High-dose versus low-dose intravenous nitroglycerine for sympathetic crashing acute pulmonary edema: a randomised controlled trial

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ABSTRACT

Objectives Sympathetic crashing acute pulmonary edema (SCAPE) is a subset of heart failure with a dramatic presentation. The unique physiology of this condition requires a different management strategy from the conventional practice. The trial objective was to compare the efficacy of high-dose and low-dose GTN in patients with SCAPE.

Methods This was an open-label randomised control trial conducted in a tertiary care teaching hospital in India from 11 November 2021 to 30 November 2022. Consenting participants were randomised to high-dose GTN or conventional low-dose GTN. The primary outcome was symptom resolution at 6 hours and 12 hours. Secondary outcomes included intubation rates, admission rates, length of hospital stay, and any short-term adverse effects of GTN and major adverse cardiac events (MACE) at 30 days.

Results Fifty-four participants were included (26 high-dose GTN, 26 low-dose GTN). At 6 hours, symptom resolution was seen in 17 patients (65.4%) in the 'high-dose' group, compared with 3 (11.5%) in the 'low-dose' group (p<0.001). At 12 hours, 88.5% of patients had a clinical resolution in the 'high-dose' arm versus 19.5% in 'low-dose' arm . The low-dose group had longer median hospital stay (12 hours vs 72 hours), more frequent MACE (3.8% vs 26.9%, p=0.02) and a higher intubation rate (3.8% vs 19.2%, p=0.08). The only short-term adverse effect seen was a headache in both the groups.

Conclusion In SCAPE, patients receiving high-dose GTN (>100 mcg/min) had earlier symptom resolution compared with the conventional 'low dose' GTN without any significant adverse effects.

Trial registration Clinical trial registry of India (CTRI/2021/11/037902).

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Sympathetic crashing acute pulmonary oedema (SCAPE) is a distinct subset of heart failure, where several observational studies have shown benefit of aggressive treatment with higher doses of nitroglycerine (GTN).

WHAT THIS STUDY ADDS

⇒ In this randomised controlled trial, there was a significant shorter time to improvement in patients receiving high-dose GTN without observing an increase in serious adverse events compared with those receiving conventional-dose GTN.

⇒ Length of hospital stay was shorter in the high-dose group.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This small trial suggests that high-dose GTN improves outcomes in SCAPE.

⇒ Larger trials are required to study safety outcomes with adequate statistical power.

INTRODUCTION

Background

Sympathetic crash acute pulmonary oedema (SCAPE) is a life-threatening condition due to the increased systemic vascular resistance and rapid redistribution of fluid caused by a sympathetic surge.[1] Studies have shown that the renin-angiotensin-aldosterone system activation results in higher peripheral vascular resistance and increased sodium and water reabsorption. This worsens cardiac function along with a decrease in pulmonary venous return. As a result, intravascular fluid shifts into the pulmonary interstitium and alveoli, causing hypoxia, dyspnoea and further sympathetic surge.[2 3] Management of these patients is challenging due to the dramatic presentation as the patient is hypoxic, restless and agitated.

Emergency physicians have used nitroglycerine (GTN) in varying doses with and without bi-level positive airway pressure (BIPAP) for patients with SCAPE successfully.[4–6] All available formulations of nitrates, including oral, intravenous and transdermal, share a similar haemodynamic effect and cause a substantial reduction in right and left ventricular filling pressure, systemic vascular resistance, systemic BP, an increase in cardiac output, and little or no change in heart rate.[7 8] In its conventional dose of 5–40 mcg/min, GTN causes venodilation, but in high doses, it causes arterial vasodilation, reducing the afterload as well.[9] This combined preload and afterload reduction reduces cardiac work and improves forward flow, relieving patients. Fearful of the adverse effects of giving high-dose GTN, many clinicians still follow the the traditional method of giving diuretics, assuming

the patient is in volume overload along with lower doses of GTN.[10–12]

The American College of Emergency Physicians, in their updated policy in 2022 on acute heart failure syndromes, gave a class C recommendation on using high-dose GTN in acute heart failure syndrome and elevated BP.[13] The current recommendations are based on a few trials[6 14 15] and several observational studies/case series.[4 5 16]

This trial was undertaken to compare the efficacy of conventional 'low-dose GTN' with 'high-dose GTN' in patients with SCAPE and highlight any adverse effects associated with high-dose GTN.

METHODS

Study design and setting

This was an open-label, parallel, pragmatic randomised controlled trial conducted in the ED of a tertiary care teaching hospital in India, with a daily footfall of 400–450 patients. The study was conducted from 11 November 2021 to 30 November 2022. The investigation conforms with the principles outlined in the *Declaration of Helsinki*. The trial was prospectively registered in the Clinical trial registry of India (CTRI/2021/11/037902).

Selection of participants

Patients aged >18 years having acute onset shortness of breath were screened for eligibility. Patients with onset of symptoms <6 hours, arrival systolic BP (SBP) ≥160 mm Hg and diastolic BP (DBP) ≥100 mm Hg or a mean arterial pressure (MAP) of ≥120 mm Hg, an RR ≥30/min, and SpO_2 <90% with bilateral crepitation on chest auscultation were diagnosed with SCAPE. These clinical criteria for SCAPE were based on the previous two published studies.[4 16] If the patient could not give consent due to illness, consent was taken from the legally authorised representative before recruiting the patient. The exclusion criteria were acute myocardial infarction (AMI), history of hypersensitivity to GTN, use of sildenafil within 24 hours or tadalafil use within 48 hours, moderate to severe aortic stenosis, or hypertrophic cardiomyopathy. Patients requiring immediate endotracheal intubation on ED arrival, as decided by the treating team were excluded.

Intervention and control arm

Participants were randomly assigned in a 1:1 ratio to a 'high-dose' GTN group (600–1000 mcg bolus followed by starting infusion rate of 100 mcg/min) or a 'low-dose' GTN group (no bolus, and a starting infusion rate of 20–40 mcg/min). Block randomisation was done using computer-generated sequences, with four patients in a block. Opaque, sealed envelopes containing a card with the treatment allocation were kept in a box at emergency and allocated to each patient in sequence. The investigators did not know the randomisation sequence until the treatment groups were assigned. Both groups were given BIPAP support with an initial inspiratory positive airway pressure of 12 mm Hg and expiratory positive airway pressure of 6 mm Hg. The pragmatic nature of the study meant that the intervention could not be performed in a blinded fashion for either the physician or patient. In our ED, patients are first seen by a junior emergency physician (EP) trainee at the triage, where initial assessment is done. The patients presenting with acute breathlessness, who are hypoxic, are triaged red according to our institutional protocol[17] and are immediately shifted to the resuscitation bay on oxygen by face mask, where a senior emergency physician would screen these patients for eligibility. After taking consent, this physician would allocate the treatment according to the randomisation and complete the entire management in the emergency. In the low-dose GTN arm, the patients did not receive bolus GTN, and GTN was started at infusion rates of 20–40 mcg/min, which the EP could titrate based on the patient's clinical condition. The maximum infusion rate in the low-dose group was fixed at 250 mcg/min as the arterial vasodilation effect predominates above that dose. In the high-dose arm, a bolus dose of GTN was given, followed by infusion rates starting from 100 mcg/min, with EP titrating the rates according to the patient's clinical response. The detailed flow of treatment protocol used in both groups is described in online supplemental eFigure - 1. All patients were managed in the high-dependency unit of the ED, with close monitoring of their vitals. If the patient developed hypotension (SBP <90 mm Hg), the GTN infusion would be immediately stopped and restarted once the BP stabilises. In patients developing headaches, 1 gm of intravenous paracetamol was given. The emergency physician performed point-of-care ultrasonography (POCUS) in real time during the initial assessment to determine the inferior vena cava (IVC) collapsibility/distensibility. The ejection fraction was calculated after the resolution of symptoms once the heart rate was normalised.

After the resolution of symptoms, a cardiology consultation was taken for each patient and their oral medications were optimised based on the current American Heart Association (AHA)/European Society of Cardiology (ESC) guidelines.[18 19] Patients could be discharged from the ED if they reported subjective improvement, a resting HR <100 bpm with a oxygen saturation of ≥95% in room air, no hypotension when standing up, and there was no or moderate worsening of renal function (chronic renal disease might be present). An early outpatient follow-up was arranged after discharge, and patients with Chronic Kidney Disease (CKD) on dialysis were sent for regular haemodialysis sessions.

Outcomes

The co-primary outcomes were the resolution of symptoms at 6 hours and 12 hours. The criteria for resolution of symptoms included meeting at least two of the following (A–C): (A) *Resolution of tachypnoea*—RR decrease by 25% or RR ≤24/min, (B) *BP resolution*—SBP ≤160 mm Hg and DBP ≤100 mm Hg or MAP ≤120 mm Hg, (C) *Resolution of hypoxia*—saturation of ≥90% on room air and ≥95% on supplemental oxygen; along with subjective improvement in their symptoms.[4 16] Patients were asked to rate their improvement on a 7-point Likert Scale, ranging from 'markedly worse' to 'no change' to 'markedly better'.[20] Subjective improvement was defined as a one-step change towards the 'markedly better' direction. Secondary outcomes included the need for invasive mechanical ventilation, ED disposition (admission or discharge), the length of ED stay, the length of hospital stay, and any major adverse cardiac event (MACE) (AMI, stroke, cardiovascular death and heart failure). Safety outcomes considered were the complications associated with giving high-dose GTN.

Sample size estimation

We defined effect size as the absolute risk difference of symptom resolution at 6 hours between the treatment arms. Since no studies compared the clinical efficacy of high-dose GTN with low-dose GTN, we calculated the sample size from two previously published studies. In a previous study published by our team, high-dose GTN resolved symptoms at 6 hours in 96% of patients.[4] In the Acute study of clinical effectiveness of Nesiritide

in decompensated heart failure (ASCEND-HF) Trial, low-dose GTN (standard treatment) improved symptoms considerably within 6 hours in 42% of patients with acute heart failure.[21 22] To detect an absolute risk difference of 54% with a power of 90%, continuity correction and a significance threshold of 0.01, we would need a sample size of 46. We aimed to enrol at least 52 patients (26 in each arm) to account for attrition and loss to follow-up.

Data collection

Information regarding age, gender, arrival time, presenting symptoms, comorbid illness, vitals at presentation and POCUS examination findings (IVC assessment and ejection fraction) were collected by the treating team. The total cumulative dose calculation of GTN required within 3 hours and 12 hours of admission and outcomes, as mentioned above, were collected by the research team, who were not involved in patient care.

All analyses were performed on an intention-to-treat principle. Categorical variables (gender, arrival shift of the day, presenting symptoms, fluid assessment, resolution at 6 hours, resolution at 12 hours, intubation requirement, ED disposition, MACE at 30 days, and any adverse events) were presented in number and percentage (%). The χ^2 test was used to find any statistical difference among study arms. The co-primary endpoints of 'resolution at 6 hours and 12 hours' were analysed using Benjamini-Hochberg analysis (BH) to adjust the false discovery rate.[23] All continuous variables (age, vitals, ejection fraction, cumulative dose within 6 hours and 12 hours, length of ED stay, and length of hospital stay) were assessed for normality of distribution using Shapiro-Wilk test. All the above-mentioned continuous variables were non-normally distributed; hence, the Mann-Whitney U test was used to investigate the difference in the study arms. The resolution of symptoms over time (6 hours and 12 hours from ED arrival) was compared using Kaplan-Meier curves. Statistical difference was assessed using the Mantel-Cox log-rank test. All the information was collected in Microsoft Excel (V.16), and statistical analysis was conducted in the IBM SPSS Statistics for Mac (V.24). All the statistical tests were applied in a two-tailed manner, with a value of $p<0.05$ considered statistically significant. The trial protocol and detailed statistical plan are available in the online supplemental file.

Patient and public involvement

No patient was involved.

Data monitoring and safety endpoints

An internal monitoring committee was constituted with two clinical faculty and one biostatistician, with the objective of monitoring any serious adverse events related to high-dose GTN and if patients in the low-dose group had a higher incidence of mortality than the high-dose group. All other procedures remain unaffected, and the patient was not excluded from the study.

RESULTS

Characteristics of study subjects

During the study period, 169 patients with symptoms and signs that suggested SCAPE were screened for eligibility by the emergency team. We excluded 102 patients who did not meet the case definition of SCAPE and those requiring immediate intubation on arrival. Nine patients met one of the exclusion criteria, and three declined to consent to participate in the study. Thus, 52 patients were finally enrolled and randomised (figure 1).

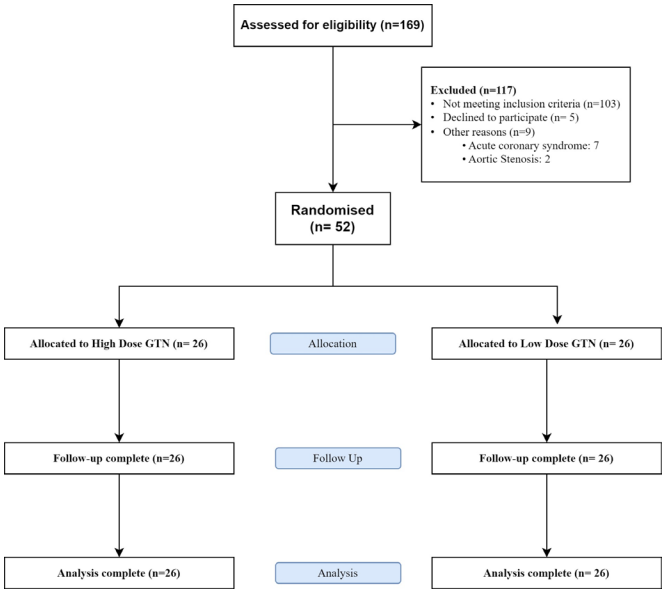

Figure 1 Consolidate Standards of Reporting Trials (CONSORT) flow diagram. (#GTN: Nitroglycerin)

The baseline characteristics of the patients were similar in the two groups (table 1). Most of the patients had a history of hypertension. Chronic kidney disease (CKD) was the most common comorbid illness in both arms. The mean duration from the onset of symptoms to arrival to the ED was 2.5 hours in the high-dose group and 3.5 hours in the low-dose group. Thirty-four patients came to the ED between 21:00 hours and 08:00 hours. Twenty-one out of the 52 patients were euvolaemic/hypovolaemic at presentation, as determined by bedside POCUS evaluation of IVC diameter and collapsibility.

Main results

The haemodynamic response to GTN in both groups is depicted in figure 2. The cumulative dose of GTN administered within 3 hours was higher in the 'high-dose' arm; however, the cumulative dose of GTN administered within 12 hours was greater in the 'low-dose' arm. Details of GTN dosing are shown in table 2. The median dose of diuretics (furosemide) received in both groups was similar (40 (40–60) mg $p=0.57$).

At 6 hours, there was resolution of symptoms in 17 out of 26 patients (65.4%) in the 'high-dose' group compared with 3 out of 26 (11.5%) in the control group ($p<0.001$). Similarly, at 12 hours, 88.5% of patients were clinically resolved in the 'high-dose' arm compared with 19.2% in the control group (risk difference 69.3%, 95% CI 49.7% to 88.7%, $p<0.001$). The differences remained statistically significant after adjusting for the false discovery rate using the BH method for the analyses at 6 hours and 12 hours. Details about the outcomes are presented in table 3. The self-assessed change in dyspnoea by the Likert Scale revealed a significant improvement in symptoms in the high-dose group at 6 hours and 12 hours (online supplemental efigure 2). The rate of clinical resolution of symptoms was also significantly greater in the high-dose GTN group than in the low-dose group (log-rank $p<0.001$, for both 12 hours and 24 hours follow-up) (figure 3).

More patients were intubated in the 'low-dose' group than in the 'high-dose' group (19.2% vs 3.8%), though this was not statistically significant (risk difference −15.4%, 95% CI −32.2 to 1.4, $p=0.08$). The proportion of patients requiring admission

Table 1 Baseline characteristics of the study population

Baseline characteristics	High-dose GTN (n=26) Median (IQR) or n (%)	Low-dose GTN (n=26) Median (IQR) or n (%)
Age (in years)	42 (30–48)	47 (42–55)
Gender (male)	14 (53.8)	14 (53.8)
Duty shift		
Morning (08:00 to 14:00)	4 (15.4)	3 (11.5)
Afternoon (14:00 to 21:00)	3 (11.5)	8 (30.8)
Night (21:00 to 08:00 next day)	19 (73.1)	15 (57.7)
Breathlessness duration	2.5 (2–4)	3.5 (2–5)
Comorbidities		
Hypertension	24 (92.3)	26 (100)
Chronic kidney disease	18 (69.2)	19 (73.1)
Diabetes	5 (19.2)	8 (30.8)
Coronary artery disease	2 (7.7)	4 (15.4)
Dilated cardiomyopathy	2 (7.7)	0 (0)
Postrenal transplant	1 (3.8)	0 (0)
Vitals at presentation		
Respiratory rate (per min)	38 (35–40)	36 (34–40)
Oxygen saturation (in %)	80 (76–85)	85 (78–87)
Pulse rate (per min)	125 (120–140)	120 (110–136)
SBP (mm Hg)	210 (196–230)	200 (188–210)
DBP (mm Hg)	126 (120–140)	126 (110–134)
Ejection fraction (%)	50 (40–50)	50 (35–50)
Furosemide received (mg)	40 (40–60)	40 (40–60)

All the categorical variables are depicted in n (%), and continuous variables are depicted in median (IQR).

DBP, diastolic BP; GTN, nitroglycerine; SBP, systolic BP.

from ED, the length of stay in ED, overall hospital stay, and the incidence of MACE was significantly higher in the 'low-dose' arm than in the 'high-dose' arm. The eight patients with MACE within 30 days had heart failure. The only short-term adverse effect in both groups was headache (3 in the high-dose group and 11 in the low-dose group). None of the patients developed hypotension in either of the study arms.

DISCUSSION

The findings of this study suggest that high-dose GTN significantly improves outcomes in patients with SCAPE without any significant short-term and long-term side effects. The low-dose group had a longer time to resolution, more incidences of mechanical ventilation and increased length of stay in the hospital. Our study demonstrates that early intervention with high-dose GTN leads to rapid resolution of symptoms in patients with SCAPE.

Different institutes have successfully used various doses of GTN in different formulations (sublingual/intravenous bolus/high-dose infusions) to treat patients with SCAPE.[4 5 16] Our ED has successfully used the high-dose GTN protocol (bolus dose followed by high-dose infusions) with BIPAP in patients with SCAPE.[4] This study highlights the significant difference in the outcome of patients receiving high-dose compared with 'conventional' low-dose GTN. A larger trial comparing high-dose and conventional-dose GTN, including patients >75 years, found no difference in outcomes (mortality/MACE/re-admissions) in the treatment versus control groups at 30 days.[24] The trial used a combination of vasodilatory strategies. In comparison, our study revealed a significant improvement in outcomes in the group with early aggressive vasodilatation using only intravenous nitrates.

The baseline characteristics in both groups were similar, and notably, the median age of patients in both the groups in our study was in the 40s. The prevalence of young hypertensives in our country is significantly higher than in the West.[25 26] About 65% of patients presented at night. Patients with diabetes and chronic kidney disease are at risk for nocturnal hypertension due to autonomical dysfunction, leading to sympathetic surge.[27] Patients on dialysis tend to have refractory hypertension on multiple antihypertensives, and even one missed session triggers SCAPE in them. The diuretic strategy used previously for SCAPE in these patients assumes that they were fluid overloaded. This strategy may not work in patients with SCAPE as they are not necessarily hypervolaemic; 40% of patients in our study were either euvolaemic or hypovolaemic. The median diuretic dose received in both groups was similar, and the treating physician did not direct their treatment based on the patient's volume status. The onset of action of furosemide is around 1 hour, and it requires a very large dose (>500 mg/day) in patients with end-stage renal disease to have any effect.[28] High-dose GTN, on the other hand, rapidly reduces afterload and improves cardiac output, increasing the perfusion of kidneys and causing diuresis.

Our study suggests that the high-dose GTN strategy in patients with SCAPE appears to work on the principle of 'hit fast, hit hard' because the low-dose group received three times more GTN at the end of 12 hours compared with the high-dose group. This blunted response in the low-dose group could be due to complex neurohormonal counter-regulation known as pseudo-tolerance and intrinsic vascular processes, termed vascular tolerance.[29] Receiving prolonged therapy of GTN causes endothelial dysfunction, which desensitises the vasodilator response to nitric oxide, a phenomenon called cross-tolerance.[30] It also causes permanent changes in vasculature, and cessation of nitrate therapy can cause a withdrawal or rebound effect.[29] This could explain the higher incidence of MACE in the low-dose group, where patients presented again with heart failure within 30 days of the first episode.

The short-term adverse effects of GTN include hypotension, palpitation, headache, dizziness and syncope.[9] Headache was the only side effect patients experienced in both groups, with a higher incidence in the low-dose group, likely because of the prolonged duration of treatment. Paracetamol was given to relieve the patient of the headache. There was no incidence of hypotension in either group. This highlights that GTN may be safely given, even in high doses, though the study was not powered for safety outcomes.

In this study, the length of hospital stay was significantly shorter in the high-dose GTN group. Most patients in this group were discharged from ED after brief observation following resolution. Thus, high-dose GTN could potentially reduce the need for hospitalisation, and relieve some of the burden on an already stretched healthcare system.

The significant advantage for patients with CKD is the reduced chance of hospital-acquired infections, as they are prone to infections and higher mortality due to immunocompromised status.[31]

Limitations

The study had the limitation of being an open-label trial with a small sample size. Therefore, the results must be interpreted as exploratory and hypothesis-generating. Though we found

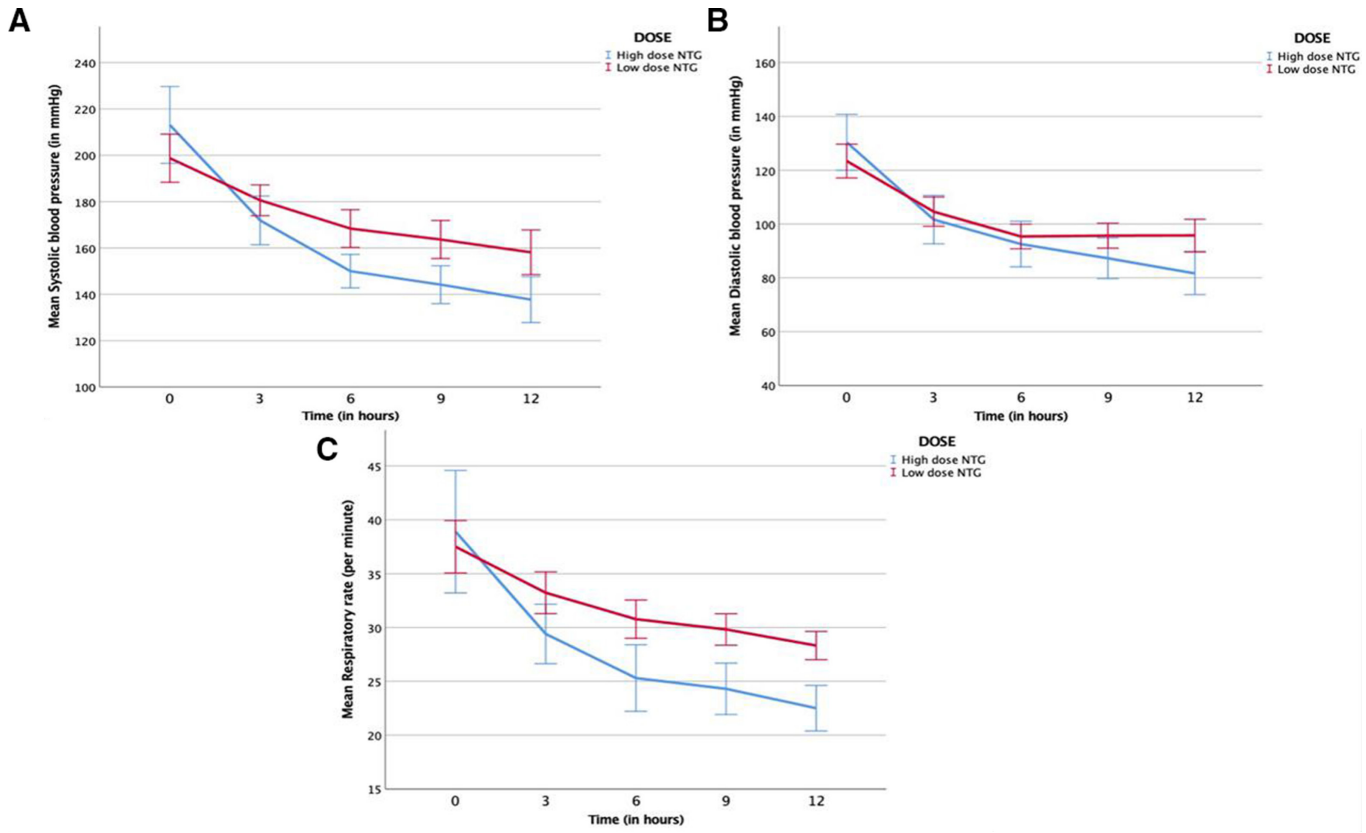

Figure 2 Response of GTN to haemodynamic parameter in both groups (A) Systolic BP (B) Diastolic BP (C) RR. #NTG (nitroglycerine). Line diagram showing the trend of median haemodynamic parameter with time (bars show the IQR).

a significant difference in both groups, the effect size in small studies is overestimated and is not likely to be repeated. The study was not powered for safety outcomes. The investigators were involved in the management of cases, which may have introduced bias in the unblinded assessment of dyspnoea. A significant proportion of patients had chronic kidney disease, which is usually refractory to antihypertensives, so a marked fall in BP on starting high doses of GTN is not seen. Although these are a subset of patients who frequently present in SCAPE, multicentre studies focusing on patients with SCAPE with normal kidney functions and reduced ejection fraction could better qualify for the adverse effects of high-dose GTN.

In conclusion, for patients presenting to ED with SCAPE, high-dose GTN (>100 mcg/min) may be helpful in early resolution and favourable outcomes compared with the conventional 'low dose' GTN.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by AIIMS ethics committee IECPG: 560/23.09.21 Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

Table 2 Cumulative dose of GTN (in mg) received in 3 hours and 12 hours in both the study arms

Dose	High-dose GTN (n=26)	Low-dose GTN (n=26)	
GTN dose (in milligrams)	Median (IQR)	Median (IQR)	P value
Cumulative dose within 3 hours	17.9 (15.6–21.8)	10.9 (7.2–16.8)	0.001
Cumulative dose within 12 hours	26.1 (16.3–54.8)	89.7 (45.0–118.8)	0.004

All the categorical variables are depicted in n (%), and continuous variables are depicted in median (IQR).
*Statistically significant.
GTN, nitroglycerine.

Table 3 Comparison of outcomes in the study arms

Outcome variables	High-dose GTN (n=26) Median (IQR) or n (%)	Low-dose GTN (n=26) Median (IQR) or n (%)	Risk difference (95% LCL, UCL)	P value
Resolution by 6 hours	17 (65.4)	3 (11.5)	53.9 (31.2 to 75.9)	<0.001*†
Resolution by 12 hours	23 (88.5)	5 (19.2)	69.3 (49.7 to 88.7)	<0.001*†
Intubation required	1 (3.8)	5 (19.2)	−15.4 (−32.2 to 1.4)	0.08
ED disposition				
Admission	3 (11.5)	15 (57.7)	46.2 (23.5 to 68.8)	0.002*
Discharged	23 (88.5)	11 (42.3)		
Length of ED stay (in hours)	11 (6–14.5)	24 (16–28.5)	–	<0.001*
Length of hospital stay (in hours)	12 (6–21)	72 (25.5–172.5)	–	<0.001*
MACE at 30 days	1 (3.8)	7 (26.9)	−23.1 (−41.6 to −4.5)	0.02*

All the categorical variables are depicted in n (%), and continuous variables are depicted in median (IQR).
*Statistically significant.
†Benjamini-Hochberg adjustment for the co-primary outcomes of symptom resolution at 6 hours and 12 hours showed a significant difference in the endpoint among the treatment groups.
GTN, nitroglycerine; LCL, Lower Confidence Level; MACE, major adverse cardiac events; UCL, Upper Confidence Level.

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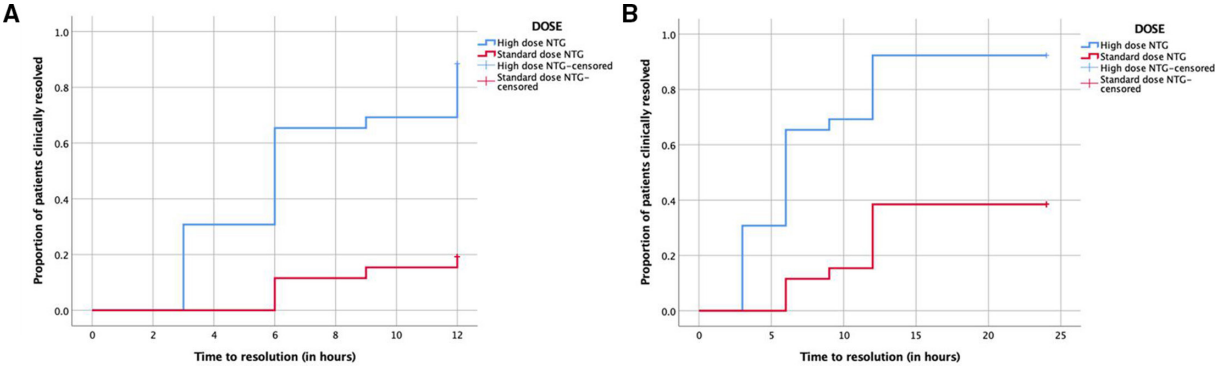

Figure 3 Kaplan-Meier curve showing the resolution of symptoms over time in both the groups, at 12 hours follow-up (A) and 24 hours follow-up (B). #NTG: Nitroglycerine.

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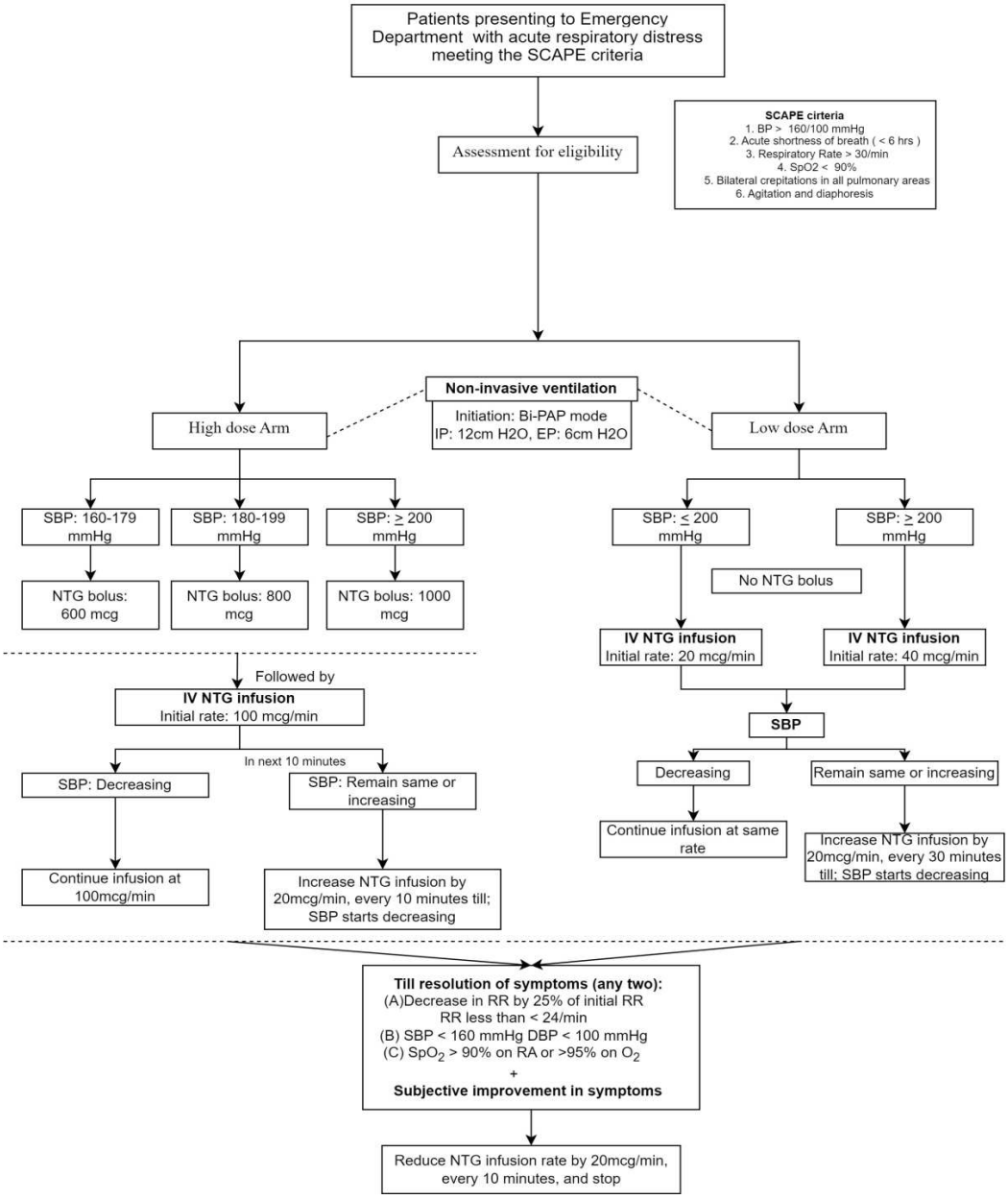
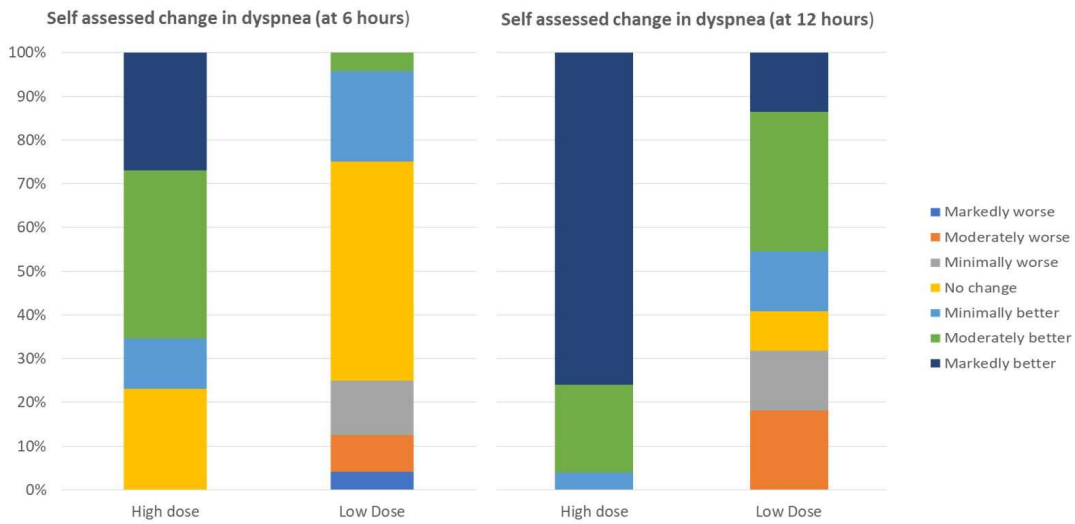


eFigure - 1: Sympathetic crashing acute pulmonary edema (SCAPE) treatment protocol

FOOTNOTES: NTG –intravenous nitroglycerine, BP – blood pressure, SBP – systolic BP, DBP – diastolic BP, RR – respiratory rate (per minute), Bi-PAP – bilevel positive airway pressure, IP – inspiratory pressure, EP – expiratory pressure, mcg – micrograms.



eFigure 2**:** Subjective change in dyspnea as assessed by 7 point likert scale

Appendix 1: Study Protocol & Statistical Plan

High-dose versus low-dose intravenous nitroglycerine for sympathetic crashing acute pulmonary edema: A randomized controlled trial

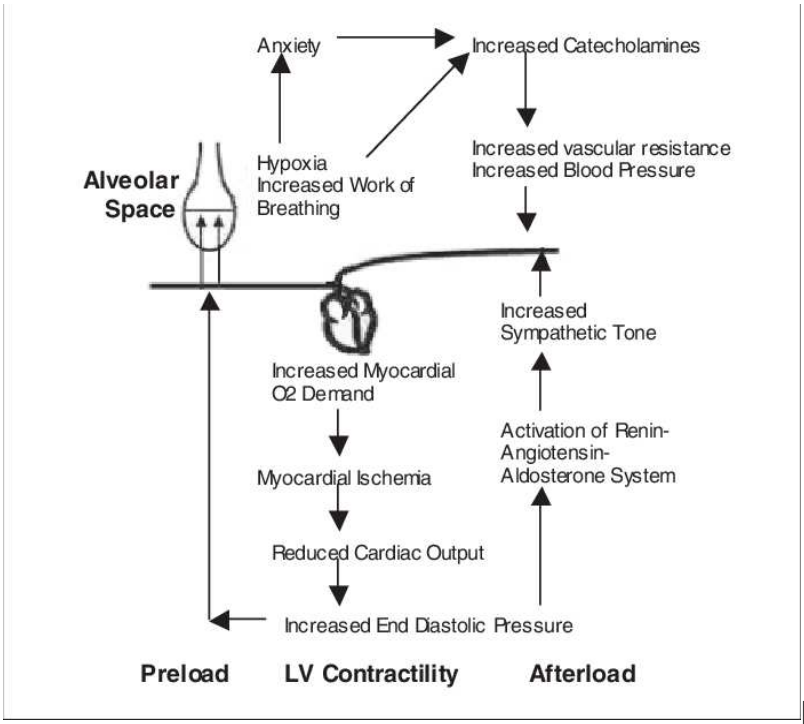
This document includes the detailed statistical plan

Introduction

Acute Heart Failure Syndrome (AHFS) is defined as new onset or gradual or rapidly worsening heart failure signs and symptoms requiring urgent therapy irrespective of the underlying cause (e.g : ischemic event) or precipitant (e.g :severe hypertension), pulmonary and systemic congestion due to elevated ventricular filling pressures with or without decrease in cardiac output.[1]bAcute heart failure has become an increasingly frequent reason for hospital admission during the last 2 decades and clearly represents a major health problem. Despite improvements in therapy, the mortality rate in patients with Heart failure has remained unacceptably high. Hence require early detection and rapid management [2].

Sympathetic Crashing Acute Pulmonary Edema (SCAPE) is the extreme end of acute pulmonary edema spectrum . The spectrum of patients presenting with AHFS is wide, ranging from mild pulmonary edema to cardiogenic shock. It is known by several names such as Flash pulmonary edema, Crashing pulmonary edema, Severe acute pulmonary edema etc.

Pathogenesis of Acute pulmonary edema is as follows :



[3]

It is associated with the combination of marked increase in systemic vascular resistance superimposed on insufficient systolic and diastolic myocardial functional reserve. This resistance results in increased left ventricular diastolic pressure causes increase in the pulmonary venous pressure, which results in fluid shift from the intravascular compartment into the pulmonary interstitium and alveoli, resulting in the syndrome of pulmonary edema. It is the fluid redistribution rather than fluid overload that precipitates SCAPE.

Therefore, the emphasis in treating pulmonary edema has shifted from diuretics (ie., furosemide-because patient may be euvolemic/hypovolemic) to vasodilators (ie, high-dose nitrates) combined with noninvasive positive airway pressure(NIV) ventilation and rarely inotropes. SCAPE develops over minutes-to-hours into a life-threatening condition.

Increased sympathetic tone adversely affects the pulmonary circulation by increasing permeability and/or provoking stress failure of the pulmonary capillaries. Other factors contributing to flash pulmonary edema include decreased nitric oxide and increased endothelin activity. Hence SCAPE is a better term since the main pathology is surge in sympathetic activity. [4]

Definition

Sympathetic Crashing Acute Pulmonary Edema(SCAPE):

The diagnosis of SCAPE will be done according to diagnostic criteria:

Diagnostic Criteria:

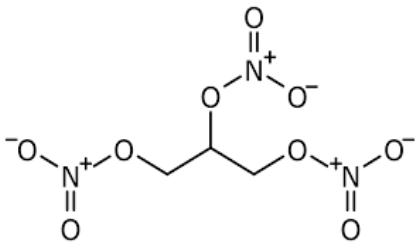
Essential Criteria

1. **Blood Pressure ≥ 160/100 mmHg.**
2. **Acute onset of respiratory distress < 6 hours**
3. **Bilateral rales or crepitations**
4. **Bedside Ultrasound – Bilateral B-lines in all pulmonary fields**

Clinical Features that are seen:

1. Extremely agitated or restless , Tachypnea >30/minute
2. Hypoxia <90% on room air <95% on oxygen
3. Dyspnea – Use of accessory muscles or air hunger
4. Diaphoresis

Nitroglycerin (NTG) is the most effective, predictable, and rapidly-acting medication available for preload reduction. Several studies demonstrated greater efficacy and safety and a faster onset of action



with NTG than with furosemide or morphine sulfate.[5]

NTG at lower doses (10-20 mcg/min) cause preload reduction and at higher doses (>100mcg/min) cause after load reduction. Use of nitrates in SCAPE differs from that of other varieties of AHFS i.e Intense sympathetic activity causes both venous and arterial tone to increase significantly causing diastolic failure. The main aim is to decrease the afterload at the earliest to cut the vicious cycle caused by sympathetic upsurge. Thus, initiating the treatment with low-dose nitrates (venodilatory doses) with gradual titration doesn't mitigate the underlying pathophysiology. [4]

Aggressive decrement of preload and afterload in the ICU by intravenous nitrates seems to improve initial outcome (5-7). Cotter et al. compared low vs. high doses of intravenous nitrates in combination with diuretics in acute HF with pulmonary edema. Aggressive vasodilatation was associated with a reduced number of myocardial infarctions, higher oxygen saturation and reduced endotracheal intubations rates (7). Comparable results supporting aggressive vasodilatation in acute HF were achieved by Sharon et al. who compared high-dose intravenous nitrates versus BiPAP (non-invasive) ventilation combined with standard treatment in patients with pulmonary edema due to acute HF. Patients treated by aggressive vasodilatation had lower mortality rates, lower incidence of myocardial infarction and lower requirement for intubation as compared to the patients in the BiPAP group (8)

Few studies on high dose NTG in SCAPE patients

1)Nashed, A. H., & Allegra, J. R. (1995). Intravenous nitroglycerin boluses in treating patients with cardiogenic pulmonary edema. The American Journal of Emergency Medicine, 13(5), 612–613. doi:10.1016/0735-6757(95)90189-2 :

They have done a case series on High dose of NTG in Cardiogenic pulmonary edema.24 patients were included in the study. Results were as follows : 83 % of patients experienced significant improvement in clinical outcome when treated with IV NTG boluses. The bolus

protocol produced a steady overall decrease in SBP with no episodes of hypotension (SBP <90 mm Hg) in 24 cases. Intubation was required only in 1 patient

2). Yi-Ting Hsieh a, Tai-Ying Lee et al. Treating acute hypertensive cardiogenic pulmonary edema with high-dose nitroglycerin Turk J Emerg Med 2018 Mar; 18(1): 34–36.

It is a case series. They presented three SCAPE patients who were successfully treated with high-dose nitroglycerin (NTG) and Bilevel positive airway pressure (BiPAP) ventilation. All three patients presented with respiratory failure on arrival but rapidly improved after treatment and did not require endotracheal intubation or admission to the intensive care unit (ICU). High-doses of NTG are well tolerated in their patients. Sublingual NTG (NITROSTAT 0.6 mg/tab) were given without success. High-dose NTG Push-doses (1 mg every 2 minutes) and BiPAP were used and patients recovered.

3) SamanthaPaone, Leigha Clarkson et al Recognition of Sympathetic Crashing Acute Pulmonary Edema (SCAPE) and use of high-dose nitroglycerin infusion; The American Journal of Emergency Medicine Volume 36, Issue 8, August 2018, Pages 1526.e5-1526.e7.

They have presented a case report where their patient presented with shortness of breath, hypertension and tachycardia with a positive finding of B-lines during bedside ultrasound. Using their SCAPE-nitro protocol, High Dose NTG(HDN) was administered in a safe and effective manner. The patient's symptoms resolved within 6 min of receiving HDN and required no further pharmacological management.

4)Fermín López-RiveraHector R. CintrónMartínez,Christian Castillo LaTorre et al Treatment of Hypertensive Cardiogenic Edema with Intravenous High-Dose Nitroglycerin in a Patient Presenting with Signs of Respiratory Failure: A Case Report and Review of the Literature Am J Case Rep. 2019; 20: 83–90.Published online 2019 Jan 21.

The case report has highlighted that hypertensive cardiogenic pulmonary should be diagnosed and managed as early as possible, and distinguished from respiratory failure due to other causes. Although pharmacokinetic and pharmacodynamic studies support the improved therapeutic role for high-dose IV nitroglycerin (>100 mcg/min) when prescribed for hypertensive cardiogenic pulmonary edema, physicians still use high-dose furosemide. High-dose nitroglycerin can reduce the need for tracheal intubation, does not affect renal function, and does not increase intensive care unit admission rates, which as occur with furosemide treatment. They have recommended premedication with nitroglycerin and an ACE-inhibitor followed by the use of furosemide once clinical stability has been achieved, as this strategy can reduce the adverse cardiovascular and renal effects of furosemide.

5) Mallick, Piyush; Upadhyay, Surjya; Senthilnathan, TS; Waleed et al A PROTOCOL OF BOLUS-DOSE NITROGLYCERIN AND NON-INVASIVE VENTILATION TO AVERT INTUBATION IN EMERGENCY DEPARTMENT ACUTE PULMONARY EDEMA Critical Care Medicine: December 2011 - Volume 39 - Issue 12 - p 67

They have done a small, single centre cohort study of hypertensive crashing acute pulmonary edema patients who were initially deemed to require immediate invasive airway management, intubation was avoided using a protocol combining NPPV (Non-invasive positive pressure ventilation) and boluses of the vasodilator nitroglycerin. Adverse events were not seen with their protocol.

41 patients were consecutively enrolled. Mean dose of 1588 mcg (range 800-28,000 mcg). None (0%) of the patients required intubation. Marked improvements in their respiratory parameters seen. 2 patients had transitory dips in SBP < 100, which resolved spontaneously

6) Levy, P., Compton, S., Welch, R., Delgado, G., Jennett, A., Penugonda, N., … Zalenski, R. (2007). Treatment of Severe Decompensated Heart Failure With High-Dose Intravenous Nitroglycerin: A Feasibility and Outcome Analysis. Annals of Emergency Medicine, 50(2), 144–152. doi:10.1016/j.annemergmed.2007.02.022

It was a nonrandomized open label trial single arm study of High dose NTG . 29 patients were included in this study whose SBp ≥160 mmHg or Mean arterial Bp is ≥ 120 mmHg and refractory to initial therapy. Patients received 2mg bolus dose followed by high dose every 3 min upto maximum 10 doses.They concluded that High Dose NTG administration is associated with decrease ICU admission, endotracheal intubation and had a promising resolution of symptoms.

7) : R. Mathew et al., High-Dose Nitroglycerin Bolus for Sympathetic Crashing Acute Pulmonary Edema: A Prospective Observational Pilot Study, Journal of Emergency Medicine, https://doi.org/10.1016/j.jemermed.2021.05.011

It was a prospective observational pilot study including 25 patients who were treated with NIV and High Dose NTG. The mean bolus dose of NTG given was 825mcg and mean cumulative dose 35mg .11 patients had resolution of symptoms at 3 hours of therapy,24 patients were discharged from ED, 1 patient was intubated and shifted to ICU.

8) Wang, K., & Samai, K. (2019). Role of high-dose intravenous nitrates in hypertensive acute heart failure. The American Journal of Emergency Medicine, 158324. doi:10.1016/j.ajem.2019.06.046 :

It is a systematic review of 2 RCTs, 3 prospective studies, 2 retrospective cohorts, 2 case series and 1 case report. They have concluded that High dose NTG is appropriate in H-AHF patients presenting with severe respiratory distress and SBp ≥ 160 mmHg or MAP ≥ 120 mmHg.

JUSTIFICATION FOR THE CONDUCT OF THE STUDY

This study will be the first of its kind in one of the India's high flow Emergency department. **SCAPE** (Sympathetic Crashing Acute Pulmonary Edema) is an extreme spectrum of Acute Hypertensive Heart failure. It has a dramatic onset and rapid course. Hence urgent identification and management is required. High dose NTG along with NIV is believed to achieve preload and afterload reduction.

There is a scarcity of medical literature (only case reports and case series) on the use of high dose NTG in SCAPE. These low evidence based studies concluded the safety and efficacy of high dose nitroglycerine in terms of reduced need of invasive mechanical ventilation and symptomatic improvement. Levy et al study on treatment of acute decompensated heart failure with high dose NTG stated endotracheal intubation occurred in 13.8%(95%CI 4.8% to 29.5%) of patients treated with high dose NTG and 26.7%(95% CI 15.5% to 40.8%) of the non-intervention patients. (9)

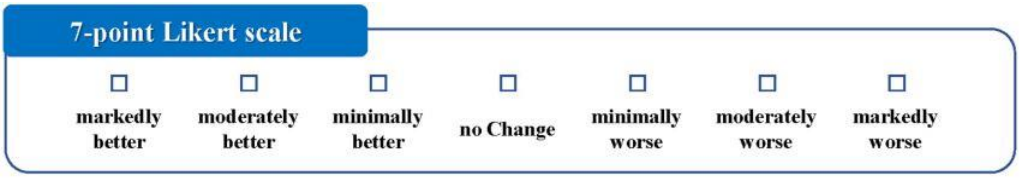
Hence the main aim of this study is to assess the safety of high dose of NTG, It's complications and outcome compared to standard low dose in SCAPE patients in a randomized controlled study.

Study Objective

1. Primary Objectives:

To compare the resolution of symptoms (outcome) at 6 hours and 12 hours (co-primary end points)

The criteria for resolution of symptoms included meeting at least 2 of the following (A-C):
A) *Resolution of tachypnea* - RR decrease by 25% or RR less than or equal to 24/min,
B) *Blood pressure resolution* - systolic BP (SBP) $\leq$ 160 mmHg DBP $\leq$ 100 mmHg,
C) *Resolution of hypoxia* –saturation of >90% on room air and >95% on supplemental oxygen;
Along with subjective improvement in their symptoms. The 7-point Likert scale was used to quantify the subjective improvement (10). 'Subjective improvement' was defined as at least one step improvement in the direction towards 'markedly better'.



2. Secondary Objectives:

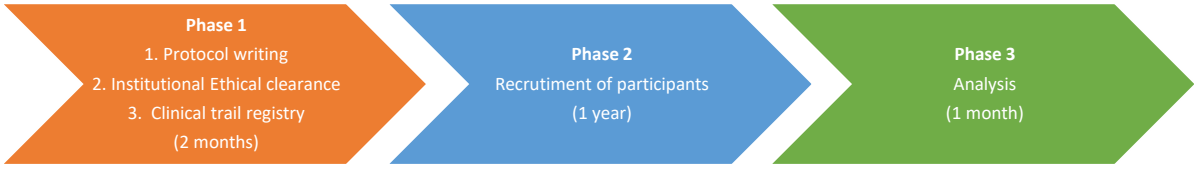
1. To assess the need of Invasive Mechanical Ventilation in both arms
2. To compare the number of ICU admissions
3. To assess short term adverse events of using high dose NTG
4. To assess MACE (Major Adverse Cardiovascular Events) in both arms at 30 days

Study Design

The trial was designed as **prospective randomized control trial** to be conducted in the emergency room of All India Institute of Medical Sciences, New Delhi, India; a tertiary care teaching hospital with average footfall of 400-450 patients per day in the emergency department.

Timeline of Study

Study period: September 2021 to December 2022



Study Subjects

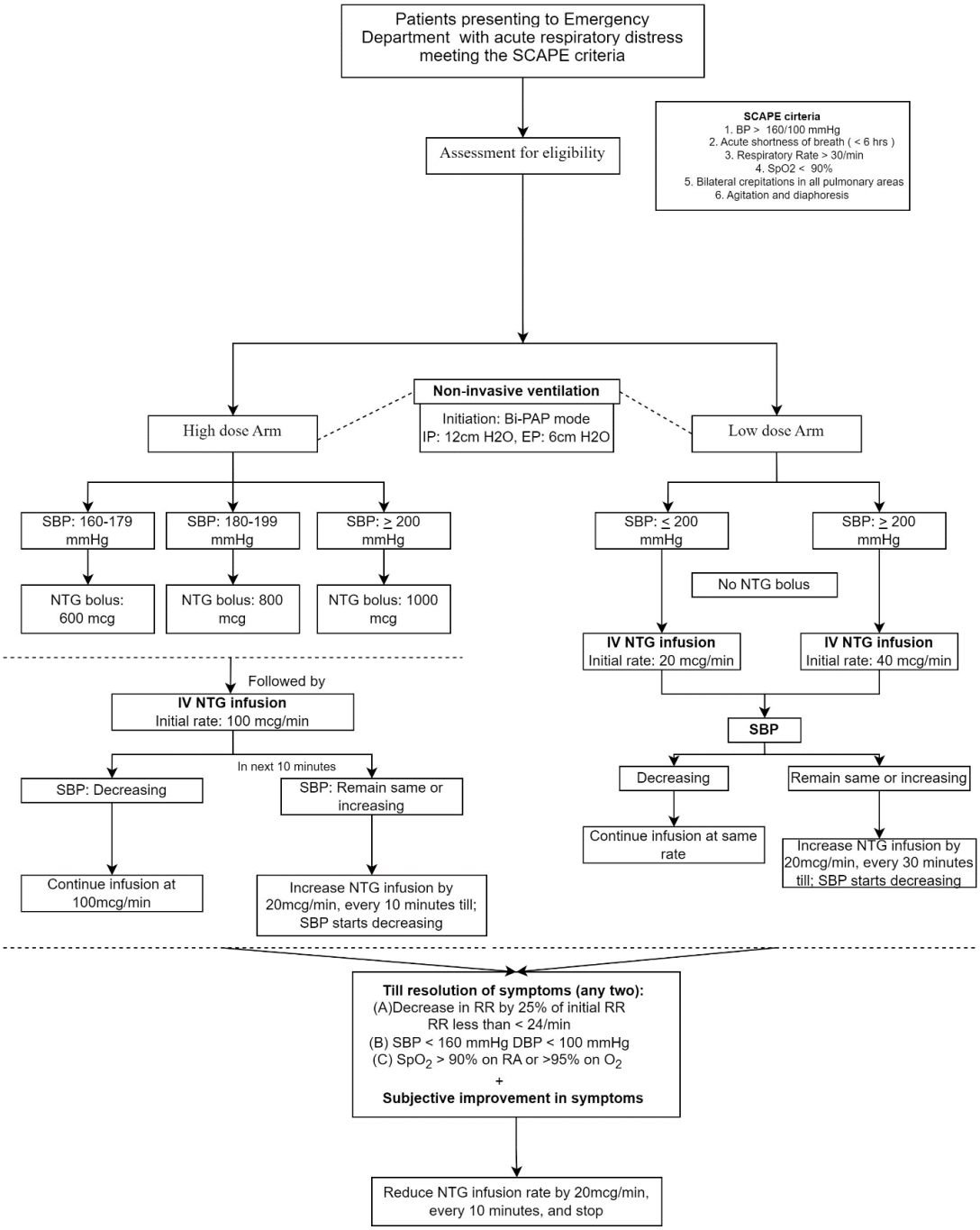
Inclusion criteria

1. Patients coming to ER with
    a. Acute shortness of breath (< 6 hrs)
    b. BP > 160/100 mmHg
    c. Respiratory Rate > 30/min
    d. SpO2 < 90%
    e. Bilateral crepitations in all pulmonary areas
    f. Agitation and diaphoresis
2. Patients / Legally authorised representative willing to give valid consent

Exclusion criteria

1. Patients brought in Cardio- Respiratory Arrest or History of trauma
2. Age < 18 years
3. STEMI/NSTEMI as primary diagnosis
4. History of hypersensitivity to NTG
5. Use of Phosphodiesterase V inhibitors within 48 hours
6. Patients with moderate to severe AS, HOCM
7. Pregnancy
8. Acute aortic dissection

Treatment protocol



Randomization

Patients who fulfil all of the inclusion criteria and none of exclusion criteria will thoroughly be informed about study protocol and informed consent will be obtained.

The eligible patients will be randomized to Intervention group who will receive high dose NTG and Control group who will receive low dose NTG on 1:1 basis. Randomization will be done by using computer generated sequences and block randomization methods will be used - Opaque, sealed envelopes containing a card mentioning treatment allocation namely “Standard group” or “Modified group” will be kept in a box at emergency and will be allocated to each patient in sequence. This randomized sequence will be prepared by using MS Excel. Blinding to the patients or investigator cannot be done due the nature of interventions in this study.

Patient Safety

Nitro-glycerine has many adverse effects of significance, most resulting from the vasodilatory effects of the medication. These include:

- Dizziness
- Weakness
- Palpitations
- Vertigo
- Headaches
- Nausea
- Vomiting
- Diaphoresis
- Syncope

Many of these adverse effects are secondary to the hypotensive effects of nitro-glycerine.

If systolic blood pressure should fall below the target of 90 mm Hg and signs or symptoms of arterial hypotension occur, then NTG infusion will be immediately stopped and a 250 ml bolus of fluid will be given to the patient. If there is persistent hypotension even after stoppage of NTG and IV bolus the treatment will be stopped. In case of severe headache, IV paracetamol will be given to the patient for relief of symptoms and if there is no improvement in the headache then the infusion will be stopped.

At any time in the study the use of further treatment including loop diuretics, morphine or fentanyl or any other drugs or non-pharmacological therapies will always be dependent on the clinical conditions and will be at the discretion of the treating physician.

Non-invasive hemodynamic monitoring will be performed every 10 minutes during the first hour, every 30 minutes in the second to the sixth, and hourly till the time NTG infusion is being given. Continuous recording of a three-channel ECG and transdermal oxygen saturation provided by automated monitoring systems will be applied as clinically indicated.

A trail safety board will be constituted which will monitor any untoward side effects associated with the treatment given. If there are findings that indicate that a further participation in the study would lead to a disproportionate risk for the patient's health or life, the patient may be excluded from the study.

In case of an adverse event or a serious adverse event (e. g. symptomatic hypotension, acute coronary syndrome, or death etc.) or known or unexpected side effects related to the study medication the treatment with the concerning medication will be suspended. All other procedures remain unaffected and the patient will not be excluded from the study.

Definition of Adverse Events according to the International Conference of Harmonization (ICH)

An **Adverse Event (AE)** is any untoward medical occurrence in a patient or clinical investigation subject, who has been administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medical (investigational) product.

A **Serious Adverse Event (SAE)** means an adverse event that requires either inpatient hospitalization, prolongation of existing hospitalization, is a congenital anomaly / birth defect, results in persistent or significant disability or incapacity, is life threatening, or results in death.

A **Suspected Unexpected Serious Adverse Reaction (SUSAR)** is defined as a serious adverse event / drug reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigators Brochure for an unapproved investigational medicinal product)

Follow up

Patient will be followed up telephonically till 30 days post discharge for any Major Adverse Cardiac event (MACE). A four point MACE (CVD events, admission for Heart Failure, ischemic cardiovascular [CV] events, cardiac death) will be used for the purpose of this study.

Data Management and Statistical Plan

- Analysis type: Intention to treat

Sample Size

We defined effect size as the absolute risk difference of symptom resolution at 6 hours between the treatment arms. Since no studies compared the clinical efficacy of high-dose GTN with low-dose GTN, we calculated the sample size from two previously published studies. In a previous study published by our team, high-dose GTN resolved symptoms at 6 hours in 96% of patients[11]. In the ASCEND-HF trial, low-dose GTN (standard treatment) improved symptoms considerably within 6 hours in 42% of patients with acute heart failure [12,13]. To detect an absolute risk difference of 54% with a power of 90%, continuity correction, and a significance threshold of 0.01, we would need a sample size of 46. We aimed to enrol at least 52 patients (26 in each arm) to account for attrition and loss to follow-up.

Statistical hypothesis for the trial objectives:

- Primary objective:
  - There is one coprimary endpoint i.e., resolution of symptoms at 6 hours and 12 hours, from the time of randomisation.
  - The criteria for ‘resolution of symptoms’ is defined in the Objectives section.
  - The null hypothesis is that there is no difference in the outcome, in the ‘High-dose NTG’ versus ‘Low-dose NTG’ group.
- Secondary objectives:
  - To assess the need of Invasive Mechanical Ventilation, compare the number of ICU admissions, the short term adverse events of using high dose NTGand the number of MACE in both arms at 30 days
  - The null hypothesis is that there is no difference in the outcome, in the ‘High-dose NTG’ versus ‘Low-dose NTG’ group

Interim analysis:

- There are no interim analyses planned for this study.
- An internal committee will be responsible for reviewing the progress of the study at regular intervals to ensure subject safety and study integrity. The board will meet at intervals, when approximately 15 and 30 subjects had been randomized and had 30 day follow-up information

Demographics and baseline characteristics:

- Descriptive statistics by treatment group will be provided for age, gender, duty shift, presenting symptoms, comorbidities, vitals at presentation, diuretics dose used, and point-of-care ultrasound (POCUS) examination findings.
- Categorical variables described below, will be presented in terms of frequency distribution (number and proportion i.e., n and %) by treatment group:
  - Gender (male, female)
  - Duty shift when the patient was randomised:
    - Morning shift (8AM to 2PM)
    - Afternoon shift (2PM to 9PM)
    - Night shift (9PM to next day 8AM)
  - Presenting symptoms:
    - Breathlessness
    - Diaphoresis
    - Chest pain
    - Cough
    - Fever
  - Comorbid illness of the patient:
    - Hypertension
    - Chronic kidney disease (and stage)

- Diabetes mellitus
- History of Coronary artery disease: any prior percutaneous intervention, acute myocardial infarction, coronary artery bypass grafting, or diagnosed coronary artery disease in coronary angiography
- History of heart failure
- Diagnosed case of dilated cardiomyopathy
- Post-renal transplant
- Chronic liver disease

▪ Fluid status examined by inferior vena cava (IVC) assessment using POCUS:

- Hypervolemia (IVC > 2cm and < 50% collapsible)
- Euvolemia (IVC > 2cm and > 50% collapsible; or IVC < 2cm and < 50% collapsible)
- Hypovolemia (IVC < 2cm and > 50% collapsible)

o Quantitative variables, described below, will undergo normality testing (Shapiro-Wilk test). Data will be presented in the format of mean and standard deviation, if all the variables are normally distributed. In cases where some of the variables or all variables are found to have non-normal distribution, data will be presented as median values and interquartile range (25th and 75th percentiles).

▪ Age (in years)

▪ Breathlessness duration (in hours)

▪ Vitals at presentation (documented in the case sheet at triage)

- Respiratory rate (calculated manually for 1 minute)
- Oxygen saturation (in %, using pulse oximeter)
- Pulse rate (per minute)

- Systolic and diastolic blood pressure (in mmHg, using non-invasive blood pressure cuffs)

- Ejection fraction (by eyeballing method in POCUS)

- The difference in the categorical variables among treatment groups will be analysed using the Chi-square test.
- The difference in the normally distributed quantitative variables among the treatment groups will be analysed using the Student's t-test.
- Whereas, non-normally distributed qualitative variables will be analysed using the Mann-Whitney U test.
- A two-tailed level of significance (p) at 0.05 will be used for the above-mentioned tests to compare the demographics and baseline characteristics.

Discontinuation / completion of information:

- A subject may be withdrawn from the study for the following reasons:
  - Loss to follow-up
  - Withdrawal of consent
- The numbers of subjects randomized, treated, and completed Day 30, follow-up will be summarized by treatment group. Reasons for early discontinuation will also be summarized by the treatment group.

- **Compliance:**
  - Nursing chart captures the NTG bolus administration date/time, total bolus dose administered in mg, initial infusion start date/time, ongoing infusion rate at 3, 6, 9, 12 hours of starting the treatment, final infusion stop date/time and cumulative dose administered at 3 hours and 12 hours.
  - All this information will be collected from these paper-based nursing charts.

- In addition, reasons for interruption and total duration (in minutes) of interruptions, and reasons for premature discontinuation of NTG infusion are captured.

- **Extent of exposure:**
  - Exposure to study drug will be summarized by treatment group using the following variables:
    - Number of subjects receiving NTG bolus
    - Total number of hours receiving any amount of NTG (i.e., last dose stop date/time minus the first dose stop/date time minus total interruptions). Total duration in hours, defined as the last dose stop date/time minus the first dose stop/date time
    - Number of subjects with study drug infusion interruptions
    - Number of subjects with premature study drug terminations
    - Primary reason for study drug infusion interruptions
    - Primary reason for premature study drug terminations

- **Concomitant medications**
  - Intravenous diuretic (furosemide) dose used during the acute management was collected.Common cardiovascular medication usage is collected from randomization to hospital.

- **Protocol deviations:**
  - Protocol Deviations will be summarized by the treatment groups which will include, randomization of ineligible subjects (based on inclusion/exclusion criteria) and intravenous NTG bolus administration apart from the study specified protocol.

Efficacy outcomes analysis:

- *Primary objective:*
  - There is one coprimary endpoint i.e., resolution of symptoms at 6 hours and 12 hours.
  - Resolution of symptoms at 6 hours and 12 hours will be presented as frequency distribution (n and %), as these are dichotomous data.
  - The primary analysis method used for these dichotomous data will be Chi-square test.
    - To understand BH procedure, we have to define FDR first. Using an alpha level of 0.05, there's only a 5% chance of making a false discovery with any individual test conducted on a single endpoint, but if we are conducting one or more tests on more than one outcomes, we would expect about 5 of the 100 tests to lead to false discoveries. This is called as false discovery rate (FDR). The FDR is statistically defined as the rate of false positive results compared to all positives. The BH procedure is done to control FDR in the studies with coprimary endpoints
    - The Benjamini-Hochberg (BH) procedure will be used to adjust the false discovery rate for the coprimary endpoint. The acceptable false discovery rate is set at 0.05 (f). (11) In the first step, p-value (from Chi square test) of each of the endpoints (6-hour resolution and 12-hour resolution) will be ranked (k) from low to high.
    - Total number of outcomes being analysed here is two.
    - Hence, the BH adjusted significance level will be calculated using the formula: (k*f/2)
    - The p-value of chi square tests will be compared with the corresponding BH adjusted significance level. If the p-value is

less than the BH-adjusted significance level, the null hypothesis will be rejected.

- The coprimary endpoint will be considered significant, only if both the 6-hour and 12-hour resolution were found to be significant in BH procedure.

- BH procedure overview:

BH procedure steps	BH procedure to control FDR in this study
Step 1: Conduct all statistical tests and find the p-value for each test or endpoint.	Resolution at 6 hours has a p-value = 0.0005 Resolution at 12 hours has a p-value = 0.0001
Step 2: Arrange the p-values in order from smallest to largest, assigning a rank to each one – the smallest p-value has a rank of 1, the next smallest has a rank of 2, etc.	Ranking of p-values: Rank-1: Resolution at 12 hours (p – 0.0001) Rank-2: Resolution at 6 hours (p – 0.0005)
Step 3: Calculate the Benjamini-Hochberg critical value for each p-value, using the formula (i/m)*Q, where i – rank, m – number of tests or endpoints, and Q – predefined acceptable FDR.	We have predefined the acceptable FDR as 0.05. Calculating BH critical values: Rank-1: For resolution at 12 hours: (i/m)*Q = (½)*0.05 = 0.025. Rank-2: For resolution at 6 hours: (i/m)*Q = (2/2)*0.05 = 0.05

- *Secondary objectives:*
  - To assess the need of Invasive Mechanical Ventilation (yes, no):
    - This will be presented in frequency distribution (n and %)
    - Chi-square test will be used to compare between the treatment groups and will be considered significant if $p < 0.05$.
  - To compare the number of ICU admissions (yes, no):
    - This will be presented in frequency distribution (n and %)
    - Chi-square test will be used to compare between the treatment groups and will be considered significant if $p < 0.05$.

- To assess short term adverse events of using high dose NTG:
    - This will be presented in frequency distribution (n and %)
    - Chi-square test will be used to compare between the treatment groups and will be considered significant if $p < 0.05$.
- To assess MACE (Major Adverse Cardiovascular Events) in both arms at 30 days:
    - This will be presented in frequency distribution (n and %)
    - Chi-square test will be used to compare between the treatment groups and will be considered significant if $p < 0.05$

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PARTICIPANT INFORMATION SHEET (PIS)

(Patient or Legally authorized relative)

TITLE OF THE STUDY : High dose vs low dose NTG in the management of SCAPE – A Randomized Controlled Trial .

This is an important form. Before you make a decision to take part in the study, it is important that you understand

why the study is being conducted and what will it involve . If you have any query, feel free to ask your doctor. Your signature in the consent form means you wish to take part in the trial.

1) **Why is this study being done ?** You have presented to Emergency department with

condition called SCAPE(Sympathetic Crashing Acute Pulmonary Edema) . The main purpose of this study is to compare the resolution of symptoms with the use of High dose NTG(nitroglycerin) vs Low dose NTG . This study is novel of its kind as minimal evidence is available for this condition . SCAPE has a rapid and dangerous course , needs immediate recognition and management . Hence this study will guide us whether this new method of administering High dose NTG will resolve the symptoms and reduce the complications.

2) **What will happen in this study ?** When you present to Emergency Department, after you give valid consent you will be randomized to either Intervention group or control group . You will be triaged as RED and shifted to Red area. All monitors attached and vitals including SpO2 , Respiratory rate , Pulse Rate, Blood Pressure will be checked at regular intervals. Your blood will be drawn for investigations : ABG, CBC, LFT, RFT, Troponin I, NT pro BNP. Bedside ultrasound using POCUS is done. NIV and standard care is provided to all patients. NTG is started according to the group you assigned. If any adverse event occurs, NTG is stopped and required treatment will be provided.
3) **What is SCAPE?** It is a condition where your sympathetic nervous system is firing at increased rate causing increasing load on heart having symptoms – extremely agitated , breathlessness , palpitations , BP $\geq$ 160/100 mmHg. It has a rapid worsening course . High dose NTG is observed to be beneficial as it reduces after load compared to low dose NTG. Hence this study helps in better understanding of this condition and management.
4) **Expected duration of the subject participation :** From presenting to emergency department with symptoms of SCAPE to resolution of symptoms
5) **What are the benefits for you/or for the society ?** No medical compensation or insurance will be provided to the study participants. This study will provide insight into management aspects and will help in knowing the outcomes which can contribute to the better understanding about the condition. Patient will neither be paid for participating in the study and nor will it alter the outcome of the treatment that is going on.

6) **What are the complications/risks of participating in the study?** NTG (nitroglycerin) has few side effects like Hypotension, Headache, syncope, Flushing, Meth-hemoglobinemia, bradycardia. No medical compensation or insurance will be

provided to the study participants. In the event of any injury to the subject resulting from any research procedure, medical treatment will be provided without any cost in the department of Emergency Medicine, AIIMS, New Delhi. All patients will be provided with standard care. The data acquired during the process will be analyzed and gained information will be used in better understanding about the disease and its treatment .The data will be acquired after your willful consent.

7) **Maintenance of confidentiality:** During your participation in the study, information related to the patients' health and contact details will be taken. All this information will be maintained in strict confidence during study period. At the time of publication of the study, your personal details will not be disclosed.
8) **Do I have to take part?** It is your wish to participate in the study. If you decide to take part, you will be given this information sheet and consent form to sign. You are free to withdraw from the study anytime you want. If you have decided to withdraw, your care and treatment won't be effected in any way.
9) **Cost and source of investigations:** cost for conducting this research will be borne by the department.

If you have further queries, please contact

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AIIMS, New Delhi
9990345682

PARTICIPANT INFORMATION CONSENT FORM : (PICF)

Participant identification number for this trial: ……

Title of the project: High dose vs low dose NTG in management of SCAPE.
Name of the candidate: Dr. Naazia Siddiqua Tel no. 9246595679
Name of the chief guide: Dr. Nayer Jamshed Tel no. 9990345682
The contents of the information sheet dated …….. that was provided have been read carefully by me /explained in detail to me, in a language that I can comprehend and I have fully understood the contents. I confirm that I have had the opportunity to ask

questions. The nature, purpose of the study, its potential risks / benefits, expected duration of the study and other relevant details of the study have been explained to me in detail. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reasons, without my medical care and legal right being affected. I understand that the information collected about the patient for participation in this research and sections of any medical notes may be looked at by responsible individuals from AIIMS . I give permission for these individuals to have access to my records. I agree to take part in the above study.

Date: ……..

(Signature / left thumb impression of patient)

Place: …….. Name of the patient……

Complete postal address: ……

……

This is to certify that above consent has been taken in my presence.

Date: …….

Signatures of principal investigator

Place: …….

1) Witness -1 2) witness-2

Name : …….. Name: ……