

## PAIN LITERATURE

J Pain. 2008 Oct 29. [Epub ahead of print]

### **A Prolonged Nitric Oxide-Dependent, Opioid-Mediated Antinociceptive Effect of Hyperbaric Oxygen in Mice.**

**Zelinski LM, Ohgami Y, Chung E, Shirachi DY, Quock RM.**

**Hyperbaric oxygen (HBO(2)) therapy is reported to cause pain relief in several conditions of chronic pain.**

A single 60-minute session of HBO(2) treatment produced a prolonged antinociceptive effect in mice that persisted for 90 minutes after cessation of treatment. The HBO(2)-induced antinociception was significantly attenuated by pretreatment before HBO(2) exposure with the opioid antagonist naltrexone, the nonspecific nitric oxide synthase (NOS)-inhibitor N(G)-nitro-L-arginine methyl ester (L-NAME), and the selective neuronal NOS-inhibitor S-methyl-L-thiocitrulline (SMTC) but not the selective endothelial NOS-inhibitor N(5)-(1-iminoethyl)-L-ornithine (L-NIO). The antinociception was also significantly reduced by central pretreatment with a rabbit antiserum against dynorphin(1-13) but not by rabbit antisera against either beta-endorphin or methionine-enkephalin. The prolonged antinociceptive effect at 90 minutes after HBO(2)-induced treatment was also significantly attenuated by naltrexone but not L-NAME administered 60 minutes after HBO(2) treatment but before nociceptive testing. These findings indicate that the antinociception that persists for 90 minutes after HBO(2) exposure is mediated by nitric oxide (NO) and opioid mechanisms but that the NO involvement is critical during the HBO(2) treatment and not at the time of nociceptive testing. **These results are consistent with the concept that HBO(2) may induce an NO-dependent release of opioid peptide to cause a long-acting antinociceptive effect. PERSPECTIVE: This article presents evidence of a persistent antinociceptive effect of hyperbaric oxygen treatment that is mediated by opioid and NO mechanisms. Further elucidation of the underlying mechanism could identify molecular targets to cause a longer-acting activation of endogenous pain-modulating systems.**

Curr Pain Headache Rep. 2006 Apr;10(2):95-100.

### **Hyperbaric oxygen therapy in chronic pain management.**

**Yildiz S, Uzun G, Kiralp MZ.**

Chronic pain is one of the frequently encountered clinical problems that is difficult to cure. **Hyperbaric oxygen (HBO) therapy has been reported in chronic pain syndromes with promising results. In this review, we focus on the effectiveness of HBO in fibromyalgia syndrome, complex regional pain syndrome, myofascial pain syndrome, migraine, and cluster headaches. HBO may be beneficial if appropriate patients are selected.** HBO is a reliable method of treatment. However, physicians performing HBO must be aware of oxygen toxicity. Another problem regarding HBO is the scarcity of centers administering it. Further research is required focusing on the optimal treatment protocol, the cost/benefit ratio, and the safety of HBO in chronic pain management.

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Pain Physician. 2005 Apr;8(2):157-61.

### **Effects of hyperbaric oxygen on skin blood flow and tissue morphology following sciatic nerve constriction.**

**Mychaskiw G 2nd, Pan J, Shah S, Zubkov A, Clower B, Badr A, Zhang JH.**

**BACKGROUND:** Constriction of the sciatic nerve by loose ligation produces an inflammatory neuropathic injury. This represents an animal model for peripheral mononeuropathy. Oxygen-derived free radicals are suspected to play an important role in the pathogenesis of ischemia/reperfusion injury, leading to neurogenic inflammation. Hyperbaric oxygen (HBO) has been used anecdotally to treat clinically similar conditions in humans, but specific effects on the animal model have not been well studied.

**OBJECTIVE:** This study in a rat model examined the effects of hyperbaric oxygen on skin blood flow and tissue morphology by light and electron microscopy following sciatic nerve constriction. **DESIGN:** A scientific investigation in a rat model. **METHODS:** In this study, the neuropathic injury was established by loose ligation of the rat sciatic nerve. The animals were divided into three groups, sham (S, n=8), ligation but no treatment (LN, n=8) and ligation and treatment with hyperbaric oxygen (LT, n=8). The treatment group (n=8) received hyperbaric oxygen treatment immediately following the injury and daily for four additional days at the same time interval. One hundred percent O<sub>2</sub> at 3 atmospheres absolute pressure (66 feet sea water) was administered for two hours. The hindpaws of the rats were observed by light microscopy, electron microscopy, laser Doppler flowmetry (LDF), and clinically for the presence of edema. **RESULTS:** Untreated animals demonstrated marked tissue edema following sciatic constriction, whereas animals that received hyperbaric oxygen had minimal to no edema. The sham group demonstrated normal histology. The group not treated with hyperbaric oxygen demonstrated swollen mitochondria (2-3 times), with loss of cellular integrity, multiple vacuole formation in both nerve and muscle tissue, widened sarcomeres in muscle, and degenerative changes in the nerve myelin sheaths. The group treated with hyperbaric oxygen demonstrated preservation of cellular structure including mitochondrial integrity, no vacuole formation, and maintenance of normal, easily identifiable nerve structure. The sham group had no change of skin blood flow. Skin blood flow of LT group was decreased immediately after ligation (p<0.05) and recovered to baseline level before ligation on Day 5 after four hyperbaric oxygen treatments. Skin blood flow of LN group was decreased immediately after ligation (p<0.01) and did not recover (p<0.01). **CONCLUSION:** This study evaluated tissue changes after nerve injury caused by loose ligation of the sciatic nerve in rats. Hyperbaric oxygen treatment following sciatic nerve injury reduced tissue edema, improved skin blood flow, and preserved muscle and neuronal ultrastructural integrity.

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J Int Med Res. 2004 May-Jun;32(3):263-7.

**A new treatment modality for fibromyalgia syndrome: hyperbaric oxygen therapy.**

**Yildiz S, Kiralp MZ, Akin A, Keskin I, Ay H, Dursun H, Cimsit M.**

Fibromyalgia syndrome (FMS) is characterized by longstanding multifocal pain with generalized allodynia/hyperalgesia. There are several treatment methods but none has been specifically approved for this application. We conducted a randomized controlled study to evaluate the effect of hyperbaric oxygen (HBO) therapy in FMS (HBO group: n = 26; control group: n = 24). Tender points and pain threshold were assessed before, and after the first and fifteenth sessions of therapy. Pain was also scored on a visual analogue scale (VAS). There was a significant reduction in tender points and VAS scores and a significant increase in pain threshold of the HBO group after the first and fifteenth therapy sessions. There was also a significant difference between the HBO and control groups for all parameters except the VAS scores after the first session. We conclude that HBO therapy has an important role in managing FMS.

J Int Med Res. 2004 May-Jun;32(3):258-62.

**Effectiveness of hyperbaric oxygen therapy in the treatment of complex regional pain syndrome.**

**Kiralp MZ, Yildiz S, Vural D, Keskin I, Ay H, Dursun H.**

In this double-blind, randomized, placebo-controlled study we aimed to assess the effectiveness of hyperbaric oxygen (HBO) therapy for treating patients with complex regional pain syndrome (CRPS). Of the 71 patients, 37 were allocated to the HBO group and 34 to the control (normal air) group. Both groups received 15 therapy sessions in a hyperbaric chamber. Pain, oedema and range of motion (ROM) of the wrist were evaluated before treatment, after the 15th treatment session and on day 45. In the HBO group there was a significant decrease in pain and oedema and a significant increase in the ROM of the wrist. When we compared the two groups, the HBO group had significantly better results with the exception of wrist extension. In conclusion, HBO is an effective and well-tolerated method for decreasing pain and oedema and increasing the ROM in patients with CRPS.

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J Trauma. 1996 Aug;41(2):333-9.

### **Hyperbaric oxygen therapy in the management of crush injuries: a randomized double-blind placebo-controlled clinical trial.**

**Bouachour G, Cronier P, Gouello JP, Toulemonde JL, Talha A, Alquier P.**

Hyperbaric Oxygen (HBO) therapy is advocated for the treatment of severe trauma of the limbs in association with surgery because of its effects on peripheral oxygen transport, muscular ischemic necrosis, compartment syndrome, and infection prevention. However, no controlled human trial had been performed until now to specify the role of HBO in the management of crush injuries. Thirty-six patients with crush injuries were assigned in a blinded randomized fashion, within 24 hours after surgery, to treatment with HBO (session of 100% O<sub>2</sub> at 2.5 atmosphere absolute (ata) for 90 minutes, twice daily, over 6 days) or placebo (session of 21% O<sub>2</sub> at 1.1 ata for 90 minutes, twice daily, over 6 days). All the patients received the same standard therapies (anticoagulant, antibiotics, wound dressings).

Transcutaneous oxygen pressure (PtCO<sub>2</sub>) measurements were done before (patient breathing normal air) and during treatment (HBO or placebo) at the first, fourth, eighth, and twelfth sessions. The two groups (HBO group, n = 18; placebo group, n = 18) were similar in terms of age; risk factors; number, type or location of vascular injuries, neurologic injuries, or fractures; and type, location, or timing of surgical procedures. Complete healing was obtained for 17 patients in the HBO group vs. 10 patients in the placebo group (p < 0.01). New surgical procedures (such as skin flaps and grafts, vascular surgery, or even amputation) were performed on one patient in the HBO group vs. six patients in the placebo group (p < 0.05). Analysis of groups of patients matched for age and severity of injury showed that in the subgroup of patients older than 40 with grade III soft-tissue injury, wound healing was obtained for seven patients (87.5%) in the HBO group vs. three patients (30%) in the placebo group (p < 0.05). No significant differences were found in the length of hospital stay and number of wound dressings between groups. For the patients with complete healing, the PtCO<sub>2</sub> values of the traumatized limb, measured in normal air, rose significantly between the first and the twelfth sessions (p < 0.001). No significant change in PtCO<sub>2</sub> value was found for the patients whose healing failed. The Bilateral Perfusion Index (BPI = PtCO<sub>2</sub> of the injured limb/PtCO<sub>2</sub> of the uninjured limb) at the first session increased significantly from 1 ata air to 2.5 ata O<sub>2</sub> (p < 0.05). In patients with complete healing, the BPI was constantly greater than 0.9 to 2.5 ata O<sub>2</sub> during the following sessions, whereas the BPI in air progressively rose between the first and the twelfth sessions (p < 0.05), reaching normal values at the end of the treatment. In conclusion, this study shows the effectiveness of HBO in improving wound healing and reducing repetitive surgery. **We believe that HBO is a useful adjunct in the management of severe (grade III) crush injuries of the limbs in patients more than 40 years old.**