A Randomized Crossover Evaluation of Antianginal Efficacy and Safety of Nitrolingual-Spray and Nitroglycerin Tablet Form in Coronary Artery Disease Patients

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Key Words

Coronary artery disease · Treadmill exercise test · Nitroglycerin · Clinical trial

Abstract

Twenty-eight coronary artery disease patients with more than 50% stenosis in at least one major coronary artery completed this randomized crossover clinical trial for the comparison of efficacy and safety of Nitrolingual-Spray and nitroglycerin (NTG) tablets. Exercise time was lengthened to 399.1 s (spray) or 408.5 s (tablets), compared to a baseline of 387.3 s. Ischemic burden decreased to about –4.0 mm with both forms, compared to –7.5 mm at baseline (ANOVA: $p = 0.003$). The ischemic time improved to 137.2 s (spray) or 152.9 s (tablets), compared to 253.4 s at baseline (ANOVA: $p = 0.005$). Patients taking tablets experienced more episodes of hypotension and/or headache compared to patients taking the spray. Nitrolingual-Spray is as effective and safe as NTG tablets for the treatment of symptomatic coronary heart disease.

Introduction

Sublingual nitroglycerin (NTG) is an established therapy for the treatment of effort angina [1]. Nonetheless, the pharmacological activity of NTG tablets diminishes gradually, particularly if it is not properly stored [2–6]. Tallett [7] suggested that patients have NTG tablets dispensed at least every 12 weeks, even when following instructions for optimal storage. Lack of knowledge about the tablet form limits the usefulness of the drug [8, 9]. New formulations of NTG with greater stability are now available.

Several clinical trials have demonstrated that NTG spray has a more rapid action of angina relief than NTG tablets [10–13] due to its rapid absorption [14]. We conducted a randomized crossover clinical trial in Taiwan to compare the antianginal efficacy and safety of the most commonly used NTG tablets (0.6 mg) with a new spray formulation (Nitrolingual-Spray, 0.4 mg per puff; Pohl Boskamp, Hohenlockstedt, Germany) for treatment of coronary artery disease (CAD) patients with myocardial ischemia, documented by a treadmill exercise test (TxT).

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Patients and Methods

Thirty CAD patients with ≥50% stenosis in at least one of the three major coronary arteries were recruited into this randomized crossover clinical trial. All patients gave informed consent. The hospital ethics review committee had approved the study. There were 25 men and 5 women (average age, 59.4 ± 8.5 years; table 1). All patients had symptomatic angina, documented CAD by coronary angiography, and a positive TxT. Patients with any of the following criteria were excluded: myocardial infarction within the previous 6 months, congestive heart failure (NYHA ≥3), symptomatic valvular heart disease, or cardiomyopathy.

All patients performed a TxT without NTG tablets or spray to establish baseline performance. They were then randomly assigned to either the spray-to-tablet or tablet-to-spray groups (fig. 1). In the spray-to-tablet group, patients underwent a TxT immediately after

Fig. 1. Study protocol. — ST group: 1 puff (0.4 mg) of NTG oral spray → 1 tablet (0.6 mg) of sublingual NTG. --- TS group: 1 tablet (0.6 mg) of sublingual NTG → 1 puff (0.4 mg) of NTG oral spray.

taking one 0.4-mg NTG spray puff. After resting for at least 30 min, the patients took an NGT 0.6-mg tablet sublingually and then performed another TxT. In the tablet-to-spray group, the drug form application was reversed. All TxT were performed using the standard Bruce protocol. ST-segment depression of at least 1.0 mm was considered significant for exercise-induced ischemia. The stress test was considered negative if at least 85% of the predicted maximal heart rate (defined as 220 – age in years) was achieved without significant ST-segment changes. Those patients with maximal heart rates <85% of the predicted rate were excluded from the study. The end point of the TxT was extreme fatigue and exhaustion.

We compared the following variables of the two groups to baseline exercise performance: (1) exercise duration: the time from start to maximal exercise; (2) ischemic burden: total ST-segment depression during exercise, and (3) ischemic time: time duration from appearance to disappearance of ST-segment depression during exercise and resting periods. Secondary end points compared to baseline included rate-pressure product (RPP), blood pressure patterns, and adverse effects such as hypotension, palpitation, headache, and dizziness.

Efficacy was assessed in terms of exercise capacity by symptom-limited exercise time, total work performed, time to onset of angina, and ST-segment change.

Statistical Analysis

All values are presented as means ± SD. The results were analyzed for exercise period 1 and then for period 2, as a crossover design. Data were grouped by drug form and then analyzed. Analysis of variance was used to test the differences of measurements among baseline, and NTG spray and tablet treatments. The differences in test variables between NTG spray and tablets were analyzed using linear regression, with random effect incorporated in the model. Significance of differences in adverse events was tested using the χ^2 or Fisher's exact test. p values <0.05 were considered significant for all parameters tested.

Table 1. Demographic characteristics of the study subjects

	ST group (n = 15)	TS group (n = 15)
Men	12	13
Women	3	2
Age, years (mean ± SD)	59.2 ± 19.8	59.6 ± 5.6
Range	40–75	47–70
Body weight, kg (mean ± SD)	69.07 ± 12.56	69.06 ± 6.42
Body height, cm (mean ± SD)	165.6 ± 8.1	168.8 ± 5.8
History of angina	10	10
Hypertension	7	8
Diabetes mellitus	4	1
Hyperlipidemia	13	9
Smoking		
Yes	3	3
No	6	7
Quit	6	5

ST = 1 puff (0.4 mg) of NTG oral spray → 1 tablet (0.6 mg) of sublingual NTG; TS = 1 tablet (0.6 mg) of sublingual NTG → 1 puff (0.4 mg) of NTG oral spray.

Results

Of the 30 patients enrolled, 28 completed the protocol, and 2 patients withdrew because of severe headache while taking NTG tablets. The two treatment groups were similar in basic demographic characteristics (table 1). The mean heart rate, systolic blood pressure, diastolic blood pressure and RPP were similar among baseline, NTG spray, and NTG tablet treatment (table 2).

The duration of exercise increased from 387.3 s at baseline to 399.1 s with NTG spray treatment and 408.5 s with NTG tablet treatment ($p = 0.26$; table 2). The average ischemic burden was reduced from -7.50 mm at baseline to -3.97 mm with NTG tablets and -4.04 mm with NTG spray (ANOVA: $p = 0.003$). While the two treatment groups showed similar reductions in ST-segment depression, ischemic burden in both treatment groups was significantly less at baseline (fig. 2a). The average ischemic time was also shortened with both forms of NTG compared with baseline (ANOVA: $p = 0.005$, table 2, fig. 2b).

Two patients in the NTG spray group did not develop ST depression of >1 mm, even at the end of exercise. Thus, we used the heart rate and blood pressure values at the peak of exercise as indicators of ischemia development. The time required before ischemia developed during exercise was prolonged in both treatment groups (355.4 s with NTG spray and 336.9 s with NTG tablets) compared to baseline (287.6 s, $p = 0.30$, table 2). Average heart rate, systolic blood pressure and RPP during ischemia were significantly higher with NTG spray than with NTG tablets. Figure 2c shows that greater stresses were required to develop ischemia in the spray group than in the tablet group.

There were no significant differences in the frequency and types of reported adverse events between the two treatment groups; nonetheless, more patients experienced hypotension, headache, and dizziness with NTG tablets (5 patients) than with NTG spray (0 patients; table 3).

Table 2. Comparison of hemodynamic parameters in patients at baseline, with NTG spray, and NTG tablet groups

	Baseline (n = 28)	Spray (n = 28)	Tablet (n = 28)	Difference spray vs. tablet	p value
<i>Initial</i>					
HR	77.8 ± 13.1	76.1 ± 12.1	78.9 ± 12.9	-2.7	0.18
SBP	135.5 ± 21.5	134.5 ± 12.3	131.0 ± 14.4	3.5	0.14
DBP	80.7 ± 11.6	82.4 ± 10.8	78.6 ± 7.3	3.7	0.11
RPP	10,528.4 ± 2,303.4	10,233.7 ± 1,852.0	10,397.6 ± 2,475	-156.2	0.68
<i>Peak</i>					
HR	143.3 ± 16.9	143.5 ± 17.8	144.0 ± 18.2	-0.6	0.70
SBP	172.1 ± 29.4	171.0 ± 27.6	170.3 ± 24.3	0.06	0.99
DBP	80.7 ± 14.4	80.2 ± 11.3	80.9 ± 11.8	-0.7	0.75
RPP	24,676.7 ± 4,941.4	24,580.3 ± 5,317.3	24,529.4 ± 4,829.3	-48.5	0.95
Duration of exercise, s	387.3 ± 102.3	299.1 ± 99.8	408.5 ± 91.1	-10.2	0.26
Ischemic burden, mm*	-7.5 ± 5.1	-4.04 ± 3.8	-3.97 ± 3.5	-0.07	0.86
Ischemic times, **	253.4 ± 183.7	137.2 ± 116.3	152.9 ± 101.7	-15.7	0.34
<i>Conditions of ischemic development</i>					
Time to ischemia, s	287.6 ± 114.6	355.4 ± 111.2	336.9 ± 152.1	18.5	0.30
HR	127.1 ± 15.9	131.7 ± 19.5	125.2 ± 19.17	6.42	0.009
SBP	163.9 ± 20.7	171.5 ± 25.3	156.9 ± 24.5	14.64	0.005
DBP	80.8 ± 12.1	83.3 ± 19.8	77.4 ± 10.2	5.89	0.15
RPP***	20,915.4 ± 4,127.5	22,741.0 ± 5,563.5	19,826.8 ± 5,251.1	2,914.2	0.002

Crossover analyses were also performed to compare the means of various variables between spray and tablet groups, with p values.

HR = Heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; ischemic burden = total ST-segment depression; ischemic time = time from ST depression appearance to disappearance. ANOVA * $p = 0.0028$, indicating total ST depression among the three treatments were significantly different. ** $p = 0.0054$, *** $p = 0.046$.

Fig. 2. Comparisons of ischemic burden (**a**), ischemic time (**b**), and RPP (**c**) at the onset of ischemia.

Discussion

This crossover clinical trial compared the effectiveness of NTG spray and tablets for treatment of exercise-induced ischemia in CAD patients. The results demon-

strated that exercise duration, total ST-segment depression, and ischemic time were improved with both spray and tablet forms compared with baseline. There were significant differences in heart rate, blood pressure, and RPP during exercise-induced ischemia between the two treat-

Table 3. Adverse events with NTG spray and tablet treatments

Adverse events	NTG spray (n = 30)	NTG tablets (n = 30)
Hypotension*	0	5
Palpitations	0	3
Headache	1	5
Dizziness	1	5
Edema	0	0
Nausea	0	0
Fatigue	0	1

Two patients withdrew due to severe headache with the tablet form. * p = 0.051 (Fisher’s exact test).

ments. Patients taking the spray form seemed to tolerate higher stress before ischemia developed than patients taking the tablet form.

Previous clinical trials have reported several differences in efficacy between the two NTG spray and tablet formulations [10, 12]. NTG spray has a longer shelf life with no stability problems, but NTG tablets carried by patients are often out of date and have decreased efficacy [5, 9]. While both tablet and spray NTG are convenient to use, the spray form may have a greater advantage, as it causes fewer headache and hypotension episodes than the tablet form. Although this was an actively controlled study, it was not double-blinded and, therefore, there may have been some information bias on the part of the observers or patients. However, the similar distributions of demographic and risk factors in both groups implies

that the comparison is acceptable. In comparing NTG tablets (0.6 mg) with the metered-dose NTG spray (0.4 mg), the difference in formulation might account for the improved results in the NTG spray group in our study. Lee et al. [14] reported an earlier onset of action with NTG spray compared to tablets. We did not find significant differences between spray and tablet forms, except when ischemia developed.

Crossover designs reduce between-individual variance and improve the efficiency of the sample size [15]. On the other hand, crossover studies may suffer from carry-over effect and/or period effect. Because the elimination half-life following both sublingual administration of NTG spray and tablets ranges from 2.5 to 4.4 min [14], a carry-over effect was avoided by taking a long enough rest before undergoing the next crossover treatment. The period effect was adjusted by a model fitting technique, incorporating random effect into the fitted linear regression model.

Based on the efficacy, adverse effects, storage convenience, and hemodynamic parameters, Nitrolingual-Spray should be considered as a therapy for CAD patients with angina pectoris. It may be a superior preparation compared to the tablet form and may have clinical advantages.

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