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Original Article

The Movahed protocol and algorithm for preventing intubation in patients with acute or sympathetic crashing acute pulmonary edema (SCAPE) without cardiogenic shock by repeated administration of buccal nitroglycerin ointments

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Abstract: Patients presenting with severe acute cardiogenic pulmonary edema with hypoxia commonly require intubation until heart failure treatments take effect. A new term describing similar condition is called sympathetic crashing acute pulmonary edema (SCAPE). It is also called Flash pulmonary edema. Immediate pre- and afterload reduction can abort intubation. Using rapid repeated buccal administrations of nitroglycerin ointments can prevent intubation by rapidly reducing pre- and afterload as long as systolic blood pressure remains adequate without cardiogenic shock. A case series of 6 patients who needed intubation due to severe cardiogenic pulmonary edema and hypoxia despite 100% 02 administration without the presence of cardiogenic shock were successfully treated with repeated buccal administration of nitroglycerin ointments. Approximately half of an inch of nitroglycerin ointment (nitropaste) was buccally administrated every 60 seconds as long as repeated blood pressure measurements every minute before each repeated administration remained above 120 mmHg. Complete response with resolution of dyspnea with minimal oxygen requirement achieved in less than 30 minutes in all patients. Intubation was prevented in all 6 patients. No adverse events occurred in any of the patients. A treatment protocol and algorithm are developed based on these patients and reported cases in the literature for prevention of intubation in these patients. Rapid repeated buccal administration of nitroglycerin ointment is highly effective in preventing intubation and mechanical ventilation in patients with any acute pulmonary edema or SCAPE and hypoxia without cardiogenic shock.

Keywords: Congestive heart failure, acute pulmonary edema, nitropaste, sympathetic crashing acute pulmonary edema, SCAPE, flash pulmonary edema, nitroglycerin, nitroglycerin ointment, topical nitroglycerin

Introduction

Patients presenting with severe acute cardiogenic pulmonary edema with hypoxia commonly require intubation until heart failure treatments take effect. A new term describing this similar condition is called sympathetic crashing acute pulmonary edema (SCAPE) [1]. SACAPE is the extreme end of acute pulmonary edema presentation. It is also called Flash pulmonary edema. These patients have an abrupt redistribution of fluid in the lungs requiring immediate significant after- and preload reduction. Acute cardiogenic pulmonary edema is related to left ventricular failure leading to increases in the feeling pressure and pulmonary congestion. If not rapidly treated, severe hypoxia will develop, and mechanical ventilation will be necessary until congestion is resolved. Rapid pre- and afterload reduction can lead to a very quick reversal of pulmonary edema and hypoxia thus preventing intubation. Nitroglycerin has been safe for reducing pre- and post-load as long as blood pressure can tolerate it [2]. Rapid administration of high doses of nitroglycerin is crucial to reverse acute congestion. Numerous reports using intravenous nitroglycerin have been reported to be very successful in this setting [3-6]. However, it is not quickly available and requires intravenous access. Nitroglycerin ointment has the best pharmacodynamic and pharmacokinetic properties as it is widely available

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Table 1. Patients characteristics

Age	Gender	Race	HTN	DM	CAD	CRF	SBP BT	SBP AT	Causes of SCAPE	O2 sat BT	O2 Sat AT
70	M	C	Y	N	Y	Y	160	120	Diastolic heart failure	80%	100% on 4 L O2
72	F	C	Y	Y	Y	Y	170	130	Contrast induced nephropathy	82%	98% on 4 L O2
75	M	C	Y	N	N	N	190	120	Severe Aortic Regurgitation	85%	100% on 4 L O2
46	M	C	Y	N	N	Y	170	130	Dialysis with fluid overload	86%	98% on 4 L O2
78	M	C	Y	Y	Y	Y	200	110	Post coronary intervention	85%	100% on 4 L O2
68	M	H	Y	Y	Y	Y	180	130	Dialysis with fluid overload	86%	100% on 4 L O2

M = male, F = female, SBP = Systolic blood pressure, BT = before treatment, AT = after treatment, O2 sat = O2 saturation, L = liter, SCAPE = sympathetic crashing acute pulmonary edema, C = Caucasian, H = Hispanic, DM = presence or history of DM, HTN = presence or history of hypertension, CAD = presence or history of coronary artery disease, CRF = presence or history of chronic renal failure.

and rapidly absorbed by buccal administration [7, 8]. The successful use of buccal nitroglycerin ointment in patients with severe cardiogenic pulmonary edema has been used successfully in many published case reports but is rarely utilized and hardly known in the medical community. Hereby, six cases of successful buccal nitroglycerin ointment administration are reported in patients suffering from severe cardiogenic pulmonary edema with hypoxia on maximal oxygen therapy thus preventing intubation and the need for mechanical ventilation in all of these patients. This report is followed by a review of the literature. Furthermore, a treatment protocol and algorithm are developed based on these patients and reported cases in the literature for prevention of intubation in these patients. **Table 1** summarizes the clinical characteristics of these patients.

Case descriptions

Case 1

A 70-year-old male was admitted with diastolic heart failure from the emergency department. He had a normal ejection fraction. After transfer to the medical floor, the patient suffered from severe pulmonary edema with oxygenation dropping to the mid-80 s despite 100% oxygen therapy. Physical examination revealed severe bilateral rales all the way to the upper lung. His systolic blood pressure (SBP) was in the 160-180 mmHg range. The respiratory therapist was called for immediate intubation while receiving 40 mg of IV furosemide. An immediate 1/2 of an inch of buccal nitroglycerin ointment (nitro paste) was applied to his oral mucosa every 60 seconds with a recheck of his SBP every minute before each nitro ointment administration to make sure SBP remains above 120 mmHg. Within 20 minutes of treatment, respiratory distress resolved. O2 sat increased to 100% on 2 liters of oxygen and intubation was avoided. Further diuretic and BP treatment gradually resolved his heart failure over the next couple of days. The patient had no adverse event to buccal nitro ointment administration.

Case 2

A 72-year-old female patient presenting with unstable angina underwent coronary angiography and stenting. Post-procedure, the patient suffered from acute contrast-induced nephropathy leading to severe congestive heart failure and pulmonary edema with hypoxia. Her O2 saturation dropped to the 80 s despite 100% oxygen administration. Her SBP was > 140 mmHg. While the respiratory therapist was underway to perform intubation, she received an immediate 1/2 of an inch of buccal nitroglycerin ointment every minute while checking SBP before each administration. SBP dropped gradually from 170 to 120 mmHg within 30 minutes. Her respiratory distress and pulmonary edema resolved, and intubation was avoided. Her O2 saturation was raised to 100% on 4-liter O2. She had no adverse event. Later she responded to high doses of IV diuretic and IV nitro with the resolution of heart failure.

Case 3

A 75-year-old male was admitted with congestive heart failure secondary to severe aortic valve regurgitation from the emergency department. Upon arrival on the medical floor, while

receiving IV diuretic therapy, the patient suffered from severe respiratory distress and pulmonary edema. His 02 saturation dropped to the 70 s. The pt was put on 100% non-rebreather without resolution of hypoxia. A respiratory therapist was called for intubation. The patient was immediately treated with repeated doses of 1/2 of an inch of buccal nitroglycerin ointment every 60 seconds with repeated BP measurements before each administration every minute to make sure SBP remained > 120 mmHg. His SBP from 190 mmHg gradually was reduced to 120 mmHg. Within 20 minutes, respiratory distress resolved with a rise of 02 saturation to 100% on 4-liter 02. Intubation was avoided and the patient tolerated the treatment well. Later, he responded well to IV diuresis and underwent successful aortic valve surgery.

Case 4

A 46-year-old male was admitted to ICU with worsening renal failure leading to congestive heart failure. He had a normal ejection fraction. He had a Swan-Ganz catheter in place showing a wedge pressure of 30 mmHg. He failed diuretic therapy and developed worsening heart failure and pulmonary edema. His 02 sat on 100% oxygen on BIPAP dropped to the 80 s and his wedge pressure rose to 45 mmHg. The patient was prepared for intubation. He immediately received 1/2 of an inch of buccal nitroglycerin paste every 60 seconds with repeated blood pressure checks every minute. His wedge pressure decreased with each treatment with a final wedge of 18 mmHg in 30 minutes. His respiratory distress completely resolved after 30 minutes with 02 saturation improvement to 100% on 4 liters of 02. His SBP normalized from 170 mmHg to 130 mmHg. Later, IV nitro was started to keep his pre- and after-load low, and intubation was aborted. Later the patient underwent dialysis and did well. No adverse event occurred.

Case 5

A 78-year-old male underwent PCI to his LAD for unstable angina. Post PCI, he suffered from respiratory distress and severe pulmonary edema. His SBP was 170-200 mmHg range. While awaiting intubation, 1/2 of an inch of buccal nitroglycerin ointment was administrated every 60 seconds with repeated SBP checks every minute before the next nitroglycerin ointment administration. His SBP remained above 120 mmHg. His respiratory distress and pulmonary edema gradually resolved with the normalization of his SBP. Intubation was avoided. Later, he responded well to diuretics and had no adverse reaction to buccal nitroglycerin administration.

Case 6

A 68-year-old male on dialysis presented with acute anterior ST-elevation Myocardial infarction (STEM). He underwent successful PCI to 100% occluded proximal LAD. Post PCI, he developed severe pulmonary edema. His 02 saturation dropped to 83% with severe hypertension with SBP in the 170-190 mmHg range. His ejection fraction was 45%. Immediate buccal ½ of an inch nitroglycerin ointment was administered every 60 seconds with blood pressure measurement before each repeat administration every minute. His SBP gradually dropped to the 130 mmHg range with complete resolution of his hypoxia and respiratory distress within 20 minutes. Intubation was avoided. The patient had no adverse events. Urgent dialysis was started later which resolved his congestive heart failure.

Summarizing the above patients' characteristics, all patients had severe hypertension that could allow the use of high-dose buccal nitroglycerin administration and significant hypoxia related to severe pulmonary edema.

Discussion

Acute cardiogenic pulmonary edema is a life-threatening condition requiring immediate treatment. A new term describing similar condition is called sympathetic crashing acute pulmonary edema (SCAPE) [1]. Usual treatment such as intravenous diuretic therapy will take time to reduce congestion and rarely will prevent intubation in severe pulmonary edema with severe hypoxia on maximal oxygen therapy or BIPAP. Morphine administration can be helpful but by suppressing respiratory drive it can worsen respiratory failure and hypoxia. It is also not a very strong pre- and afterload reducer and has rarely prevented intubation. Any agents that can rapidly and safely reduce pre- and afterload is ideal for this situation. Nitroglycerin is an ideal drug in this setting. At low doses, nitroglycerin induces only vasodilatation in the

venous system. However, as the dose is gradually increased, it will lead to arterial vasodilatation [2]. Therefore, it will cause preload and afterload reduction thus lowering elevated left ventricular filling pressures and elevated systemic vascular resistance.

The use of rapid repeated administration of intravenous nitroglycerin in a prehospital setting of patients with pulmonary edema and hypertension has been safe and effective in preventing intubation [3-8]. In a series of 41 patients, high-dose intravenous nitroglycerin was a much more effective treatment compared to low doses in patients with pulmonary edema [5]. In the largest case series of using high-dose intravenous nitroglycerin, Housman et al. [6] found that high dose nitroglycerin infusion (≥ 100 μg/min) strategy for the management is a safe and more effective alternative to low-dose infusion in patients with severe pulmonary edema.

Sublingual nitroglycerin theoretically could be used for this purpose but a tablet of 0.2 which equals 200 micrograms of nitro is a very low dose. In patients with severe pulmonary edema, at least up to 800-5000 micrograms of nitro boluses are required to be rapidly effective. This would translate to about 4-20 nitroglycerin sublingual tablets with each treatment. This will make giving sublingual nitro impractical and will make nursing personnel very resistant to providing these high doses. Furthermore, due to dry mouth related to hyperventilation, sublingual nitro will take much longer time to resolve. Bussmann et al. [9] successfully gave up 0.8 to 2.4 mg of nitroglycerin sublingually at intervals of 5 to 10 minutes as proof of concept that rapid nitro administration can avoid intubation in acute heart failure. However, the superiority of buccal nitro ointment regarding pharmacodynamics and ease of use in comparison to sublingual nitroglycerin will be discussed later. As mentioned earlier, high doses of IV nitroglycerin have been effective in patients with acute pulmonary edema [3-5]. Bosc et al. used up to 3 milligrams (3000 micrograms) IV successfully in such a patient [10]. Stemple et al. [11] described 4 patients with severe cardiogenic pulmonary edema that was started mostly with 400 micrograms IV nitro per minute with rapid up titration to 800 micrograms per minutes. Using their protocol, they could avoid intubation in all 4 of their patients. High-dose intravenous nitroglycerin has been also successful in a prehospital setting [12, 13]. However, it is important to notice that ordering and mixing intravenous nitroglycerin by a pharmacist will take time and again pharmacists and nursing personnel will be very reluctant to follow physicians' orders to start very high doses of IV nitroglycerin due to unfamiliarity with such a high dosing.

Nitro ointment, commonly called nitropaste, is widely available with excellent rapid resorption and pharmacodynamics if it is administrated buccally. In patients with severe pulmonary edema, rapid pre- and afterload reduction is very important to improve oxygenation by reducing pulmonary edema. Buccal administration of nitroglycerin ointment is the ideal drug for this purpose as it has a high and rapid absorption rate during buccal administration and is very effective in reducing pre- and afterload with minimal adverse events.

Buccal administration of nitro ointment has been shown to be superior compared to other nitroglycerin agents in patients with angina [14-18]. In patients with chronic congestive heart failure buccal administration of nitroglycerin ointment has also been shown to be superior to other forms of nitroglycerines with rapid onset, longer duration of drug effect and superior hemodynamic response [19-25]. Abrams [20] studied a variety of nitroglycerin formulations, including sublingual, buccal, oral tablets, capsules, topical creams, ointments, patches, tapes, and inhalable sprays. As it can be seen in **Table 2**, buccal nitroglycerin ointment was superior in comparison to other forms. It had a rapid onset of effect within 2 minutes with a long-sustained effect ranging from 30-300 minutes making it an ideal formulation for rapid administration of high doses.

Nitroglycerin ointment contains approximately 15 mg of nitroglycerin per one inch of paste that can rapidly absorbed by buccal application simulating intravenous nitroglycerin administration. Giving a quarter of an inch (the tip of an index finger, **Table 2**) of buccal nitroglycerin ointment (if SBP > 120 but < 140) about 3-4 mg (3000-4000 micrograms) of nitroglycerin can be given rapidly with each administration. By administrating half an inch (half of the distal phalanx of the index finger, **Figure 1**) of buccal

Table 2. Dosage and kinetic of various nitroglycerin formulations (with permission from Am J Cardiol 1985; 58: 12A)

Medication	Usual Recommended Dosage	Onset of Action (min)	Peak Action (min)	Duration
Sublingual NTG	0.3-0.8 mg	2-5	4-8	10-30 min
Sublingual ISDN	2.5-10 mg	5-20	15-60	45-120 min*
Buccal NTG	1-3 mg	2-5	4-10	30-300 min**
Oral ISDN	10-60 mg	15-45	45-120	2-6 h***
Oral NTG	6.5-19.5 mg	20-45	45-120	2-6 h***
Oral PET	40-80 mg	60	60-120	3-6 h
NTG Ointment (2%)	½-2 in	15-60	30-120	3-8 h
NTG Discs (Transdermal)	10-20 mg	30-60	60-180	Up to 24 h†

ISDN = Isosorbide dinitrate; NTG = nitroglycerin; PET = pentaerythrityl tetranitrate; min = Minutes; h = hours; mg = milligrams; in = inch. *8 Up to 3 to 4 hours in some studies. **Effect persists as long as tablet is intact. ***Some acute dosing studies have demonstrated effects up to 8 hours. †Data are conflicting regarding 24-hour effects.

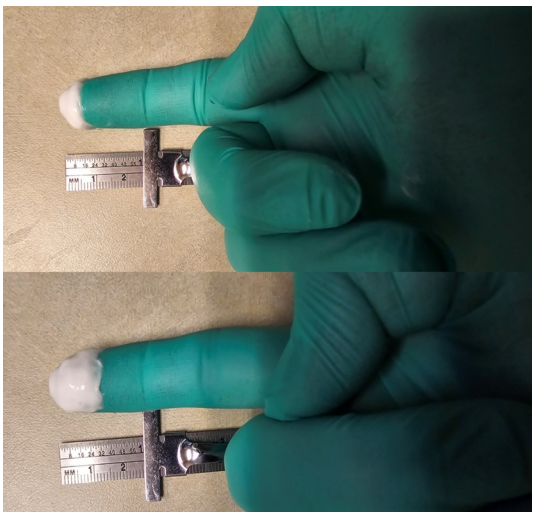

Figure 1. It shows a simple way to administrate recommended nitroglycerin ointment in patients with severe cardiogenic pulmonary edema without cardiogenic shock. Quarter of inch (for SBP 120-140) would be equal to tip of the index figure and or half of an inch (SBP > 140) would be half of the distal index finger phalanx.

nitroglycerin ointment (for SBP > 140) 6-7 mg (6000-7000 micrograms) can be given rapidly that can induce quick pre- and afterload reduction thus dramatically reducing pulmonary congestion. An important part of this treatment is the presence of adequate blood pressure. This is the reason that this type of treatment should not be initiated in patients with cardiogenic shock or marginal SBP < 120 mmHg. Therefore, SBP must be rechecked every minute before each buccal administration to make sure SBP remains above 120 mmHg before the next buccal nitroglycerin administration.

In the setting of acute pulmonary edema without cardiogenic shock, there are case reports and case series that have demonstrated the effectiveness and safety of buccal nitroglycerin application [23-28] including repeated very high initial doses of one inch (equal to 15,000 micrograms) of nitroglycerin treatment without causing hypotension [26]. Unfortunately, this very effective treatment of patients with acute hypoxic pulmonary edema without cardiogenic shock is barely utilized as the medical communities are not aware of this lifesaving treatment. Every time I have used this method, every single medical staff including nurses, residents, fellows, and cardiology attendings were unaware of this treatment and were surprised about its usage and effectiveness. These cases are the largest reported case series in this regard showing very effective and safe use of buccal nitroglycerin ointment.

Due to ease of use, safety, and efficacy, the use of buccal nitroglycerin ointment should be encouraged and be the standard of care in patients presenting with severe cardiogenic hypoxic pulmonary edema without cardiogenic shock to avoid imminent intubation and mechanical ventilation. Based on these patients and reported cases in the literature, a treatment protocol and algorithm are developed for prevention of intubation in these patients which can be seen in **Figure 2**.

Conclusion

Rapid repeated buccal administration of nitroglycerin ointment is highly effective in preventing intubation and mechanical ventilation in

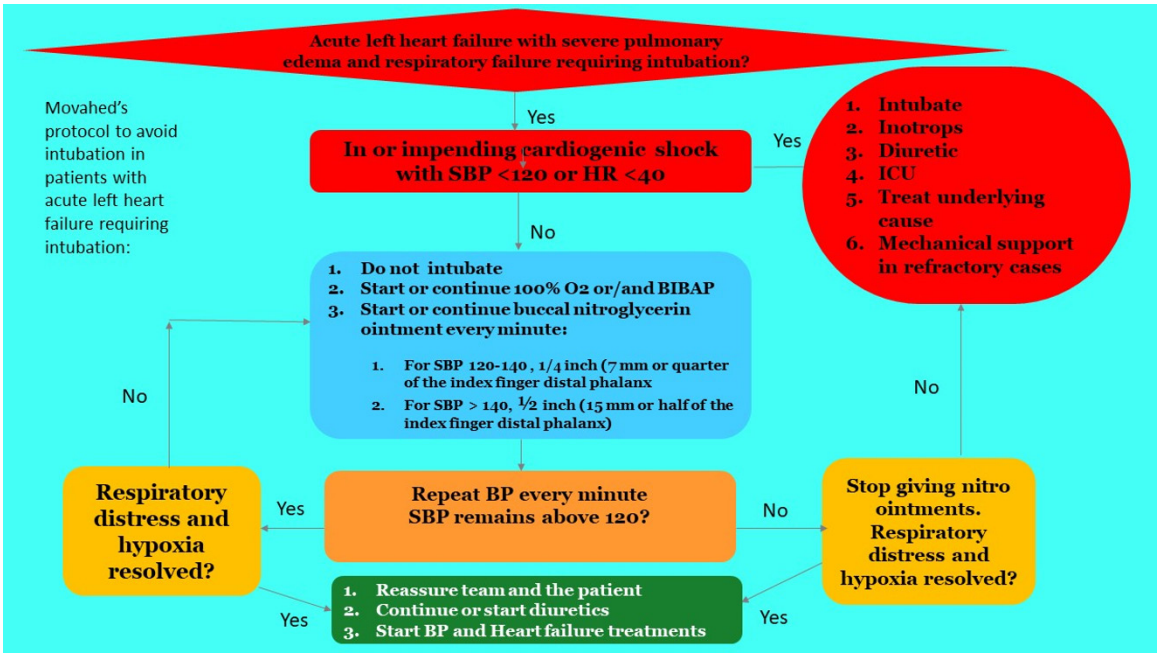

Figure 2. Protocol and algorithm for repeated buccal nitroglycerin ointment administration in patients with any acute or sympathetic crashing acute pulmonary edema (SCAPE) without cardiogenic shock.

patients with any acute or sympathetic crashing acute pulmonary edema (SCAPE) without cardiogenic shock.

Limitation

This protocol is developed based on case reports from this manuscript and published data. Randomized trials are needed to validate this protocol. Furthermore, the majority of reported cases had an ejection fraction above 35%. It is not known how often patients with severely reduced ejection fraction will have adequate blood pressure when presenting with severe pulmonary edema in order to be eligible for this protocol.

Disclosure of conflict of interest

None.

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