Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eContext. Research in Context Panel

EVIDENCE BEFORE THIS STUDY

Risk for postextubation respiratory failure and reintubation is usually stratified in two groups, with patients being classified as low-risk or high-risk according to the presence of at least one high-risk factor for reintubation. There is a possible preventive role for noninvasive mechanical ventilation in patients at high risk for reintubation.

Two previous randomized trials compared the efficacy and safety of high-flow oxygen therapy after extubation to conventional oxygen therapy in a general population of mechanically ventilated patients including high-risk patients. However, in both these studies, the sample size analyzed was underpowered to detect a reduction in the reintubation rate.

To our knowledge, only one study (BiPOP) has compared high-flow to noninvasive mechanical ventilation (NIV). This study aimed to elucidate whether high-flow therapy was noninferior to NIV in preventing or treating hypoxemic postextubation respiratory failure in patients after cardiothoracic surgery.

ADDED VALUE OF THIS STUDY

This is the first randomized trial comparing high-flow conditioned oxygen therapy to NIV that is powered to detect a noninferior effect of high-flow compared to NIV in the reintubation rate of a selected population of mechanically ventilated patients at high risk for postextubation respiratory failure and reintubation. The results show that high-flow conditioned oxygen therapy is noninferior to NIV in terms of postextubation respiratory failure and reintubation rate in this group of patients.

IMPLICATIONS OF ALL THE AVAILABLE EVIDENCE

The noninferior efficacy of high-flow conditioned oxygen therapy in preventing postextubation respiratory failure and reintubation in high-risk patients is an important finding for improving the weaning process in critically ill patients.

An additional benefit is the lack of adverse events. Knowledge of the feasibility of this approach will probably spread the use of preventive treatments after extubation in high-risk patients, possibly reducing costs.

Finally, the reduced postextubation respiratory failure rate in patients receiving high-flow conditioned oxygen therapy suggests that not all high-risk patients are suitable for NIV after extubation. Future research will focus on selecting subgroups of patients who could have specific benefits from NIV or high-flow therapy.

eAppendix 1. Criteria for spontaneous breathing trial failure

Criteria for spontaneous breathing trial failure were agitation, anxiety, depressed mental status, diaphoresis, cyanosis, evidence of increasing respiratory effort, increased accessory muscle activity, facial signs of distress, dyspnea, PaO_2 lower than 60 mmHg or SpO_2 lower than 90% on inspired fraction of oxygen higher than .5, $PaCO_2$ higher than 50 mmHg or increased more than 8 mmHg from baseline value, arterial pH lower than 7.32 or decreased more than .07 from baseline value, respiratory rate higher than 35 breaths per minute or increased more than 50% from baseline value, heart rate higher than 140 beats per minute or increased more than 20% from baseline value, systolic arterial pressure higher than 180 mmHg or increased more than 20% from baseline value, systolic arterial pressure lower than 90 mmHg, or cardiac arrhythmias.

REFERENCES:

1.- Boles JM, Bion J, Connors A, et al. Weaning from mechanical ventilation. Eur Respir J 2007; 29:1033-1056.

eAppendix 2. Risk factors and diagnosis for postextubation laryngeal edema

Patients were considered at high risk for postextubation laryngeal oedema if they had at least two of the following: female gender, orotracheal intubation lasting 3 days or longer, and difficult intubation. These patients underwent an auscultation cuff-leak test as reported by Cheng et al.[1] When no leak or only a mild leak was heard through a stethoscope (excluding cases in which the leak was heard without a stethoscope), a cuff-leak volume test was performed, according to the protocol reported previously.[2] In brief, the actual tidal volume at expiration was measured before and after deflation of the endotracheal tube cuff. Patients with a cuff leak volume >24% of tidal volume during inflation received 20 mg intravenous methylprednisolone every 4 hours during 12 hours and extubation was delayed for that period.[3]

REFERENCES:

1.- Cheng KC, Hou CC, Huang HC, Lin SC, Zhang H. Intravenous injection of methylprednisolone reduces the incidence of postextubation stridor in intensive care unit patients. Crit Care Med 2006; 34:1345-1350.

2.- Sandhu RS, Pasquale MD, Miller K, Wasser TE. Measurement of endotracheal tube cuff leak test to predict postextubation stridor and need for reintubation. J Am Coll Surg 2000; 190:682-687.

3.- Fan T, Wang G, Mao B, Xiong Z, Zhang Y, Liu X, Wang L, Yang S. Prophylactic administration of parenteral steroids for preventing airway complications after extubation in adults: meta-analysis of randomised placebo controlled trials. BMJ 2008;337:a1841.

eAppendix 3. Comorbidity index

Comorbidities were categorized based on the Charlson Comorbidity Index.[1-3] Having two or more comorbidities in separate components was considered a high-risk factor, but two comorbidities in the same component were counted as one.

Arterial hypertension included patients without diabetes or renal disease who had systolic pressures >140 mmHg and/or diastolic pressures >90 mmHg, patients with controlled hypertension, and patients with diabetes or renal disease who had systolic pressures >140 mmHg and/or diastolic pressures >80 mmHg.

Heart disease

Myocardial infarction was defined as one or more definite or probable myocardial infarctions. These patients were hospitalized for chest pain or an equivalent clinical event and had electrocardiographic and/or enzyme changes. Patients with electrocardiographic changes alone with no clinical signs of infarction were not designated as having had an infarction.

Hospitalized or treated for heart failure was defined as congestive heart failure. These patients had exertional or paroxysmal nocturnal dyspnea and their symptoms responded to digitalis, diuretics, or afterload-reducing agents (or they showed improvement on physical examination after taking one of these medications). Patients who had no response and no evidence of improvement of physical signs with treatment were not considered to have heart failure.

Angina included patients with chronic exertional angina, those who had coronary artery

bypass grafts, and those initially admitted with unstable angina.

Arrhythmia included patients with chronic atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias requiring chronic treatment.

Valvular disease included patients with hemodynamically significant aortic stenosis and/or insufficiency, with significant mitral stenosis and/or insufficiency, with prosthetic aortic or mitral valves, with asymmetric septal hypertrophy requiring treatment, or with tricuspid insufficiency.

Cardiogenic shock or cardiopulmonary resuscitation included patients with these events before admission to the ICU.

Peripheral vascular disease included patients with intermittent claudication, those who had had a bypass for arterial insufficiency, those with gangrene or acute arterial insufficiency, and those with a treated or untreated thoracic or abdominal aneurysm measuring 6 cm or more.

Neurologic disease

Cerebrovascular accident or transient ischemic disease included patients with minor or no residual symptoms.

Hemiplegia included patients with hemiplegia or paraplegia resulting from a cerebrovascular accident or other conditions.

Alzheimer's disease, dementia of any cause, or serious cognitive impairment included patients with moderate-to-severe chronic cognitive deficit resulting in impaired function, regardless of the cause.

Other neurologic conditions included patients with Parkinson's disease, uncontrolled seizures, or syncope without an identified cause.

Respiratory disease

Chronic obstructive pulmonary disease (COPD) included patients diagnosed with COPD who had ongoing symptoms such as dyspnea or cough on light or moderate activity. This included patients who were dyspneic on light activity, with or without treatment, and those who were dyspneic on moderate activity despite treatment, as well as patients who were dyspneic at rest despite treatment, those who required constant oxygen, those with CO_2 retention, and those with a baseline PO_2 below 50 torr.

Asthma included patients diagnosed with asthma who had ongoing symptoms such as dyspnea or cough on light or moderate activity. This includes patients who were dyspneic on light activity with or without treatment and those who were dyspneic with moderate activity despite treatment, as well as patients who were dyspneic at rest despite treatment.

Other respiratory conditions included patients with interstitial lung disease, chronic restrictive lung disease, pulmonary embolism disease, vascular disease or severe pulmonary hypertension (>40 mmHg) of any cause resulting in severe exercise restriction (e.g., unable to climb stairs or perform household duties).

Smoking habit included active smokers consuming >10 cigarettes/day with >10 pack years.

Diabetes mellitus included all patients with diabetes treated with insulin or oral hypoglycemic agents, but not those treated with diet alone. Patients with gestational

diabetes were not considered diabetic. This classification also included patients with end-organ damage (retinopathy, neuropathy, nephropathy) attributable to diabetes.

Renal disease included patients with moderate renal insufficiency patients with a serum creatinine >3 mg/dl. Severe renal disease included patients on dialysis, those who had undergone transplantation, and those with uremia.

Liver disease included patients with mild liver disease (chronic hepatitis (B or C) or cirrhosis without portal hypertension), those with moderate liver disease (cirrhosis with portal hypertension, but without bleeding) and those with severe liver disease (ascites, chronic jaundice, portal hypertension or a history of variceal bleeding, or liver transplant).

Cancer

Lymphoma included patients with Hodgkin's disease, lymphosarcoma, Waldenstrom's macroglobulinemia, myeloma, or other lymphomas.

Leukemia included patients with acute or chronic myelogenous leukemia, acute or chronic lymphocytic leukemia, or polycythemia vera.

Solid organ tumor included patients with solid tumors without documented metastases, including breast, colon, lung, prostate, melanoma, and a variety of other tumors.

Metastatic cancer included patients with metastatic solid tumors, including same locations as previously detailed.

Other diseases

Peptic ulcer disease included patients who have required treatment for gastric or peptic ulcers, including those who have bled from ulcers.

Rheumatic or connective tissue disease included patients with systemic lupus erythematous, polymyositis, mixed connective tissue disease, rheumatoid arthritis, polymyalgia rheumatica, vasculitis, sarcoidosis, Sjogren's syndrome, or any systemic vasculitis.

HIV or AIDS included patients with definite or probable AIDS, i.e. AIDS-related complex, as well as asymptomatic HIV-positive patients.

Decubitus ulcers, peripheral skin ulcers, or repeated episodes of cellulitis included partial thickness loss of skin over legs or back with open ulcers or two or more episodes of cellulitis requiring treatment with antibiotics, regardless of etiology.

Depression included patients who were receiving treatment for depression, whether pharmacologic or psychotherapy, and those with signs indicating probable or definite depression.

Coagulopathy included patients with coagulation disorders and those with circulating anticoagulants for any medical condition.

Other endocrine diseases included patients with hypopituitarism, adrenal insufficiency, or recurrent acidosis.

Inflammatory bowel disease included patients with ulcerative colitis, Crohn's disease, or regional enteritis.

Gastrointestinal bleeding included patients with bleeding requiring transfusions from causes other than ulcer disease.

Alcoholism was defined as a regular intake of more than 80 g of alcohol per day.

Other causes of reduced resistance to infection included patients who had undergone treatments that suppress resistance to infection, such as immunosuppression, chemotherapy, radiation, long-term or recent high dose steroids, as well as those with a disease that is sufficiently advanced to be considered a cause of suppressed resistance to infection, such as splenectomy before ICU admission.

Major surgery within two months prior to admission.

Previous antibiotic therapy for at least 2 weeks within two months prior to admission.

REFERENCES:

1.- Ho KM, Finn J, Knuiman M, and Webb SAR. Combining multiple comorbidities with Acute Physiology Score to predict hospital mortality of critically ill patients: a linked data cohort study. Anesthesia 2007; 62:1095-110.

2.- Ho KM, Knuiman M, Finn J, Webb SA. Estimating long-term survival of critically ill patients: the PREDICT model. PLoS ONE 3(9): e3226. Doi:10.1371/journal.pone.0003226

3.- Esper AM, and Martin GS. The impact of comorbid conditions on critical illness. Crit Care Med 2011; 39:2728-2735,

eAppendix 4. Definition of ventilator-associated pneumonia and tracheobronchitis

Ventilator-associated pneumonia (VAP) was defined as fever (temperature >38ºC) or altered leukocyte count (>12,000/mL or <4,000/mL) plus new onset of purulent endotracheal secretions or change in sputum, with new and progressive or persistent infiltrate or consolidation or cavitation and a significant pathogen culture (>10^5 cfu/mL in semiquantitative endotracheal aspirate, >10^4 cfu/mL in bronchoalveolar lavage fluid, or >10^3 cfu/mL in protected brush specimens).[1] Ventilator-associated tracheobronchitis (VAT) was defined by the same criteria but without new infiltrates.[2]

REFERENCES:

1.- Niederman MS, Craven DE, Bonten MJ. American Thoracic Society and Infectious Diseases Society of America (ATS/IDSA). Guidelines for the management of adults with hospital acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005; 171:388–416.

2.- Craven DE, Chroneou A, Zias N, Hjalmarson KI. Ventilator associated tracheobronchitis. Chest 2009; 135:521–528.

eAppendix 5. Definition of persistent postextubation respiratory failure

In both study groups, patients were reintubated for persistent postextubation respiratory failure if they met at least one of the following criteria, after they had undergone the assigned treatment by the treating physician for at least one hour, without fulfilling immediate reintubation criteria:

1. Lack of improvement in pH or in the partial pressure of carbon dioxide or fall in GCS scale >2 points.

2. Lack of improvement in signs suggestive of respiratory-muscle fatigue or worsening including the appearance of unequivocal signs of respiratory-muscle fatigue, such as maintained active contraction of the expiratory muscles, asynchronous motion of the rib cage and abdomen, respiratory alternans, or active contraction of the sternocleidomastoid.

3. Hypotension, with a systolic blood pressure below 90 mm Hg for more than 30 minutes despite adequate volume challenge, use of vasopressors, or both.

4. Copious secretions that could not be adequately cleared or that were associated with acidosis, hypoxemia, and changes in mental status or persistent or worsening signs of respiratory-muscle fatigue.

5. Decrease to SpO_2 <85% despite the use of a high FiO_2 (>.5).

Patients fulfilling these criteria were reintubated, but the final decision to reintubate was made by the treating physician or evaluated by a consensus committee excluding the investigators. The single most relevant reason for reintubation from the list was recorded. If two or more criteria were present, the reason for reintubation was assigned in the following order of preference: presence of copious secretions, respiratory

acidosis, hypoxemia, signs of respiratory-muscle fatigue, and hypotension for selection of cause of reintubation.

eAppendix 6. Details of the multivariable logistic regression analysis for the primary outcome of reintubation rate

The purpose of the anticipated multivariable analysis was to confirm that the marginal OR (1.25; 95%CI: 0 – 1.74) is similar to the OR conditioned to covariables (1.23; 95%CI: 0 – 1.76).

Baseline variables associated with reintubation in the univariate analysis with a level of statistical significance <.1, and included in the multivariable analysis were:

- Risk factors for reintubation: APACHE II on extubation day, not-simple weaning, inability to deal with respiratory secretions.
- Comorbidities: vascular disease.
- Diagnosis at ICU admission: medical respiratory primary failure (pneumonia).

	Successful extubation n=478	**Reintubated n=126**	**p**
Age, mean (SD), y	64 (16)	65 (13)	.64
Men, Nº (%)	303 (63.7)	85 (67.5)	.46
Risk factors for reintubation, Nº (%)			
Time under MV >7 days	156 (32.6)	65 (51.6)	<.001
APACHE II at extubation, median (IQR)	8 (8-12)	12 (9-14)	<.001
Not simple weaning	107 (22.4)	53 (42.1)	<.001
Moderate-to-severe COPD	86 (18)	30 (23.8)	.16

Intubated for heart failure	37 (7.7)	10 (7.9)	.99
More than 1 comorbidity	330 (69)	92 (73)	.45
Body mass index >30	97 (20.3)	28 (22.2)	.62
Older than 65 y	276 (57.7)	72 (57.1)	.92
Airway patency problems	13 (2.7)	4 (3.2)	.76
Inadequate secretions management	84 (17.6)	48 (38.1)	<.001
Comorbidities, Nº (%)			
Body mass index >25	366 (76.6)	90 (71.4)	.25
Arterial hypertension	277 (57.9)	64 (50.8)	.16
Heart disease	160 (33.5)	36 (28.6)	.34
Neurologic disease	123 (25.8)	33 (26.2)	.91
COPD	93 (19.5)	31 (24.6)	.21
Other respiratory disease	140 (29.4)	44 (34.9)	.23
Diabetes mellitus	135 (28.2)	44 (34.9)	.16
Cancer	89 (18.6)	24 (19)	.89
Vascular disease	28 (5.9)	15 (11.9)	.03
Renal failure	61 (12.8)	18 (14.3)	.66
Hepatic disease	43 (9)	17 (13.5)	.14
Other comorbid conditions	63 (13.2)	18 (14.3)	.77
Diagnosis at admission, Nº (%)			
Respiratory primary failure	163 (34.1)	56 (44.4)	.04
ARDS	40 (8.4)	13 (10.3)	.48

Respiratory tract infection	56 (11.7)	29 (23)	.002
Exacerbated COPD	40 (8.4)	8 (6.3)	.58
Airway patency problem	10 (2.1)	3 (2.4)	.74
Nonrespiratory primary failure	320 (66.9)	89 (70.6)	.45
Neurologic	113 (23.6)	30 (23.8)	.99
Cardiologic	73 (15.3)	17 (13.5)	.67
Trauma	39 (8.2)	13 (10.3)	.47
Traumatic brain injury	21 (4.4)	7 (5.6)	.63
Surgical	187 (39.1)	45 (35.7)	.53

Abbreviations: MV, mechanical ventilation; COPD, chronic obstructive pulmonary disease.

The multivariate analysis showed the following results:

	Beta	Std. error	p	OR	95%CI
High-flow vs NIV	-.20	.21	.35	1.23	.81 to 1.88
Not simple weaning	.39	.24	.10	1.49	.92 to 2.39
Inadequate secretions management	.81	.24	.001	2.26	1.39 to 3.67
Vascular disease	.59	.37	.11	1.81	.86 to 3.77
Respiratory tract infection	.65	.28	.02	1.92	1.11 to 3.36
APACHE II (per point)	.07	.03	.03	1.08	1.01 to 1.15
Length of MV (per day)	.04	.02	.01	1.05	1.01 to 1.09
Hospital	.87	.37	.06	2.39	1.16 to 4.92
Constant	-3.42	.61	0	N/A	N/A

Hosmer-Lesmeshow test p=0.513 and the 3.65% of the points had studentized residuals >2.

eAppendix 7. Sensitivity analyses

Sensitivity analyses:

- To exclude bias in our main result due to delayed reintubation, we performed a sensitivity analysis including reintubation up to 7 days after extubation: 67 patients (23.1%) in the high-flow group vs 60 (19.1%) in NIV group, difference between groups 4%, unilateral 95%CI: -∞ to 9.5%.

- To exclude a possible inclusion bias due to the lack of an evidence-based model predicting risk for reintubation, we performed a sensitivity analysis focused on the reintubation of patients with only one risk for reintubation:

- 3/36 patients (8.3%) in the high-flow group vs 4/39 (10.3%) in the NIV group, difference -1.9%, unilateral 95%CI: -∞ to 10.2 and bilateral 95%CI: -16.3 to 12.9.

The number of patients according to the number of high-risk factors in every group:

Number of risk factors, Nº (%)	**High-flow group n=290**	**NIV group n=314**
1	36 (12.4)	39 (12.4)
2	80 (27.6)	78 (24.8)
3	80 (27.6)	83 (26.4)
4	47 (16.2)	64 (20.4)
5	31 (10.7)	34 (10.8)
6	13 (4.5)	12 (3.8)
7	3 (1)	4 (1.3)