Review

The Relevance of the Use of NO-therapy in Traumatology and Rehabilitation Medicine

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Abstract: The purpose of this review is to familiarize with the possibilities of using NO-containing gas streams in traumatology and restorative medicine. It reflects the main mechanisms of action of nitric oxide, methods of exogenous delivery of NO and the clinical experience of Russian doctors on the use of NO therapy. The theoretical and clinical data presented in the review substantiate the effectiveness of the use of NO gas streams in injuries and their complications such as scarring processes and chronic osteoarthritis.
Nitric oxide is a gas molecule with a wide range of biological effects - bactericidal, vasodilating, pro- and anti-oxidative, pro- and anti-apoptotic and pro-proliferative. It also has the ability to activate neutrophils and macrophages, potentiate collagen synthesis, which significantly accelerates full-fledged regeneration.

Keywords: NO – therapy, rehabilitation therapy, nitric oxide, NO – containing gas flow.

Citation: Shestakov D.; Igrunkova A.; Kryuchkova, K.; Chekulaev P.; Zaborova, V. The relevance of the use of NO-therapy in traumatology and rehabilitation medicine**.** Journal of Clinical Physiology and Pathology (JISCPP) 2023; 2(2): 30-34.

https://doi.org/10.59315/JISCPP.2023-2-2.30-34

Academic Editor: Igor Kastyro

Received: 13.03.2023
Revised: 27.04.2023
Accepted: 09.05.2023
Published: 30.06.2023

Publisher's Note: International Society for Clinical Physiology and Pathology (ISCPP) stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. Introduction

According to data from (Sheu et al 2016) in the USA annually, in 4.3 million cases, injuries sustained at sports facilities or in places of active recreation required a doctor's consultation, while 3.2 million people repeatedly sought medical help. In approximately 230,000 cases, patients required hospitalization. Thus, athletes and people who lead an active lifestyle make up a fairly large part of the patients of traumatologists and sports doctors [1]. The need for daily training, a long period of rehabilitation, and high risks of post-traumatic complications require doctors to search for new methods of helping this group of patients.

Nitric oxide (NO) is a well–known gaseous molecule that regulates many physiological and pathophysiological processes in the body, which made it possible to single out a separate clinical direction – NO therapy. Currently, exogenous nitric oxide is used in surgery, oncology, dermatology, ophthalmology, otolaryngology and many other specialties (Huerta S., 2015, Shekhter A.B., 2020, Chernysheva M. M., 2018).

Currently, it is known that NO synthases are represented by three isoenzymes that are encoded by different genes, have different localization and are involved in a variety of physiological and pathological processes. Two isoenzymes, endothelial (eNOS) and neuronal (nNOS) are constitutive, they provide continuous formation of low concentrations of NO through cyclic guanosine monophosphate (cGMP) in vascular endothelial cells and neurons, respectively. Inducible NOS (iNOS) is produced only in response to the action of pathogens - lipopolysaccharides and proinflammatory cytokines (for example, interferon, INF-α, tumor necrosis factor (TNF)), etc.), which are generated by neutrophils and macrophages in response to damage [4, 5]. In the wound and in inflammatory processes, NO levels increase in the first hours after injury and reach a peak on day 2 [3, 6–9]. It is known that NO derivatives can play an anti-inflammatory role (Feelisch M., 2008, Hsu C. C. et al., 2017). Nitric oxide has direct and indirect effects, which is determined by its concentrations in tissues [2, 10, 11].

The main causes of nitric oxide deficiency in wounds are hyperglycemia, insufficiency of the synthetic cell system, weak or excessive exogenous stimulation of immune system cells, which is accompanied by impaired function of chemokines and cytokines necessary for leukocyte and macrophage migration, synthesis of regenerative factors, angiogenesis and fibroblast activation [12-14]. In view of this, the study of exogenous ways to increase the concentration of NO in wounds is an effective and promising direction in medicine.

The purpose of this review is to analyze the works devoted to the problem of treatment of traumatic injuries, including those related to sports with the help of exogenous NO.

2. Experience

Experience of practical application of exogenous NO-therapy for injuries:

The use of NO-therapy has already been studied in patients with moderate to severe rheumatoid arthritis (n =76), in whom traditional treatment was insufficiently ineffective. The course of therapy using the plasma-chemical device "Plason", which generates high concentrations of nitric oxide (500 ppm), included 10-12 daily procedures, for 5-8 minutes for each affected joint. The treatment was carried out through intact skin. Most patients repeated the same course after 3-4 months. As a result, patients noted the complete disappearance of pain, edema, hyperemia, restoration of joint mobility after 5-8 procedures, laboratory parameters normalized in the same time period. The patients did not take anti-rheumatic drugs, they had no relapses a year after treatment. link.

The use of Plason in the same regimen was also successful in 83% of patients with various forms of osteoarthritis with synovitis of the knee, shoulder and hip joints. Patients (n = 43) noted a decrease in the severity of edema after 2-3 procedures and pain after 3-5 procedures. Joint mobility improved after 4-10 procedures. The positive effect persisted for a year after treatment, which made it possible to reduce the dose of drugs (Vasilets V. N. et al., 2015).

The technique was used in both football players with bruises (n = 19) and track and field runners with tendovaginitis (n = 12). Before that, athletes received traditional physiotherapy procedures for 2-6 weeks, but they did not always have a pronounced positive effect. Blowing of the NO-CGF grass area (containing gas flow) was carried out for 10 seconds per 1 cm2. The course of therapy was 6-8 days. As a result, pain intensity decreased statistically significantly after the first session. After the fourth session, the athletes were able to start full-fledged training [61].

NO-therapy was performed in patients with injuries and inflammatory changes in the ligaments and tendons of the knee and shoulder joints, feet, menisci of the knee joint; muscles of the lower leg, hips and shoulders. NO-CGF (containing gas flow) was used in the maximum mode, for 10-15 seconds per 1 cm2 of the affected area. The course of therapy included 8-12 sessions. Significant pain relief during movement and reduction of edema was observed after 2-3 sessions. After 4-6 sessions of NO-therapy, the range of motion in the joints was restored and athletes could resume training [66].

In patients with injuries to the tendons of the hand with an open fracture of the clavicle, an open fracture of the mandible, intraoperative tissue treatment with a Plason apparatus was performed in the mode of coagulation and stimulation. In the early postoperative period, the NO-therapy regimen was used. As a result, patients noted a decrease in soft tissue edema in the area of surgery and a decrease in the intensity of pain syndrome. The use of NO-CGF for wound treatment after removal of metal structures (8 patients) allowed to reduce the number of hematomas and seromas in the postoperative period [65].

NO-therapy was performed intraoperatively for 1-3 minutes with plastic surgery of the tendons of the hand (3 cases) and tendon transplantation from the forearm (2 cases). In the postoperative period, the Plason device was used in the mode of stimulation and NO-therapy for 2-3 minutes daily. As a result, in all cases, wound healing occurred by primary tension, the severity of edema and pain syndrome was moderate [46].

3. Discussion

The use of NO-therapy has shown its effectiveness in traumatological patients, including those with various forms of osteoarthritis, as well as patients with rheumatoid arthritis. At the same time, these nosologies have a high social significance, since they often occur in young patients, especially in athletes, which is manifested by pain, functional disorders and a decrease in physical activity. However, the role of nitric oxide in these diseases is not fully defined. At the cellular level, the manifestations of posttraumatic osteoarthritis are characterized by apoptosis of chondrocytes and osteoblasts, the release of a large number of pro-inflammatory mediators (IL-1, IL-6, TNF-I and others), changes in the extracellular matrix (decrease in glycosaminglycans, collagen, increased activity of matrix metalloproteinases) (Punzi L. et al., 2016, Sward P. et al., 2013, Golovach I. Yu., & Egudina E. D., 2019).

It is known that in the acute phase of the inflammatory process, surface zone chondrocytes actively express an enzyme involved in the synthesis of NO–inducible NO-synthase (iNOS). iNOS formation is also induced by mechanical and biochemical factors, including inflammatory mediators such as IL-1α and TNF-Ɉ. NF-κβ (Vuolteenaho K. et al., 2007). At the same time, specific inhibition of iNOS and nitric oxide synthesis reduces the intensity of catabolic processes implemented by IL-1a, matrix metalloproteinases and peroxynitrite.

At the same time, NO derivatives can play an anti-inflammatory role and, according to some authors, do not matter in the progression of joint lesions (Feelisch M., 2008, Hsu C. C. et al., 2017). In particular, the introduction of exogenous nitric oxide or activation of iNOS contributed to the synthesis of collagen types I and II, an increase in proteoglycans in tissues (Xia W. et al., 2004, Shi H.P. et al., 2007, Abramson S., 2008).

Moreover, in most studies on the role of nitric oxide in the pathogenesis of osteoarthritis, we are talking about the primary etiology of the disease, and not about post-traumatic (Studer R. et al., 1999, Vuolteenaho K. et al., 2007, Leonidou A. et al., 2018). Studies on the effect of NO-containing gas flow to stimulate the regeneration of articular cartilage in post-traumatic osteoarthritis have not yet been conducted. It would be interesting to study the functional activity of joints before and after treatment with NO-containing gas streams (including long-term results of articular cartilage regeneration in an experiment) in experimental modeling of post-traumatic osteoarthritis. In addition, conducting a comprehensive morphological, morphometric and immunohistochemical study will allow us to study the possibilities of reducing inflammation and stimulating the regeneration of articular cartilage with NO-therapy, as well as to justify the effectiveness of NO-therapy in the treatment of knee joint and periarticular injuries.

The study of functional and subjective changes in the state, as well as the dynamics of interleukin levels IL-1, IL-6, IL-8, IL-10, C-reactive protein in patients with posttraumatic osteoarthritis before and after nitric oxide therapy can contribute to the development of practical recommendations for the use of nitric oxide in traumatology and rehabilitation medicine.

5. Conclusions

According to the literature, NO has a wide range of biological effects and can promote tissue regeneration in a short time. NO-therapy has found its application for the treatment of various pathological conditions and diseases. However, the possibility of using NO-therapy in restorative medicine is an urgent, but extremely poorly studied problem that requires comprehensive studies to determine the leading mechanisms of action of nitric oxide, optimal therapy regimens, and to determine indications and contraindications for its use.

Author Contributions: Conceptualization, V.Z.; methodology, software, D.S.; validation, formal analysis, K.K.; investigation, P.C.; resources, data curation, A.I.; writing—original draft preparation, K.K. and A.I.; writing—review and editing, D.S.; visualization, supervision, V.Z.; project administration, A.I. All authors have read and agreed to the published version of the manuscript."

Funding: This study was not supported by any external sources of funding.

Informed Consent Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Ethics Committee of Sechenov University (protocol number 05-19 dated 25 November 2019).

Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest: The authors declare no conflict of interest.

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