Prehospital High-dose Sublingual Nitroglycerin Rarely Causes Hypotension

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Abbreviations:
ADHF: acute decompensated heart failure
APE: acute pulmonary edema
CHF: congestive heart failure
ED: emergency department
EMS: Emergency Medical Services
ePCR: electronic patient care report
IV: intravenous
MSN: multiple sublingual nitroglycerin tabs
SBP: systolic blood pressure

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Abstract

Introduction: High-dose intravenous nitroglycerin is a common in-hospital treatment for respiratory distress due to congestive heart failure (CHF) with hypertension. Intravenous (IV) nitroglycerin administration is impractical in the prehospital setting. In 2011, a new regional Emergency Medical Services (EMS) protocol was introduced allowing advanced providers to treat CHF with high-dose oral nitroglycerin. The protocol calls for patients to be treated with two sublingual tabs (0.8 mg) when systolic blood pressure (SBP) was >160 mm Hg, or three sublingual tabs (1.2 mg) when SBP was >200 mm Hg, every five minutes as needed.

Hypothesis/Problem: To assess the protocol's safety, the incidence of hypotension following prehospital administration of multiple simultaneous nitroglycerin (MSN) tabs by EMS providers was studied.

Methods: This study was a retrospective cohort study of patients from a single commercial EMS agency over a 6-month period. Records from patients with at least one administration of MSN were reviewed. For each administration, the first documented vital signs pre- and post-administration were compared. Administrations were excluded if pre- or post-administration vital signs were missing.

Results: One hundred case-patients had at least one MSN administration by an advanced provider during the study period. Twenty-five case-patients were excluded due to incomplete vital signs. Seventy-five case-patients with 95 individual MSN administrations were included for analysis. There were 65 administrations of two tabs, 29 administrations of three tabs, and one administration of four tabs. The mean change in SBP following MSN was -14.7 mm Hg (SD = 30.7; range, +59 to -132). Three administrations had documented systolic hypotension in the post-administration vital signs (97/71, 78/50 and 66/47). All three patients were over 65 years old, were administered two tabs, had documented improved respiratory status, and had repeat SBP of at least 100. The incidence of hypotension following MSN administration was 3.2%.

Discussion: High-dose oral nitroglycerin administration is a practical alternative to IV nitroglycerin in the prehospital setting when administered by advanced providers. The prehospital protocol for high dose oral nitroglycerin was demonstrated to be safe in the cohort of patients studied. Limitations of the study include the relatively small sample size and the inability to identify hypotension that may have occurred following the cessation of data collection in the field.

Conclusion: Hypotension was rare and self-limited in prehospital patients receiving MSN.

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Introduction

Congestive heart failure (CHF) affects approximately 5.7 million patients in the US, with one in nine death certificates mentioning heart failure.[1] Patients presenting with acute decompensated heart failure (ADHF) require urgent medical intervention to reduce the morbidity and mortality associated with rapid cardiopulmonary deterioration. Current treatment guidelines for ADHF include nitrates, morphine, diuretics, non-invasive ventilation and, when necessary, intubation and mechanical ventilation.[2] Nitroglycerin is a systemic vasodilator that acts preferentially on the venous system to reduce cardiac preload. At higher doses it also acts on the arterial system, reducing afterload and improving cardiac output, making it an ideal treatment for patients in ADHF who tend to have high vascular resistance and hypertension.[3]

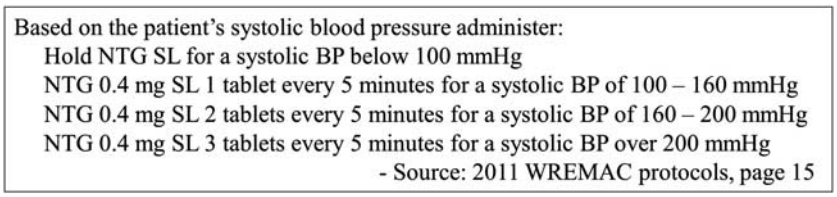

Figure 1. Regional Protocol

Administration of high-dose nitroglycerin is an effective treatment that has been shown to improve the respiratory symptoms associated with ADHF, and decrease the incidence of death due to myocardial infarction and mechanical ventilation, particularly when initiated early.[4-6] Such doses are generally administered intravenously in the hospital setting, but the practical considerations of IV nitroglycerin storage and administration preclude the routine use of this medication in the prehospital setting.

A new protocol was recently developed by the New York State Western Regional Emergency Medical Advisory Council allowing paramedics to administer high-dose nitroglycerin for CHF using multiple sublingual tablets dosed according to patient blood pressure (Figure 1). Patients were treated with two sublingual tabs (0.8 mg) every five minutes when systolic blood pressure (SBP) was >160 mm Hg or three sublingual tabs (1.2 mg) every five minutes when SBP was >200 mm Hg.

One of the potential hazards of MSN administration in the field is hypotension following MSN administration. The current study is a retrospective analysis of prehospital data to determine the safety of the new protocol. Pre- and post-administration changes in systolic blood pressure were analyzed to address this issue.

Methods

Study Design

This study was a retrospective cohort study utilizing electronic prehospital patient care report (ePCR) data from a single large commercial provider.

Human Subject Review

This study was approved by the University at Buffalo Health Sciences Institutional Review Board.

Protocol and Study Population

Nitroglycerin 0.4 mg sublingual tabs (Nitro Stat, Parke-Davis, New York, New York USA) were utilized by New York State certified EMT-CCs (Emergency Medical Technicians-Critical Care) and paramedics during prehospital patient care. A computerized search for all documented prehospital nitroglycerin patients during the study period (January-June 2012) was performed. Case-patients were defined as those who received emergency medical services that resulted in at least one instance of MSN administration. The number of MSN administrations varied for each case-patient in the study. For each MSN administration, the timed set of vital signs immediately preceding and following (pre and post) was reviewed. The ePCR system documents time in one minute intervals. In instances where vital signs and medication administration had the same time stamp, it was assumed that the vitals were taken pre-MSN administration.

Analysis

MSN administrations were excluded from the analysis when pre or post vital signs were missing. Case-patients for whom no MSN administrations had complete pre and post vital signs data were eliminated. In case-patients who received multiple MSN administrations, each administration with complete vital signs was included in the analysis, but administrations with incomplete data were excluded. Data were entered into and analyzed in Microsoft Excel 2010 version 14.0 (Microsoft Corporation, Redmond, Washington USA).

Outcome

The primary endpoint was change in systolic blood pressure following each MSN administration. Blood pressure was measured in mm Hg. Hypotension was defined as systolic blood pressure (SBP) < 100. Administrations that resulted in hypotension were further reviewed.

Results

During the 6-month study period, there were 1,446 patients with any documented nitroglycerin administration, including basic life support (BLS) medication assists. One hundred patients had at least one instance of multiple simultaneous nitroglycerin administration by an advanced provider. Ninety-five MSN administrations in 75 case-patients had documented pre and post administration vital signs and were included in the analysis (Figure 2).

The average age of the case-patients was 65.7 (range 34-90) years. The patients were 54.7% male, 13.7% had documented chest pain, and 96.8% had documented shortness of breath.

Sixty-eight percent (65/95) of MSN administrations were of two tabs (Figure 3) administered simultaneously with a mean change in SBP of -16.4 mm Hg (SD = 31.9; range, +26 to -132). Thirty-one percent (29/95) of MSN administrations were of three tabs (Figure 4) administered simultaneously with a mean change in SBP of -10.1 mm Hg (SD = 28.1; range +59 to -79). A single MSN administration of four tabs occurred with a change in SBP of -31 mm Hg.

The average time between pre-administration vital signs and MSN administration was 4.2 minutes (SD = 3.7; range, 0-17). The average time between MSN administration and post administration vital signs was 4.6 minutes (SD = 2.7; range 1-12).

Systolic hypotension was documented in the post-administration vital signs of three patients (Table 1). The overall rate of post-MSN administration hypotension was 3.2% (3/95).

The first case-patient was a 68-year-old Caucasian male with complaints of respiratory distress and chest pain. After treatment with two sublingual nitroglycerin tablets, his blood pressure decreased from 186/104 to 97/71. A follow-up blood pressure taken eight minutes later was 119/73. The patient remained

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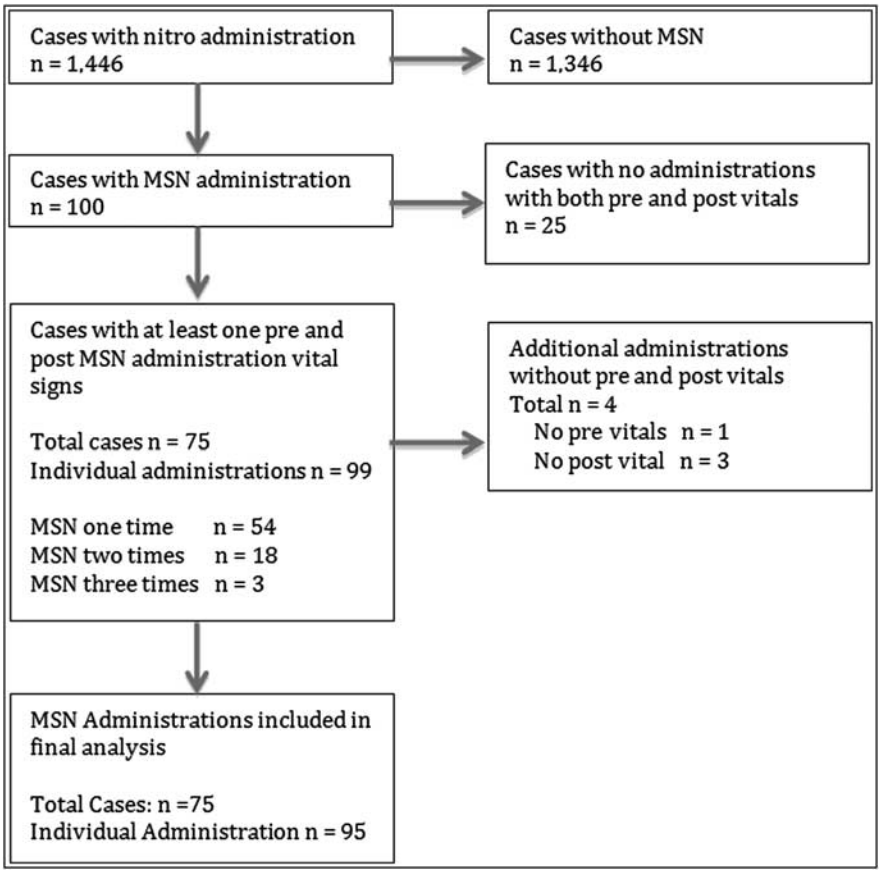

Figure 2. Inclusion Diagram

stable and was transported to the hospital emergency department (ED) without incident.

The second case-patient was an 82-year-old Caucasian female being treated for shortness of breath and congestive heart failure. After treatment with two sublingual nitroglycerin tablets, her breathing improved but her blood pressure decreased from 185/91 to 66/47. Seven minutes later, a follow-up blood pressure was recorded at 100/56.

The third case-patient was a 71-year-old Caucasian female in severe respiratory distress. She was treated with two sublingual nitroglycerin tablets, after which her breathing slightly improved but her blood pressure decreased from 210/145 to 78/50. Seven minutes later, her blood pressure was recorded as 180/120. She remained stable and was transferred to the hospital ED without incident.

Based on documented pre-administration vital signs, adherence to the MSN administration protocol was inconsistent. Three case-patients were administered MSN following a documented SBP <160. None of these administrations resulted in hypotension.

Limitations

The study examined patients to whom MSN was administered. There were likely other patients treated during the study period for whom MSN was indicated but not administered. Similarly, more than one MSN administration may have been indicated for a patient based on the recommended five minute dosing, but only one MSN administration was administered.

The study was a retrospective review of prehospital data collected for clinical, non-research purposes. In the data set, vital signs were recorded separately from interventions and were not specifically linked to the administration of nitroglycerin. Vital signs also were not documented at fixed intervals, and other interventions may have taken place between pre and post vital signs. Other sets of vital signs that were obtained, but not documented, may have affected the care of the patients. This would explain some instances where the quantity of MSN administered seemed inconsistent with the protocol. Alternatively, other instances may represent protocol deviations.

This system of documentation may underestimate the frequency of hypotension by not capturing early hypotension that resolved prior to the documented set of vital signs or late hypotension that occurred after the last documented prehospital vital signs.

Discussion

Prompt recognition of ADHF symptoms and early initiation of appropriate therapy reduces morbidity and mortality and improves outcomes.[6,7] However, the accurate diagnosis of ADHF and acute pulmonary edema (APE) may be challenging, particularly in the prehospital environment. Distinguishing between the respiratory distress symptoms of APE, chronic obstructive pulmonary disease (COPD) exacerbations, and pneumonia is often difficult or impossible on purely clinical grounds.

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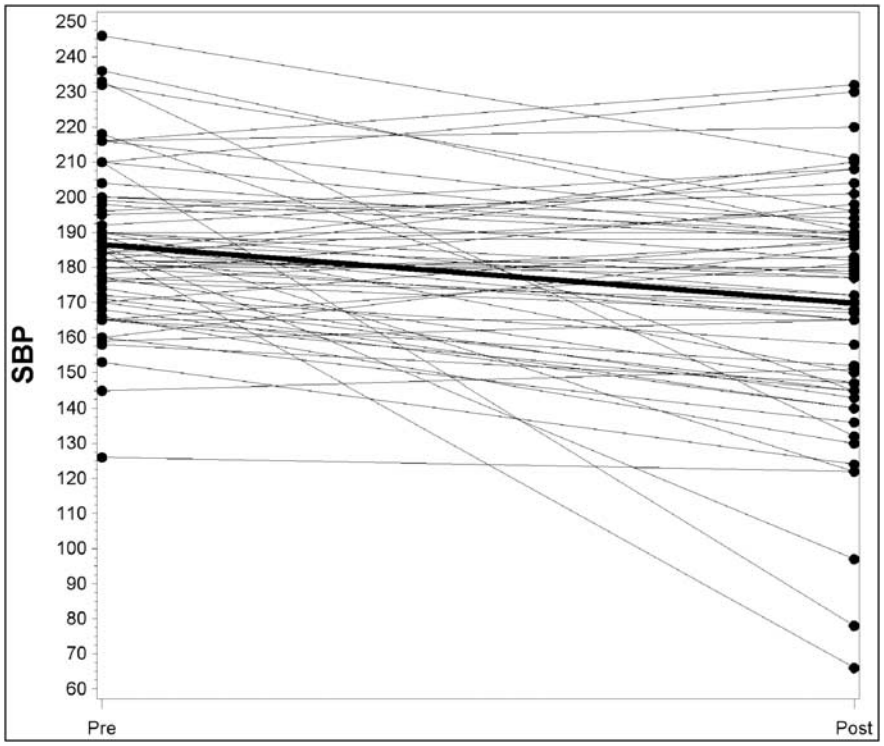

Figure 3. Pre/Post Systolic Blood Pressure for Administration of 2 Tabs Simultaneously

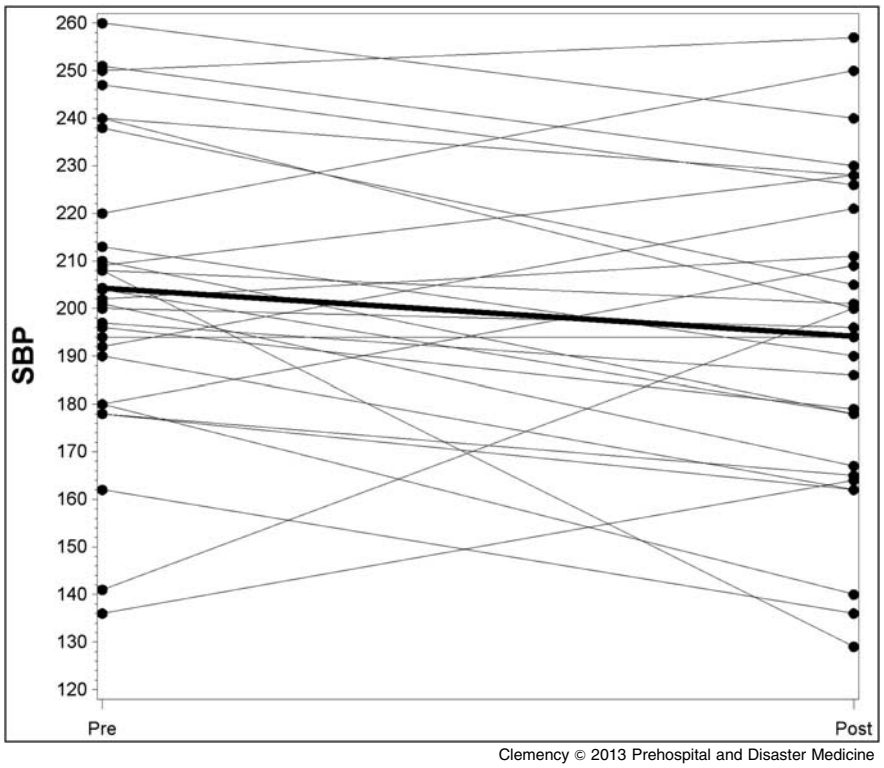

Figure 4. Pre/Post Systolic Blood Pressure for Administration of 3 Tabs Simultaneously

Patients or bystanders may provide inadequate medical history or inaccurate history of present illness due to severe clinical symptoms. Even heart failure itself can be subdivided into several heart failure syndrome classifications, each with a distinct symptom profile and unique pathophysiology.[7] Treatment decisions in the setting of such diagnostic uncertainty may impose additional risks on a patient, yet must be made without delay to prevent further respiratory compromise.

Previous studies have examined the safety of different treatment algorithms in presumed ADHF in the prehospital setting.[8–11]

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	No.	Mean SBP Δ	95% CI	Range	Incidence of Hypotension
2 tablets	65	-16.5	-8.6, -24.4	+26, -132	3
3 tablets	29	-10.1	+0.6, -20.8	+59, -79	0
4 tables	1	-31.0	N/A	N/A	0
All	95	-14.7	-8.5, -21.0	+59, -132	3

Table 1. Change in Systolic Blood Pressure by Number of Nitroglycerin Tablets Administered

Mattu et al report that the use of standard-dose nitroglycerin by EMS personnel is not associated with adverse consequences, even if the diagnosis is incorrect.[10] The current study addresses the safety of high-dose nitroglycerin administered as multiple sublingual tablets in an undifferentiated population of patients in respiratory distress. Although three case-patients (representing 3.2% of MSN administrations) developed hypotension following MSN administration, these episodes fully resolved and respiratory symptoms improved. This suggests that the protocol is a safe and potentially beneficial treatment option for prehospital patients in presumed ADHF and is unlikely to result in an adverse outcome if the etiology is other than heart failure.

Current guidelines for the treatment of decompensated heart failure include the use of non-invasive ventilation, diuretics, and morphine in addition to nitrates.[2] The current study does not control for the effects of these additional treatments on patient outcome. It is possible that these therapies may have been responsible for the documented episodes of hypotension, or that the combination of nitroglycerin with other medications and/or non-invasive ventilation contributed to the overall change in the patients' clinical and hemodynamic parameters, including those with improvement without hypotension. Furthermore, there is no available data on patient outcomes once they arrived in the emergency department, so it is possible that late episodes of hypotension caused by MSN have been missed.

The current study was designed to review the safety of a newly-established protocol for the treatment of ADHF. The study demonstrated a low incidence of hypotension, an important adverse event. Although long-term outcome data on the study population are not available, based on the infrequent development of hypotension, it is reasonable to conclude that the use of MSN is a safe and acceptable treatment alternative to high-dose IV nitroglycerin in the prehospital setting. Further investigation is also required to determine the effectiveness of initiating high-dose nitroglycerin prior to ED arrival relative to other available prehospital treatment options.

Conclusion

Hypotension was rare and self-limited in this retrospective cohort of prehospital patients receiving MSN for acute ADHF exacerbation with hypertension. Further study regarding the effectiveness of this prehospital intervention is needed.

Acknowledgement

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