Bone marrow edema syndrome/transient osteoporosis of the hip joint and management with the utilization of hyperbaric oxygen therapy

Athanasios N. Ververidis^a, Konstantinos Paraskevopoulos^{b,*}, Anthimos Keskinis^b, Nikolaos Adrianos Ververidis^c, Reichan Molla Moustafa^a, Konstantinos Tilkeridis^a

^a Department of Orthopaedic Surgery, Medical School, Democritus University of Thrace, University General Hospital of Alexandroupolis, 68100, Alexandroupolis, Greece

^b Medical School, Democritus University of Thrace, University General Hospital of Alexandroupolis, 68100, Alexandroupolis, Greece

^c Medical School, University of Cyprus, Ioanni Giapouna 4, 1057, Nicosia, Cyprus

ARTICLE INFO

Keywords:

Hip
Transient osteoporosis
Osteonecrosis
Avascular necrosis
Hyperbaric oxygen therapy
Core decompression

ABSTRACT

Transient osteoporosis of hip (TOH) is a self-limited condition that affects young and middle aged women or men. The clinical manifestation is characterized by sudden or gradual onset of pain that is exacerbated on weight-bearing and at night. The treatment of TOH is either conservative or surgical. Conservative regimens include restriction of weight-bearing, pharmacological agents such as prostacyclin analogues (iloprost), non-steroid anti-inflammatory drugs (NSAIDs), extracorporeal shock wave and hyperbaric oxygen therapy (HBOT). Surgical intervention includes drilling or core decompression. The aim of this article is to review the clinical entity of TOH (clinical presentation, pathophysiology, diagnosis) and to further discuss the off-label utilization of HBOT as an alternative treatment regimen in patients suffering from TOH that fail to respond to other conservative methods.

1. Introduction

The clinical entity of transient osteoporosis of hip (TOH) was initially described in 1959 by Curtiss in 3 pregnant women with symptomatology of hip/thigh pain and radiological findings of demineralization of the hip joint which resolved spontaneously after delivery.¹ TOH is considered a rare, benign and self-limited condition which is characterized by demineralization, bone marrow edema (BME) of the proximal femur and eventually complete resolution after several months.^{2,3} Most common site of involvement is the hip joint, but many other joints such as the knee, ankle, shoulder, elbow, wrist and other smaller joints can be affected.⁴ The syndrome typically affects middle aged men and women in the third trimester of pregnancy or the immediate postpartum period, while non-pregnant cases have been reported as well.^{2,5} A handful of authors consider TOH as a different form of avascular necrosis (AVN), but it generally remains unclear and its clinical significance is frequently underestimated.^{3,6} Throughout the literature, many acronyms have been used to describe the term of TOH, such as regional migratory osteoporosis (RMO), transient bone marrow edema syndrome (TBMES) and reflex sympathetic dystrophy (RSD).⁶ BME pattern is an area of decreased signal density on T1 weighed

images and increased signal intensity on fat-suppressed, T2 weighed, and short tau inversion recovery sequences, without evidence of local lesions specific of AVN. It can only be detected by magnetic resonance images (MRI) and rarely by plain radiographs and computed tomography (CT) as a region of localized osteopenia.^{7–9} BME pattern is detected in a variety of other conditions except of TOH which include infections, malignancies, osteoarthritis, inflammation and trauma.¹⁰ In the clinical practice, it is important to differentiate between reversible (TOH, RSD, RMO) and irreversible disorders (AVN) that are associated with BME patterns on MRI, which are self-limited and need early surgical intervention respectively.¹⁰ TOH is of unknown cause and history of trauma is absent.⁶ The treatment modalities for the management of TOH include conservative treatment with restriction of weight bearing activities, pharmacological agents such as non-steroid anti-inflammatory drugs (NSAIDs), bisphosphonates and prostacyclin derivative iloprost, extracorporeal shock wave therapy, hyperbaric oxygen therapy (HBOT) and surgical intervention using core decompression.^{3,11} In this literature review article we will attempt to discuss the clinical entity of TOH (clinical presentation, pathophysiology, diagnosis) and to further analyze the off-label utilization of HBOT as an alternative treatment regimen in patients suffering from TOH that fail

* Corresponding author.

E-mail addresses: averver@otenet.gr (A.N. Ververidis), paraskevopouloskonstantinos@hotmail.com (K. Paraskevopoulos), anthimos13@hotmail.com (A. Keskinis), nickleever@gmail.com (N.A. Ververidis), reyhanmollamustafa@hotmail.com (R. Molla Moustafa), tilkerorth@icloud.com (K. Tilkeridis).

<https://doi.org/10.1016/j.jor.2020.03.062>

Received 26 March 2020; Accepted 28 March 2020

Available online 31 March 2020

0972-978X/ © 2020 Professor P K Surendran Memorial Education Foundation. Published by Elsevier B.V. All rights reserved.

Table 1
Studies including the use of HBOT on patients suffering from TOH.

Author	Year	N	Gender	Age	HBO (S, ATA, mps)	Follow-up	Overall Results
Capone et al. ¹¹	2011	22	M:F = 20:2	44.8	40S/2.2 ATA/90 mps	2 y	Short term superiority/long term not significantly different compared to control group
Guler et al. ²⁶	2015	18	M:F = 12:6	34.3 ± 4.3	30S/2.5 ATA/120 mps	17.8 ± 5.3 m	Clinical & radiological improvement
Yagishita et al. ²⁷	2016	5	–	–	27.8 ± 4.7S	–	Not significant improvement
Kesikburun et al. ²⁴	2015	2	M:F = 1:1	42.5	15S/2.4 ATA/120 mps	2 m	Clinical & radiological improvement
Elahi et al. ²⁵	2018	1	M:F = 1:0	47	30S/2.5 ATA/90 mps	2 y	Clinical & radiological improvement
Mutluoglu et al. ²⁶	2012	1	M:F = 0:1	33	30S/2.4 ATA/120 mps	10 w	Clinical & radiological improvement
Sahni and Gupta ²⁹	2016	1	M:F = 1:0	32	50S/2.4 ATA/90 mps	2 m	Clinical & radiological improvement
Domachevsky et al. ³⁰	2004	1	M:F = 1:0	33	90S/2.5 ATA/90 mps	6 m	Clinical & radiological improvement

Abbreviations: M = male; F = female; S = sessions; mps = minutes per session; m = month; w = weeks; y = years; ATA = atmosphere absolute pressure.

Table 2
Undersea and hyperbaric medicine Society's indications for HBOT.¹⁷

Air or gas embolism
Acute decompression sickness
Acute carbon monoxide poisoning (including poisoning complicated by cyanide poisoning)
Gas gangrene (clostridial myositis, myonecrosis)
Crush injury, compartment syndrome, acute traumatic ischemias
Refractory osteomyelitis
Osteoradionecrosis, soft tissue radiation necrosis
Intracranial abscesses
Necrotizing soft tissue infection (e.g. Fournier's gangrene)
Severe blood loss/anaemia
Compromise graft or flap preservation
Idiopathic sudden sensorineural hearing loss
Thermal burns
Enhance healing of selected problem wounds

to respond to other conservative methods (Table 1).

2. Clinical features - workup

The clinical manifestation of TOH is variable, but most commonly includes a sudden or gradually onset of a non-traumatic pain which is localized in the groin, anterior thigh, buttocks or in the lumbar region.^{3,4,12} Patient's pain is exacerbated by weight-bearing and alleviated on rest but it worsens at night, and may be more severe than AVN as well. Movement of hip joint is painful but range of motion is usually not affected.^{3,4} Pain is attributed to the increase in the intraosseous pressure, venous hypertension, microfracture, increased bone turnover and periosteal irritation.¹³ Generally, there is a discrepancy regarding the severity of clinical symptomatology compared to the more silent clinical signs that are elucidated on examination.⁵ TOH is a self-limited disorder that lasts about 4–24 months without the need of intervention. A rare but potential complication may be the progression to AVN.³ This self-limited syndrome is historically characterized by 3 stages. The first stage comprises the sudden onset of pain that is localized in the hip joint and is associated with limping. Hip is tender on palpation. In the second stage there is a non-progression of symptomatology that lasts a couple of months characterized by demineralization of femoral head, neck and intertrochanteric region without joint space narrowing on plain radiographs. MRI could be a reasonable diagnostic tool to depict the lesion associated with TOH. Last stage includes the complete clinical and radiological resolution.^{2,3}

The etiology of the disorder remains unknown. On the other hand, several predisposing factors are implicated including pregnancy, alcohol abuse, tobacco, corticosteroids, hypothyroidism, hypophosphatasia, osteogenesis imperfect, low testosterone, low vitamin D, and specific occupations such as physicians.^{13,14}

Histological specimens reveal a focal region of altered bone trabeculae architecture covered by osteoid seams and active osteoblasts associated by formation of callus. Nearby tissues are characterized by the presence of edema, fibrosis, hemorrhage and vascular congestion

without findings compatible to AVN.¹⁵

AVN remains the most important disorder that should be separated from TOH in order to avoid unnecessary surgical intervention. Differentiation between these 2 clinical entities is considered a clinical challenge, especially in early stages of AVN where both radiological and clinical findings may be identical.^{2,13} MRI is a diagnostic tool that could facilitate the distinction between them: AVN is associated with subchondral lesion (crescent sign), single line sign with edema on T1 images and double line sign with edema on T2 images or femoral head deformity.³ Pathognomonic for AVN is the presence of reactive interface that separates the necrotic lesion from the surrounding femoral head.⁴

3. Hyperbaric oxygen therapy - overview

In clinical practice, HBOT has been utilized as a treatment regimen in a variety of medical disorders including traumatic ischemia, non-healing ulcers, and osteoradionecrosis but with uncertain results.¹⁶ There are specific indications published by Undersea and Hyperbaric Medicine Society regarding the use of HBOT (Table 2). HBOT is an intriguing method in which the individual is subjected to 100% oxygen inhalation inside a chamber where the pressure is adjusted to greater than 1 atm absolute (ATA). In fact, for clinical purposes the pressure protocols are typically set above 1.4 ATA with pressures ranging between 1.5 and 3.0 ATA and exposure time ranging from 60 to 120 min with up to 3 sessions of HBOT daily, depending on the indication of use.^{16–18} The exposure to such high levels of oxygen increases the hemoglobin saturation, therefore leading to 10–20 fold increase of oxygen amount dissolved in plasma, and better oxygen delivery to the tissues. In particular, the great oxygen levels trigger the oxygen cascade to the intracellular environment and produces therapeutic or even toxic effects to the tissues. The therapeutic effects are divided into 3 major groups which are comprised of the consequences of hydrostatic pressure and removal of inactive gas from the tissues, the effects of supra-physiological arterial tensions of oxygen and oxygenation of dysfunctional hypoxic tissues.^{16,17} The HBOT is applied inside a compression vessels called the hyperbaric chambers which may be high pressure multi-place chambers, high pressure mono-place chambers or low pressure mono-place chambers.^{16,17} In the mono-place chambers only a single patient is allowed while in the multi-place chambers, multiple patients can be exposed to the high levels of oxygen which is delivered through face masks, hoods or even endotracheal tubes.¹⁸ As with any clinical intervention, the application of hyperbaric oxygen entails risks and complications that are directly related to either the high tension of the oxygen or the high pressure in the chamber. Exposure to high oxygen pressure causes toxicity, which is directly relative to the exposure time. Oxygen toxicity is due to the production of ROS which act as mutagens and potentially carcinogenic agents. Since patients undergoing HBOT are not been exposed for a long period of time, this has the effect of activating antioxidant mechanisms that could reverse the damage that can be caused by the action of ROS, thus providing a

protective role.¹⁹ The complications that are related to the exposure to high ATA are usually experienced when the ATA is above 4, but relatively safe levels are considered those below 3 ATA with 120 min being the threshold of exposure. Potential side effects include barotrauma, confinement anxiety and visual disorders, while the most common is disorders related to middle ear equalization mechanisms. Furthermore, the use of HBOT has absolute contraindications which include pneumothorax, restrictive respiratory disorders, and patients receiving chemotherapy. Therefore, all patients should be carefully subjected into pre-exposure examination to exclude patients with such conditions.¹⁹

AVN of femoral head is a common orthopedic disorder affecting mainly young and middle aged people.²⁰ It occurs when the intraosseous blood circulation is interrupted, which leads to decreased vascular supply inside the femoral head and ischemia leading to subsequent necrosis.²¹ The causes of osteonecrosis are divided into 3 main groups including idiopathic, secondary (steroid use) and trauma causes.²⁰ HBOT has been applied in the clinical practice as a non-operative option for the management of early stage AVN of the femoral head.^{20,21} HBOT could improve the intraosseous microcirculation of the femoral head in patients with AVN by targeting the underlying pathophysiology. In the early stages of AVN, HBOT helps to provide high oxygen pressures (oxygenation) in the hypoxic tissues, reduces BME, and induces angiogenesis. The reduction of intraosseous pressure is associated with pain relief and venous drainage restoration, which therefore improves microcirculation. Bone resorption, revascularization and osteogenesis are the late effects of HBOT.^{20–22}

4. Discussion

It has been presented by many authors that histological specimens in early stage of AVN is preceded by BME as seen on MRI, while others suggest that TOH is potentially another form or an early reversible stage of AVN.^{6,21,23} Therefore, the application of HBOT in off-label use in patients with TOH has been attempted with beneficial effects by reducing intraosseous edema with vasoconstriction and increasing bone repair.²⁴ Consequently, HBOT has been utilized as a potential treatment in those patients suffering from TOH.²⁵ In a prospective study conducted by Capone et al., 44 consecutive patients were included with clinical and radiological signs compatible with TOH. The patients were randomly divided into 2 groups of 22 patients each. The control group was assigned to be treated with acetaminophen or non-steroid anti-inflammatory drugs (NSAIDs) and protective weight bearing while the HBOT group was treated with the same regimen plus HBOT administration. The protocol of HBOT administration included a total of 40 sessions with each session breathing 100% oxygen at 2.2 ATA for 90 min 2 patients were excluded from HBOT group due to barotrauma related to therapy. MRI at 3 months showed resolution of BME in 55.0% of the patients in HBOT group and 28% in the control 1. Free of pain was achieved in 70% of HBOT group patients after 3 months of follow-up while all of control group patients had mild pain and discomfort especially during activities. After 24 months of follow-up, all patients were free of pain.¹¹ In another study that was carried out by Guler et al., 18 patients were assessed with diagnosis of TOH. All patients were treated with conservative regimen including the use of crutches, pharmacological agents (classical anti-inflammatory drugs for pain relief) in combination with HBOT administration. The HBOT was given in a total of 30 sessions at 2.5 ATA for 90 min each session. At the final follow-up (17.8 ± 5.3 months) all patients were clinically and radiologically improved with no signs of AVN and no complications related to HBOT.²⁶ In a study by Yagishita et al., 5 cases of TOH treated with HBOT were examined. The average time to achieve normal hip range motion was 15.4 ± 7.8 weeks and pain relief was 16.6 ± 4.0 weeks while MRI normal findings were achieved 22.0 ± 2.5 weeks. The authors concluded that the HBOT did not significantly improve recovery of TOH.²⁷ In a case series study conducted by Kesikburun et al. including 2 cases of patients suffering from TOH, HBOT was

administered. The patients received a total of 15 sessions (range 10–20) at 2.4 ATA for 120 min per session. After a follow-up of 2 months both radiological and clinical resolution of BME and pain were achieved respectively.²⁴ Throughout the literature a handful of case reports have been published, utilizing the alternative of HBOT on patients affected by TOH. In all studies, the administration of HBOT led to improvement/complete resolution of MRI findings, pain relief and to an increase of the range of motion in the hip joint.^{25,28–30}

A handful of studies have compared the use of conservative treatment (NSAIDs, iloprost, paracetamol) with the surgical method of core decompression. Core decompression seemed to offer a faster recovery, less chance of recurrence and better pain control compared with patients that were administered NSAIDs or paracetamol.¹⁴ On the other hand patients that were treated with iloprost had equal or better results regarding the treatment of TBMEs compared with patients that were subjected into surgical core decompression.²³

5. Conclusions

To our knowledge this is the first review article that analyzes the current studies that have been published referring to the management of TOH using HBOT, from 2004 to 2018. We searched throughout the literature and detected 8 studies that included a total of 51 patients treated with HBOT. Most studies were case series/reports (6/8 studies included 5 or less patients). Those studies seem that HBOT has been successfully utilized to achieve resolution of pain, BME on MRI and improvement in range of motion in patients suffering from TOH that failed to respond to other conservative methods. The disadvantage of the method may be the time that is required to achieve remission (15–90 sessions) but on the other hand it may be a potential alternative in patients that fail to respond to other conservative treatments. Furthermore, there are no studies in the literature that compare the application of HBOT and core decompression in patients that are affected with TOH. Nevertheless, due to the fact that only a handful of studies have been reported regarding the use of HBOT in TOH and none that compares HBOT with surgical core decompression, further investigation is needed in order to decide whether the use of HBOT is indeed an alternative method to treat patients with TOH that failed to other conservative approaches. We report a lack of standardized guidelines with respect to the use of HBOT in patients suffering from TOH.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

No potential conflict of interest relevant to this article was reported.

Acknowledgements

None.

References

- Curtiss PH, Kincaid WE. Transitory demineralization of the hip in pregnancy: a report of three cases. *J Bone Jt Surg Am.* 1959;41-A:1327–1333.
- Szwedowski D, Nitek Z, Walecki J. Evaluation of transient osteoporosis of the hip in magnetic resonance imaging. *Pol J Radiol.* 2014;79:36–38.
- Aprato A, Conti A, Triolo P, Piana R, Masse A. Transient osteoporosis of the hip: state of the art and review of literature. *Fortune J Rheumatol.* 2019;1(3) 021-027.
- Hofmann S. The painful bone marrow edema syndrome of the hip joint. *Wien Klin Wochenschr.* 2005;117(4):111–120.
- Rocchetti March M, Tovaglia V, Meo A, Pisani D, Tovaglia P, Aliberti G. Transient osteoporosis of the hip. *Hip Int.* 2010;20:297–300 03.
- Korompilias AV, Karantanas AH, Beris AE. Transient osteoporosis. *J Am Acad Orthop*

- Surg.* 2008;16(8):480–489.
7. Manara M, Varenna M. A clinical overview of bone marrow edema. *Reumatismo*. 2014;66(2):184–196.
 8. Hayes CW, Conway WF, Daniel WW. MR imaging of bone marrow edema pattern: transient osteoporosis, transient bone marrow edema syndrome, or osteonecrosis. *Radiographics*. 1993;13:1001–1011 discussion 1012.
 9. Ververidis AN, Paraskevopoulos K, Tilkeridis K, Riziotis G, Tottas S, Drosos GI. Surgical modalities for the management of bone marrow edema of the knee joint. *J Orthop.* 2020;17:30–37.
 10. Korompilias AV, Karantanas AH, Lykissas MG, Beris AE. Bone marrow edema syndrome. *Skeletal Radiol.* 2009;38(5):425–436.
 11. Capone A, Podda D, Ennas F, Iesu C, Casciu L, Civinini R. Hyperbaric oxygen therapy for transient bone marrow oedema syndrome of the hip. *Hip Int.* 2011;21(2):211–216.
 12. Cano-Marquina A, Tarín JJ, García-Pérez MÁ, Cano A. Transient regional osteoporosis. *Maturitas*. 2014;77(4):324–329.
 13. Asadiipooya K, Graves L, Greene LW. Transient osteoporosis of the hip: review of the literature. *Osteoporos Int.* 2017;28(6):1805–1816.
 14. Bashairreh KM, Aldarwish FM, Al-Omari AA, et al. Transient osteoporosis of the hip: risk and therapy. *Open Access Rheumatol.* 2020;12:1–8.
 15. Vande Berg BC, Lecouvet FE, Koutaïsoff S, Simoni P, Malghem J. Bone marrow edema of the femoral head and transient osteoporosis of the hip. *Eur J Radiol.* 2008;67(1):68–77.
 16. Barilaro G, Francesco Masala I, Parracchini R, et al. The role of hyperbaric oxygen therapy in orthopedics and rheumatological diseases. *Isr Med Assoc J.* 2017;19(7):429–434.
 17. Bennett MH, Mitchell SJ. Emerging indications for hyperbaric oxygen. *Curr Opin Anaesthesiol.* 2019;32(6):792–798.
 18. Lam G, Fontaine R, Ross FL, Chiu ES. Hyperbaric oxygen therapy: exploring the clinical evidence. *Adv Skin Wound Care.* 2017;30(4):181–190.
 19. Memar MY, Yekani M, Alizadeh N, Baghi HB. Hyperbaric oxygen therapy: antimicrobial mechanisms and clinical application for infections. *Biomed Pharmacother.* 2019;109:440–447.
 20. Koren L, Ginesin E, Melamed Y, Norman D, Levin D, Peled E. Hyperbaric oxygen for stage I and II femoral head osteonecrosis. *Orthopedics.* 2015;38(3):e200–e205.
 21. Reis ND, Schwartz O, Militianu D, et al. Hyperbaric oxygen therapy as a treatment for stage-I avascular necrosis of the femoral head. *J Bone Jt Surg Br.* 2003;85(3):371–375.
 22. Camporesi EM, Vezzani G, Bosco G, Mangar D, Bernasek TL. Hyperbaric oxygen therapy in femoral head necrosis. *J Arthroplasty.* 2010;25(6 Suppl):118–123.
 23. Aigner N, Petje G, Schneider W, et al. Bone marrow edema syndrome of the femoral head: treatment with the prostacyclin analogue iloprost vs. core decompression: an MRI-controlled study. *Wien Klin Wochenschr.* 2005;117(4):130–135.
 24. Kesikburun S, Uran A, Demir Y, Guzelkucuk U, Ergozen S, Tan AK. Transient osteoporosis of the hip and hyperbaric oxygen therapy: a report of two cases. *Turk J Phys Med Rehab.* 2015;61:80–83.
 25. Elahi MM, Syed F, Qaadri S, Elahi H, Khan A, Elahi M. Successful and rapid resolution of transient osteoporosis of the hip (TOH) with hyperbaric oxygen therapy (HBOT): a case report. *J Clin Case Rep.* 2018;8(5):1124.
 26. Guler O, Ozyurek S, Cakmak S, Isyar M, Mutlu S, Mahiroglu M. Evaluation of results of conservative therapy in patients with transient osteoporosis of hip. *Acta Orthop Belg.* 2015;81(3):420–426.
 27. Yagishita K, Jinno T, Koga D, et al. Transient osteoporosis of the hip treated with hyperbaric oxygen therapy: a case series. *Undersea Hyperb Med.* 2016;43(7):847–854.
 28. Mutluoglu M, Sonmez G, Sivrioglu AK, Ay H. There may be a role for hyperbaric oxygen therapy in transient osteoporosis of the hip. *Acta Orthop Belg.* 2012;78(5):685–687.
 29. Sahni T, Gupta S. Case report: treatment of bone marrow edema of the femoral head with hyperbaric oxygen therapy. *Apollo Med.* 2016;13:59–62.
 30. Domachevsky L, Keynan Y, Militianu D, Goldenberg I, Adir Y. Transient osteoporosis associated with hyperhomocysteinemia: a possible role for hyperbaric oxygen therapy. *Undersea Hyperb Med.* 2004;31(3):275–279.