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Hyperbaric Oxygen Treatment Is Comparable to Acetylsalicylic Acid Treatment in an Animal Model of Arthritis

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Abstract: Approximately 1 in 5 adults in the United States are affected by the pain, disability, and decreased quality of life associated with arthritis. The primary focus of treatment is on reducing joint inflammation and pain through a variety of pharmacotherapies, each of which is associated with various side effects. Hyperbaric oxygen therapy is an alternative treatment that has been recommended to treat a variety of inflammatory diseases, ranging from chronic brain injury to exercise induced muscle soreness. The purpose of this set of experiments was to explore the effect of hyperbaric oxygen therapy on joint inflammation and mechanical hyperalgesia in an animal model of arthritis, and compare these effects to treatment with aspirin. Hyperbaric oxygen therapy significantly reduced both joint inflammation and hyperalgesia. As compared with aspirin treatment, hyperbaric treatment was equally as effective in decreasing joint inflammation and hyperalgesia.

***Perspective:** This article reports that hyperbaric oxygen treatment decreases pain and inflammation in an animal model of arthritis. The effect of hyperbaric oxygen treatment is very similar in magnitude to the effect of acetylsalicylic acid treatment. Potentially, hyperbaric oxygen could be used to treat pain and inflammation in patients with arthritis.*

***Key words:** Analgesia, antinociception, carrageenan, inflammation, nociception, arthritis.*

Arthritis, literally meaning "inflammation of the joint," encompasses over 100 rheumatic diagnoses, with osteoarthritis and rheumatoid arthritis being the most prevalent. Currently, approximately 1 in 5 adults in the United States are clinically diagnosed with some form of arthritis.[11] With the growing aging population in the United States, the number of patients suffering from arthritis is expected to increase from approximately 46 million in 2005 to 65 million in 2030.[8] Pain from arthritis may lead to job loss, sick days, decreased quality of life, and permanent disability. Of the 46 million patients that are affected by arthritis in 2006, approximately 7% report a limit in their daily activity due to arthritic pain.[11]

In general, treatment for arthritis is focused on symptom management. Typically pain and inflammation are treated with nonsteroidal anti-inflammatory drugs (NSAIDS) and corticosteroids, which provide limited pain relief and can have deleterious long-term side effects.[13] The most common complications involve nausea, vomiting, diarrhea, and stomach ulcers. In addition to the well-documented gastrointestinal side effects, nonsteroidal anti-inflammatory drugs are also associated with increased risk for high blood pressure and acute urinary retention.[16,19] The risk for serious complications goes up with age, frequency of use, and strength of dose, making long term chronic pain patients more likely to have these injurious side effects. Novel therapies are needed for patients where NSAIDS are ineffective or are contraindicated.

Hyperbaric oxygen treatment (HBO) is an innovative therapy that involves administering 100% oxygen at a pressure greater than atmospheric pressure at sea level.[6] The combination of increased pressure and oxygen allows the blood to transport more oxygen to tissue by dissolving it in the plasma. The treatment leads to new vascular growth, vasoconstriction and hyperoxygenation, making it an effective therapy for a variety of ailments including delayed onset muscle soreness,[1,4] fi-

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bromyalgia,[20] complex regional pain syndrome,[7] and chronic brain injury.[5]

Hyperbaric oxygen therapy has demonstrated efficacy in decreasing edema and hyperalgesia in inflammatory conditions.[5,15,18] The beneficial effects of hyperbaric oxygen therapy on inflammation make it an attractive treatment option for patients with chronic arthritis. Despite these indications for benefit, relatively few researchers have explored the effects of hyperbaric oxygen treatment on arthritis, and those that have provide mixed results.[2,9,12,14,17] Additional research is needed to explore the effects of HBO on hyperalgesia and inflammation.

Therefore, the primary purpose of this set of experiments is to explore the efficacy of HBO on decreasing inflammation and altering mechanical sensation in an animal model of arthritis. Experiment 1 compares mechanical hypersensitivity and joint diameter in animals that receive hyperbaric oxygen treatment or sham treatment. In an effort to compare the magnitude of the effect of HBO to current treatments, a separate study was conducted to evaluate the effect of aspirin on the animal model of arthritis used in experiment 1. Experiment 2 compares mechanical paw withdrawal thresholds (MPWT) and joint diameter in animals that receive aspirin or saline injection.

Materials and Methods

Ninety-two male Sprague-Dawley rats (Harlan, Indianapolis, IN) between 60 and 90 days old were used for this set of experiments. The arthritic condition was induced via a 0.12 mL intra-articular injection of 2% carrageenan (Sigma-Aldrich, St. Louis, MO) suspended in saline in the left knee joint.

Paw diameter was measured utilizing Vernier calipers. Percentage differences were calculated based on post-treatment differences as compared with pretreatment measures. Hyperalgesia was assessed using the up/down method[3] of MPWT with 8 von Frey monofilaments (4, 6, 10, 18, 40, 78, 141, and 217 mN). Each trial began with the 1 second application of a 10 mN von Frey, and if no response was detected then the next highest force was applied. If there was a withdrawal response, then the next lowest force was applied. This procedure was repeated until either no response was made at the highest force, or there had been 4 von Frey stimuli applied after the initial response. Withdrawal thresholds were calculated using the following formula: $[Xth]\log = [vFr]\log + ky$, where [vFr] is the force of the last von Frey used, $k = 0.2487$, which is the average interval (in log units) between the von Frey monofilaments, and y is the value that depends upon the pattern of withdrawal responses. Three MPWT trials were conducted, and the scores were averaged across trials to determine mean left and right paw values for each animal.

Hyperbaric oxygen treatment involved exposing animals to 100% oxygen at a pressure of 2.4 atmospheres absolute (ATA) for 90 minutes in a hyperbaric chamber. A control group was placed in the hyperbaric chamber but did not receive treatment. Aspirin treatment involved an intraperitoneal injection of a 15 mg/mL solution in a volume of 10 mL/kg. Control animals were intraperitoneally administered a 10 mL/kg dose of saline. The behavioral experimenter was blind to treatment condition in both experiments. Approval was obtained from the University of Texas at Arlington Institutional Animal Care and Use Committee, and all animals were treated in accordance with the guidelines set forth by the International Association for the Study of Pain.[21]

Baseline threshold values and volume measures were taken on the morning before treatment, and animals received intra-articular injection that evening. Pretreatment mechanical paw withdrawal threshold and paw diameter measurement were performed the morning after injection, between 15 to 16 hours after the injection. To ensure effective induction of inflammatory condition, only animals with a 10% difference in paw diameter and 25% difference in mechanical paw withdrawal threshold between preinjection and pretreatment measures were included in the study. Based on these criteria, a total of 32 animals in experiment 1 and 12 animals in experiment 2 were dropped before treatment. Immediately after completion of the pretreatment measures animals were placed in the chamber for hyperbaric oxygen or sham treatment (experiment 1), or received aspirin or saline injection (experiment 2). Paw diameter and mechanical paw withdrawal thresholds were measured immediately after treatment and every hour for a total of 5 hours after treatment. Percent difference scores were calculated for paw diameter based on change from pretreatment. The results were analyzed utilizing Statistica 6 for Windows TM (StatSoft, Tulsa, OK). Significance was set at $P < .05$, and Fisher LSD post hoc tests conducted where indicated. Experiment 1 and experiment 2 were not run concurrently, and were executed by different experimenters. Analytic comparisons were first conducted among control and experimental animals within each experiment. A second set of analyses were performed in an effort to compare the efficacy of hyperbaric treatment to aspirin treatment. For this set of analyses the control groups for each experiment were combined (sham treated and saline injected animals), and analytic comparisons among the combined control group and the hyperbaric and aspirin treated animals were conducted.

Results

Experiment 1

Paw diameter results are presented in Fig 1a. One-way analysis of variances (ANOVAS) revealed no significant preinjection group differences ($F_{1,22} = 0.03$, $P = .87$) or pretreatment group differences ($F_{1,22} = 0.66$, $P = .43$). An overall mixed design analysis (group $\times$ time) with 2 levels of group (hyperbaric-treated, sham-treated) and 6 levels of time (post-treatment time 0 to post-treatment measure 5) revealed a significant main effect for group ($F_{1,22} = 8.18$, $P < .01$) and time ($F_{5,110} = 3.37$, $P < .01$). No significant interaction was detected ($F_{5,110} = 1.35$, $P = .25$).

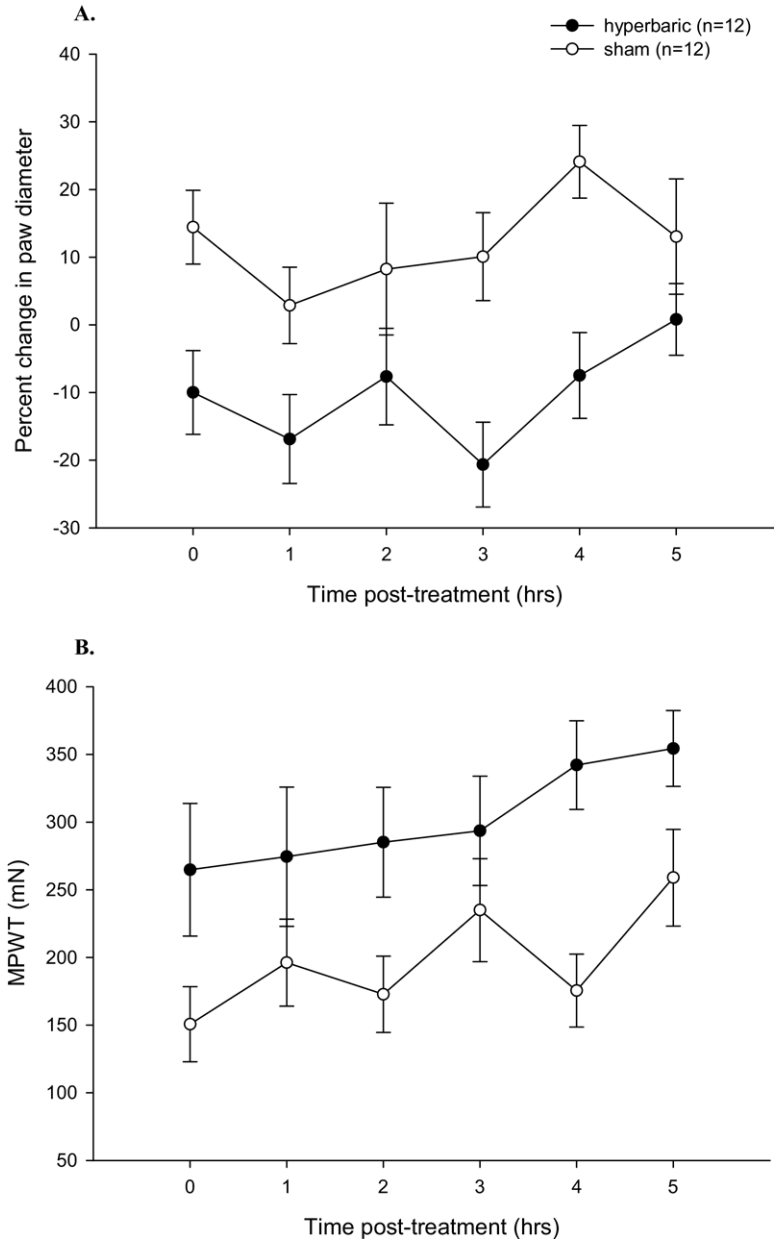

Figure 1. A, Mean (±SEM) percent change of paw diameter after intra-articular injection of carrageenan in hyperbaric oxygen or sham-treated animals. Sham-treated animals had significantly more inflammation as compared with hyperbaric-treated animals. **B,** Mean (±SEM) mechanical paw withdrawal threshold after intra-articular injection of carrageenan for hyperbaric oxygen or sham-treated animals. Mechanical paw withdrawal threshold measurements were performed immediately after treatment (time 0) and at 1-hour intervals up to 5 hours after treatment, and then averaged within groups. Hyperbaric-treated animals were significantly less hyperalgesic than sham-treated animals.

Hyperbaric-treated animals had overall smaller paw diameter than sham-treated animals.

Mechanical paw withdrawal results are presented in Fig 1b. One-way ANOVAs revealed no significant preinjection group differences ($F_{1,2} = 0.10$, $P = .75$) or pretreatment group differences ($F_{1,22} = 0.05$, $P = .83$). An overall mixed design analysis (group × time) with 2 levels of group (treatment, sham) and 6 levels of time (pretreatment to post-treatment measure 5) revealed a significant main effect for condition ($F_{1,22} = 7.10$, $P < .05$) and a main effect for time ($F_{5,110} = 3.26$, $P < .01$). No significant interaction was detected ($F_{5,110} = 0.96$, $Pp = .44$). Hyperbaric oxygen–treated animals had an overall decrease in mechanical hypersensitivity as compared with sham-treated animals.

Experiment 2

Paw diameter results are presented in Fig 2a. One-way ANOVAs revealed no significant preinjection group differences ($F_{1,20} = 1.31$, $P = .27$) or pretreatment group differences ($F_{1,20} = 0.14$, $P = .71$). An overall mixed design analysis (group × time) with 2 levels of group (aspi-

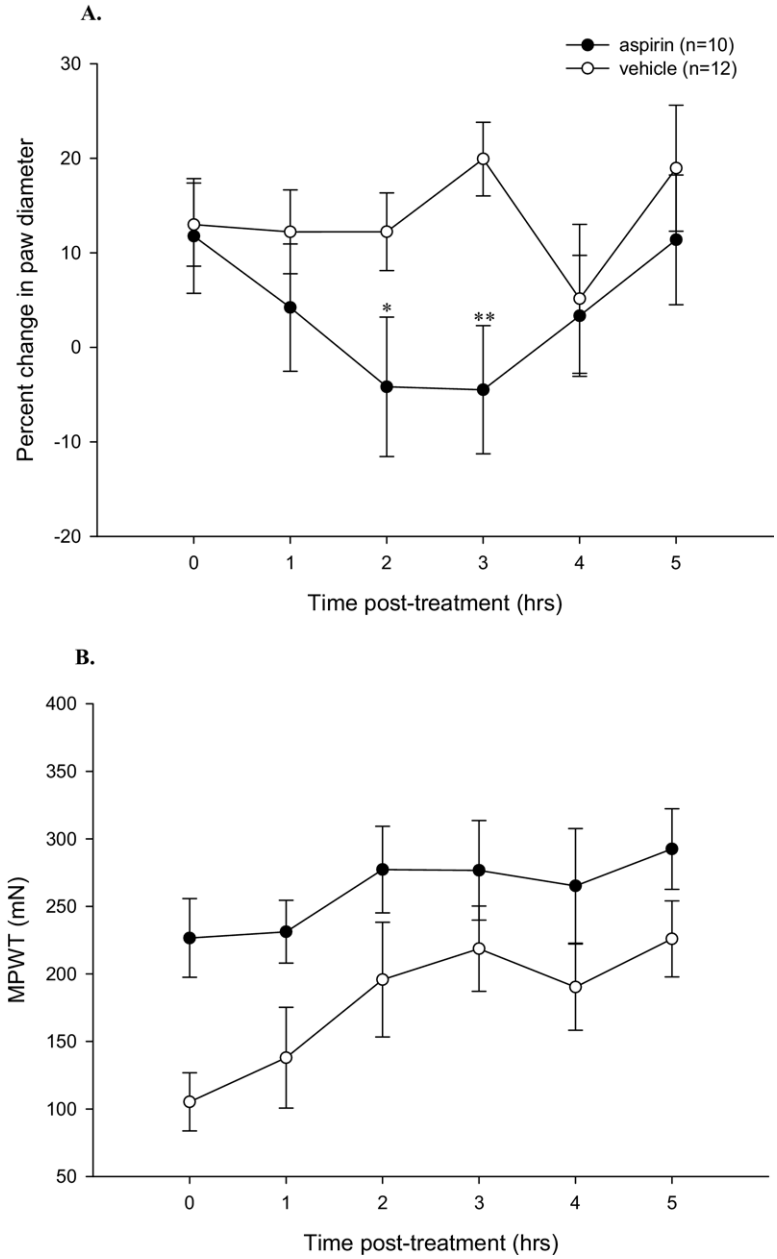

Figure 2. A, Mean (±SEM) percent change of paw diameter after intra-articular injection of carrageenan in aspirin or saline-injected animals. Aspirin-injected animals were significantly different at time point 2 and 3 as compared with vehicle-injected animals (*$P <$ .01, **$P <$ .001). **B,** Mean (±SEM) mechanical paw withdrawal threshold after intra-articular injection of carrageenan for aspirin and saline-injected animals. Mechanical paw withdrawal threshold measurements were performed immediately after treatment (time 0) and at 1-hour intervals up to 5 hours aftertreatment and then averaged across time. Aspirin-treated animals were significantly less hyperalgesic compared with saline-injected control animals.

rin-injected, saline-injected) and 6 levels of time (post-treatment time 0 to post-treatment measure 5) revealed no main effect for group ($F_{1,20} = 2.23$, $P = .15$) or time ($F_{1,20} = 2.26$, $P = .05$); however a significant group by time interaction ($F_{1,20} = 2.31$, $P < .05$) was detected. Post hoc tests indicated that aspirin-treated animals had significantly less inflammation compared with vehicle-injected animals at 2 and at 3 hours after treatment.

Mechanical paw withdrawal results are presented in Fig 2b. One-way ANOVAs revealed no significant pre-injection group differences ($F_{1,20} = 0.78$, $P = .39$) or pre-treatment group differences ($F_{1,20} = 0.04$, $P = .84$). An overall mixed design analysis (group × time) with 2 levels of group (treatment, sham) and 6 levels of time (pre-treatment to post-treatment measure 5) revealed a significant main effect for condition ($F_{1,20} = 7.95$, $P < .05$) and a main effect for time ($F_{5,100} = 3.71$, $P < .01$). No significant interaction was detected. Aspirin treatment was associated with a decrease in pain, as indicated by higher MPWT scores compared with vehicle-treated animals.

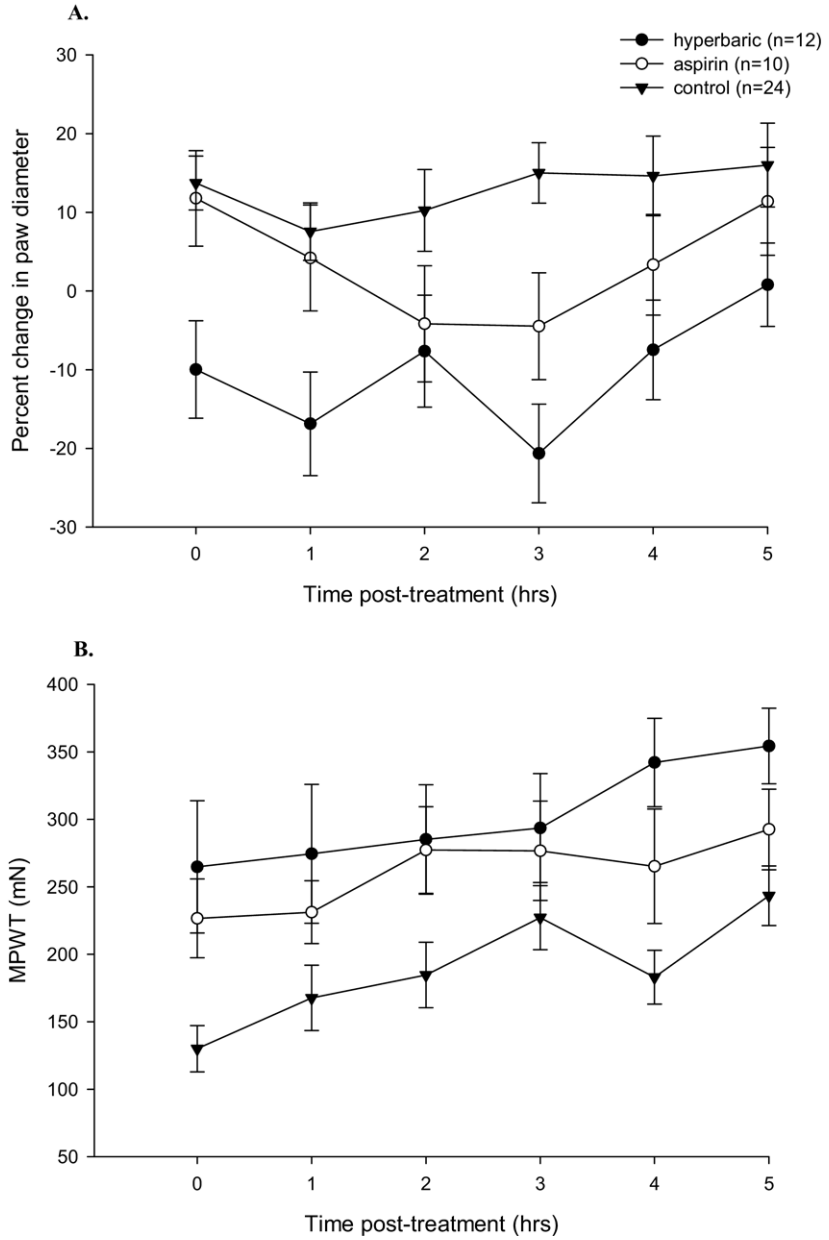

Figure 3. A, Mean (±SEM) percent change of paw diameter after intra-articular injection of carrageenan in control (saline-injected and sham-treated), aspirin, and hyperbaric-treated animals. Post hoc results indicated aspirin and hyperbaric were significantly different as compared with control animals. **B,** Mean (± SEM) percent change of paw diameter after intra-articular injection of carrageenan in control (saline-injected and sham-treated), aspirin, and hyperbaric-treated animals. Mechanical paw withdrawal threshold measurements were performed immediately after treatment (time 0) and at 1-hour intervals up to 5 hours after treatment and then averaged across time. Control animals were significantly more hyperalgesic than hyperbaric and aspirin-treated animals.

Combined Experimental Analyses

In an effort to compare the efficacy of hyperbaric oxygen treatment with aspirin treatment, control animals from experiment 1 and experiment 2 were combined to form an overall control group, and analytic comparisons were made among the collapsed control group, aspirin-treated, and hyperbaric-treated animals. Before collapsing the control groups, analyses were conducted to determine if there were significant differences among the 2 groups. Analysis of variance indicated no significant differences between sham- or saline-treated animals for either mechanical paw withdrawal ($F_{1,22} = 0.44$, $P = .52$), or paw diameter ($F_{1,22} = 0.04$, $P = .84$). It should be noted that these 2 experiments were run separately, and thus are drawn from different samples. As a result, analyses should be interpreted with caution.

Paw diameter results are presented in Fig 3a. A mixed group by time analysis was conducted with 3 levels of group (combined control, aspirin-injected, hyperbaric-treated), and 6 levels of time (0–5). A significant main effect for group ($F_{2,43} = 7.16$, $P < .001$) and time ($F_{5,215} = 3.77$, $P = .01$), but no significant interaction ($F_{10,215} =$

1.42, $P = .17$) was detected. Post hoc comparisons indicated that both the hyperbaric oxygen treated and aspirin injected animals had significantly less inflammation than the combined control group.

Mechanical paw withdrawal results are presented in Fig 3b. A mixed group by time analysis was conducted with three levels of group (combined control, aspirin-injected, hyperbaric-treated), and 6 levels of time (0–5). A significant main effect for group ($F_{2,43} = 8.18$, $P < .001$) and time ($F_{5,215} = 4.94$, $P = .001$), but no significant interaction ($F_{10,215} = 0.63$, $P = .79$) was detected. Post hoc comparisons indicated that both the hyperbaric oxygen–treated and aspirin-treated animals had significantly less mechanical hypersensitivity than control animals.

Discussion

The purpose of this study was to explore the efficacy of HBO on decreasing inflammation and altering mechanical sensation in an animal model of arthritis. In experiment 1, it was found that mechanical hypersensitivity and joint diameter in animals that receive hyperbaric oxygen treatment was significantly decreased compared with sham treatment. Similarly and as expected, experiment 2 found that mechanical hypersensitivity and joint diameter in animals that received aspirin treatment were significantly decreased compared with vehicle treatment. In an effort to compare the magnitude of the effect of HBO to the aspirin treatment, a separate analysis found that HBO treatment was as effective as aspirin treatment to decrease inflammation and mechanical hypersensitivity in an animal model of arthritis.

Although HBO treatment might be a viable option for the treatment of arthritis, the mechanisms by which the treatment acts to decrease pain and inflammation remain unclear. Arthritic joints are characterized by hypoxemia, caused in part by increased metabolic demands for oxygen and decreased blood flow due to increased intra-articular pressure. The ability of hyperbaric oxygen therapy to increase delivery and uptake of oxygen by tissue indicates potential therapeutic effects for arthritis.[10]

Based on these indications for potential benefit, Rui-Change,[12] Lukich et al,[9] and Davis et al[2] conducted clinical research on the effects of HBO on patients with arthritis. Rui-Chang[12] and Lukich et al[9] both report positive effects of treatment. Rui-Chang[12] report that only 8.1% of a group of 37 patients receiving HBO therapy for rheumatoid arthritis showed no improvement in pain, swelling, and mobility, and Lukich et al[9] report overall improvement in immune function in patients receiving HBO therapy. One drawback of both of these studies is that all participants received treatment, and thus experimenters were not blind to condition. Only 1 double-blinded trial has been conducted to assess the effects of HBO on rheumatoid arthritis, and it found no overall improvement of mobility, strength, or immune function for 8 patients receiving HBO as compared with 2 receiving sham treatment.[2]

Animal models of disease allow researchers more control than may often be obtained in clinical evaluations, and a few studies utilizing animal models of arthritis provide evidence that hyperbaric oxygen therapy decreases clinical signs of joint inflammation. Warren et al[17] evaluated the effects of hyperbaric oxygen therapy in rats subcutaneously injected with microbial tuberculosis in the tail. In this adjuvant model of rheumatoid arthritis, rats develop inflammation in 1 or more joints and the number of affected joints and degree of inflammation is noted. Rats were administered hyperbaric oxygen therapy at various time points after injection. The authors report a positive correlation between time of treatment and severity of symptoms: The sooner rats received treatment the lower the degree of inflammation. In addition, Seilanov et al[14] evaluated the effects of HBO on adjuvant arthritis in mice. They report mice treated with HBO were less likely to develop symptoms of adjuvant arthritis than to mice in a control group.

These initial studies in the adjuvant model of arthritis indicate HBO therapy may be an effective treatment at decreasing inflammation; however, neither study addresses the effect HBO treatment has on pain thresholds. Although inflammation and pain thresholds are correlated, distinct mechanisms are involved in each.[18] The purpose of this set of experiments was to explore the effect of hyperbaric oxygen therapy on joint inflammation and hyperalgesia in an animal model of arthritis, and compare these effects to aspirin treatment. As expected, based on previous findings,[18] both HBO and aspirin treatment decreased hyperalgesia and inflammation as compared with control animals in the animal model of arthritis. Future studies will examine the mechanisms or HBO treatment on inflammation and pain processing and will also examine if HBO treatment is effective to treat other chronic pain conditions.

In summary, the present results indicate that hyperbaric oxygen therapy was at least as effective as aspirin in decreasing mechanical paw withdrawal thresholds and joint inflammation. Based on these results, additional clinical trials to evaluate the efficacy of hyperbaric therapy on patients suffering from chronic arthritis are needed. Although hyperbaric therapy may not be a cost-effective option for all patients, it may provide an alternative therapy in persistent cases, or when NSAIDS are contraindicated. Future research should focus on identifying patients that would benefit most from hyperbaric oxygen, as well as evaluate the efficacy of various combination therapies.

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