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Journal
Menopause The Journal of The North American Menopause Society, 23(3)

ISSN
1072-3714

Authors
Huang, Alison J
Cummings, Steven R
Schembri, Michael
et al.

Publication Date
2016-03-01

DOI
10.1097/gme.0000000000000520

Peer reviewed

Published in final edited form as:

Menopause. 2016 March ; 23(3): 330–334. doi:10.1097/GME.0000000000000520.

Continuous Transdermal Nitroglycerin Therapy for Menopausal Hot Flashes: A Single-Arm Dose-Escalation Trial

Alison J. Huang, MD, MAS[1], **Steven R. Cummings, MD, MPH**[2], **Michael Schembri, BA**[3], **Eric Vittinghoff, PhD**[4], **Peter Ganz, MD**[1], and **Deborah Grady, MD, MPH**[1]

[1]Department of Medicine, University of California, San Francisco, California

[2]San Francisco Coordinating Center, California Pacific Medical Center Research Institute

[3]Department of Obstetrics and Gynecology, University of California, San Francisco, California

[4]Department of Epidemiology and Biostatistics, University of California, San Francisco, California

Abstract

Objective—To describe the efficacy and tolerability of continuous nitroglycerin for treatment of hot flashes.

Methods—Peri- and postmenopausal women reporting at least 7 hot flashes per day were recruited into a single-arm, dose-escalation trial of continuous transdermal nitroglycerin. Participants were started on a generic 0.1 mg/hr nitroglycerin patch applied daily without patch-free periods. Over four weeks, participants escalated dosage weekly to 0.2, 0.4, or 0.6 mg/hr as tolerated, then discontinued nitroglycerin during the final week. Changes in hot flash frequency and severity were assessed using symptom diaries. Paired t-tests examined change in outcomes between baseline and maximal-dose therapy as well as after discontinuation of nitroglycerin.

Results—Of the 19 participants, mean age was 51.4 (±4.3) years. Women reported an average 10.6 (±3.0) hot flashes and 7.1 (±3.8) moderate-to-severe hot flashes per day at baseline. Eleven women escalated to 0.6 mg/hr, three to 0.4 mg/hr, two to 0.2 mg/hr, and one remained on 0.1 mg/hr nitroglycerin. Two discontinued nitroglycerin before the first outcomes assessment. Among the remaining 17 women, the average daily frequency of hot flashes decreased by 54% and the average frequency of moderate-to-severe hot flashes decreased by 69% from baseline to maximum-dose therapy ($P<0.001$ for both). After discontinuing nitroglycerin, participants reported an average 23% increase in frequency of any hot flashes ($P=0.041$) and 96% increase in moderate-to-severe hot flashes ($P<0.001$).

Conclusions—Continuous nitroglycerin may substantially and reversibly decrease hot flash frequency and severity. If confirmed in a randomized blinded trial, it may offer a novel non-hormonal hot flash treatment.

Keywords

hot flashes; vasomotor symptoms; nitroglycerin; nitrate tolerance; nitric oxide

Correspondence may be addressed to: Alison Huang, MD, MAS, University of California San Francisco, Women's Health Clinical Research Center, 1545 Divisadero Street, Box 0320, San Francisco, CA 94115. Phone: (415)-514-8697. Fax: (415) 353-8666. ahuang@ucsfmed.org.

Introduction

Over two thirds of U.S. women experience hot flashes (a.k.a. vasomotor symptoms) during menopause, and up to a quarter suffer from symptoms severe enough to require treatment.[1,2] Although estrogen therapy is effective in suppressing hot flashes, it is associated with increased long-term risk of cardiovascular and thromboembolic events when combined with progestogen to prevent endometrial hyperplasia.[3,4] Additionally, estrogen therapy is contraindicated in women with estrogen-sensitive cancers and those with hot flashes in the setting of selective estrogen receptor modulator or aromatase inhibitor therapy. As a result, there is widespread interest in identifying non-hormonal treatments for hot flashes that are not only effective, but safe and easy to use.

Although most other attempts to identify non-hormonal treatments for hot flashes have focused on potential central nervous system triggering mechanisms, the final physiologic pathway underlying the hot flash is peripheral vasodilation. Clinical studies have shown that nitric oxide (NO) plays an important role in mediating peripheral vasodilation during hot flashes, with local cutaneous blockade of NO synthase suppressing hot flash-related vasodilation.[5-7] One pharmacologic agent with direct and potent effects on NO-mediated vasodilation is nitroglycerin, an organic nitrate that is widely used to treat chest pain in patients with coronary disease. Intermittent use of nitroglycerin triggers release of NO, promotes vascular smooth muscle relaxation, and triggers vasodilation. However, *continuous* use of nitroglycerin rapidly leads to tolerance to the drug's vasodilatory effects as well as cross-tolerance to endogenous nitrates, as a result of enhanced NO degradation.[8-13] While this tolerance limits the usefulness of nitroglycerin for chest pain, it offers a potentially innovative approach to treating hot flashes, since women who develop cross-tolerance should experience a marked reduction in hot flashes due to suppression of NO-mediated peripheral vasodilation.

To explore the potential efficacy and tolerability of continuous nitroglycerin for hot flashes, we conducted a single-arm, dose-escalation trial in peri- and postmenopausal women.

Methods

Participants were recruited from the San Francisco Bay area in 2013 and 2014 using a combination of community-based media efforts (newspaper advertisements, community fliers), targeted mailings to female patients at the University of California San Francisco (UCSF) Medical Center with diagnostic codes suggestive of hot flashes, and recruitment from a database of past research participants interested in women's health studies. Eligible women had to be between 40 and 60 years of age and report an average of at least 7 hot flashes per 24 hours on a validated 7-day screening symptom diary.[14-16] Women also had to report 9 or fewer menstrual periods in the past year or a history of bilateral oophorectomy, or to have measured serum follicle stimulating hormone levels >30 mU/mL. Women were excluded if they reported using other clinical treatments for hot flashes in the past 3 months (e.g., hormone therapy, selective serotonin or norepinephrine reuptake inhibitors, clonidine, gabapentin) or if they were already using nitrate-based medications. To avoid enrolling

women who might need to use nitroglycerin for chest pain or who might be at increased risk of chest pain with withdrawal of nitrate therapy, study staff excluded women reporting a history of coronary disease, hypertrophic cardiomyopathy, diabetes mellitus, or two or more risk factors for coronary disease (i.e., smoking, hypertension, or hyperlipidemia with clinician-directed pharmacologic treatment). Also excluded were women with a history of chronic headache, known sensitivity to adhesives, or blood pressure less than 100/60 mmHg. All participants provided informed consent according to the protocol approved by the institutional review board of UCSF.

Generic nitroglycerin patches from Mylan Pharmaceuticals Inc. in the four existing commercially-available doses (0.1, 0.2, 0.4, and 0.6 mg/hr) were purchased by the UCSF Compounding and Research Support Pharmacy and distributed to participants on a weekly basis. All eligible participants were initially instructed to apply a 0.1 mg/hr patch on a daily basis to any clean, dry, hairless area of skin on the body except the extremities below the knee or elbow for 1 week. Participants applied a new patch just before bedtime, immediately after removing the old patch, and were instructed to avoid any patch-free episodes that might interfere with development of tolerance. Those who were successful in applying and changing the 0.1 mg/hr patch for 1 week but continued to report persistent bothersome hot flashes subsequently underwent dose escalation on a weekly basis to 0.2, 0.4, or 0.6 mg/hr as tolerated. Women who reported being completely satisfied with the improvement in their hot flashes or had concerns about side effects on a higher-dose patch were permitted to remain at a lower dose. Dose escalation was therefore designed to be participant-directed and to reflect both symptom control and medication tolerability, as would be expected in clinical practice. During the final study week, women were instructed to wean off nitroglycerin over a 1-3 day period, by switching to a lower patch dose on each successive day until they were no longer taking nitroglycerin, to allow assessment for post-treatment rebound in hot flashes. Adherence was tracked by medication diaries, in which participants directly affixed their used patches to the diary after removing them and indicated the date and time that patches were changed.

Hot flash frequency and severity were measured using a validated symptom diary shown to have good test-retest reliability and sensitive to change in past trials of hot flash interventions.[14-17] During each week of the study, women were instructed to record each hot flash they experienced and rate its severity as: (1) mild (sensation of heat without sweating), (2) moderate (sensation of heat with sweating, not preventing activity), or (3) severe (severe sensation of heat and sweating, resulting in cessation of activity); severity definitions were provided with the diary. To facilitate real-time recording of symptoms, the diary was designed to be small and portable, and women were instructed to carry the diary with them during the day and keep it at their bedside at night. Participants also received $25 in gift cards for each completed diary returned during the study.

The primary clinical outcome of the study was change in the average daily frequency of any hot flashes (averaged over each 7-day diary period). Diary data were also used to assess change in daily frequency of moderate-to-severe hot flashes as a secondary outcome. A cumulative 7-day hot flash severity score was also calculated for each week of the study by summing the severity rating for each hot flash reported over each 7-day diary period.[15,16]

Paired t-tests were used to examine average change in outcomes between baseline and maximal-dose therapy, as well as between maximal-dose therapy and after discontinuation of nitroglycerin treatment. Normal distribution of change values was confirmed using Shapiro-Wilk tests. Changes between baseline and each dose of nitroglycerin (0.1, 0.2, 0.4, and 0.6 mg/hr) were evaluated for women who used any of these doses for at least a 7-day period; dose effects were tested both categorically and linearly using linear models with repeated measures. All analyses were carried out in SAS Version 9.4 (SAS Institute, Cary, NC).

Safety was assessed by systematically querying participants about any negative changes in health at all follow-up visits following initiation of therapy; all negative changes reported were recorded as adverse events on standardized forms. Participants were also given telephone numbers to call study coordinators in between scheduled visits to report additional adverse events. Resting blood pressure and heart rate were also measured at baseline and each follow-up visit, with intent to discontinue therapy in participants with blood pressure <90/60 mgHg or in those with blood pressure <100/60 mmHg and symptoms suggestive of hypotension. Women were informed in advance about headache, lightheadedness, and/or low blood pressure as potential side effects of nitroglycerin, and also were given a one-page pamphlet on strategies for managing these symptoms.

Results

Of the 119 women who inquired about the study, 64 were found ineligible, and 36 failed to complete screening procedures or ultimately opted not to enroll. The most common reasons for ineligibility were insufficient frequency of hot flashes (N=22), use of exclusionary medications (N=16), and exclusionary medical conditions (N=7). Of the 19 enrolled participants, mean (±SD) age was 51.4 (±4.3) years, and 8 (42%) were racial/ethnic minorities (including 4 Asian, 3 Black, and 1 Latina). Three (16%) had undergone bilateral oophorectomy. Six (32%) were using aromatase inhibitors, and 4 (21%) were using selective estrogen receptor modulators. Mean body mass index (BMI) was 25.2 (±4.5) kg/m^2, with 3 women (16%) being overweight (BMI ≥25 kg/m^2) and 3 (16%) being obese (BMI ≥30 kg/m^2). On average, women reported 10.6 (±2.1) hot flashes and 7.2 (±3.7) moderate-to-severe hot flashes per day, and the mean 7-day hot flash severity score was 20.0 (±7.7). Mean systolic and diastolic blood pressure were 129.9 (±16.9) and 79.1 (±12.5) mmHg, respectively.

Of the 19 women who started on nitroglycerin, two (10%) developed headache on the initial 0.1 mg/hr dose, leading them to discontinue treatment before the first outcomes assessment. Of the remaining 17 women, 11 (65%) opted to escalate to 0.6 mg/hr, 3 (18%) escalated to 0.4 mg/hr, 2 (12%) escalated to 0.2 mg/hr, and one (6%) chose to remain on 0.1 mg/hr.

Among the 17 women completing the 6-week study, the average daily frequency of any hot flashes decreased from 10.7 (±3.1) at baseline to 5.0 (±2.5) at highest dose (54% average decrease, P for paired t-test <.01) [Figure 1]. The average daily frequency of moderate-to-severe hot flashes decreased from 7.7 (±3.8) at baseline to 2.3 (±2.6) at highest dose (69% average decrease, P for paired t-test <.01). Average 7-day hot flash severity scores also

decreased from 20.4 (±7.7) to 8.5 (±6.0) at highest dose (58% decrease, P for paired t-test <. 01).

Among the 17 women providing outcomes data, higher doses of nitroglycerin therapy were associated with greater reduction in frequency of hot flashes [Table 1]. Average reduction in daily frequency of any hot flashes from baseline was 28% for 0.1 mg/hr, 34% for 0.2 mg/hr, 39% for 0.4 mg/hr, and 53% for 0.6 mg/hr dose (P <.01 for linear trend with increasing dose). Average reduction in daily frequency of moderate-to-severe hot flashes was 35% for 0.1 mg/hr, 39% for 0.2 mg/hr, 54% for 0.4 mg/hr, and 65% for 0.6 mg/hr dose (P <.01 for linear trend).

After women discontinued nitroglycerin, the average daily frequency of any hot flashes was 6.0 (±3.5) (23% average increase compared to maximal-dose therapy, P = 0.041)[Figure 1]. The average daily frequency of moderate-to-severe hot flashes was 4.4 (±3.5) per day (96% average increase from maximal-dose therapy, P <0.001).

Eleven participants reported adverse events during the study, including 5 with headache, 3 with lightheadedness, 3 with nausea, 2 with rash, and 1 with palpitations (categories not mutually exclusive). Among the 17 women who tolerated the initial dose of nitroglycerin, none discontinued treatment due to adverse events, regardless of highest dose achieved. No serious adverse events (defined as death, disability, or hospitalization) were reported during the study. Average blood pressure was 127/79 (±14/9.2) mmHg, 129/78 (±17/9.7) mmHg, 130/81 (±16/10) mmHg, and 125/77 (±13/11) mmHg on 0.1 mg, 0.2 mg/hr, 0.4 mg/hr, and 0.6 mg/hr nitroglycerin, respectively, and no women had medication withheld for low blood pressure.

Discussion

These results suggest that continuous nitroglycerin has the potential to substantially reduce the frequency of hot flashes, particularly moderate to severe flashes, in peri- and postmenopausal women. Over a 4-week period, women reported an average 54% decrease in frequency of any hot flashes, 69% reduction in frequency of moderate-to-severe hot flashes, and 58% decrease in cumulative hot flash severity scores between baseline and maximum tolerated therapy (ranging from 0.1 to 0.6 mg/hr). Although this trial did not include a placebo group, the magnitude of improvement in hot flashes among women taking continuous nitroglycerin exceeded that reported in multiple prior trials of non-hormonal pharmacologic therapies.[18-22] Furthermore, participants reported an average 22% increase in frequency of any hot flashes and 81% increase in frequency of moderate-to-severe hot flashes after discontinuation of nitroglycerin, demonstrating that improvements observed on nitroglycerin did not result solely from reversion to the mean.

Our findings also suggest that improvement in hot flashes associated with nitroglycerin may be dose-dependent, with significantly greater reductions in the frequency and severity of symptoms with increasing dose. Nevertheless, some women reported substantial improvements in their symptoms at low doses (e.g., 0.2 mg/hr or less) and opted not to further escalate therapy. Additionally, dose escalation was performed sequentially over time,

and the effects of higher dose nitroglycerin therapy may have been partially influenced by longer duration of treatment.

Results also suggest that continuous transdermal nitroglycerin therapy may be tolerated well by many, but not all peri- or postmenopausal women with hot flashes. Headache is a known potential side effect of nitroglycerin that limits its use for treatment of ischemic chest pain, and primary nitroglycerin-induced headache thought to be caused by medication-induced vasodilation of intracranial blood vessels.[23] While the risk of headache should be lower among patients who use the medication continuously and thus develop tolerance to its vasodilatory effects, 5 participants in this trial reported headache at some point in the study, and two developed headache that led them to discontinue treatment within a few days of starting the lowest dose. Nevertheless, findings suggest that women who are able to tolerate 0.1 mg/hr nitroglycerin are likely to be able to continue therapy for at least a month, and in most cases to escalate to higher-dose therapy on 0.2, 0.4, or 0.6 mg/hr.

Limitations of this study include its modest size, single-arm design, and relatively short duration of follow-up. Exclusion of women with a known history of or multiple risk factors for coronary disease also precluded assessment of safety in that population. Future larger, randomized, and blinded trials are indicated to test the efficacy and safety of continuous nitroglycerin over longer periods of treatment in a broader array of postmenopausal women.

Conclusion

Given the potential long-term adverse effects of hormone therapy, many women are interested in non-hormonal treatments for hot flashes. This study provides preliminary evidence that continuous nitroglycerin therapy may offer a novel and potentially effective treatment for hot flashes, presumably by targeting peripheral vasodilation mechanisms.

Acknowledgments

Funding: This research was supported by a grant from the Mt. Zion Health Fund. Dr. Huang is additionally supported by the Paul B. Beeson Career Development Award in Aging Research from the National Institute on Aging (1K23AG038335) and the American Federation for Aging Research. Dr. Grady is additionally supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through UCSF-CTSI Grant Number UL1 TR000004.

Potential conflicts of interest: Dr. Huang has received funding from Pfizer, Inc. to conduct research unrelated to hot flashes through research grants awarded through UCSF.

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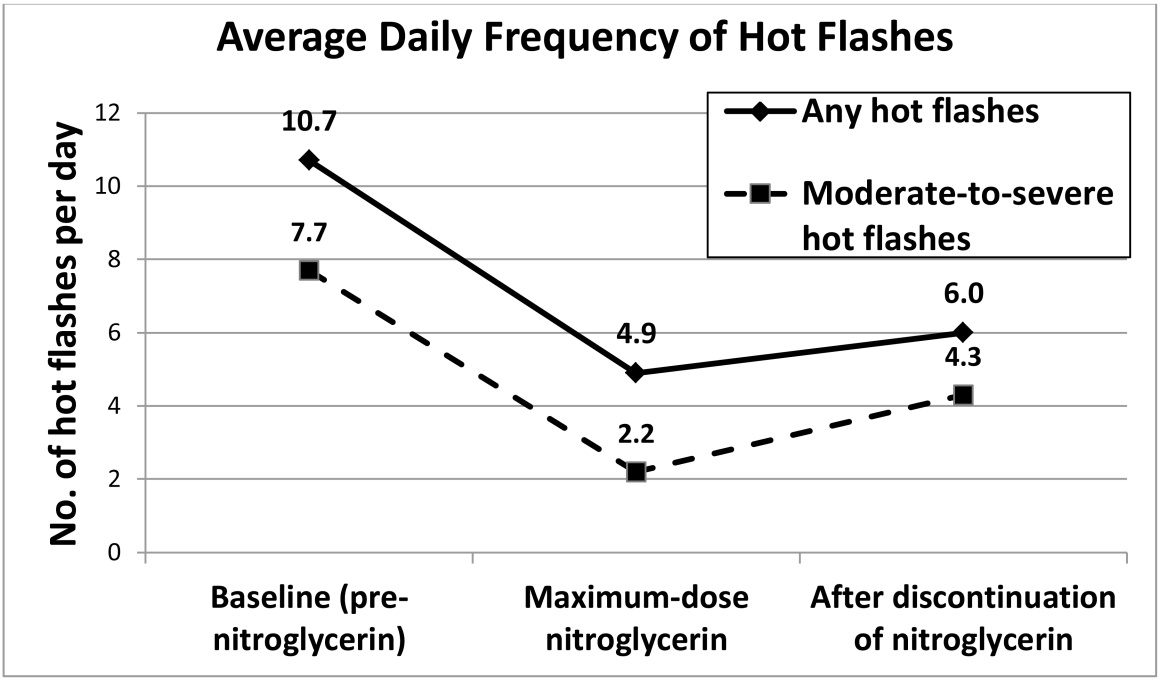

Figure 1.

Hot flash frequency and severity were assessed by symptoms diaries in which women recorded each hot flash they experienced and rated its severity as mild, moderate, or severe. The average daily frequency of 1) any hot flashes, and 2) moderate-to-severe hot flashes, was determined over a 7-day period at baseline (pre-treatment), during successive 7-day periods on each dose of nitroglycerin, and during a 7-day period during weaning and discontinuation of nitroglycerin. Among the 17 participants providing outcomes data, maximum dose of nitroglycerin was 0.6 mg/hr for 11 women, 0.4 mg/hr for 3 women, 0.2 mg/hr for 2 women, and 0.1 mg/hr for one woman.

Table 1

Changes in Average Daily Frequency of Hot Flashes from Baseline, by Nitroglycerin Dose

Dose (mg/hr)	Number of participants*	Change in any hot flashes			Change in moderate-severe hot flashes		
		Number/day	% Change	P-value**	Number/day	% Change	P-value**
0.1	17	-3.0 (3.5)	-28%	0.003	-2.7 (3.2)	-35%	0.003
0.2	16	-3.6 (3.6)	-34%	0.001	-2.9 (3.0)	-39%	0.002
0.4	14	-4.0 (3.5)	-39%	<0.001	-4.0 (3.4)	-54%	<0.001
0.6	11	-5.3 (3.2)	-53%	<0.001	-4.7 (3.2)	-65%	<0.001

* Data are from women who provided at least one week of outcomes data on at least one dose.

** P for paired t-test assessing change in average daily frequency from baseline