

1-1-2012

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YALÇIN ÖNEM

VEDAT TURHAN

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Recommended Citation

ÖNEM, YALÇIN and TURHAN, VEDAT (2012) "Comments on: In vitro efficacy of hyperbaric oxygen therapy against *Leishmania tropica* promastigotes and amastigotes," *Turkish Journal of Medical Sciences*: Vol. 42: No. 7, Article 30. <https://doi.org/10.3906/sag-1205-74>
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Comments on: “In vitro efficacy of hyperbaric oxygen therapy against *Leishmania tropica* promastigotes and amastigotes”

Yalçın ÖNEM¹, Vedat TURHAN²

We read with great interest the paper by Koru et al. (1), in which in vitro efficacy of hyperbaric oxygen (HBO) therapy against *Leishmania tropica* promastigotes and amastigotes was investigated. We applaud their efforts to seek new treatments for leishmaniasis, which is an important health problem in Turkey. However, we have some concerns regarding the clinical usability of HBO therapy in the treatment of leishmaniasis.

Due to its antiinfective properties, HBO therapy is frequently used in the treatment of certain infectious diseases (gas gangrene, necrotizing fasciitis, diabetic foot infections, etc.) and its effectiveness has also been investigated in several other indications such as fungal and parasitic infections (2). In their study, Koru et al. exposed *L. tropica* promastigotes and amastigotes in culture dishes to 3 different HBO therapy protocols of 2 h, 4 h, and 6 h. The dose of HBO therapy is determined by 2 measures, the duration and the pressure of the treatment. Due to pulmonary and neurologic toxicity of HBO therapy, the highest operating pressure is 2.8 ATA and the duration of oxygen breathing periods does not exceed 2 h. From this perspective, only the 2-h HBO protocol in the study of Koru et al. was clinically relevant and the 4-h and 6-h HBO protocols are not applicable to humans due to the risk of oxygen toxicity. When we look at the data from the 2-h HBO experiments, we see that HBO therapy for 2 h did not affect motility and viability of *L. tropica* promastigotes (Figure 1 in the paper of Koru et al.). Moreover, in contrast to 4-h and 6-h HBO protocols, HBO therapy for 2 h did not show significant cytotoxicity on *L. tropica* promastigotes (Figure 3 in the paper of Koru et al.) and *L. tropica* amastigotes (Figure 5 in the paper of Koru et al.). Additionally, despite the fact that HBO therapy for 2 h reduced growth of *L. tropica* promastigotes, it did not reach statistical significance, as shown in Figure 4 in the paper of Koru et al.

On the other hand, the partial pressure of oxygen in human tissues during HBO therapy will never reach the same level of that in the culture dishes. As Koru et al. have shown, the beneficial effects of HBO therapy are related to reactive oxygen species and free radicals, and the amount of oxidative products produced by HBO therapy is directly proportional to the partial pressure of oxygen. Therefore, the efficacy of HBO therapy against *L. tropica* promastigotes and amastigotes will be lower in human tissues compared to that in culture dishes.

We think that the efficacy of HBO therapy at 2.5 ATA for 2 h against *L. tropica* promastigotes and amastigotes is limited. However, combination of HBO therapy with antimicrobial drugs may be an alternative approach (3). As recommend by Koru et al., we think that future studies should investigate the efficacy of the combination of HBO therapy and antiparasitic drugs, which reduce the levels of antioxidant enzymes in parasites.

Received: 19.05.2012 – Accepted: 15.06.2012

¹ Department of Internal Medicine, Gülhane Military Medical Academy Haydarpaşa Teaching Hospital, 34668 İstanbul – TURKEY

² Department of Infectious Disease and Clinical Microbiology, Gülhane Military Medical Academy Haydarpaşa Teaching Hospital, 34668 İstanbul – TURKEY

Correspondence: Yalçın ÖNEM, Department of Internal Medicine, Gülhane Military Medical Academy Haydarpaşa Teaching Hospital, 34668 İstanbul – TURKEY
E-mail: nemya90@gmail.com

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Author's Response

Özgür KORU, Soykan ÖZKOÇ, Kemal ŞİMŞEK, Gürkan MERT, Hakan AY, Seray TÖZ, Mehmet TANYÜKSEL

We would like to thank to Önem and Turhan for their comments. In our in vitro study, we assessed the effective dose and duration of hyperbaric oxygen (HBO) application that could be tolerated by humans on *Leishmania tropica* promastigote and amastigote forms and detected the cytotoxic effect of HBO, which began 2 h after treatment and reached a maximum level after 6 h in treated groups. Promastigotes that are in the infective stage, injected by sandflies, transform in macrophages and other types of mononuclear phagocytic cells into the tissue stage of the parasite (1). Therefore, only amastigote forms are found in human tissues and HBO's effect on promastigote forms has to be examined in vitro. Thus, "the efficacy of HBO therapy against *L. tropica* promastigotes and amastigotes will be lower in human tissues compared to that in culture dishes" is not an accurate phrase in the letter of Önem and Turhan. Most HBO treatments, including those for wound healing, last about 2 h. Treatments for acute indications, such as carbon monoxide poisoning, gas gangrene, and ischemic and traumatic crush injuries,

may last as long as 4 h, and under rare circumstances, some diving injuries may require treatment even longer than 8 h (2). Pulmonary oxygen toxicity is a very rare complication that can occur with cumulative effects in long-lasting sessions (60–80 sessions) and can improve rapidly when the exposure is terminated (3). Therefore, the comments of Önem and Turhan about HBO treatment protocol are inaccurate.

The obligate intracellular parasite *Leishmania* has developed numerous highly successful strategies for preventing activation of effective antimicrobial agents such as nitric oxide, oxygen radical generation, and cytokine production. HBO increases generation of reactive oxygen species and free radicals and inhibits the antioxidant defense mechanisms of *Leishmania* spp. (4). We believe that HBO can be effective for treatment of leishmaniasis with enhanced effects of antileishmanial drugs. Further in vivo and in vitro studies are needed for its more reliable use along with chemotherapy in the treatment of patients, as emphasized by Önem and Turhan.

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