JOURNAL OF PHARMACOLOGICAL CHEMISTRY AND BIOLOGICAL SCIENCES

Vol.: 2(2). pp. 145-157, Mar-Apr
DOI: 10.36619/jpcbs.2020.2.39.52
ISSN: 2674-886X

Clinical Applications of Nitric Oxide: Comprehensive Review

Isabeline Maria de Góis Mendes Oliveira[1]; Ricardo dos Santos Cirilo and Fausto Pierdoná Guzen [1,2]

[1] Laboratory of Experimental Neurology, Department of Biomedical Sciences, Health Sciences Center, State University of Rio Grande do Norte (UERN), Mossoró-RN, Brazil.

[2] Postgraduate Program in Biotechnology at Potiguar University (UnP) - Laureate International Universities – Natal/Brazil.

Keywords:

Nitric Oxide
Clinical Application

Abstract

Around the year of 1986 nitric oxide was no longer seen by health professionals as a highly toxic molecule and began to be considered in clinical treatments. However, the discovery of their positive functions does not mitigate their negative characteristics, because of this, research and tests are performed on the functionalities and risks, however doubts and fears are still common. In biological organisms, nitric oxide may react with molecules and attenuate various processes, whereas when in contact with a high amount of the oxide or a been exposed for too long may cause intoxication. Therefore, further research and testing with the use of oxide are required to avoid com-

plications. Hence, the objective of the present research is to present the clinical complications caused by the use of nitric oxide in various treatments.

INTRODUCTION

Nitric oxide (NO) is a simple colorless gaseous molecule at room temperature, poorly soluble in water and more in solvents that can be dissolves in cell membranes and lipid phases (QUEIROZ and BATISTA, 1998) and "Usually found in the atmosphere in small quantities, being highly toxic due to the presence of free radical that makes it a highly reactive chemical agent" (FLORA FILHO and ZILBERSTEIN, 2000, p. 265).

This is known for its polluting potential, being primarily responsible for global warming, making it unimaginable that it could bring benefits to human health, however, in 1986, researchers proved that it may have beneficial biological reactions in the human body. In fact, a reaction between NO and peroxynitrous acid results in OH and NO2, which are highly oxidizing and harmful to biomolecules. Nevertheless, NO can act as an important second messenger, activating or inhibiting several target molecules involved in different processes. Therefore, exposure to varying concentrations of NO should be closely controlled, as it may cause reversible or irreversible inhibition of these metalloproteins. (BARRETO, CORREIA and MUSCARÁ, 2005).

Oxide can be introduced into the body by inhalation or intravenously. Inhaled NO has limited action on small resistance veins and arteries and is unable to dilate large vessels, being the most recommended in clinical procedures. However, it is toxic when inhaled at high levels, producing methemoglobinemia and lung injury (ÉVORA et. al., 2002).

Cerqueira and Yoshida (2002, p. 418) present the most varied functions that nitrogen oxide can perform in the biological system, such as "mediating non-cholinergic non-adrenergic relaxation of the longitudinal and circular esophageal sphincter, stomach, duodenum, small intestine, and internal anal sphincter muscles" when in the gastrointestinal tract. In blood

vessels “it plays a role in modulating vascular diameter and vascular resistance by its ability to relax vascular smooth muscle and inhibit interactions of circulatory blood elements with the vessel wall”, among many other functions in the respiratory system and circulatory system.

According to these authors, in fact, nitric oxide provides numerous benefits in clinical treatments, when applied to the extent and with appropriate exposure time in each case, and its use is still very restricted and questioned. Moreover, NO has great toxic potential and can react in different ways in the body, because of these obstacles the studies and tests performed with the oxide are still quite restricted, allowing the existence of many doubts and questions.

In addition, it is also important to point out that the medical team itself is vulnerable to the effects of nitric oxide inhalation. Évora et. al. (2002) cite some safety measures established by the US Occupational Safety and Health Administration (OSHA) that should be adopted, such as using aluminum cylinders at 400-500 ppm NO supplemented with N2, using soda lime in the inspiratory line of the NO2 neutralizing respirator, administer low NO concentrations, do not use hospital compressed air at pre-dilution, add NO in circuit prior to ventilator blender, do not manufacture your own NO for clinical use. The concentration and the exposure time to which professionals may be exposed are also determined in order to avoid intoxication.

Many studies present the various applications of NO in clinical treatments, however, it is very restricted to talk about the problems that can trigger. Considering that the risks are high for both the patient and the team, as the oxide is extremely toxic and can be inhaled, and there are few studies on this subject focused on this perspective, the present research aims to present the clinical complications caused by the use of nitric oxide in various treatments.

METHODOLOGY

This article is a comprehensive literature review of research that entails careful

analysis of studies on the nitric oxide molecule. The study hypothesis was: "Main clinical applications of nitric oxide". For the survey of scientific productions, parameters from Lima and Mioto (2007) were used in: Health works that addressed NO applications in the medical clinic (thematic parameter); chronological parameter: articles published and indexed in databases from 1995 to the present day. The productions presented in the form of letter to the editor, communication, monograph, dissertation or thesis were excluded.

The selection of articles for this review was made by consulting three databases: ScienceDirect, Web of Science and PubMed whose searches were guided by the combination of two descriptors, applying Boolean operator (and): Nitric Oxide and Clinical Application. Applying the inclusion and exclusion criteria, 28 articles were found in the Web of Science, 6 articles in ScienceDirect and 8 articles in PubMed observing articles in duplicate. The second screening considered their reading, discarding those that were not in accordance with the thematic standard; finally, 16 articles were considered for this review.

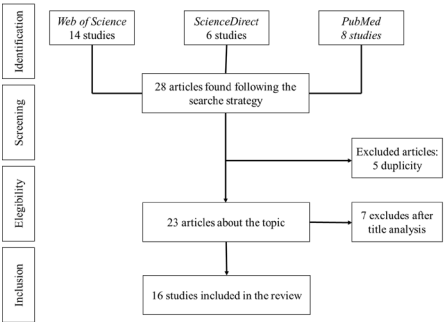

Figure 1: Flowchart representative of the article selection process / Source: authors' production, 2020.

RESULTS AND DISCUSSION

After reading the selected articles in full, it was observed that they all dealt with applications of the nitric oxide molecule in the medical clinic. The studies selected in this review are presented in table 1.

Table 1 – Articles on Clinical Applications of Nitric Oxide. Source: multiple databases.

AUTHOR	YEAR	SUMMARY
Song	2015	FeNO measurement is useful for screening, optimizing the clinical process in asthmatic patients. Biological factors, smoking, food intake interfere with the result by interfering with FeNO values, which increase with age.
Manna *et. al.,*	2014	The authors bring a new approach regarding the malefísios of nasal contact of children with nitric oxide and the benefits of its use in pediatric respiratory treatments.
Levine	2012	Conversely, insulin activates NOS, while NO / cGMP / cGK signaling increases insulin sensitivity. Inflammation generates resistance to anabolic actions of insulin, as well as vascular dysfunction with impaired nutrient delivery, resulting in a parallel interruption of metabolic-vascular insulin and NO signaling, correlating with insulin resistance and its deterioration.
Manna *et. al.,*	2012	In this work, the authors present a discussion about the influence of the use of nitric oxide in the treatment of children with respiratory problems, also addressing the effects of the uncontrolled contact of this public with gas.
Taylor	2012	FENO measurements provide complementary data that allow the clinician to decide on the appropriateness of starting or increasing the yes / no ICS treatment more intelligently and less empirically.
Dweik	2011	Consistent observations indicate that atopic individuals have higher levels of FENO while smokers tend to have lower levels. Including FENO as an outcome in clinical trials would be very helpful in understanding FENO's role in monitoring response to occupational asthma therapy.
Carraro S.,	2010	The authors discuss the effects of high or low nitric oxide concentration in the body, making a comparison between children and adults.
Zitt	2005	The present study demonstrated the usefulness of exhaled nitric oxide in the diagnosis and management of asthma, as well as in predicting response to therapy, that is, FENo has merit in the diagnosis and treatment of asthma.
Keefer,	2003	This study aims to address the beneficial properties of nitric oxide in clinical treatments.
Paoloni	2003	The results of this clinical trial demonstrated that there were significant improvements in signs and symptoms, functional tests, and results of patients with extensor tendinosis treated with nitric oxide therapy (glyceryl trinitrate application) compared with tendon rehabilitation alone.
Jacobs. et al.,	2000	The purpose of this study was to compare the use of inhaled nitric oxide (NO) x oxygen administered to newborns of gestational age greater than or equal to 34 weeks with severe respiratory disease. Although there is not a significant sample of patients analyzed, it was observed that for non-CDH patients, the favorable proportion provides very qualified evidence in favor of NO.

Pearl	2000	The present study addresses the applications of inhaled nitric oxide in acute respiratory distress syndrome, perioperative use, chronic pulmonary hypertension, newborn hypoxemic respiratory failure, sickle cell disease, and pulmonary ventilation. Addresses the importance of nitric oxide in the case of ischemia-reperfusion injury and lung transplantation.
Adatia	1995	It addresses the selective vasodilatory action of inhaled nitric oxide in children with congenital heart disease and pulmonary hypertension, also optimizing patient management, especially after surgical procedures requiring cardiopulmonary bypass. Furthermore, it demonstrates the success of adding NO to therapy in cases in which resuscitation maneuvers for the treatment of pulmonary hypertensive crises were used.
Body	1995	The biological and therapeutic roles of NO are being recognized. Prior to inhaled administration of NO, consensus on safe and accurate use is required. The potential for NO use is apparently and potentially positive for therapeutic success. However, their effectiveness and safety must be carefully assessed by testing.
Frostell and Zapol	1995	The effects of inhaled NO exposure resulted in a reduction in pulmonary hypertension in several patients with primary pulmonary hypertension. A variety of cells in the human respiratory system, including endothelial cells, are found to contain NO synthase. Blockage of this pathway by an arginine analog (NG-monomethyl-L-arginine) causes increased pulmonary vascular resistance (PVR).
Mupanemunda	1995	The use of inhaled NO may be a significant advance factor in the management of the respiratory system disorders addressed. However, significant gaps remain in understanding NO toxicology and pharmacology.

Levine (2012) states that vascular and metabolic health are linked, since insulin receptor and nitric oxide synthase (NOS) are expressed in vascular endothelium, where they regulate vascular tone, as well as skeletal and cardiac muscle in the processes. metabolic Insulin receptor and NOS are anatomically and functionally linked. Working reciprocally, insulin activates NOS, and NO / cGMP / cGK signaling increases insulin sensitivity, but there are cases of inflammation that generates anabolic insulin resistance, but also vascular dysfunction with impaired nutrient delivery, in effect, disruption. parallel to metabolic--vascular insulin and NO. Endothelial dysfunction compromises insulin sensitivity, resistance, worsening endothelial function and the degree of endothelial dysfunction correlates with severity insulin resistance and contribute to its deterioration. In cases of Stress and chronic inflammation, dysfunctional NO and insulin resistance manifest, affecting several tissues.

Manna et. al. (2012) reaffirms the feasibility of using

oxide, especially with regard to the treatment of children with respiratory problems, such as asthma, bronchitis and pneumonia, considering that it is not invasive, thus not causing discomfort or trauma in the pediatric public. However, the same author, two years later, in a new study on the same theme, states that, in some upper airway disorders, the clinical utility of nasal nitric oxide is questionable (MANNA et. Al., 2014). Making oneself questioned as to the knowledge and domain of the effects of the oxide in the organism.

Thus, the authors highlighted how nitric oxide has several clinical uses. Song (2015) used fractional exhaled NO (FENo) as a biomarker of respiratory diseases, eg, Asthma. Taylor (2012), Dweik (2011) and Zitt (2005) also bring this approach to the use of NO as a marker of respiratory pathologies. In the test proposed by Zitt (2005) it was shown utility, in addition to diagnosis and management in asthma, of predicting response to therapy, thus being an important tool to incorporate in clinical care, mainly because it is a noninvasive and well tolerated method. This application was the most discussed among the papers analyzed.

Frostell and Zapol (1995) state that inhaled NO is chemically stable because it contains an unpaired electron, contributing, among other factors, to the reduction of primary pulmonary hypertension. Paoloni (2003) shows that it can also be used to treat degenerative tendinopathy by stimulating collagen synthesis in fibroblasts.

In their research, Mupanemunda (1995) and Pearl (2000) found the importance of inhaled nitric oxide in vascular regulation, cardiorespiratory disorders in infants and children, and in the management of other disorders, stating that it should be used with caution. The lack of studies in this area undermines the toxicological and pharmacological understanding of oxide in the patient's organism, which may worsen the individual's health, which is a topic discussed by all authors, with general agreement.

Jacobs et. al. (2000) and Pearl (2000) also analyzed the use of NO in pediatric treatments, however their research is aimed at evaluating the cost benefit of using NO specifically in newborns, attesting the economic viability of applying this method. Adatia (1995) attests that the use of inhaled nitric oxide in children with congenital heart disease and pulmonary hypertension indicates that nitric oxide is a selective pulmonary vasodilator that may improve patient management.

Keefer (2003) claims that, due to its chemical characteristics, this is an excellent starting point in the projection of materials capable of directing reliable and controllable flows of bioactive substances, thus being a clinical promise, which can contribute to the treatment of patients with respiratory problems, reverse vasopasm, relieve hypertension, among other contributions.

Importantly, all authors agree that, although research on the use of NO in clinical treatment has started years ago, there are still many uncertainties and questions that permeate its practical use, and further research and tests.

Bearing in mind that, among unknown consequences, the high or low concentration of NO in the nasal passages can aggravate the patient's situation and or generate other problems. In his research, CARRARO S. (2010) states that low concentrations of NO can cause or aggravate cases of sinusitis and fibrosis.

It is interesting to note the evolution of studies, findings and development of successful therapies involving nitric oxide over the years. From this perspective, when analyzing the studies carried out in the early years of research on NO, as early as the 1990s, Body et al raises the possibility of using such a molecule in therapy, after reporting its action in various systems in the body. A concern described by the author in addition to investments in new studies that enable NO to be used for the treatment of some pathologies is about the safety of this use. In the same year

Frostel et al and Mupanemunda take a more specific approach and direct the study line for treatment using inhaled nitric oxide for the treatment of respiratory diseases. One of the first discoveries about the action of nitric oxide was about its vasodilatory action and it is precisely about this function that Adatia addressed in 1995.

In the 2000s, Pearl already talks about the importance of NO in cases of ischemic injuries and lung transplants, while addressing the numerous actions of NO also in other respiratory diseases, further evidence that previous studies have had success in their survey and questions. Following the same line of study on NO and respiratory system, Jacobs et. al compares the use of inhaled nitric oxide (NO) x oxygen administered to newborns and allows us to state that the findings provide qualified evidence in favor of nitric oxide.

In 2003, A research developed by Paoloni, showed improvements in extensor tendinosis treated with nitric oxide therapy, showing a new look at new therapies. The supply of exogenous topical nitric oxide to the degenerate tendon may replace reduced nitric oxide levels or its synthesizing enzyme, so this application of topical nitric oxide can stimulate fibroblast wounds by increasing collagen synthesis and remodeling. Despite being an innovative work with its satisfactory results, the author raises the importance of rehabilitation and concomitance treatment programs for its success.

From 2005 to 2012 authors Zitt, Dweik and Taylor developed research on exhaled nitric oxide, thus showing the diagnostic and management possibilities of respiratory system pathologies such as asthma. In this case NO assumes an important role, now monitoring, enabling adjustments in therapy. Also in 2012, Levine writes about the link between NO and insulin and how there may be an endothelial dysfunction that is related to the severity of insulin resistance and contributes to its deterioration and may develop into coronary heart disease.

In 2015, Song already talks about the usefulness in screening favoring the patient's clinical process and makes it clear that there may be interference in the measurement of exhaled nitric oxide by factors such as smoking.

CONCLUSIONS

From the above considerations, it can be stated that nitric oxide tends to revolutionize clinical treatments, promoting significant improvements, being more viable even economically, however, it has a high toxic content, requiring rigorous care in its use and application, in order to avoid worsening the condition of patients or even intoxication of professionals.

Given this, the need for further research and testing on the means of application, the purposes and especially the precautions that should be taken is reinforced.

REFERENCES

ADATIA, David L.Wessel. Clinical Applications of Inhaled Nitric Oxide in Children with Pulmonary Hypertension. **Advances in Pharmacology**, v. 34, 1995.

ARTEAGA-TRONCOSO, Gabriel. **Intracervical application of the nitric oxide donor isosorbide dinitrate for induction of cervical ripening**: a randomised controlled trial to determine clinical efficacy and safety prior to first trimester surgical evacuation of retained products of conception/ Gabriel Arteaga-Troncoso, Alejandro Villegas-Alvarado, Aurora Belmont-Gomez, Francisco J. Martinez-Herrera, Roberto Villagrana-Zesati, Fernando Guerra-Infantea. BJOG: an International Journal of Obstetrics and Gynaecology December, v. 112, p. 1615 – 1619, 2005.

BARRETO, Ricardo de L.; CORREIA, Carlos Roque D.; MUSCARÁ, Marcelo N. **Óxido nítrico**: propriedades e potenciais usos terapêuticos. Quím. Nova, v. 28, n° 6, São Paulo, 2005.

BODY, S.C. **Nitric Oxide**: Delivery, Measurement, and Clinical Application/ S. C. Body, P. M. Hartigan, S. K. Shernan, V. Formanek, W. E. Hurford. Journal of Cardiothoracic and Vascular Anesthesia, v. 9, n° 6, 1995.

CARRARO S. Clinical application of nasal nitric oxide measurement/ Carraro S., Cutrone C., Cardarelli C., Zanconato S., Baraldi E. **Int. J. Immunopathol Parmacol**, 2010.

CERQUEIRA, Nereide Freire; YOSHIDA, Winston Bonetti. Óxido Nítrico. Revisão. **Acta Cirúrgica Brasileira**, v. 17, n° 6, 2002.

DWEIK, Raed A. **An Official ATS Clinical Practice Guideline**: Interpretation of Exhaled Nitric Levels (Feno) for Clinical Applications/ Read A. Dweik, Peter B. Boggs, Serpil C. Erzurum, Charles G. Irvin, Margaret W. Leigh, Jon O. Lundberg, Anna-Carin Olin, Alan L. Plummer, D. Robin Taylor. Am J Respir Crit Care Med, v. 184, p. 602 – 6015, 2011.

ÉVORA, Paulo Roberto B. A utilização do óxido nítrico inalado em cirurgia cardíaca: atualização e análise crítica/ Paulo Roberto B. Évora, Fernanda Viaro, Maurício Shigeo Oshiro, Daniel Gonçalves de Souza. **Rev Bras Cir Cardiovasc**, v. 17, n° 3, 2002.

FLORA FILHO, R.; ZILBERSTEIN, B. Óxido nítrico: o simples mensageiro percorrendo a complexidade. Metabolismo, síntese e funções. **Revista Ass Med Brasil**, v. 46, n° 3, 2000.

FROSTELL, Claes G.; ZAPOL, Warren M. Inhaled Nitric Oxide, Clinical Rationale and Applications. **Advances in Pharmacology**, v. 34, 1995.

HAYASHI, Nariyuki. Application of a Novel Technique for Clinical Evaluantion of Nitric Oxide-Induced Free Radical Reactions in ICU Patients/ Nariyuki Hayashi, Akira Utagawa, Kasaku Kinoshita, Toru Izumi. **Cellular and Molecular Neurobiology**, v. 19, n° 1, 1999.

JACOBS, P. A cost-effectiveness analysis of the application of nitric oxide versus oxygen gas for near-term newborns with respiratory failure: Results from a Canadian randomized clinical P. Jacobs; N. N Finner; C. T. M. Robertson; P. Etches; E. M. Hall; L. D. Saunders. **Critical Care Medicine**, v. 28, n° 3, 2000.

KEEFER, Larry K. Progress toward clinical application of the nitric oxide. **Annu. Rev. Pharmacol. Toxicol**, v. 43, n° 585, 2003.

LEVINE, Arlene Bradley; PUNIHAOLE, David; LEVINE, T. Barry. **Characterization of the Role of Nitric Oxide and Its Clinical Applications**. Turning Basic Research into Clinical Success. Cardiology, 2012.

MANNA, Angelo. Clinical Application of Nasal Nitric Oxide Measurement in Pediatric Airway Diseases/ Angelo Manna, Silvia Montella, Mauro Maniscalco, Marco Maglione, Francesca Santamaria. **Pediatric Pulmonology**, 2014.

MANNA, Angelo. Clinical application of exhaled nitric oxide measurement in pediatric lung diseases/ Angelo Manna, Carlo Caffarelli, Margherita Varini, Carlotta Povesi Dascola, Silvia Montella, Marco Maglione, Francesco Sperlì, Francesca Santamaria. **Italian Journal of Pediatrics,** v. 38, n° 74, 2012.

MUPANEMUNDA, R. H. Inhaled nitric oxide: clinical applications. **Current Paediatrics**, v. 5, n° 21, 1995.

OVODOV, Konstantin J.; PEARL, Ronald G. **Nitric Oxide:** Clinical Applications. Seminars in Anesthesia, Perioperative Medicine and Pain, v 19, n° 2, p: 88-97, 2000.

PAOLONI, Justin A. **Topical Nitric Oxide Application in the Treatment of Chronic Extensor Tendinosis at the Elbow**: A Randomized, Double-Blinded, Placebo-Controlled Clinical Trial/ Justin A. Paoloni; Richard C. Appleyard, Janis Nelson, George A. C. Merrell. The American Journal of Sports Medicine, v. 31, n° 6, 2003.

ROMERO, R. **Clinical Application of Nitric Oxide Donors and Blockers**. Perinatology Research Branch NICHD, Wayne State University, Hutzel Hospital, Department of Obstetrics and Gynecology, 4707 St Antoine Boulevard, Detroit, MI 48201, USA. 2016.

ROSSAINT, Rolf. **Inhaled Nitric Oxide for the Adult Respiratory Distress Syndrome**/ Rolf Rossaint, Konrad J. Falke, Frank López, Klaus Slama, Ulrich Pison, Warren M. Zapol. v. 328, n° 6.

SAAVEDRA, Joseph E.; KEEFER, Larry K. **Nitrogen-Based Diazeniumdiolates**: Versatile Nitric Oxide-Releasing Compounds in Biomedical Research and Potential Clinical Applications. Journal of Chemical Education, v. 78, n° 12, 2002.

SONG, Woo-Jung. C**linical Application of Exhaled Nitric Oxide Measurements in a Korean Population**/ Woo-Jung Song, Ji-Won Kwon, Eun-Jin Kim, Sang-Min Lee, Sae-Hoon Kim, So-Yeon Lee, Sang-Heon Kim, Heung-Woo Park, Yoon-Seok Chang, Woo Kyung Kim, Jung Yeon Shim, Ju-Hee Seo, Byoung-Ju Kim, Hyo Bin Kim, Dae Jin Song, Gwang Cheon Jang, An-Soo Jang, Jung-Won Park, Ho-Joo Yoon, Joo-Shil Lee, Sang-Heon Cho, Soo-Jong Hong. Allergy Asthma Immunol Res., v. 7, n° 1, 2015.

ZITT, Myron. **Clinical Applications of Exhaled Nitric Oxide for the Diagnosis and Management of Asthama:** A Consensus Report. Clinical Therapeutics, v. 27, n° 8, 2005.