RESEARCH ARTICLE

# Effects of hyperbaric oxygen therapy on recovery acceleration in Japanese professional or semi-professional rugby players with grade 2 medial collateral ligament injury of the knee: A comparative non-randomized study

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## ABSTRACT

**Introduction:** The effects of hyperbaric oxygen ($HBO_2$) therapy on sprains, ligament injuries, and muscle strains have been reported in several animal studies. In a dog model of compartment syndrome and in a rat contused skeletal muscle injury model, the significant effects of $HBO_2$ therapy on the reduction of edema and muscle necrosis have been reported. In basic research $HBO_2$ therapy stimulated fibroblast activity to improve the healing process. Because of this it expected that $HBO_2$ therapy might improve focal edema and pain in the acute phase and accelerate the healing of injured tissues in athletes with a medial collateral ligament (MCL) injury of the knee. This study aimed to examine the short-term effects of $HBO_2$ application subjectively, and the long-term effects of $HBO_2$ therapy in Japanese professional or semi-professional rugby players with grade 2 MCL injury of the knee.

**Methods:** Thirty-two professional or semi-professional rugby players with grade 2 MCL injury of the knee were investigated. First, in the $HBO_2$ group (n=16), $HBO_2$ therapy was performed during the acute phase. Visual analog scales (VASs) immediately before and after $HBO_2$ therapy on the same day were compared. Next, we retrospectively evaluated the time to return to play in the $HBO_2$ (n=16) and non-$HBO_2$ (n=16) groups.

**Results:** VAS scores for pain while walking immediately before and after $HBO_2$ therapy on the same day were 37.4 ± 20.1 (mean ± standard deviation) and 32.4 ± 21.8, respectively ($p<0.001$). The VAS scores for pain while jogging were 50.7 ± 25.6 and 43.9 ± 25.0, respectively ($p<0.001$). The time to return to play was 31.4 ± 12.2 days in the $HBO_2$ group and 42.1 ± 15.8 days in the non-$HBO_2$ group, indicating a significant difference between the groups ($p<0.05$).

**Conclusion:** $HBO_2$ therapy may reduce pain and accelerate the return to play in athletes with grade 2 MCL injury of the knee in this non-randomized study.

## INTRODUCTION

After sustaining injuries during sports, athletes are usually required – and desire – to return to competition rapidly. In particular, high-level athletes are required to return to play as soon as possible. Therefore, safe and effective, multidisciplinary treatments should be established. Athletes prefer such therapies, as they accelerate their return to competition.

Injury to the medial collateral ligament (MCL) of the knee is a frequently encountered sports injury. The incidence rate of MCL injury during sports activity ranges from 0.04 to 3.1 MCL injuries per 1,000 hours of athlete exposures (AEs) [1-3]. Moreover, the incidence rate during rugby competitions is relatively high [1].

As with other soft-tissue injuries, MCL injury undergoes four stages of healing. These include: hemorrhage,

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inflammation, repair, and remodeling [4,5]. The acute inflammatory phase is characterized by edema, pain, and a limited range of motion, which prevents affected individuals from returning to sports activities. A rapid reduction of pain and tissue edema at the injured site during the acute phase would accelerate the healing potential and reduce the time to return to previous levels of competition.

Hyperbaric oxygen ($HBO_2$) therapy has been noted as effective for wound healing and soft tissue injury, including crush injury and compartment syndrome [6-10]. The effects of $HBO_2$ therapy on soft tissue injuries during sports activities, including sprains, ligament injuries, contusions, and muscle strains, have been reported by several basic and clinical studies [11].

In the acute phase, $HBO_2$ therapy improves hypoxic tissue microcirculation following a reduction in edema. In a dog model of compartment syndrome, significant effects of $HBO_2$ therapy on the reduction of edema and muscle necrosis have been reported [11-13] In animal research $HBO_2$ therapy stimulated fibroblast activity to improve the healing process [14], and promoted ligament healing and maximum failure load after injury in the remodeling phase in a rat model [15-17]. Clinically, $HBO_2$ therapy may provide short-term effects such as reducing edema and pain in athletes with acute ankle sprain, as shown in a pilot study [29]. James, et al. first documented the quantitative effectiveness of $HBO_2$ therapy in sports injuries. In this preliminary report the actual days of unfitness compared to the estimated days assessed by the club physiotherapist resulted in a 70% decrease in injury time for returning to football activities in Scotland [36].

We reasoned therefore that $HBO_2$ therapy might help improve focal edema and pain in the acute phase and accelerate the healing of injured tissues in athletes with MCL injury of the knee. However, Barata, et al. documented a literature review that demonstrates that although results have proven to be promising in terms of using $HBO_2$ as a treatment modality in sports-related injuries, these studies have been limited due to the small sample size, lack of blinding, and issues with randomization [22]. As there have been few quantitative evaluations of $HBO_2$ therapy for MCL injury, $HBO_2$ effectiveness has not been clarified in detail.

This comparative non-randomized study aimed to evaluate the clinical efficacy of $HBO_2$ therapy in athletes with grade 2 MCL injury of the knees. The subjects in this study included professional or semi-professional rugby players. The primary outcome was defined as the short-term effects of $HBO_2$ therapy in the $HBO_2$ group in the acute phase of injury in terms of subjective VAS evaluation compared immediately before and after $HBO_2$ therapy. The secondary outcome was defined as the long-term effects of $HBO_2$ in terms of the time to return to play compared between the $HBO_2$ and non-$HBO_2$ groups.

## MATERIALS AND METHODS

This study was approved by the institutional review board of Tokyo Medical and Dental University in 2007. Each subject in the $HBO_2$ group provided written informed consent before participating in the study and starting $HBO_2$ therapy. This study was undertaken in full accordance with the ethical standards in the Declaration of Helsinki.

### Subjects

A total of 32 professional or semi-professional rugby players with grade 2 MCL knee injury that occurred during sports activity and during the rugby season that extended from June to January were investigated in this study. All subjects belonged to the "Top League" Japanese rugby league, which is the top category of the Japanese Rugby Federation.

The diagnosis of grade 2 MCL injury was made via clinical examination by the authors, who were the team medical doctors. Their specialty was orthopedics and sports medicine, and they possessed a keen ability to diagnose injuries accurately.

The grade of MCL injury was judged by manual examination as follows, and any right-left asymmetry was considered a positive finding:

A) **grade 1:** negative instability in the manual valgus stress test at full extension and at 30 degrees of knee flexion, and positive tenderness at the injured MCL site;
B) **grade 2:** negative instability in the manual valgus stress test at full extension, and positive instability in this test at 30 degrees of flexion; and
C) **grade 3:** positive instability in the manual valgus stress test at full extension and at 30 degrees of flexion (Table 1).

Exclusion criteria included a past history of MCL injury and/or other knee joint injuries including anterior cruciate ligament injury or meniscus injury.

From 2007 to 2011 all the patients with grade 2 MCL injury during the acute phase within six days of injury

**Table 1. Diagnosis of the grade of MCL injury**

| | instability by manual valgus test | | tenderness |
|---|---|---|---|
| | at full extension | at 30 degrees of flexion | at the injured MCL site |
| Grade 1 | (–) | (–) | (+) |
| Grade 2 | (–) | (+) | (+) |
| Grade 3 | (+) | (+) | (+) |

in four teams were referred to our hospital. All the cases were included in this study. All the cases were enrolled, consented, and underwent treatment with $HBO_2$ therapy ($HBO_2$ group, n=16). From 2001 to 2006, patients with grade 2 MCL injury were not administered $HBO_2$ therapy and were determined as the non-$HBO_2$ group (n=16). The data in the non-$HBO_2$ group were collected from their team doctors or their trainers.

### Hyperbaric oxygen therapy protocol

The $HBO_2$ chamber in our hospital is a multiplace unit capable of holding 16 patients (NHC-412-A, Nakamura Tekko-Sho Corp., Tokyo, Japan). In this series $HBO_2$ therapy was performed using 2.8 atmospheres absolute (ATA) (283.6 kPa) for 60 minutes. In the $HBO_2$ group (n=16), $HBO_2$ application started as soon as possible, including the same day of injury (Day 0). Each patient received a total of five $HBO_2$ treatments within 10 days after injury.

### Treatment and rehabilitation protocol post injury

All subjects underwent treatment assuming that they would be participating in a competitive match within the same season. The treatment and rehabilitation protocols after injury continued to be non-surgical and included initial rest, cryotherapy, compression, elevation, and restriction of weight bearing in the acute phase within 72 hours [31]. Patients were advised on early rehabilitation, including early range of motion and strengthening exercise of the quadriceps and hamstrings in a standard fashion. Weight bearing was permitted as soon as possible with use of a hinged knee brace when the athlete had moderate or severe pain [31-33]. Finally, after patients' muscle strength, proprioception, agility, and cardiopulmonary function had recovered to levels that were comparable to the contralateral side, the patients were permitted to return to play. The medical staff members for all teams checked this protocol, and confirmed their treatments according to this protocol.

### Evaluation

#### *Short-term effects of $HBO_2$ therapy on the subjective evaluation of pain: VAS evaluation*

First, in the $HBO_2$ group, VAS scores were used to subjectively evaluate pain. These scores were compared immediately before and after $HBO_2$ therapy on the same day, which means that we assessed differences in the 117-minute treatment. In the VAS evaluation, such question items of *pain at rest*, *pain while walking*, and *pain while jogging* were included. VAS scores consisted of 100 points at full marks, with the worst condition being 100 points and no complaint being 0 points.

### Long-term effects of $HBO_2$ therapy on time to return to play

Second, time to return to play in the $HBO_2$ (n=16) and non-$HBO_2$ (n=16) groups was compared. The day of return to play was determined as the day the athlete participated in a competitive match. In the non-$HBO_2$ group the time to return to play was retrospectively investigated through the team medical records, to which two of the authors had access as medical team doctors. In addition, we analyzed time to return to play regarding teams and field positions in all cases (n=32). We also analyzed time to return to play regarding teams, positions, number of $HBO_2$ treatments and early or late application of $HBO_2$ in the $HBO_2$ group (n=16).

### Statistical analysis

In this study data were shown as mean ± SD. Statistical analyses were performed using the Wilcoxon signed rank test for the VAS evaluation, and the Mann-Whitney U test for the evaluation of time to return to play between the $HBO_2$ and non-$HBO_2$ groups, and time to return to play regarding positions, length of $HBO_2$ treatment time and early or late $HBO_2$ application. The Kruskal-Wallis test was performed for the evaluation of time to return to play among the teams.

All data were analyzed using SPSS version 19.0 (IBM, Armonk, New York, U.S.). The significance level for statistical analysis was set at $p<0.05$.

## RESULTS

### Demographics of the subjects

**$HBO_2$ group:** Mean age of subjects in the $HBO_2$ group was 27.2 ± 3.3 (range; 22-32) years and all were male. Subjects in the $HBO_2$ group belonged to these teams: A (six patients); B (four patients); C (three patients); or D (three patients) among 14 teams in the top Japa-

**Table 2. Patient distribution**

| | n | age (years) | height (cm) | body weight (kg) | position | | affected side | |
|---|---|---|---|---|---|---|---|---|
| | | | | | forwards (n) | backs (n) | right (n) | left (n) |
| $HBO_2$ | 16 | 27.2 ± 3.3 (22-32) | 182.l ± 9.3 | 97.3 ± 14.4 | 11 | 5 | 8 | 8 |
| Non-$HBO_2$ | 16 | 27.0 ± 2.0 (24-31) | 180.5 ± 7.5 | 89.0 ± 10.9 | 6 | 10 | 8 | 8 |

nese rugby league. Rugby positions were distributed as: 11 forwards and five backs, with the right knee affected in 8 patients and the left knee affected in eight patients (Table 2). The mean number of days from injury to the first $HBO_2$ session was 2.2 ± 1.4 (range; 0-6) days. Five $HBO_2$ treatments were recommended. However, average number of $HBO_2$ sessions was 4.6 ± 0.7 (range; 3-5). In total, 73 courses of $HBO_2$ were performed in 16 patients (three treatments in two patients, four treatments in three patients, five treatments in 11 patients).

**Non-$HBO_2$ group:** Mean age was 27.0 ± 2.0 (range; 24-31) years and all were male. Subjects in the non-$HBO_2$ group belonged to teams A (six patients) or C (10 patients). Rugby positions were distributed as follows: six forwards and 10 backs, with the right knee affected in eight patients and the left knee affected in eight patients (Table 2). Two of the authors were medical doctors from teams A and C, respectively. They managed the medical protocol and records including the recovery process and time to return to play. There were no statistical differences in age, body weight, or height between the $HBO_2$ and non-$HBO_2$ groups.

### VAS evaluation in the $HBO_2$ group

We used 58 VAS scores obtained from 13 patients for analysis, excluding three subjects for whom there was insufficient data. The VAS scores regarding pain at rest immediately before and after $HBO_2$ therapy on the same day were: 18.8 ± 17.7 and 17.3 ± 16.4, respectively ($p=0.11$), for pain while walking; 37.4 ± 20.1 and 32.4 ± 21.8, respectively ($p<0.001$); and for pain while jogging, 50.7 ± 25.6 and 43.9 ± 25.0, respectively ($p<0.001$) (Figure 1).

### Time to return to play between the $HBO_2$ group and the non-$HBO_2$ group

All subjects were able to participate in a competitive match after injury within the same season. Time to return to play was 31.4 ± 12.2 (range; 10-58) days in the $HBO_2$ group and 42.1 ± 15.8 (range; 18-71) days in the non-$HBO_2$ group (Figure 2). There was a significant difference between the two groups ($p<0.05$).

### Time to return to play regarding teams, positions, number of $HBO_2$ treatments, and early or late application of $HBO_2$

Regarding time to return to play there were no significant differences among the teams, but there were statistical differences between positions (Table 3). Regarding the number of $HBO_2$ treatments, time to return to play was 21.6 ± 9.6 (range; 10-38) days in the three- or four-treatment $HBO_2$ group (n=5) and 35.8 ± 9.9 (range; 25-58) days in the five-treatment $HBO_2$ group (n=11). There was a significant difference between the groups ($p<0.05$). Regarding early or late $HBO_2$ application, time to return to play was 27.9 ± 9.3 (range; 10-41) days in the early $HBO_2$ group within two days after injury (n=11) and 39.0 ± 13.1 (range; 23-58) days in the delayed $HBO_2$ group three to five days after injury (n=5). There were no significant differences between the groups.

## DISCUSSION

The healing process of soft tissue injury, which includes MCL injury, is divided into the inflammatory or acute, proliferative, and remodeling phases. In the acute or inflammatory phase, focal injured soft tissue is characterized by tissue hypoxia microvascular dysfunction, tissue ischemia and hypoxia, and edema [5]. $HBO_2$ therapy can mitigate resolve tissue hypoxia by increasing dissolved oxygen tension. MCL injury in the acute phase is also characterized by edema, pain, and limited range of motion; hence, rapid reduction of pain and tissue edema at the injured site in the acute phase could also accelerate the healing process and return to play.

Skyhar, et al. reported the effects of $HBO_2$ on tissue edema and necrosis of muscle in the dog compartment model associated with hemorrhagic hypotension. They concluded that those findings might be the results of improvement of oxygenation of hypoxic tissue and reduction of edema, which came from reductions in serum and hematocrit leakage, resorption of extracellular fluid, and improvement in local circulation [11]. They mentioned that the mechanisms – i.e., hyperoxygenation and vasoconstriction [12] – were similar to those of the

**FIGURE 1**
**VAS scores immediately before $HBO_2$ and after $HBO_2$**

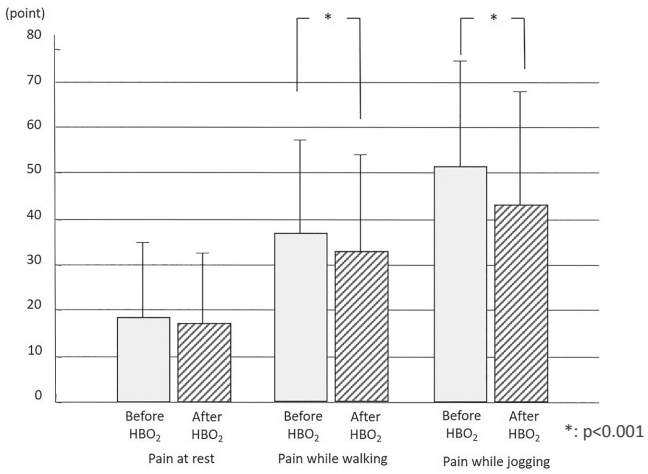
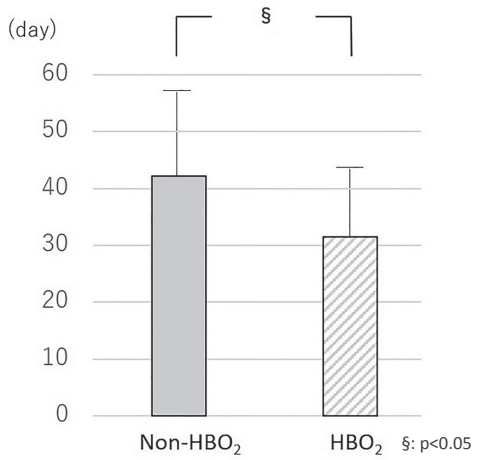



**FIGURE 2**
**Time to return to play in the non-$HBO_2$ and $HBO_2$ groups**




dog compartment syndrome model in the normotensive state reported by Strauss, et al.

Using a rat contused skeletal muscle injury model Oyaizu, et al. reported that $HBO_2$ therapy reduced muscle wet weight, and decreased the extracellular space and vascular permeability, which resulted in rapid reduction of edema [30].

Regarding the effects of $HBO_2$ therapy on ligament healing, the results of several animal research studies have been reported. Horn, et al. used a rat model of surgical MCL laceration with $HBO_2$ therapy exposure at 2.8 ATA for 1.5 hours a day for five days after surgery [15]. Maximum failure load and stiffness at two, four, six and eight weeks were analyzed. The maximum failure load and stiffness at four weeks in the $HBO_2$ group were statistically greater than in the control group. Moreover, the $HBO_2$ group reached normal levels at four weeks. However, the $HBO_2$ group at six weeks was not statistically different from the control group, which suggested that $HBO_2$ therapy accelerated the return to normal ligament level.

Mashitori, et al. created a 2-mm segment of MCL in a rat model and applied $HBO_2$ therapy at 2.5 ATA for two hours a day for five days. Maximum failure load and type I procollagen gene expression at 14 days in the $HBO_2$ groups statistically increased in conjunction with $HBO_2$ application[16]. Ishi, et al. examined the effects of three different $HBO_2$ exposures on the healing of rat patellar ligament injury: $HBO_2$ exposures included 1.5 ATA for 30 minutes, 2.0 ATA for 30 minutes, and 2.0 ATA for 60 minutes once a day and for 10 sessions. After two weeks, $HBO_2$ therapy at 2.0 ATA for 60 minutes was

**Table 3. Time to return to play regarding the teams and positions**

| | $HBO_2$ | | | | non-$HBO_2$ | | | |
|---|---|---|---|---|---|---|---|---|
| Team | Number | Forwards (n) | Backs (n) | subtotal | Number | Forwards (n) | Backs (n) | subtotal |
| A | 6 | 27.3±11.0 (4) | 43.5±5.5 (2) | 32.5±12.0 (6) | 6 | 52.0±19.0 (2) | 40.3±11.3 (4) | 44.2±15.4 (6) |
| B | 4 | 25.5±2.5 (2) | 26.5±3.5 (2) | 26.0±3.1 (4) | | | | |
| C | 3 | 31.5±6.5 (2) | 58 (1) | 40.3±13.6 (3) | 10 | 42.5±14.5 (4) | 39.7±15.3 (6) | 40.8±15.1 (10) |
| D | 3 | 27.3±11.0 (3) | | 27.3±11.0 (3) | | | | |
| Total | 16 | 27.6±26.6 (11)* | 41.2±12.0 (5)* | 31.4±12.2 (16) | 16 | 45.7±16.7 (6) | 39.9±13.9 (10) | 42.1±15.8 (16) |

statisitical difference between forwards and backs *: p<0.05 (average ± SD days)

the most effective, resulting in enhanced extracellular matrix deposition as measured by collagen synthesis [17]. Possible mechanisms of action of $HBO_2$ on ligament injury include reduction of edema and swelling, and promotion of fibroblast proliferation in the scar tissue to produce more type I procollagen mRNA[16].

Clinical reports of the time loss due to MCL injury had been variously documented. The time loss in grades 2 and 3 MCL injury in the U.S. Military Academy study was reported as 29 days [2], and the Union of European Football Association injury study reported 23 ± 23 days of layoff time in 346 MCL injuries [34]. Derscheid, et al. reported a mean return to football within 20 days in patients with grades 1 or 2 MCL injuries who were treated non-operatively [35]. Regarding rugby, especially in high-level rugby players at a professional or semi-professional level, Dallalana, et al. reported knee injuries in the English professional rugby union, and documented a time loss of 41 days in grade 2 MCL injury [1].

However, clinical data is scarce regarding the short- and long-term effects of $HBO_2$ therapy in patients with MCL injury. Moreover, little is known regarding its effect in accelerating recovery time. Only Soolsma reported the effects of $HBO_2$ therapy on functional recovery during the fourth, fifth and sixth week after injury using a double-blind controlled study. However, this study has not been published as an original article but only as a university report [28].

This study is the first clinical report regarding the short-term effects of $HBO_2$ therapy on subjective symptoms and the long-term effect of $HBO_2$ therapy on return to play, comparing an $HBO_2$ group with a non-$HBO_2$ group. Time to return to play is influenced by many factors, including the athletic event; field position; circumstances of schedule; other conventional treatment protocols, including RICE (rest, ice, compression and elevation) treatment at the acute phase; and post-injury rehabilitation protocol. In this study, in order to minimize the effect of subject bias, all subjects were professional or semi-professional rugby players who belonged to the same top category of the Japanese Rugby Federation.

In this study, the VAS scores regarding pain while walking and jogging were significantly reduced, which indicated an increase in the short-term effect of $HBO_2$ therapy. The VAS scores for pain at rest were not significantly different between immediately before and after $HBO_2$ therapy, but the VAS scores while walking and jogging were significantly different. Walking and bending the knee joint increased the tissue pressure, and this increase exacerbated the knee pain around the MCL. $HBO_2$ application helps reduce edema and tissue pressure and would have effects on reduction of VAS scores during walking and jogging.

The time to return to play in the non-$HBO_2$ group was 42.1 days, which is consistent with the Dallalana, et al. report on conventional treatment in professional rugby players. Thus, it was considered that the control group of non-$HBO_2$ therapy in this study was suitable, and the time to return to play of 31.4 days in the $HBO_2$ group was judged as significantly valuable data in regard to the long-term effects of $HBO_2$ therapy on the acceleration of recovery. Regarding number of $HBO_2$ treatments, there was a significant difference between the three- or four-treatment $HBO_2$ group and the five-treatment $HBO_2$ group. We speculated that the subjects in the five-treatment $HBO_2$ group might include cases of greater severity.

## LIMITATIONS

We recognize several limitations of this study. First, this was not a prospective comparative study, and it is not possible to exclude that factors related to the intervention, including a possible placebo effect, may have confounded the results. The number of subjects was small, and the injury periods of the $HBO_2$ and non-$HBO_2$ groups were different. The subjects in this study belonged to the top-level category; however, the $HBO_2$ group included four teams, whereas the non-$HBO_2$ group included only two teams. The results showed the wide range of recovery time, which might include mild and severe cases of grade 2 MCL injury for the subjects in this study. In addition, it will be necessary to examine differences in the effects of $HBO_2$ therapy on injured tissue compared to non-injured healthy tissue, as well as conventional therapies such as RICE treatment and/or use of orthotics.

The VAS evaluations immediately before and after $HBO_2$ therapy had the possibility to show only the effects of the 117-minute rest. The VAS scores of the patients who had not received $HBO_2$ and simply had 117 minutes of rest would be more appropriate as a control. In addition, the VAS evaluation in the non-$HBO_2$ limb would be performed hopefully for comparing the effects of $HBO_2$ on the healthy limb and injured limb in the future.

$HBO_2$ can have positive effects on MCL injuries. However, practitioners should be cautious in using $HBO_2$ therapy for off-label sports medicine injuries.

## CONCLUSION

We examined the effects of $HBO_2$ therapy on professional or semi-professional Japanese rugby players with grade 2 MCL injury that occurred during sports activities. $HBO_2$ therapy could have a short-term effect on pain reduction during the acute phase, and a long-term effect on acceleration of recovery with a decreased time to return to play. ■

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For the remaining authors none were declared.

## REFERENCES

1. Dallalana RJ, Brooks JH, Kemp SP, Williams AM. The epidemiology of knee injuries in English professional rugby union. Am J Sports Med 2007;35(5):818-830.

2. Roach CJ, Haley CA, Cameron KL, Pallis M, Svoboda SJ, Owens BD. The epidemiology of medial collateral ligament sprains in young athletes. Am J Sports Med 201;42(5):1103-1109.

3. Swenson DM, Collins CL, Best TM, Flanigan DC, Fields SK, Comstock RD. Epidemiology of knee injuries among U.S. high school athletes, 2005/2006-2010/2011. Med Sci Sports Exerc 2013;45(3):462-469.

4. Creighton RA, Spang JT, Dahners LE. Basic science of ligament healing. Medial collateral ligament healing with and without treatment. Sports Med Arthrosc Rev 2005;13(3):145-150.

5. Järvinen TA, Järvinen TL, Kääriäinen M, Kalimo H, Järvinen M. Muscle injuries: biology and treatment. Am J Sports Med 2005;33: 745-764.

6. Weaver LK. Undersea and Hyperbaric Medical Society. Hyperbaric Oxygen Indications. 13th edition. Best Publishing Company, 2014.

7. Bouachour G, Cronier P, Gouello JP, Toulemonde JL, Talha A, Alquier P. Hyperbaric oxygen therapy in the management of crush injuries: a randomized double-blind placebo-controlled clinical trial. J Trauma 1996;41(2):333-339.

8. Strauss MB. The effect of hyperbaric oxygen in crush injuries and skeletal muscle-compartment syndromes. Undersea Hyperb Med 2012;39:847-855.

9. Kanhai A, Losito JM. Hyperbaric oxygen therapy for lower extremity soft-tissue injuries. J Am Podiatr Med Asssoc 2003; 93:298-306.

10. Yamada N, Toyoda I, Doi T, Kumada K, Kato H, Yoshida S, Shirai K, Kanda N, Ogura S. Hyperbaric oxygenation therapy for crush injuries reduces the risk of complications: research report. Undersea Hyperb Med 2014;41(4):283-289.

11. Skyhar MJ, Hargens AR, Strauss MB, Gershuni DH, Hart GB, Akeson WH. Hyperbaric oxygen reduces edema and necrosis of skeletal muscle in compartment syndromes associated with hemorrhagic hypotension. J Bone Joint Surg Am 1986;68(8):1218-1224.

12. Strauss MB, Reduction of skeletal muscle necrosis using intermittent hyperbaric oxygen in a model compartment syndrome. J Bone Joint Surg Am 1983;65(5):656-662.

13. Strauss MB, Hargens AR, Gershuni DH, Hart GB, Akeson WH. Delayed use of hyperbaric oxygen for treatment of a model anterior compartment syndrome. J Orthop Res 1986;4(1):108-111.

14. Brismar K, Lind F, Kratz G. Dose-dependent hyperbaric oxygen stimulation of human fibroblast proliferation. Wound Repair Regen 1997;5:147-150.

15. Horn PC, Webster DA, Amin HM, Mascia MF, Werner FW, Fortino MD. The effect of hyperbaric oxygen on medial collateral ligament healing in a rat model. Clin Orthop Relat Res 1999;360: 238-242.

16. Mashitori H, Sakai H, Koibuchi N, Ohtake H, Tashiro T, Tamai K, Saotome K. Effect of hyperbaric oxygen on the ligament healing process in rats. Clin Orthop Relat Res 2004;423:268-274.

17. Ishii Y, Ushida T, Tateishi T, Shimojo H, Miyanaga Y. Effects of different exposures of hyperbaric oxygen on ligament healing in rats. J Orthop Res 2002;20:353-356.

18. Staples J, Clement D. Hyperbaric oxygen chambers and the treatment of sports injuries. Sports Med 1996;22:219-227.

19. Staples JR, Clement DB, Taunton JE, McKenzie DC. Effects of hyperbaric oxygen on a human model of injury. Am J Sports Med 1999;27:600-605.

20. Babul S, Rhodes EC. The role of hyperbaric oxygen therapy in sports medicine. Sports Med 2000;30:395-403.

21. Babul S, Rhodes EC, Taunton JE, Lepawsky M. Effects of intermittent exposure to hyperbaric oxygen for the treatment of an acute soft tissue injury. Clin J Sports Med 2003;13:138-147.

22. Barata P, Cervaens M, Resende R, Camacho O, Marques F. Hyperbaric oxygen effects on sports injuries. Ther Adv Musculoskelet Dis 2011;3:111-121.

23. Best TM, Loitz-Ramage B, Corr DT, Vanderby R. Hyperbaric oxygen in the treatment of acute muscle stretch injuries: results in an animal model. Am J Sports Med 1998;26:367-372.

24. Gregorevic P, Lynch GS, Williams DA. Hyperbaric oxygen improves contractile function of regenerating rat skeletal muscle after myotoxic injury. J Appl Physiol 2000;89:1477-1482.

25. Webster AL, Syrotuik DG, Bell GJ, Jones RL, Hanstock CC. Effects of hyperbaric oxygen on recovery from exercise-induced muscle damage in humans. Clin J Sports Med 2002;12:139-150.

26. Horie M, Enomoto M, Shimoda M, Okawa A, Miyakawa S, Yagishita K. Enhancement of satellite cell differentiation and functional recovery in injured skeletal muscle by hyperbaric oxygen treatment. J Appl Physiol 2014;116:149-155.

27. Borromeo CN, Ryan JL, Marchetto PA, Peterson R, Bove AA. Hyperbaric oxygen therapy for acute ankle sprains. Am J Sports Med 1997;25:619-625.

28. Soolsma SJ. The effect of intermittent hyperbaric oxygen on short term recovery from grade II medial collateral ligament injuries. Thesis, University of British Columbia, 1996, Vancouver.

29. Yagishita K, Oyaizu T, Aizawa J, Enomoto M. The effects of hyperbaric oxygen therapy on reduction of edema and pain in athletes with ankle sprain in the acute phase: A pilot study. Sport Exerc Med Open J 2017 3(1):11-16.

30. Oyaizu T, Enomoto M, Yamamoto N, Tsuji K, Horie M, Muneta T, Sekiya I, Okawa A, Yagishita K. Hyperbaric oxygen reduces inflammation, oxygenates injured muscle, and regenerates skeletal muscle via macrophage and satellite cell activation. Sci Rep. 2018 Jan 22;8(1):1288. doi: 10.1038/s41598-018-19670-x.

31. Chen L, Kim PD, Ahmad CS, Levine WN. Medial collateral ligament injuries of the knee: current treatment concepts. Curr Rev Musculosketet Med 2008;1(2):108-113.

32. Miyamoto RG, Bosco JA, Sherman OH. Treatment of medial collateral ligament injuries. J Am Acad Orthop Surg 2009;17(3): 152-161.

33. Marchant MH Jr, Tibor LM, Sekiya JK, Hardaker WT Jr, Garrett WE Jr, Taylor DC. Management of medial-sided knee injuries, part 1: medial collateral ligament. Am J Sports Med 201;39(5):1102-1113.

34. Lundblad M, Waldén M, Magnusson H, Karlsson J, Ekstrand J. The UEFA injury study: 11-year data concerning 346 MCL injuries and time to return to play. Br J Sports Med 2003;47(12):759-62

35. Derscheid GL, Garrick JG. Medial collateral ligament injuries in football. Nonoperative management of grade I and grade II sprains. Am J Sports Med 1981;9(6):365–8

36. James PB, Scott B, Allen MW. Hyperbaric oxygen therapy in sports injuries. Physiotherapy 1993;79(8):571-2