pain of uncertain aetiology to determine the clinical significance of the symptoms. GTN can also be used alone or in combination with other agents to decrease the number of ischaemic episodes in patients with proven CAD or ischaemic cardiomyopathy with a high degree of effectiveness.² Nitrates undergo biotransformation with the subsequent liberation of exogenous nitric oxide, which causes vasodilatation.³ It is well known that GTN causes headache in a significant portion of the patients who initially receive it. However, the particular frequency of headache in patients with and without obstructive CAD has not been reported. We postulated that headache occurs much more often in patients without obstructive CAD or atherosclerosis caused by normal vasodilatory reserve in the systemic arterioles, especially in the cerebral circulation.

METHODS

Patient population

Four hundred patients who underwent diagnostic cardiac catheterisation procedures at Park Ridge Hospital, Rochester, New York, USA, were screened for this study. The study followed the guidelines of our institution review board concerning the confidentiality and safety of the patients. The patients' responses to GTN administration were documented if sublingual GTN caused any significant headache within one hour after the administration of the drug. The dose of sublingual GTN was 0.4 mg. Our patients were not advised of possible headache before GTN use. Patients with documented hypotension (systolic blood pressure < 100 mm Hg) or headache within six hours before any GTN use were excluded. Patients with a known history of chronic headache, long term GTN use, documented CAD, prior myocardial infarction, any myocardial revascularisation or heart valve procedures, and congestive heart failure were excluded from the study. A total of 118 patients met the criteria to be enrolled in the study. Coronary angiographic procedures were performed within one month of the initial GTN use.

Coronary angiography

The left and right coronary arteries were visualised in multiple standard views and qualitatively analysed by experienced operators. The results were classified as positive for obstructive CAD if lumen obstruction was greater than 50% diameter in any one or more of the coronary arteries or major branches; and negative for obstructive CAD if the lumen obstruction was none, minimal, or less than 50% diameter obstruction. The invasive and interventional

cardiologists independently recorded coronary angiograms and analysed the results. These cardiologists were not part of this study and were not aware of the different headache responses to GTN use in our patients with chest pain.

Statistical methods

We analysed binary variables with Pearson's χ^2 test and Yates's corrected χ^2 test when expected frequencies were below 10. Differences in the means of continuous measurements were tested by Student's *t* test. All statistical analyses were performed with the SPSS statistical software for Windows, version 7.5 (SPSS Inc, Chicago, Illinois, USA). Significance was declared at the 0.05 level.

RESULTS

Study cohort

Four hundred consecutive patients were screened and 118 patients were included for final analysis (66 men and 52 women). The age ranged from 36–88 years. The mean (SD) age was 62.5 (12.7) years. Patients with obstructive CAD were significantly older than the non-obstructive CAD subgroup. All the other traditional vascular risk factors were not significantly different between patients with and without obstructive CAD (table 1).

Thirty patients had normal coronary arteries. Eighty eight patients (75%) had obstructive CAD with lumen narrowing greater than 50% diameter in any one or more of the left or right coronary arteries or their major branches. Headache was observed in 36% of all the patients (42 patients). In patients without obstructive CAD, 73% reported significant episodes of headaches after GTN use compared with 23% of patients with obstructive CAD ($p < 0.001$) (table 2).

DISCUSSION

Our study investigated headache response and possible differential vasodilatation during GTN treatment in patients with chest pain of unknown origin. Although clinicians are aware that nitrates can cause significant headache, our study is the first to research systemically the exact frequency of headache in patients with and without CAD documented by coronary angiography. Tattersall *et al*⁴ reported post-marketing surveillance of a transdermal GTN patch in over 1000 patients with angina. The incidence of severe headache that led to GTN patch withdrawal was 7.1% and decreased with time of usage. We observed a 23% incidence of headache after GTN use in patients with documented CAD and a significantly higher incidence of headache in 73% of patients with normal coronary arteries or minimal CAD ($p < 0.001$). Nitrates can dilate epicardial coronary arteries and collateral vessels in patients with obstructive CAD.^{5,6}

Table 1 Baseline characteristics of patients with coronary artery disease (CAD) versus no obstructive CAD

	CAD positive (n = 88)	CAD negative (n = 30)	p Value
Age (years)	65.51 (12.09)	54.83 (11.24)	<0.01
Sex (male/female)	52/36	14/16	0.237
Systolic BP (mm Hg)	150.68 (30.17)	141.35 (21.27)	0.180
Diastolic BP (mm Hg)	83.56 (15.79)	83.13 (14.72)	0.911
Diabetes mellitus (yes/no)	18/70	4/26	0.387
Smoking (yes/no)	31/56	9/21	0.719
Total cholesterol (mmol/l)	4.92 (1.1)	5.0 (1.0)	0.797
LDL cholesterol (mmol/l)	2.80 (0.82)	3.0 (0.84)	0.365
HDL cholesterol (mmol/l)	1.18 (0.33)	1.26 (0.33)	0.427
Triglycerides (mmol/l)	2.02 (1.65)	1.55 (0.86)	0.372

Data are mean (SD) or number.

BP, blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein.

Table 2 Occurrence of headache in patients with or without CAD

		Headache		Total
		Absent	Present	
CAD	Absent	8	22 (73%)	30
	Present	68	20 (23%)	88
Total		76	42 (36%)	118

Pearson χ^2 value = 24.99, n = 118, $p < 0.001$.

It is quite possible that nitrates selectively dilate coronary arteries to a larger extent than cerebral arterioles in patients with obstructive CAD. Lai *et al*⁷ used high resolution ultrasonography to evaluate the vascular elasticity of the common carotid arteries at sites with and without atheromatous plaque before and after sublingual GTN administration. They concluded that the prevalence of carotid atheromatous plaque was highly correlated with that of CAD and that carotid vascular elasticity to GTN use was decreased in patients with severe CAD.⁷ Their observation may support our theory that GTN causes less frequent headache in patients with atherosclerosis caused by impaired cerebral arterial dilatation. Adams *et al*⁸ reported similar findings in 800 patients at risk for atherosclerosis. On multivariate analysis, diabetes mellitus, increasing age, male sex, large vessel size, and reduced endothelium dependent dilatation were all independently associated with impaired GTN related vasodilatation.⁸ The baseline characteristic risk factor analysis of our study population did show that the obstructive CAD group was older, which is not an unexpected finding, but we observed no significant differences in the frequency of smoking or diabetes mellitus, or in blood pressure or lipid profiles. Thus, our results of GTN induced headache in patients with and without obstructive CAD seem not significantly influenced by the differences in the baseline vascular risk factor profiles. Lundman *et al*⁹ found that transient triglyceridaemia decreased vascular reactivity in young healthy men. GTN induced brachial artery vasodilatation decreased from 20.5 (5.8)% to 11.5 (3.2)% ($p < 0.002$) before and after one hour infusion of systemic fat emulsion. The vasodilator response to GTN is impaired in the brachial artery of patients with CAD consistent with functional abnormalities in smooth muscle dilatation in adults with atherosclerosis.¹⁰

Chest pain evaluation is a routine and an important part of clinical cardiology. Treadmill exercise testing with ECG monitoring alone or in conjunction with echocardiographic or radionuclide perfusion imaging, and pharmacological stress test with cardiac imaging, are widely used as diagnostic tools aiding in the clinical decision making process.^{11–15} Non-invasive cardiac tests generally offer reliable diagnostic and prognostic information if selected appropriately.^{16–18} However, even these sophisticated tests have limitations in sensitivity and specificity. ECG treadmill testing is known to cause frequent false positive findings in female patients.^{19–21} According to our hypothesis, absence of headache after the initial GTN use may predict CAD. Therefore, the screening test is positive if headache is absent and negative if headache is present. The sensitivity of our screening test was 77% and specificity was 73%. Positive predictive value was 89% and negative predictive value was 52%. The likelihood ratio was 2.898 for positive test results (absence of headache) and 0.31 for negative test results (presence of headache). Our results may help clinicians in risk stratification in the initial probability assessment of patients with chest pain of unknown aetiology or suspected CAD. This simple clinical tool may help guide subsequent diagnosis and the treatment

of patients in a more cost effective manner by augmenting the prediction of the pre-test probability of CAD. In patients with nitrate induced headache and an otherwise low coronary risks profile, such as a low clinical score based on a large Mayo Clinic study,²² outpatient cardiac testing may be considered for further evaluation of the aetiologies of chest pain while minimising patients' risk of cardiac events. Patients with positive coronary risk factors and chest pain who do not have headache after initial nitrate treatment seem to have a high likelihood of obstructive CAD. Thus, the presence or absence of headache in patients with chest pain who received sublingual GTN can offer a rapid and inexpensive tool in assisting risk assessment of possible obstructive CAD. Our "headache test" had a sensitivity of 77% for predicting underlying obstructive CAD if no headache was associated with GTN use and a specificity of 73% in predicting the absence of significant CAD if headache developed after GTN administration. This simple clinical method in a limited number of patients seems complementary to other more sophisticated non-invasive stress testing in detecting obstructive CAD.^{12 14 18} Furthermore, the patients' sex does not affect this easy test, which is particularly important for female patients, who often present more diagnostic challenges in non-invasive cardiac assessment of CAD. Since GTN can certainly exacerbate some types of headaches, such as cluster or migraine headache, we were careful not to include any patients in the study with an established diagnosis of any particular type of headache or any chronic headache. Larger or multicentre clinical studies in the future may offer further insights into the results of our observation and expand our understanding about the vascular biology of GTN induced headache in patients with chest pain syndrome.

Study limitations

We studied a relatively small patient series. Even though we screened 400 patients, we decided to include only patients without previously documented CAD and without a history of any chronic headache or nitrate exposure. We did not have a vigorous protocol to define and quantify headache. Since the overall purpose of our study was to compare the patients with and without headache, we felt that the lack of quantification should not affect the end points of our study. There may be a selection bias, since all our patients underwent cardiac catheterisation procedures. A prospectively designed study of a different patient population such as patients presenting to the emergency room or undergoing stress testing may offer further insights about the validity and mechanism of GTN induced headache in patients with chest pain. We chose this particular group of patients in order to have the coronary anatomical information uniformly available for clarity of the data.

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