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High-dose nitroglycerin infusion description of safety and efficacy in sympathetic crashing acute pulmonary edema: The HI-DOSE SCAPE study

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ABSTRACT

Background: Sympathetic crashing acute pulmonary edema (SCAPE) is a medical emergency in which severe, acute elevation in blood pressure results in acute heart failure and fluid accumulation in the lungs. Without prompt recognition and treatment, the condition often progresses rapidly to respiratory failure necessitating intubation and intensive care unit (ICU) admission. In addition to non-invasive positive pressure ventilation (NIPPV), high-dose nitroglycerin (HDN) has become a mainstay of treatment; however, an optimal dosing strategy has not been established.

Objective: The purpose of this study was to describe the characteristics and outcomes of patients who received an HDN infusion (≥ 100 μg/min) for the management of SCAPE in the Emergency Department (ED) of a large urban academic medical center. Outcomes were also analyzed to determine predictors of safety and efficacy including use of adjunct medication therapies.

Results: There were 67 adult patients who received HDN infusion for SCAPE from January 1, 2018 to December 31, 2018. The median (IQR) systolic blood pressure (SBP) on initiation of HDN infusion was 211 (192–233) mmHg. Patients were 63% male, 84% black, 51% had a history of heart failure (HF), and 36% had end-stage renal disease (ESRD). IV nitroglycerin (NTG) was initiated at a median (IQR) dose of 100 (100—200) mcg/min with median (IQR) peak rate in the first hour of 200 (127.5–200) mcg/min and an absolute maximum observed rate of 400 μg/min overall. 73% of patients received NIPPV, 48% sublingual (SL) or IV bolus nitroglycerin before HDN infusion, 58% loop diuretic, and 34% angiotensin-converting enzyme inhibitor (ACE—I) or angiotensin II receptor blocker (ARB). Rates of ICU admission, intubation, acute kidney injury (AKI) at 48 h, and hypotension were 37%, 21%, 13%, and 4% respectively.

Conclusion: This is the largest to date study describing the use of an HDN infusion (≥100 μg/min) strategy for the management of SCAPE. HDN infusion may be a safe alternative strategy to intermittent bolus HDN.

1. Introduction

Sympathetic crashing acute pulmonary edema (SCAPE) is a medical emergency in which severe, acute elevation in blood pressure (BP) may manifest as acute heart failure (HF) and fluid accumulation in the lungs [1]. Without prompt recognition and treatment, the condition often progresses rapidly to respiratory failure necessitating intubation and intensive care unit (ICU) admission [1]. High-dose nitroglycerin (HDN) has emerged as a common treatment strategy however, an optimal dosing strategy has not been established and there is a lack of consensus on the use of adjunct therapies, such as loop diuretics and ACE—Is [1,2].

Studies to date have primarily described the use of intermittent HDN bolus doses alone, low-dose infusions (≤60 μg/min) alone, or a combination of the two [3,4]. However, there is limited published evidence regarding the use of HDN infusions (≥100 μg/min) outside of one case report and a case series recently published by Stemple et al. [5,6].

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CI, confidence interval; HDN, high-dose nitroglycerin (HDN); IQR, interquartile range; NIPPV, non-invasive positive pressure ventilation; NTG, nitroglycerin; SCAPE, sympathetic crashing acute pulmonary edema; SaO2, oxygen saturation; SBP, systolic blood pressure (SBP); SD, standard deviation; SL, sublingual.

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Additionally, little is known about factors that may predict outcomes when using HDN SCAPE treatment, particularly regarding use of adjunct therapies such as angiotensin-converting enzyme inhibitors (ACE—Is) and loop diuretics. There is a need to characterize the use of HDN infusions, adjunct therapies, and outcomes in SCAPE, and to determine predictors of safety and efficacy.

The primary purpose of this study was to describe the characteristics and outcomes of patients who received an HDN infusion (≥100 μg/min) for the management of SCAPE in the emergency department (ED) of a large urban academic medical center. Secondarily, outcomes were analyzed to determine thesafety of adjunct medication therapies.

2. Methods

2.1. Study design and setting

This study was a retrospective chart review conducted at an adult emergency department located within a large, tertiary care academic medical center that sees 55,000–60,000 patient visits annually. The study was deemed exempt by the local institutional review board.

2.2. Study protocol

Patients who received an HDN infusion (≥100 μg/min) in the ED between January 1, 2018 and December 31, 2018 were screened for the following inclusion criteria: age 21–89 years, initial systolic blood pressure (SBP) ≥160 mmHg, HDN infusion (rate ≥100 μg/min within the first hour of infusion), and respiratory distress noted by ED physician (including notation of pulmonary edema, SaO2 ≤90%, Non-invasive positive pressure ventilation (NIPPV), or respiratory rate ≥30 breaths/min). No exclusion criteria were applied. Patients with multiple ED visits over the study period could be included more than once.

Electronic medical records were used to collect baseline characteristics including age, sex, body mass index (BMI), vital signs, comorbidities, and home medications. Comorbidities and home medications were based on ED physician note documentation. Ejection fraction (EF) was collected for patients with documented HF if available on echocardiogram from index hospitalization or within the previous six months. Data were collected on interventions for SCAPE received in the ED, including timing and dosing. Interventions included NIPPV, use of sublingual (SL) or intravenous (IV) bolus NTG prior to HDN infusion, initial and maximum HDN rates within the first hour, loop diuretics, and ACE—Is or angiotensin II receptor blockers (ARBs). All loop diuretic doses were converted into oral furosemide equivalents using a conversion of 40 mg PO furosemide = 20 mg IV furosemide = 20 mg IV/PO torsemide = 1 mg IV/PO bumetanide. Data on loop diuretic use was collected for 48 h after ED presentation to correlate to acute kidney injury (AKI) and need for ongoing diuresis. No data were collected regarding pre-hospital interventions received due to the lack of available retrospective data.

Our ED HDN guideline created in 2017 permits an IV bolus dosing of 200 μg with the initiation of an infusion. Because our institution does not have an order set for SCAPE, initial dosing and titration practices vary. General practice at our institution is to start an HDN infusion with or without an IV NTG bolus and rapidly up-titrate the rate as needed to achieve resolution of symptoms. The institutional IV administration guidelines recommend a maximum infusion rate of 300 μg/min. All titrations are done at the recommendation of the bedside clinician.

2.3. Outcome measures

Outcomes data were collected including initial and lowest SBP while receiving HDN infusion, the incidence of intubation, hypotension (SBP < 90 mmHg), AKI within 48 h (defined as serum creatinine [SCr] increase ≥0.3 mg/dL in 48 h per Kidney Disease Improving Global Outcomes [KDIGO] guidelines), disposition level of care, and length of stay (LOS) [7]. Patients with end-stage renal disease (ESRD) on hemodialysis were excluded from the AKI outcome.

2.4. Data analysis

Descriptive statistics were reported for the population of patients. Categorical variables were expressed as frequencies and percentages. Continuous variables were expressed as means or medians where appropriate. Differences between groups were calculated using statistical tests appropriate for categorical (Chi square test or Fisher's exact test) and continuous variables (Mann-Whitney *U* test). A p-value of <0.05 was considered statistically significant.

To explore potential predictor variables related to adjunct therapies received, rates of a composite unfavorable outcome of intubation, hypotension, or AKI within 48 h were compared between groups by intervention received in the ED: IV NTG ≥ 200 μg/min within the first hour, SL or IV bolus NTG prior to infusion, loop diuretic, and ACE-I/ARB.

3. Results

3.1. Screening and eligibility

A total of 90 patient visits received an HDN infusion (≥ 100 μg/min) in the ED during the study period and were screened for inclusion. Of these 90 patient visits, 23 were excluded, with the most common reasons for exclusion being initial SBP < 160 mmHg and HDN infusion not ≥100 μg/min within the first hour respectively. The remaining 67 patient visits were included in the study.

3.2. Overall population

Demographic and baseline characteristics including comorbidities and selected home medications documented in the ED physician note are summarized for the overall patient population in Table 1. Included patients were predominantly black and male. Overall, approximately one-half of the patients had documented history of HF before presentation and nearly one-third had ESRD. Of those with HF, approximately

Table 1
Overall Population: Baseline Characteristics.

Baseline Characteristics	$n = 67$
Male – n (%)	42 (63)
Black race – n (%)	56 (84)
Age, yrs. – mean (±SD)	59 (±11)
BMI, kg/m^2 – mean (±SD)	28.3 (±7.9)
SBP on NTG initiation, mmHg – median (IQR)	211 (192–233)
Initial SaO2, % – median (IQR)	98 (94–99)
Initial SCr, mg/dL – median (IQR)	2.12 (1.33–9.56)
No history of ESRD	1.45 (0.94–1.99)
ESRD	11.05 (8.80–13.03)
Comorbidities:*	
HF – n (%)	34 (51)
EF ≤ 40%** – n (%)	18 (53)
EF > 40%** – n (%)	16 (47)
ESRD – n (%)	24 (36)
CAD – n (%)	17 (25)
Asthma/COPD – n (%)	30 (45)
Erectile dysfunction – n (%)	1 (1)
Home Medications:*	
SL nitroglycerin – n (%)	8 (12)
Loop diuretic – n (%)	11 (16)
ACE-I/ARB – n (%)	31 (46)
Thiazide-like diuretic – n (%)	6 (9)
Aldosterone antagonist – n (%)	9 (13)
Other antihypertensive – n (%)	46 (69)
Phosphodiesterase-5 inhibitor – n (%)	2 (3)

* Documented in ED provider note prior to admission.
** Documented within 6 months prior to admission or during hospitalization.

one-half had an EF ≤ 40% on echocardiogram in the six months prior to presentation or during hospitalization. The median SCrfor all patients was 2.12 mg/dL; however in the patient population without ESRD, the median SCr was lower at 1.45 mg/dL (0.94–1.99).

3.2.1. Interventions

Interventions received for SCAPE in the overall population can be seen in Table 2. Approximately half (48%) of patients received SL or IV bolus NTG prior to initiation of HDN infusion. SL doses received nearest to HDN infusion were nearly all 0.4 mg (400 μg) and IV bolus doses were primarily 100 or 200 μg, except for two patients who received an IV bolus dose of 1000 μg prior to HDN infusion. The median (IQR) initial HDN infusion rate was 100 (100–200) mcg/min, with a peak median (IQR) rate of 200 (127.5–200) mcg/min in the first hour. The most common adjunct therapies received in order of prevalence were NIPPV (73%), loop diuretic (58%), and ACE-I/ARB (34%), which corresponded to median (IQR) times to intervention of 0 (0–23) minutes, 75 (38–184) minutes, and 258 (60–481) minutes respectively.

The median (IQR) diuretic dose received in the ED in oral furosemide equivalents was 120 (80–160) mg. Patients who received a loop diuretic and had a documented loop diuretic dose on the home medication list received 3.9 times their home dose in oral furosemide equivalents in the ED on average. Of patients who received a loop diuretic in the ED (58%), only 44% received a subsequent dose between 24 and 48 h. Overall, 55% of patients received a loop diuretic within 8 h of arrival, 40% between 8 and 24 h, and 30% between 24 and 48 h with median (IQR) incremental doses in oral furosemide equivalents of 120 (80–160) mg, 160 (120—200) mg, and 160 (120–260) mg respectively.

Of patients who received an ACE-I /ARB in the ED, IV enalaprilat was used in 43% of cases. The remainder received oral therapy, which was often a resumption of home therapy.

Table 2
Overall Population: Interventions Received in ED.

Variable	n = 67
SL or IV bolus prior to NTG infusion – n (%)	**32 (48)**
SL NTG – n (%)[a]	20 (63)
0.4 mg – n (%)	19 (95)
0.8 mg – n (%)	1 (5)
IV bolus NTG – n (%)[a]	12 (38)
100 μg – n (%)	5 (42)
200 μg – n (%)	5 (42)
1000 μg – n (%)	2 (17)
IV NTG infusion ≥ 100 μg/min within first hour – n (%)	**67 (100)**
Initial rate, mcg/min – median (IQR)	100 (100–200)
Peak rate within first hour, mcg/min – median (IQR)	200 (127.5–200)
Time to IV NTG infusion, min – median (IQR)[b]	17 (10–62)
Duration of IV NTG infusion, min – median (IQR)	314 (165–641)
IV NTG ≥ 200 μg/min in first hour – n (%)	34 (51)
Loop diuretic – n (%)	**39 (58)**
Dose, oral furosemide equivalents (OFE), mg – median (IQR)	120 (80–160)
Multiple of home dose in OFE (overall, $n = 10$)	3.9
Multiple of home dose in OFE (HF subgroup, $n = 7$)	3.3
Time to loop diuretic, min – median (IQR)	75 (38–184)
ACE-I/ARB – n (%)	**23 (34)**
IV enalaprilat	10 (43)
1.25 mg	9 (90)
0.625 mg	1 (10)
Time to ACE-I/ARB, min – median (IQR)	258 (60–481)
NIPPV – n (%)[c]	**49 (73)**
Time to NIPPV, min – median (IQR)	0 (0–23)
Duration of NIPPV, min – median (IQR)	351 (180–527)

[a] Dose given nearest to initiation of NTG infusion.
[b] From ED arrival.
[c] NIPPV = Continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BPAP).

Table 3
Blood Pressure Reduction on HDN Infusion with or without Adjunct Therapies.

Initial SBP at HDN initiation	Median (IQR), mmHg
HDN only	206 (190–211)
HDN with loop diuretic only	203 (178–233)
HDN with ACE-I/ARB only	222 (210–229)
HDN with loop diuretic and ACE-I/ARB	243 (225–251)
Percent decrease from initial SBP to nadir	**Median (IQR), %**
HDN only	32 (23–44)
HDN with loop diuretic only	37 (26–50)
HDN with ACE-I/ARB only	33 (27–37)
HDN with loop diuretic and ACE-I/ARB	36 (32–45)

Overall, 24% of patients received NTG only, 42% received NTG and a loop diuretic only, 18% received NTG and ACE-I/ARB only, and 16% received NTG with a loop diuretic and an ACE-I/ARB.

3.2.2. Outcomes

The initial SBP on HDN initiation and percent reduction in SBP for those who received HDN only, HDN with a loop diuretic, HDN with an ACE-I/ARB, or HDN with a loop diuretic and ACE-I/ARB was similar (Table 3).

Only 13% of patients were discharged home, with 37% requiring an ICU, 19% intermediate care, or 20% floor level admission (Table 4). The most common unfavorable events were intubation (21%), followed by AKI (13%), and hypotension (4%) (Table 5).

3.3. Predictor variables: composite unfavorable outcome, intubation, and AKI

Select baseline characteristics between those who experienced an unfavorable outcome (intubation, hypotension, or AKI within 48 h) (31%) and those who did not (69%) can be seen in Table 6. Median (IQR) baseline SaO2 was significantly lower in those who experienced an unfavorable outcome: 94 (88–97) % vs 98 (96–100) % ($p = 0.004$). Though not statistically significant, there were proportionally fewer patients of black race in the unfavorable outcome group (71% vs 89%, $p = 0.09$) as well as patients with ESRD (19% vs 43%, $p = 0.06$).

When comparing interventions received between groups (Table 7), those with an unfavorable outcome were more likely to have received higher rates of IV NTG (≥ 200 μg/min) within the first hour (71% vs 41%, $p = 0.02$). Though not statistically significant, those with an unfavorable outcome were also more likely to have received a loop diuretic in the ED (71% vs 52%, $p = 0.14$).

4. Discussion

This study is the largest to date describing the use of an HDN infusion (≥100 μg/min) strategy for the management of SCAPE. To our knowledge, an HDN infusion strategy for SCAPE has only been described in one published case report and a four-patient case series, both of which used a higher initial IV NTG rate of 400 μg/min, with the exception of

Table 4
Overall Population: Disposition and Length of Stay.

Variable	n = 67
Admit Level of Care:	
Discharge from ED - n (%)	9 (13)
Floor - n (%)	20 (30)
Intermediate Care - n (%)	13 (19)
ICU - n (%)	25 (37)
Length of Stay:	
ED – hrs, median (IQR)	13.7 (5.4–21.8)
ICU – hrs, median (IQR)	53.2 (30.2–82.1)
Hospital – hrs, median (IQR)	82.6 (56.7–125.8)

Table 5
Overall population: unfavorable outcomes.

Variable	n = 67
Composite Unfavorable Outcome - n (%)	**21 (31)**
Intubation - n (%)	14 (21)
AKI - n (%)	9 (13)
Within 8 h - n (%)	1/9 (11)
Within 24 h - n (%)	5/9 (56)
Within 48 h - n (%)	9/9 (100)
Hypotension (SBP < 90 mmHg) - n (%)	3 (4)

one patient in the case series who was started on IV NTG at 200 μg/min [5,6]. In contrast, in the present study, patients with SCAPE were started on HDN infusions at approximately 100 μg/min and rapidly titrated up to 200 μg/min on average, with or without relatively small SL or IV bolus doses prior to infusion compared to those reported in previous studies of intermittent bolus HDN strategies. The maximum IV NTG infusion rate observed in our patient population was 400 μg/min.

Despite large and rapid decreases in SBP seen with HDN infusions in this study, there was a low rate of hypotension and no clear relationship to the development of AKI observed. However, that patients with higher initial SBP tended to receive more adjunct therapies. For example, patients who received HDN infusion with a loop diuretic and an ACE-I had a median (IQR) SBP of 243 (225–251) mmHg compared to 203 (178–233) mmHg in those who only received HDN infusion. This was not statistically significant, likely due to the small sample size, but likely corresponds to more aggressive therapy in patients with a higher presenting systolic blood pressure. Regardless of initial SBP or interventions received, SBP was decreased by approximately one-third while on HDN infusion. Rates of loop diuretic (58%) and ACE-I (34%) use were similar to those seen in previous observational studies of intermittent bolus HDN [3,4].

Although difficult to compare outcomes across studies and hospitals due to differences in institutional practices and policies, hypotheses may be generated by comparing outcomes seen in this study using an HDN infusion strategy to previous observational studies using an intermittent bolus HDN strategy with or without a low-dose infusion [3,4]. In the previous two studies, rates of intubation ranged from 8.9% to 16.9%, rate of AKI within 48 h from 6.7% to 13.8%, rate of hypotension from 1.9% to 6%, ICU admission from 37.9% to 83%, and hospital LOS from 3.7 days to 5.0 days [3,4]. In the present study, rate of intubation overall was higher than previous studies at 21%, but rates of ICU admission and hospital LOS were slightly lower at 37% and 3.4 days respectively. Patients who required intubation in our study had a median initial SaO2 of 92% (76–97%) compared with those who were not intubated 98% (96–100%). Rates of AKI and hypotension were within the range of the previous studies. There was a high rate of NIPPV (73%) use and the average baseline SBP appeared to be higher in the present study (211 mmHg vs 186–206 mmHg), potentially indicating a patient population with more severe SCAPE in the present study leading to a higher rate of intubation.

A larger randomized trial is warranted to directly compare an HDN intermittent bolus strategy to an HDN infusion strategy. Based on the comparatively high rate of intubations seen in this study, it may be reasonable to pursue study of higher initial infusion rates (e.g. 400 μg/min) which may prove more effective and has thus far appeared safe in a case report and case series [5,6].

Several limitations should be noted. First, due to the retrospective study design, a causal relationship between interventions received and outcomes cannot be established. Associations established should be viewed as exploratory and hypothesis-generating until prospective data becomes available. Although important between-group differences were controlled for using multivariate logistic regression, the possibility of unmeasured selection bias remains. The accuracy of baseline characteristics in this study relied upon the past medical history and home medication list documented in the initial ED physician note, which may not have been complete or up-to-date. This may explain our findings of relatively low rates of guideline-directed medical therapies despite the number of patients with documented HF. It is also possible that this disparity represents patients who were labeled as having HF due to a previous episode of SCAPE rather than having chronic HF requiring ongoing medical management.The high intubation rate in our population also may represent a more severe patient presentation than other studies rather than a potential efficacy or safety concern with the use of HDN. Data on long-term outcomes were not collected, so it is not clear if rates of AKI at 48 h correlated to true long-term harm as opposed to a transient worsening of renal function without long-term consequences [8]. Additionally, it is unknown if these patients developed AKI beyond 48 h as the study only assessed the initial 48 h of patient care. Future prospective studies should examine this subpopulation to determine if there is a true effect that may change use of interventions such as loop diuretics in SCAPE management in patients with pre-existing HF.

Table 6
Patients with Unfavorable Outcome versus without: Baseline Characteristics.

Baseline Characteristics	Unfavorable Outcome ($n = 21$)	No Unfavorable Outcome ($n = 46$)	P-value
Male – n (%)	12 (57)	30 (65)	0.53
Black race – n (%)	15 (71)	41 (89)	0.09*
Age, yrs. – mean (±SD)	58 (±10)	59 (±11)	0.51
BMI[b]**, kg/m^2 – mean (±SD)	28.2 (±8.4)	28.3 (±7.8)	0.89
SBP on NTG initiation, mmHg – median (IQR)	209 (192–230)	214 (191–233)	0.74
Initial SaO2, % – median (IQR)	94 (88–97)	98 (96–100)	0.004*
HF – n (%)	10 (48)	24 (52)	0.73
ESRD – n (%)	4 (19)	20 (43)	0.06*

* $P < 0.15$ included in later multivariate logistic regression.
[b] **Body Mass Index

Table 7
Patients with Unfavorable Outcome versus without: Interventions Received in ED.

Interventions	Unfavorable Outcome (n = 21)	No Unfavorable Outcome (n = 46)	P-value
SL or IV bolus prior to NTG gtt	8 (38%)	24 (52%)	0.29
IV NTG rate ≥ 200 μg/min in 1st hr	15 (71%)	19 (41%)	0.02**
Loop diuretic	15 (71%)	24 (52%)	0.14*
ACE-I	5 (24%)	18 (39%)	0.22
NIPPV	17 (81%)	32 (70%)	0.33

* $P < 0.15$ included in later multivariate logistic regression.
** Statistically significant.

5. Conclusion

This is the largest study to date describing the use of an HDN infusion strategy for the management of SCAPE. Although optimal initial rates and titration strategies remain unknown, the present study and other reported cases suggest HDN may be a safe alternative strategy to the use of intermittent bolus HDN.

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Declaration of Competing Interest

None.

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