

## The effects of trinitroglycerin injection on early complications of angiography

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### Abstract

**BACKGROUND:** Today, ischemic heart diseases (IHDs) are the most common diseases worldwide. Angiography is the best way to diagnose IHDs. Angiographic complications however can include death, myocardial infarction, nausea, spasm of the coronary arteries, chest pain, bradyarrhythmia, hypotension, or hypertension. This study aimed to determine the effects of a simultaneous injection of trinitroglycerin (TNG) with contrast agent on the early complications of angiography.

**METHODS:** This clinical trial was conducted in Chamran Hospital, Isfahan, Iran in 2005. Before the angiography, the study population were randomly assigned into two groups of intervention (n = 111) and placebo (n = 112). TNG was mixed with contrast material in the intervention group and distilled water was mixed with contrast agent in the placebo group to be used for angiography. Nausea, spasm of the coronary arteries, chest pain, bradyarrhythmia and the mean systolic and diastolic blood pressures were compared during and after the angiography in patients of both groups. The obtained data was analyzed by chi-square and t tests.

**RESULTS:** The mean age in the intervention and placebo groups were  $59.93 \pm 9.14$  and  $59.37 \pm 10.12$  years, respectively ( $P > 0.05$ ). The two groups were not significantly different in terms of gender distribution. The frequency of nausea was 4.5% and 6.2% in the intervention and placebo groups, respectively. The corresponding values were 0.9% and 5.4% for coronary artery spasm and 1.8% and 6.3% for chest pain. Bradyarrhythmia occurred in 7.1% of patients in both groups. There were no significant differences in the abovementioned complications. Mean values of the highest and lowest systolic and diastolic blood pressures of the intervention group were significantly different from the placebo group ( $P = 0.001$ ). Simultaneous injection of TNG and the contrast agent in this study resulted in positive findings (except for changes in blood pressure).

**CONCLUSION:** More studies are recommended with different doses of TNG, different times of injection and considering at-risk individuals.

**Keywords:** Angiography, Early Complications, Trinitroglycerin.

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### Introduction

Today, ischemic heart diseases (IHDs) are common in the world. They are the main cause of mortality, disability, and increased health care costs.<sup>1,2</sup> Coronary atherosclerosis is the most common cause of IHDs that may ultimately lead to vascular stenosis.<sup>3</sup> If this narrowing, reduces the vessel cross-section to more than 80%, the blood flow (even at rest) will be reduced. The risk of myocardial ischemia will increase with a small increase of stenosis.<sup>3</sup> The best way to diagnose IHD and coronary vessels stenosis is performing angiography which is still the best and

most important diagnostic tool despite the promotion of non-invasive diagnostic methods in the study of anatomy and physiology of cardiology.<sup>4</sup> Like any other invasive procedure, angiography has its own complications that are divided into two categories of early (during angiography) and delayed (after angiography) complications. Early complications can include death (0.11%), incidence of myocardial infarction (0.05%), complications of contrast agent sensitivity (0.37%), bradyarrhythmia (0.38%), hypotension and hypertension (0.26%).<sup>5,6</sup> Considering the increasing rate of heart diseases and consequently

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angiography, conducting research on reducing its complications is important. So far, many studies have been performed on the role of trinitroglycerin (TNG) in controlling complications during angiography and angioplasty. Their results have shown positive effects of the drug on decreasing vascular spasm.<sup>7</sup> TNG is among the short-acting nitrates which reduce the preload, after load, and myocardial oxygen requirement through dilating the vessels (especially veins). In addition, the nitrates may also relieve the spasm symptoms in vasospastic angina. This drug class is typically among the most common drugs with the least side effects in the treatment of cardiovascular diseases.<sup>8</sup> Due to the complications of angiography, especially coronary artery spasm and chest pain, perhaps TNG can be used to reduce the side effects at the time of angiography. Therefore, this study aimed to determine the effects of simultaneous injection of TNG and contrast agent at the time of angiography on early complications.

### Materials and Methods

This clinical trial (registration number: IRCT138901283733N1) was performed on 223 patients who referred to Chamran Hospital (Isfahan, Iran) for angiography in 2005. The inclusion criteria were aging 20-75 years old, no drug addiction, no history of cerebrovascular disease, and systolic blood pressure above 100 mmHg. Informed consents were obtained from the patients prior to angiography. The study population was randomly divided into the intervention and placebo groups. The randomization of the patients was performed by a nurse who was not present at the time of angiography. Patients and the physicians performing angiography were not aware of the classification. To calculate the minimum sample size required for the study, the formula, which compared the two ratios, was used. Therefore, considering a confidence interval of 95%, power factor of 75%, and estimation of the relative expected complications as 0.02 and 0.08 in the intervention and placebo groups, respectively, the required sample size in each group was calculated as 112 patients. The intervention group underwent angiography with 5 µg of TNG mixed with 150 cc of meglumine as the

contrast agent. In the placebo group, 150 cc of meglumine was mixed with distilled water. The physician who performed angiography was unaware of the injected contrast agent. The patients were studied in similar conditions and by a device with nearly identical radiation. The used TNG was similar in all patients of the intervention group. The catheter number 7 was used. Systolic and diastolic blood pressure in all patients was measured by a pressure-monitoring device (which was attached to the patient during angiography). The obtained data was recorded by a nurse. The patients with significant coronary stenosis of 75% or above were placed in the group of patients with coronary artery stenosis. All subjects with low blood pressure (less than 90 mmHg) were excluded from the study. After the angiography, a questionnaire (including questions related to complications of the contrast agent) was completed for each patient by a practitioner who had no information about the classification of the two groups of patients. The questionnaire included demographic characteristics and 6 questions regarding the incidence of nausea, chest pain (with typical characteristics of cardiac pain behind the sternum that could spread to the left or right), coronary artery spasm (contraction of muscles of the vessel wall which reduces the sudden cardiac blood supply without significant coronary stenosis), bradyarrhythmia (heart rate less than 60 beats per minute), and systolic and diastolic blood pressures of the patients (during and after the angiography). All collected data was entered into SPSS<sup>11</sup> and analyzed by chi-square and independent-t tests. P values less than 0.05 were considered as significant.

### Results

The placebo and intervention groups were not significantly different in terms of mean age ( $59.93 \pm 9.14$  vs.  $59.37 \pm 10.12$ ). Likewise, gender distribution in the two groups was similar. In addition, the frequency of nausea, spasm of coronary arteries, chest pain, and bradyarrhythmia was not significantly different between the two groups (Table 1). The mean of the highest and the lowest systolic and diastolic blood pressure in the patients in the intervention group were significantly lower than the patients in the placebo group (Table 2).

**Table 1.** Comparison of the gender and qualitative variables in the intervention and placebo groups

		<b>Intervention (n = 112)</b>	<b>Placebo (n = 111)</b>	<b>P</b>
Gender	Male	56 (50.5%)	55 (49.1%)	0.940
	Female	55 (49.5%)	57 (50.9%)	
Nausea		5 (4.5%)	7 (6.2%)	0.728
Incidence of coronary spasm		1 (0.9%)	6 (5.4%)	0.119
Presence of chest pain		2 (1.8%)	7 (6.3%)	0.103
Presence of bradyarrhythmia		8 (7.1%)	8 (7.1%)	0.985

Values are expressed as n (%).

**Table 2.** Comparing the highest and the lowest blood pressure during angiography in the intervention and placebo groups

		<b>Intervention (n = 112)</b>	<b>Placebo (n = 111)</b>	<b>P</b>
Systolic blood pressure	Highest	137.41 ± 21.3	146.98 ± 19.18	0.0010
	Lowest	129.28 ± 18.92	144.37 ± 16.88	0.0001
Diastolic blood pressure	Highest	80.71 ± 13.1	84.77 ± 10.43	0.0110
	Lowest	75.27 ± 11.77	96.8 ± 29.38	0.0001

Values are expressed as mean ± SD.

### Discussion

This study showed that simultaneous injection of TNG and contrast angiography agent resulted in more remarkable changes in systolic and diastolic blood pressure. The incidence of coronary spasm, angina, and nausea in the intervention group was lower than the placebo group. Although this difference was not statistically significant, it was clinically noteworthy. Coronary artery spasm is one of the major complications of catheterization. Fischell, et al. investigated coronary spasm in 15 patients after angioplasty. They injected 5 patients with TNG (3 minutes after angioplasty) in 5 patients. Then, all patients underwent angiography again. Coronary artery spasms were not observed in the subsequent angiographies (2, 5, 15, and 30 minutes later) in patients who had received intracoronary TNG.<sup>9</sup> Margolis et al. evaluated 1400 patients undergoing angioplasty in the intervention and control groups. In the intervention group (before the injection of contrast agent and through the catheter), 1 µg TNG was injected into the coronary arteries. The results suggested that the incidence of coronary spasm in subjects who had not received TNG was significantly higher than the intervention group (14% vs. 4%).<sup>10</sup> Attention to the pathophysiology of coronary artery spasm during the catheterization is important for the treatment. Redd et al. stated that coronary artery spasm during angioplasty occurred due to the stimulation of receptors, had muscular origin, or resulted from both mechanisms. For this reason, TNG can be effective to prevent or relieve vasoconstriction caused by angioplasty.<sup>11</sup> Chest pain is one of the other complications during coronary catheterization. Kurz et al. investigated the incidence of chest pain while placing the stent during angioplasty. In their study, the 50 patients in the intervention group received intracoronary TNG during the angioplasty. The results indicated non-significant difference in the incidence of chest pain between the two groups. However, a significant decrease was observed in the incidence of minor myocardial necrosis in the intervention group which

could have been caused by better blood supply with these drugs.<sup>12</sup>

In some studies, the effect of TNG has been mentioned in patients with suspected vasospastic angina pain or in cases of risk of coronary artery spasm during angiography.<sup>13</sup> Many previous studies have indicated the incidence of coronary artery spasm during angiography to be very rare. These studies have noted that this complication of angioplasty arose from the manipulation and further stimulation of the vessels. Since most previous studies have been performed on angioplasty, angiographic studies were rare.<sup>14,15</sup> Although in the present study, the incidence of coronary artery spasm and chest pain was lower in the intervention group, due to the insignificance of the difference, using TNG during angiography to prevent side effects is not recommended. Another complication of angiography is nausea. No specific study has been found on the effect of TNG on nausea. The results of the present study indicated no significant difference in the incidence of nausea between the two groups. Since one of the common side effects of contrast agent injection is nausea<sup>5</sup> and TNG is normally ineffective in treating nausea, the absence of a significant difference is justifiable. In this study, the incidence of arrhythmia was also similar in both groups. The origin of bradyarrhythmia may be an underlying disease or the person's susceptibility. It can be concluded that TNG had no effects in controlling the condition. The most important difference between the two groups in this study was the difference in blood pressure during angiography. The presence of statistically significant differences in the highest and lowest average systolic and diastolic blood pressure could have been the effect of TNG. As already noted, this drug is among the nitrates with vasodilatory effects. This expansion also affected the preload and afterload.<sup>6</sup> Therefore, it could be expected that TNG injections during angiography reduce blood pressure. This can be one of the important facts to be considered for recommending in patients with low blood pressure. In other words, the usage of TNG in such patients may be associated

with unwanted side effects. Therefore, attention to TNG contraindications in studies is required.

In general, the results of this study indicated no significant difference in the incidence of major complications of angiography, including coronary artery spasm and chest pain, between the two groups. However, TNG reduced blood pressure. Due to the differences in the results of various studies about the incidence of coronary artery spasm and existence of a few studies on angiography, more research is required to use different doses of TNG and injection timings. Future studies are required to consider high risk patients and pain among individuals undergoing angiography and angioplasty separately. The effects of TNG on late angiographic complications and related mortality should also be evaluated in subsequent studies. In addition, reviewing the costs and spent time of using TNG and the potential complications of the drug are among the issues that need to be evaluated.

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### Conflict of Interests

Authors have no conflict of interests.

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