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# WHEN SHOULD AND WHEN SHOULD NOT USE OXYGEN IN NEUROMUSCULAR DISEASES?

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**Abstract** Although the references warn about the adverse effects of adding $O_2$ without ventilatory support in patients with neuromuscular diseases (NMD), patients are still to be admitted to intensive care units with severe hypercapnia and $CO_2$ narcosis. The problem seems to be rediscovered as the years and generations go by. Unfortunately, many patients and their network of formal and informal caregivers are unaware of this risk, leading to significant worsening of symptoms, acute events, hospital admissions, and, in some cases, cause death. This article focuses on the dangers of $O_2$ administration and its precise indications in people with NMD. The central problem is that the administration of $O_2$ can remove the hypoxic impulse to ventilate. However other mechanisms could be involved, but the complete withdrawal of oxygen therapy is an even greater mistake if it is not supported by ventilatory assistance. It is possible to supply $O_2$ and control $CO_2$ safely. Oxygen should never be administered without constantly monitoring the $CO_2$ level. Bilevel non-invasive ventilation (BiPAP) through a buccal, nasal interface or mouthpiece is the primary measure to reverse hypoventilation and decrease $PaCO_2$. The indications for oxygen therapy in people with NMD have been agreed upon and are reserved for specific situations. To improve the care of people with NMD and avoid iatrogenic interventions, education of the health team and support in the patient's environment is required.

**Key words:** neuromuscular diseases, oxygen toxicity, carbon dioxide narcosis, hypercapnia

**Resumen** ***¿Cuándo debería y cuándo no debería utilizarse oxígeno en las enfermedades neuromusculares?*** A pesar de las referencias que advierten sobre los efectos adversos de la utilización de $O_2$ suplementario sin asistencia ventilatoria en pacientes con enfermedades neuromusculares (ENM), aún hoy continúan ingresando pacientes en unidades de cuidados intensivos con hipercapnia grave y narcosis por $CO_2$. Parecería que el problema es redescubierto según pasan los años y las generaciones. Muchos pacientes y su red de cuidadores formales e informales no son conscientes de este riesgo que puede llevar a un empeoramiento significativo de los síntomas, eventos agudos, ingresos hospitalarios y, en algunos casos, causar la muerte. Este artículo está centrado en los riesgos de la administración de $O_2$, así como en sus indicaciones puntuales en personas con ENM. El problema central es que la administración de $O_2$ puede quitar el impulso hipóxico para ventilar. Aunque otros mecanismos podrían estar involucrados, el retiro completo de la oxigenoterapia sin apoyo de asistencia ventilatoria, es un error aún mayor. Es posible administrar $O_2$ y controlar el $CO_2$ de forma segura. Nunca se debe administrar $O_2$ sin monitorear constantemente el nivel de $CO_2$. La ventilación no invasiva binivelada (BiPAP) mediante interfaz nasal bucal o boquilla, es la principal medida para revertir la hipoventilación y lograr el descenso de la $PaCO_2$. Las indicaciones de oxigenoterapia en personas con ENM han sido consensuadas y están reservadas a situaciones específicas. Para mejorar la atención de aquellos enfermos con ENM y evitar intervenciones iatrogénicas, se requiere educación al equipo de salud y contención en el entorno del paciente.

**Palabras clave**: enfermedades neuromusculares, toxicidad por oxígeno, narcosis por dióxido de carbono, hipercapnia

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**KEY POINTS**
**Current knowledge**

- Several clinical research papers have warned about the risk of oxygen toxicity and $CO_2$ narcosis in people with neuromuscular disease and respiratory muscle weakness. However, the problem is rediscovered, and patients continue to be admitted to intensive care units with severe hypercapnia and $CO_2$ narcosis.

**Contribution of the article to current knowledge**

- This article reviews the risks associated with $O_2$ administration and its precise indications in patients with neuromuscular diseases. There are ways to administer it and control $CO_2$ safely. It should never be administered without monitoring the $CO_2$ levels. Non-invasive ventilation is the primary measure for reverse hypoventilation and lower $PaCO_2$.

*Everything has been said before, but since nobody listens we have to keep going back and beginning all over again*

*Nobel Prize for Literature,* **André Gide** *in 1947*

The harmful consequences of uncontrolled $O_2$ administration in various clinical situations have been known for over 50 years[1]. High oxygen therapy causes an increase in arterial blood carbon dioxide ($PaCO_2$) in patients with chronic obstructive pulmonary disease (COPD), bronchial asthma, pneumonia, obesity and acute lung injury[2]. Nevertheless, patients continue to be admitted to intensive care units with severe hypercapnia and $CO_2$ narcosis due to uncontrolled O2 administration[3]. This is still the case. Several clinical research papers warned about this situation, but it seems that the problem has been rediscovered over the years and generations. Nothing could be more appropriate than the reflections of André Gide.

The problem of the risks of oxygen therapy has taken on such a dimension that it is possible to find mentions not only in medical articles[4, 5] but also on the websites of professionals, groups of non-governmental associations, and family of people with neuromuscular diseases (NMD)[6-11].

This article focuses on the risks of $O_2$ administration and its precise indications in people with these conditions. We refer to neurological diseases involving the brain, spinal cord, motor nerves and muscles as NMD[12]. We will focus on their chronic and progressive trajectories and acute events, both inherent to their natural evolution[13, 14].

## Benefits of oxygen therapy

In general, the benefits of oxygen therapy are beyond dispute. So far, we are not aware of any movement, spread by social networks, that is against the administration of $O_2$, as is the case with climate change, the Earth's geometry, vaccines, and even the COVID-19 pandemic. Therefore, in this section, we will limit ourselves to recalling Antoine Lavoisier, who in 1777, through experimentation, described an "essential air" in the atmosphere that he called oxygen. Six years later, to the best of our knownledge, the French physician Caillens used it on a patient with tuberculosis[15]. It was not until the 1970s that $O_2$ was used at home, and at the same time, it began to be considered a drug in gaseous form, with defined doses, administered through the airways, not always accessible, expensive and not free of side effects.

## Risks of oxygen therapy in neuromuscular diseases

Some references warn of the adverse effects of using supplemental $O_2$ (without the use of ventilatory support) in patients with NMD and respiratory muscle weakness[16-19]. Unfortunately, many patients and their networks of formal (professional) and informal (family) caregivers are unaware of this risk, which can lead to significant worsening of symptoms, acute events, hospital admissions and, in some cases, death.

## Why is supplemental O2 dangerous for people with neuromuscular diseases?

The central problem is that $O_2$ administration can remove the hypoxic drive to ventilate[4] and produce $PaCO_2$ elevation[5]. Other mechanisms may also be involved[20, 21]. Hypercapnia can manifest with various manifestations, from drowsiness to the most severe $CO_2$ narcosis. Normal individuals do not experience alterations in consciousness until the $PaCO_2$ is greater than 75 mmHg. Patients with chronic progressive hypercapnia may not experience consciousness until $PaCO_2$ exceeds 80 mmHg[22]. Hypercapnia modifies the levels of neurotransmitters related to consciousness. It has been hypothesized that there are elevated levels of glutamine and gamma-aminobutyric acid (GABA) and reduced levels of glutamate[23].

Individuals with NMD are particularly prone to respiratory disturbances during sleep[24]. If hypoventilation during sleep is significant, it produces bicarbonate retention, further depressing ventilation, and further diurnal $CO_2$ elevation[25]. If these cycles are repeated, $PaCO_2$ rises, which makes falling $SatO_2$ tempt supplemental $O_2$ to rise, further worsening hypoventilation. If any sedative is added, the stage is set for the patient to enter a coma due to $CO_2$ narcosis.

We have seen patients with various NMD, ambulatory, with or without tracheostomy (TCT), lucid, arriving at the office even walking, receiving supplemental $O_2$, with $PaCO_2$ above 120 mmHg and we have found similar or substantially higher values in patients admitted to the emergency room with $CO_2$ narcosis. Oppenheimer was quite precise regarding amyotrophic lateral sclerosis (ALS): the two therapies physicians should generally avoid in treating ALS respiratory muscle weakness are supplemental oxygen and continuous positive airway pressure (CPAP)[26]. The latest End-Stage Neuromuscular Respiratory Muscle Failure Consensus unanimously recommends neither supplemental $O_2$ nor CPAP[27].

## In patients with neuromuscular disease receiving oxygen therapy, what should we do?

Indiscriminate oxygen therapy in patients with stable NMD and chronic hypoventilation (not using ventilatory support) can precipitate $CO_2$ narcosis. However, abrupt removal is an even greater mistake because $PaO_2$ can drop lower than when oxygen therapy is initiated. The development of hypoxemia is more rapid than the resolution of hypercapnia because of the high amount of $CO_2$ accumulated in the body stores[1]. Let us take the case of a lucid young adult patient, self-valid, receiving nasal oxygen therapy, with plugged TCT (recent hospitalization for ventilatory failure due to idiopathic central alveolar hypoventilation), $SatO_2$ 93%, $PaO_2$ 76.3 mmHg, $PaCO_2$ 134 mmHg, bicarbonate 57 mEq/L[28]. With this $PaCO_2$ value considering the alveolar air equation, removing the nasal cannula would result in a $PaO_2$ of -19 mmHg if the patient could not hyperventilate before losing consciousness. These values, incompatible with life, are equivalent to suddenly climbing to the top of Mount Everest[29, 30]!

## Which patients are at risk of developing oxygen therapy-induced hypercapnia?

In COPD, the incidence and magnitude of oxygen therapy-induced hypercapnia are variable and can occur in both stable and exacerbations[31]. The mechanisms involved were analyzed[20, 21]. In patients with NMD, kyphoscoliosis or bronchiectasis, specific results suggest that study models may not be appropriate for detecting potential $O_2$-induced hypercapnia in clinical practice[2]. One of the factors contributing to these discrepancies is the $FiO_2$ used in controlled studies (known) and in clinical practice (often unknown). Current evidence of the potential for $O_2$-induced hypercapnia in NMD and various respiratory conditions supports the guideline recommendations to start oxygen therapy in all patients to avoid the risks of uncontrolled oxygen therapy[27,31].

## When should oxygen be administered to patients with neuromuscular disease? Safe administration

There are methods to safely administer supplemental $O_2$ and control $CO_2$. Pulse saturation values ($pSatO_2$) below 95% when breathing atmospheric air are associated with hypercapnia[32]. Oxygen should never be administered without constant monitoring of $CO_2$ levels. This can be done non-invasively using a capnography to measure $CO_2$ in exhaled air (end-tidal $PCO_2$, $PetCO_2$) or by determining the blood $CO_2$ level by arterial blood gas sampling. A $PetCO_2$ level > 45 mmHg is considered too high. Non-invasive bilevel ventilation (BiPAP) via buccal, nasal interface, or mouthpiece) is the most critical measure to reverse hypoventilation and achieve lowering of $PaCO_2$.

The indications for oxygen therapy in patients with NMD have been agreed upon by consensus[27] and are entirely in force. The panel of experts recommended the following in specific clinical situations:

1.- Patient is about to be intubated.

2.- Cardiorespiratory arrest and resuscitation.

3.- Hospitalized patients who cannot maintain $SatO_2$ $\geq$95% with continuous NIV and mechanical cough assistance (e.g, pneumonia).

4.- Therapeutic adequacy for patients with advanced bulbar ALS who do not accept TCT.

The adequacy of therapeutic effort and withdrawal of life support in patients in the last days of life is a particular situation in which comfort is prioritized[33]. Oxygen is widely prescribed in palliative care patients. However, there is no evidence to support this practice in relieving dyspnea unless there is some degree of reversible hypoxemia[13,34].

## Conclusions

This Editorial reviewed uncontrolled oxygen therapy-induced $CO_2$ narcosis and its precise indications in NMD patients. The following aspects are considered relevant.

- Supplemental $O_2$ is not indicated for hypoventilation in persons with NMD because, in progressive hypercapnic respiratory failure with normal lungs, $SaO_2$ falls because $CO_2$ increases. Hypoxemia of hypoventilation should not be confused with $O_2$ transfer (altered V/Q ratio).
- Oxygen administration may improve hypoxemia but masks the underlying problem, hypoventilation and prevents monitoring of $SatO_2$ from inferring $PaCO_2$ evolution.
- Oxygen can increase $CO_2$ and lead to narcosis.
- Oxygen does not provide ventilatory support to weak respiratory muscles.
- If a patient has hypoxemia due to hypoventilation, the focus should be on treating hypoventilation with non-invasive ventilatory support (with high levels of expansion).

• If secretions and atelectasis are retained, cough should be assisted manually or mechanically.

However, $O_2$ administration has a vast "advantage": it gives the patient, family, and medical team a false impression that something is being done. Improving the care of people with NMD and avoiding iatrogenic interventions requires the healthcare team's education and containment in the patient's environment.

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