Movahed protocol and algorithm for prevention of intubation in patients with acute cardiogenic pulmonary edema without cardiogenic shock by using highly effective repeated buccal nitroglycerin ointment administration.

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Introduction:

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 in reducing pre- and afterload as long as blood pressure can tolerate it. Rapid administration of high doses of nitroglycerin is crucial in order to reverse acute congestion. Nitroglycerin ointment has the best pharmacodynamic and pharmacokinetic properties for this purpose as it is widely available and rapidly absorbed by buccal administration. 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 our patients and reported cases in the literature for the prevention of intubation in these patients. Figure 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-80s despite 100% oxygen therapy. Physical examine revealed severe bilateral rales all the way to the upper lung. His systolic blood pressure (SBP) was in 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 (nitropaste) was applied to his oral mucosa every 60 seconds with recheck of his SBP every minutes 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 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 80s 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 and 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 emergency department. Upon arrival to the medical floor, while receiving IV diuretic therapy, the patient suffered from severe respiratory distress and pulmonary edema. His O2 saturation dropped to 70s. 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 O2 saturation to 100% on 4-liter O2. 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 ganze catheter in place showing a wedge pressure of 30 mmHg. He failed diuretic therapy and developed worsening heart failure and pulmonary edema. His O2 sat on 100% oxygen and BIPAP dropped to the 80s 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 O2 saturation improvement to 100% on 4 liters O2. 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 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 O2 saturation dropped to 83% with severe hypertension with SBP in the 170-190 mmHg range. His ejection fraction was 45%. Immediate buccal $\frac{1}{2}$ 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.

Discussion:

Acute cardiogenic pulmonary edema is a life-threatening condition requiring immediate treatment. 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. Sublingual nitroglycerin theoretically could be used for this purpose but a tablet of 0.2 which equals to 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 treatments. 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 (1) 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, superiority of buccal nitro ointment regarding pharmacodynamic and ease of use in comparison to sublingual nitroglycerin will be discussed later. High-doses of IV nitroglycerin have been effective in patients with acute pulmonary edema (2-4). Bosc et al. used up to 3 milligrams (3000 microgram) IV successfully in such a patient (2) Stemple et al. (3) described 4 patients with severe cardiogenic pulmonary edema that were started mostly with 400 microgram 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 IV nitroglycerin has been also successful in a pre-hospital setting (4). However, it is important to notice that ordering and mixing IV 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. Buccal administration of nitro ointment has been shown to be superior compared to other nitroglycerin agents in patients with angina (5-8) 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 (9-16). Abrams (12) 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 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 index finger, figure 1) of buccal nitroglycerin ointment, (if SBP >120 but <140) about 3-4 mg (3000-4000 microgram) of nitroglycerin can be given rapidly with each administration. By administrating half inch (half of the distal phalanx of the index finger, figure 1) of buccal nitroglycerin ointment (for SBP >140) 6-7 mg (6000-7 000 microgram) 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 has to be rechecked every minute before each buccal administration to make sure SBP remained above 120 mmHg before 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 (17-19) including repeated very high initial doses of one inch (equal to 15,000 microgram) of nitroglycerin treatment without causing hypotension (19). 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. Our case series is 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 in order to avoid imminent intubation and

mechanical ventilation. Based on our patients and reported cases in the literature, a treatment protocol and algorithm are developed for the prevention of intubation in these patients that can be seen in Figure 2.

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Table 1: Patients characteristics: BP=blood pressure, BT=before treatment, AT=after treatment, O2 sat=O2 saturation, APE=acute pulmonary edema

Age	Gender	SBP BT	SBP AT	Cause APE	O2 sat BT	O2 Sat AT
70	male	160	120	Diastolic heart failure	80%	100% on 4 liter O2
72	female	170	130	Contrast induced nephropathy	82%	98% on 4 liter O2
75	male	190	120	Severe Aortic Regurgitation	85%	100% on 4 liter O2
46	male	170	130	Dialysis with fluid overload	86%	98% on 4 liter O2
78	male	200	110	Post coronary intervention	85%	100% on 4 liter O2
68	male	180	130	Dialysis with fluid overload	86%	100% on 4 liter O2

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.
* Up to 3 to 4 hours in some studies.
** Effect persists as long as tablet is intact.
*** Some acute dosing studies have demonstrated effects to 8 hours.

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

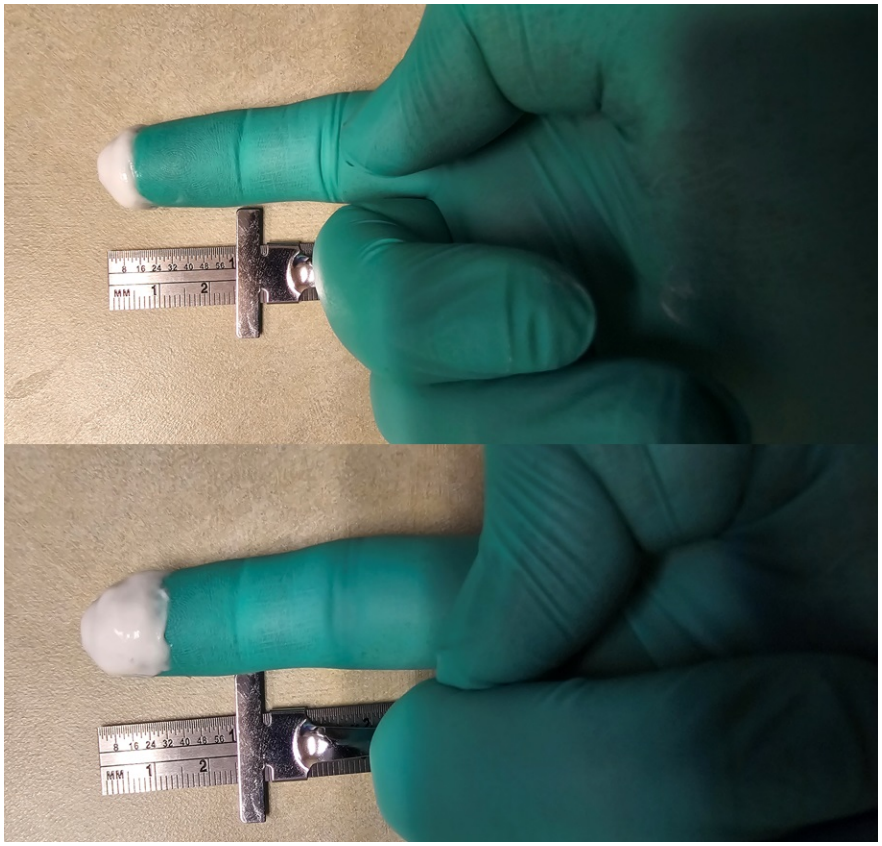

Figure 1: It shows a simple way to administrate recommended nitroglycerin ointment in patients with severe cardiogenic pulmonary edema without cardiogenic shock. Quarter of inch (for SBP120-140) would be equal to tip of the index figure and or half of an inch (SBP>140) would be half of the distal index finger phalanx.

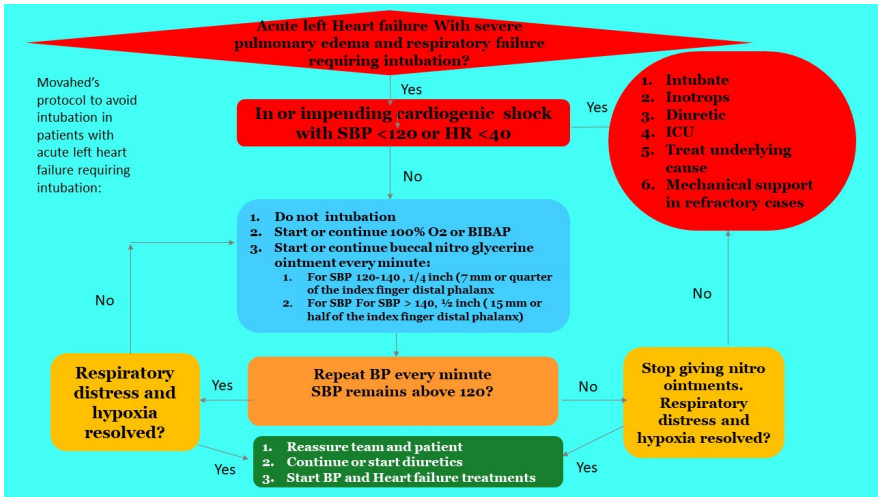

Figure 2: The Movahed protocol and algorithm for buccal nitroglycerin ointment administration in patients with severe acute cardiogenic pulmonary edema.