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Hemodynamic Effects of Nitroglycerin Ointment in Emergency Department Patients

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Abstract

Background—Nitroglycerin ointment is commonly used in the treatment of emergency department (ED) patients with suspected acute heart failure (AHF) or suspected acute coronary syndrome (ACS), but its hemodynamic effects in this population are not well described.

Objectives—Our objective was to assess effect of nitroglycerin ointment on mean arterial pressure (MAP) and systemic vascular resistance (SVR) in ED patients receiving nitroglycerin. We hypothesized that nitroglycerin ointment would result in a reduction of MAP and SVR in the acute treatment of patients.

Methods—We conducted a prospective, observational pilot study in a convenience sample of adult patients from a single ED who were treated with nitroglycerin ointment. Impedance cardiography was used to measure MAP, SVR, cardiac output (CO), stroke volume (SV), and thoracic fluid content (TFC) at baseline and at 30, 60, and 120 minutes following application of nitroglycerin ointment. Mixed effects regression models with random slope and random intercept were used to analyze changes in hemodynamic parameters from baseline to 30, 60, and 120 minutes after adjusting for age, sex, and final ED diagnosis of AHF.

Results—Sixty-four subjects with mean age 55 years (IQR 48-67) were enrolled; 59% were male. In the adjusted analysis, MAP and TFC decreased following application of nitroglycerin ointment (p=0.001 and p=0.043, respectively). CI, CO, SVR, and SV showed no change (p=0.113, p=0.085, p=0.570, and p=0.076, respectively) over time.

Conclusions—Among ED patients who are treated with nitroglycerin ointment, MAP and TFC decrease over time. However, other hemodynamic parameters do not change following application of nitroglycerin ointment in these patients.

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Conflicts of Interest: None.

Keywords

Heart failure; Nitroglycerin; Impedance cardiography

Introduction

Coronary artery disease is the leading cause of death in the United States[1], and heart failure (HF) contributes to one of every eight deaths in the United States.[2] Together, HF and acute coronary syndrome (ACS) lead to over 2.5 million hospitalizations each year, with the majority of these patients receiving initial treatment in the emergency department (ED).[3]

The American Heart Association, the European Society of Cardiology, and the Heart Failure Society of America advocate the use of intravenous vasodilators including nitroglycerin, nitroprusside, or nesiritide, in addition to diuretic therapy in patients with acute heart failure (AHF).[4-6] Similarly, the American College of Cardiology and American Heart Association recommend the use of sublingual or intravenous nitroglycerin in patients with ACS.[1] These agents cause venous and arterial dilation by increasing levels of cyclic guanosine monophosphate, which in turn decreases intracellular calcium and relaxes smooth muscle. At lower doses, nitroglycerin causes primarily venodilation; at higher doses, it also causes arterial dilation.[7] Intravenous nitroglycerin has been shown to decrease blood pressure, pulmonary capillary wedge pressure, right atrial pressure, systemic vascular resistance, and pulmonary vascular resistance while increasing cardiac output in patients with acute heart failure.[8] In acute myocardial infarction, sublingual nitroglycerin has been shown to decrease mean arterial pressure, cardiac index, and stroke volume.[9]

Nitroglycerin ointment is commonly used in United States EDs.[10] Nitroglycerin ointment exerts its effects in 15-60 minutes, with peak action at 30 to 120 minutes and an overall duration of action of 3-8 hours.[11] Limited data suggest that nitroglycerin ointment has good bioavailability and substantial hemodynamic benefits in chronic heart failure.[12,13] and stable angina.[14] However, its effectiveness in the ED management of AHF and ACS has not been well studied. To better understand its effectiveness in the ED setting, data describing acute effects are needed.

Our overall goal in this study was to determine the hemodynamic effects of nitroglycerin ointment on mean arterial pressure (MAP), systemic vascular resistance (SVR), cardiac output (CO), and stroke volume (SV) in the acute time period of treatment. Using noninvasive impedance cardiography to measure these parameters, we hypothesized that nitroglycerin ointment would result in a reduction in MAP and SVR.

Methods

Study design

We conducted a prospective observational study at a single urban, academic ED with an annual adult census of approximately 60,000 patients. This study was approved by our Institutional Review Board.

Setting and Population

We enrolled a convenience sample of patients age 18 years and older who presented to the ED between December 1, 2009, and November 30, 2010 during the hours of 8am to 5pm, and in whom the attending emergency physician suspected AHF or ACS and ordered nitroglycerin ointment for treatment. We excluded dialysis patients and those with a systolic blood pressure <90 mmHg at time of enrollment. Patients who were unable to provide informed consent were also excluded.

Study Protocol

After providing informed consent, impedance cardiography (BioZ® Dx Diagnostic System, Sonosite, Inc., Bothell, WA) was used to measure cardiac index (CI), CO, MAP, SV, SVR, and thoracic fluid content (TFC). Impedance cardiography is a noninvasive diagnostic test that gathers data from four dual sensors to calculate the resistance encountered by a current as it travels through the aorta. Dual sensors were placed bilaterally at the base of neck beneath the ear and on the chest wall, in midaxillary line at the level of the xiphoid. Eight impedance cardiography lead wires were attached to the sensors, and an oscillometric blood pressure cuff was applied to the patient's arm. Impedance cardiography measurements have been shown to correlate with Swan-Ganz catheter values.[15] A 5-minute impedance cardiography recording was performed at each time point, and hemodynamic parameters were calculated by the BioZ® Dx Diagnostic System. The system's non-invasive blood pressure measurements were taken suing a pneumatic cuff placed over the upper arm. Impedance cardiography electrodes remained on the patient between recordings, and all recordings were taken with the patient lying in approximately the same position with the head of the bed elevated at 45 degrees when possible.

Nitroglycerin 2% ointment was applied by the ED nurse to the left anterior chest wall in accordance with standard hospital procedures. Nitroglycerin usage and dose was at the discretion of the treating ED physician. Standard order sets used at the time of the study included doses of 1 inch and 2 inches. Patients who received sublingual nitroglycerin prior to ED arrival were eligible for inclusion; patients did not receive nitrates via alternative routes (sublingual, intravenous) in the ED.

Measurements

Baseline SVR, CI, CO, MAP, SV, and TFC measurements were taken before the application of nitroglycerin ointment, as well as at 30 minutes, 60 minutes, and 120 minutes following application of nitroglycerin ointment.

Outcomes

Primary outcomes were change in MAP and SVR over time following application of nitroglycerin ointment. Our sample size provided 79% power to detect a 10% change in SVR from baseline to 120 minutes following nitroglycerin application and over 80% power to detect a 4% change in MAP from baseline to 120 minutes. Secondary outcomes were the changes in CI, CO, SV, and TFC following application of nitroglycerin ointment. TFC is the reciprocal of total thoracic impedance and provides a measure of the amount of fluid within the thoracic cavity. Normal values are 21-37 $kOhm^{-1}$ for women and 30-50 $kOhm^{-1}$ for men, and substantial variation exists between individuals due to differences in body composition.

Data Analysis

Mixed effects regression models with random slope and random intercept were used to analyze changes in hemodynamic parameters from baseline to 30, 60, and 120 minutes. This model was chosen as we could not predict a standard response between individuals or within an individual over time. We adjusted for covariates including age, sex, and final ED diagnosis of AHF. These were selected based on consensus opinion among the authors as there are no definitive data on this topic. These three factors were included in the model based on consideration of variation in body fat, variation in body surface area, endothelial function, and alterations in the magnitude of effect that may occur in patients with heart failure. A sensitivity analysis including nitroglycerin dose was also performed. Data analysis was performed using STATA 12 (Stata Corporation, College Station, TX).

Results

Sixty-four patients with a median age of 55 years (IQR 48-67 years) were enrolled. The majority of subjects were male (59%) and had a history of hypertension (75%) or heart failure (64%). Most patients were treated with one inch of nitroglycerin ointment in the ED. A minority received furosemide or morphine within one hour of nitroglycerin application. AHF was the most common ED diagnosis. (Table 1.)

The mean/median values for MAP, SVR, CI, CO, SV, and TFC at baseline and times 30 minutes, 60 minutes, and 120 minutes are shown in Table 2. In the mixed effects regression model adjusting for age, sex, and final ED diagnosis of AHF, both MAP and TFC decreased following application of nitroglycerin ointment (p=0.001 and p=0.043, respectively). In contrast, CI, CO, SVR, and SV showed no change (p=0.113, p=0.085, p=0.570, and p=0.076, respectively) over time. Adding dose of nitroglycerin to the adjusted model did not alter the results.

In the multivariate models, female sex was associated with higher SVR (p=0.003) and lower CI, CO, and SV (p=0.019, p=0.001, and p=0.000, respectively). An ED diagnosis of AHF was associated with lower SV (p=0.002) and higher SVR (p=0.024).

Discussion

In this study we aimed to determine whether hemodynamic parameters change after the use of nitroglycerin ointment in the acute treatment timeframe. There is limited evidence around the changes in these parameters with nitroglycerin ointment and therefore little data surrounding the clinical effects in acute episodes of chest pain or shortness of breath. We found that MAP and TFC, but not CI, CO, SV, or SVR, change following the application of nitroglycerin ointment in ED patients with suspected AHF or ACS. Our data suggest that nitroglycerin ointment does not have significant effects on hemodynamic parameters in ED patients who present with symptoms of AHF or ACS. Our findings contrast those of Armstrong, *et al*., who showed a decrease in pulmonary capillary wedge pressure and right atrial pressure at 30 minutes following nitroglycerin application in 14 patients with New York Heart Association functional class III or IV who were refractory to therapy with digoxin and furosemide.[12] Similarly, Taylor, *et al*., showed a decrease in pulmonary capillary wedge pressure and an increase in CI following nitroglycerin ointment in 10 patients with “severe” heart failure.[13] These studies used nitroglycerin ointment at doses of one to four inches, and their small populations of patients with stable severe heart failure differ substantially from our population. Our data suggest that nitroglycerin ointment at the dose routinely used in EDs has a less pronounced, if any, effect on hemodynamic parameters in ED patients. Our data reflect the administration of nitroglycerin to patients with a broad spectrum of AHF and ACS presentations.

We did not specify surface area of nitroglycerin application; however, this enabled us to study the effectiveness (as opposed to efficacy) of nitroglycerin ointment. We may have seen no effect on hemodynamic parameters because nitroglycerin was under-dosed. One inch of nitroglycerin ointment is intended to deliver 15 milligrams of nitroglycerin over 8 hours, with peak plasma concentrations of 1.2 ng/ml reached at one hour following application.[16] Nitroglycerin infusions at 5 mcg/min and 10 mcg/min produce lower steady-state plasma concentrations of 0.5 ng/ml and 0.8 ng/ml, respectively.[17] We performed impedance cardiography at time points up to 120 minutes based on nitroglycerin's pharmacokinetic profile[11,16]; however, the peak effect of nitroglycerin may be achieved later in some patients.

Arguments for the use of nitroglycerin ointment over an intravenous infusion include its relative ease of administration and its ability to be used outside of an intermediate or intensive care unit setting. However, it remains unclear whether nitroglycerin ointment has sufficient hemodynamic effects to be used in place of an intravenous infusion.

Limitations

Our small sample size in this pilot trial from a single emergency department limits the generalizability of our findings and may have prevented us from detecting smaller yet clinically significant changes in hemodynamic parameters.

Subjects’ inclusion in the study was based on the attending physician's suspicion for AHF or ACS; thus, some patients may have had conditions mimicking these processes. However, Heart Failure Society of America guidelines state, “The diagnosis of acute decompensated HF should be based primarily on signs and symptoms”[6], and the ACC/AHA guidelines recommend that “history, physical examination, 12-lead ECG, and initial cardiac biomarker tests should be integrated” to make the diagnosis of ACS.[1] Similarly, because informed consent was required for participation, patients with the most severe presentations of AHF and ACS may not have been included.

We were unable to control for the effects of potential confounders such as pain, anxiety, dyspnea, and administration of other medications. Lastly, we used impedance cardiography to calculate hemodynamic parameters. Our results depend on the accuracy and reproducibility of measurements from the BioZ® Dx Diagnostic System.

Conclusions

Among ED patients with suspected AHF or ACS who are treated with nitroglycerin ointment, MAP and TFC decrease over time. However, other hemodynamic parameters do not change following application of nitroglycerin ointment in these patients. ED providers should consider the limited effects of nitroglycerin ointment when choosing a treatment strategy for their patients.

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Article Summary

1. Why is this topic important?

Nitroglycerin ointment is commonly used in the treatment of emergency department patients with acute coronary syndrome and acute heart failure, but its hemodynamic effects in this population remain unknown.

2. What does this study attempt to show?

This study evaluates the effects of nitroglycerin ointment on mean arterial pressure (MAP), systemic vascular resistance (SVR), cardiac output (CO), stroke volume (SV), and thoracic fluid content (TFC).

3. What are the key findings?

MAP and TFC decreased over the two hours following application of nitroglycerin ointment, but CI, CO, SVR, and SV showed no change over time.

4. How is patient care impacted?

ED providers should consider the limited effects of nitroglycerin ointment when choosing a treatment strategy for their patients.

Table 1

Baseline characteristics (N=64).

Demographics	N	%
Age (Years)*	55 (48-67)	
Male sex	38	59%
Race		
White	24	38%
Black	20	31%
Asian/Pacific Islander	3	5%
Other	10	16%
Hispanic ethnicity	6	9%
Past Medical History		
Diabetes mellitus	26	41%
Coronary artery disease	19	30%
Hypertension	48	75%
Hyperlipidemia	21	33%
Congestive heart failure	41	64%
Valvular disease	2	3%
Visit Data		
B-type natriuretic pepite (BNP) level* (pg/mL)	330 (94-1165)	
Nitroglycerin ointment dose		
0.5 inch	9	14%
1 inch	53	83%
2 inches	1	2%
Concurrent furosemide therapy**	22	34%
Concurrent morphine therapy**	13	20%
ED diagnoses‡		
Acute heart failure	31	48%
Chest pain	22	34%
Acute coronary syndrome	12	19%
Dyspnea	11	17%
Pneumonia	8	13%
COPD/asthma/acute bronchospasm	7	11%

*Data presented as median (IQR)

**Administered within one hour of nitroglycerin application

‡Patients often had more than one diagnosis.

Table 2

Hemodynamic parameters over time. (Mean/SD)

Parameter	Baseline	30 min	60 min	120 min	p-value*
SVR (dyn*s/cm5)	1630 ± 666	1652 ± 760	1584 ± 736	1617 ± 822	0.570
CI (L/min/m2)	2.7 ± 1.1	2.5 ± 1.0	2.5 ± 0.9	2.5 ± 0.9	0.113
CO (L/min)	5.9 ± 2.5	5.6 ± 2.4	5.5 ± 2.1	5.4 ± 2.1	0.085
MAP (mmHg)	106 ± 21	101 ± 21	98 ± 21	99 ± 22	**0.001**
SV (mL)	76.1 ± 33.5	72.1 ± 32.2	69.8 ± 25.1	69.3 ± 27.3	0.076
TFC (kOhm-1)	40.7 ± 12.9	40.3 ± 12.3	40.0 ± 11.9	40.2 ± 12.0	**0.043**

Data are presented as mean ± standard deviation.

SVR = Systemic vascular resistance; CI = Cardiac index; CO = Cardiac output; MAP = Mean arterial pressure; SV = Stroke volume; TFC = Thoracic fluid content.