Clinical utility of hyperbaric oxygen therapy in genitourinary medicine

Jason Gandhi[1, 2], Omar Seyam[1], Noel L. Smith[3], Gunjan Joshi[4], Sohrab Vatsia[5], Sardar Ali Khan[1, 6, *]
1 Department of Physiology and Biophysics, Stony Brook University School of Medicine, Stony Brook, NY, USA
2 Medical Student Research Institute, St. George's University School of Medicine, Grenada, West Indies
3 Foley Plaza Medical, New York, NY, USA
4 Department of Internal Medicine, Stony Brook Southampton Hospital, Southampton, NY, USA
5 Department of Cardiothoracic Surgery, Lenox Hill Hospital, New York, NY, USA
6 Department of Urology, Stony Brook University School of Medicine, Stony Brook, NY, USA

*Correspondence to: Sardar Ali Khan, M.D., FRCS, FACS, skysalik@gmail.com.
orcid: 0000-0002-4759-530X (Sardar Ali Khan)

Abstract

Hyperbaric oxygen therapy (HBOT) is a medical technique which delivers oxygen at ambient pressures to increase the amount of dissolved oxygen in the blood and oxygen distribution to tissues. There are several beneficial properties of HBOT concomitant with elevated oxygen distribution in tissue including anti-inflammation, angiogenesis through vascular endothelial growth factor proliferation, augmented fibroblast activity through fibroblast growth factor proliferation, tissue and wound repair, enhancement of lymphocyte and macrophage activity, increased male testosterone secretion, and bactericidal activity. Given its renown in treating conditions such as decompression sickness and carbon monoxide poisoning, HBOT is making gradual strides for use in genitourinary medicine due to its low risk and likeliness to achieve favorable results. Early success has been observed in the treatment of Fournier's gangrene, radiation cystitis, and interstitial cystitis via the elimination of clinical symptoms such as pain. Further indications that have exhibited positive outcomes despite HBOT's ambiguous mechanism of action include cyclophosphamide hemorrhagic cystitis, emphysematous cystitis, pelvic radiation disease, radiation-induced proctopathy, dystrophic calcification of the prostate, erectile dysfunction secondary to urethroplasty, priapism, abnormal renal morphology, blood testosterone, calcific uremic arteriolopathy, and hidradenitis suppurativa. For other indications, multicenter studies must be conducted to determine HBOT's true efficacy, mechanism of action, risks, and advantages over conventional treatments.

Key words: hyperbaric oxygen therapy; Fournier's gangrene; interstitial cystitis; hemorrhagic cystitis; radiation cystitis; priapism

doi: 10.4103/2045-9912.229601
How to cite this article: Gandhi J, Seyam O, Smith NL, Joshi G, Vatsia S, Khan SA. Clinical utility of hyperbaric oxygen therapy in genitourinary medicine. Med Gas Res. 2018;8(1):29-33.

Introduction

Hyperbaric oxygen therapy (HBOT) provides oxygen under pressure to increase tissue oxygen levels. Oxygen is administered 2 to 3 times higher than atmospheric pressure, and is resultantly distributed around infected areas; this allows the body's natural healing process to take place and repair tissue. Because HBOT stimulates signal transduction cascades by increasing reactive oxygen and nitrogen species, tissues will release prostaglandins, nitric oxide, and cytokines that exhibit pathophysiological responses towards wounds, surgery, and infections.[1] There has been a soar in demand and use for this therapy with rising incidences of diabetes and obesity. Some side effects that are related to HBOT include barotrauma, claustrophobia, anxiety, pulmonary oxygen toxicity, and seizures. Additionally, patients with chronic neurological disorders may experience a greater risk of seizures.[2] Though HBOT is well known for treating decompression sickness, gangrene, or carbon monoxide poisoning, all of its known indications for use in genitourinary medicine are presently reviewed.

Perineum

Fournier's gangrene, or scroto-perineal fasciitis, affects the fascial planes of the scrotum and perineum. It usually starts in the genitals and spreads from Buck's fascia to subcutaneous tissues (*e.g.*, anterior abdominal fascia, perineum, penis, and scrotum). Fournier's gangrene often manifests in patients who have immunodeficiency conditions such as ethilism, chronic degenerative diseases, and diabetes.[3] Though the infection is not considered idiopathic, it can be localized to a urethral, cutaneous, or rectal source and is characterized by inflammation of fatty subcutaneous tissue and edema.[4] HBOT for Fournier's gangrene includes a 90-minute daily session for 30–40 sessions in total at 2.5 atmospheres absolute (ATA).[5-7] The treatment reduces inflammation and foments antimicrobial action which allows tissue to regenerate, and additional benefits include stimulated bactericidal action of leukocytes, preservation of intracellular adenosine, enhanced fibroblast replication, promotion of neovascularization, stimulated capillary growth, vasoconstriction, and improved wound healing.[5,8] Furthermore, HBOT induces the formation of new capillaries in order to reduce local vasospasm and increases the necessary time for wound healing as well as the induced rate of collagen deposition.[5,9] A recent retrospective review of 34 cases over a period of 25 years determined that when used as adjunctive therapy to antibiotics, HBOT was able to attenuate the Fournier's gangrene mortality rate from an average of 30.8% to 20.8%.[10] Without HBOT, edema and infection secondary to Fournier's gangrene would reduce local circulation and tissue oxygenation, which would consequently impair host defenses, increase the progression of necrosis, and permit the invasion of microorganisms.[11]

Bladder

Radiation cystitis

Radiation-induced hemorrhagic cystitis, or radiation cystitis, is characterized by damage to the urinary bladder as a complication of pelvic radiation therapy.[12] The pathophysiology of radiation-induced tissue involves damage to the vascular endothelium which causes fibrosis, subsequent tissue necrosis, ischemia of the interstitium, and inflammation.[13] Some histological alterations include interstitial fibrosis, submucosal hemorrhage, and smooth muscle fibrosis. HBOT triggers a reduction of tissue inflammation, reduces capillary pressure with diminution of edema, and promotes the tissue healing process through amplification of fibroblastic activity.[14] Notably, HBOT reverses the vascular changes induced by angiogenesis. In a study conducted by Degener et al.,[15] 15 patients with radiation cystitis underwent HBOT at 2.4 atmospheres (atm; 1 atm = 101.325 kPa) for 130 minutes/day, with 34 sessions on average. The investigators demonstrated that increasing tissue oxygen levels prompted increased regeneration of urothelium. Additionally, their results suggest that hyperbaric oxygen therapy triggered the normal function of fibroblasts, granulocytes, and macrophages, helping to drive the tissue repair process. Although the group's results are indicative of a high response rate to HBOT, bladder irrigation was performed in 13% of patients to mitigate hematuric recurrence. Side effects associated with HBOT in radiation cystitis including significant hyperbaric-induced myopia, claustrophobia, ear "squeeze," and visual changes after the conclusion of HBOT.[16] Additionally, Mougin et al.[17] recently demonstrated partial or complete resolution of radiation-induced cystitis in 52% of a cohort of 71 patients with HBOT. Further research has also suggested that HBOT may be more beneficial in younger patients and may display better outcomes when started within the first six months of a radiation cystitis diagnosis.[18,19] Critically, studies have demonstrated that HBOT does not activate latent prostate cancer or cause changes in tumor growth.[20,21]

Cyclophosphamide hemorrhagic cystitis

Cyclophosphamide hemorrhagic cystitis is defined by inflammation of the bladder from an infectious or non-infectious etiology.[22] Its causative agent, acrolein, is a metabolite of cyclophosphamide, and symptoms include recurrent hematuria, urinary urgency, and suprapubic pain.[23] The role of HBOT in cyclophosphamide hemorrhagic cystitis is to enhance angiogenesis, reduce bleeding caused by vasoconstriction, help optimize immune function at the cellular level, and stimulate granulation tissue formation. HBOT stimulates angiogenesis and maintains tissue oxygenation by healing tissue hypoxia and radionecrosis. In a recent study, Kumar et al.[24] demonstrated that HBOT at 2 ATA for 60 minutes a day encouraged the healing of tissue damage and promoted capillary angiogenesis by increasing tissue oxygen levels 10- to 15-fold. Further research has also suggested that HBOT may increase the oxygen gradient in tissue surrounding damaged urothelium and this increased partial pressure diffusion gradient may enhance macrophage migration in damaged hypoxic soft tissues promoting collagen formation, neutrophil bactericidal action, and fibroblast growth.[25,26] Additionally, it has been postulated that HBOT may reduce BK viremia and viruria associated with cyclophosphamide hemorrhagic cystitis.[22]

Interstitial cystitis

Interstitial cystitis, also known as painful bladder syndrome or urgency/frequency syndrome, is a chronic condition which causes severe bladder pressure and pain. HBOT plays a role in attenuating interstitial cystitis-induced bladder inflammation through the activation of angiogenesis.[27] In a study conducted by Tanaka et al.,[28] 7 of 11 patients diagnosed with interstitial cystitis treated with HBOT exhibited improvement. Due to the nature of patient response, positive symptomatic relief varied between the trials. However, patients treated with HBOT at higher pressures experienced greater alleviation of symptoms. The most prevalent complication in this longitudinal HBOT series was reversible exudative otitis media in three patients (27%); however, no patients terminated HBOT. Strikingly, no correlation has been observed between patients' therapeutic responses and the number of HBOT sessions.[29] In the treatment of interstitial cystitis, it is suggested that HBOT hyper-saturates plasma with dissolved oxygen. Hence, this increases the concentration gradient between the circulation and surrounding tissues, allowing oxygen to enter damaged hypoxic urothelial tissues.[29] HBOT may also accelerate the growth of healthy granulation in injured tissues through stimulation of leukocytic functions, including phagocytosis and production of other growth factors related to angiogenesis.[28] A significant advantage of HBOT is the absence of any significant side effects on the bladder function or structure unlike alternative therapies such as hydrodistension or intravescical dimethyl-sulfoxide.[29]

Emphysematous cystitis

Emphysematous cystitis is a condition characterized by the presence of gas within the bladder as a result of a primary fungal or bacterial infection in the urinary tract.[30] Specifically, albumin or glucose fermentation by the urinary pathogen catalyzes gas formation in the bladder wall and lumen which may travel towards the renal parenchyma.[31] It is most common amongst elderly patients and in those who are immunocompromised. In a case study, McCabe et al.[32] reported that a 65-year-old woman experiencing debilitating fatigue underwent two HBOT sessions at 2.85 ATA in an emergency department. After 48 hours, a CT scan of her abdomen demonstrated a major decrease in bladder wall air; because of such rapid and substantial improvement in her condition, emphysematous cystitis was differentially diagnosed. Without successful HBOT treatment, it would have been difficult to conclusively predict additional symptoms or the hospital course of the patient.

Pelvis

Pelvic radiation disease

Pelvic radiation disease, in which a urologic fistula may be observed, typically occurs three months after radiotherapy for pelvic malignancies involving the bladder, prostate, or uterus.[33] The increase of oxygen to ischemic tissues in HBOT has been shown to lead to nutrient influx, fibroblast proliferation, and angiogenesis.[34] In a study conducted by Morris et al.,[35] HBOT decreased tissue hypoxia by inducing angiogenesis in bowels affected by the fibrotic and ischemic changes linked to pelvic

radiation disease. Specifically, in a patient population of 26 males and 18 females, HBOT decreased symptoms such as mucus loss, ulceration, stenosis, and tenesmus over an eight-year period. There was also a 32% calculated risk reduction associated with HBOT.

Radiation-induced proctopathy

Radiation-induced proctopathy usually manifests as a complication of pelvic external beam radiation therapy and brachytherapy and often includes a plethora of symptoms.[36,37] It is distinguished by damage to the rectum which results from radiation therapy to adjacent pelvic organs, and radiation proctitis can develop after or during a course of radiation therapy.[38] In a study by Dall'Era et al.,[36] investigators assessed the efficacy of HBOT in a sample of 27 males with radiation-induced proctopathy. The group's results demonstrated promise, with a 48% complete resolution rate for patients with bleeding following the completion of HBOT. It has been postulated that HBOT ameliorates the ischemia caused by radiation-induced obstruction of microvessels by affecting oxygen transport and tissue exchange while simultaneously stimulating an 8- to 9-fold increase in the vascular density of soft tissue. Additionally, fibroblast proliferation increases while the tissue hyperoxia decreases tissue edema.[39] Some potential side effects of HBOT in radiation-induced proctopathy are sinus barotrauma, central and pulmonary nervous system oxygen toxicity, and hyperoxia.[40]

Prostate

Dystrophic calcifications of the prostate occur in accordance with a disturbance in phosphorous or calcium metabolism.[41] These distinct calcifications manifest as tiny stones that can grow large enough to cause muscle cramps and pain in the groin. When the cell membrane leaks calcium ions, an acidic environment is created, and crystallization begins to occur. These conditions can be generally circumvented using inhibitors such as osteopontin, which prevent calcium deposition under natural conditions.[42] The mechanism of action underlying HBOT for urothelium dystrophic calcification is not yet fully understood. However, it is presumed that HBOT facilitates the delivery of oxygen to tissues unable to heal in a calcium-ion driven acidic environment. In a study by Kern & Humphreys,[2] a 71-year-old man with a history of dystrophic calcifications of the prostatic fossa, recurrent prostatitis, and urinary retention secondary to benign prostatic hyperplasia completed two rounds of HBOT following holmium-laser lithotripsy of the calcifications (37 sessions at 2.0 to 2.4 atm for the first round and 20 sessions at 2.0 atm for the second round). Results of this case demonstrate promise; following minor recurrent calcifications after the first round of therapy, the patient exhibited well healed prostatic fossa, a healthy urothelium, and marginal calcifications.

Urethra

Posterior urethral stricture disease is typically caused by straddle injury or pelvic fracture and can be corrected by reconstructive operations (*i.e.*, urethroplasty). However, a decrease in erectile function is an associated iatrogenic complication of urethroplasty.[43] HBOT has previously been shown to promote angiogenesis after surgery and aid facial nerve regeneration by means of a large increase in mean axonal diameter.[44] In the studies by Yuan et al.,[45,46] HBOT was administered for 90 minutes at an absolute pressure of 0.2 MPa (2.0 ATA). This treatment helped to stimulate the regeneration of the cavernous nerve, which is often damaged at its medial branches during dissection from the penile hilum to the prostatic area. Additionally, side effects were minimal: there were only three cases of urinary tract infections (12.5%), which were treated by antibiotics. Usually, patients that have posterior urethral strictures have abundant scar tissue leading to an increased vulnerability of the neurovascular bundle to damage during surgery. It was confirmed that the HBOT accelerated neovascularization with *in vivo* hairless mouse ear wound models.[47]

Penis

Priapism is defined as a painful erection that is persistent for more than four hours.[48] It is most common in patients with sickle cell disease. Specifically, sickle cells occlude the venous flow of blood from the corpora of the penis, and it is believed that an erection decreases oxygen tension in the corpora cavernosa and predisposes to erythrocyte sickling.[49] In a case study by Azik et al.,[50] HBOT was utilized over the course of 11 sessions in an 11-year-old boy with sickle cell disease and an erection for 72 hours. After the first application of HBOT, the patient's red cell exchange decreased from 92% to a normal range of 7.7%. Although red cell exchange transfusion benefits remain unclear, there were no HBOT-related complications in this specific case. Previously, HBOT has been successfully used for sickle cell disease complications such as painful crisis, retinopathy, and hyphema, but its mechanism of action in sickle cell disease and priapism is still under investigation.[50,51]

Kidneys

HBOT protects the kidneys against oxidative stress induced by renal ischemia perfusion. It is presumed that HBOT functions to ameliorate glomerular filtration rates against sepsis-related impairment of renal functions and inhibit pathologic neutrophil infiltration.[52] Importantly, there has been no evidence to suggest HBOT induces histopathological deformation in the kidneys – demarcated by structural impairment – including cellular swelling, proximal tubule dilatation, and flattened brush borders. In a rabbit model, it was found that HBOT protects the kidneys against oxidative stress caused by renal ischemia perfusion through inhibition of neutrophil infiltration while improving glomerular filtration rates against sepsis-related impairment of renal functions.[52] In a recent study in rats, HBOT prevented histopathological damage after renal failure and reduced creatinine levels and plasma urea as well as proximal tubular necrosis and apoptotic cell count in cisplatin-induced acute renal failure.[53] Further research is warranted to draw definitive conclusions about HBOT's efficacy in the human kidney.

Miscellaneous

Blood testosterone

HBOT may also increase blood oxygenation to stimulate testosterone synthesis. Leydig cell functions are improved by hyperoxygenation of gonadal tissue while hypoxia induces

hypogonadism.[54] Concerning the intracellular mechanisms of hyperoxygenation, HBOT increases adenosine triphosphatae and nitric oxide synthesis by interfering with mitochondrial energy cycles.[55] HBOT improves the production of local growth factors such as vascular endothelial growth factor and fibroblast growth factor while simultaneously regulating the synthesis of tumor necrosis factor as well.[55,56] Though it has been discovered that sex hormones have an impact on wound healing, the complete mechanism of action of HBOT is still under exploration.

Calcific uremic arteriolopathy (CUA)

CUA, or calciphylaxis, is the calcification of blood clots, blood vessels, and skin necrosis. Characterized by cutaneous lesions such as indurated plaques or erythematous nodules, CUA is a syndrome of small vessel calcification of unknown etiology that causes painful skin lesions.[57] HBOT has been utilized for CUA to promote wound healing, angiogenesis, and improve phagocytosis through stimulation of neutrophil activity and collagen synthesis.[58] The side effects of HBOT for CUA are minimal under a pressure of 300 atm and the duration of treatment is often less than two hours. Side effects that have been encountered include nausea, seizures, headaches, pulmonary symptoms, reversible barotrauma, and reversible myopia due to oxygen toxicity on the lens of the eye – all with rates of less than 1% in a prospective cohort study.[57]

Hidradenitis suppurativa

Hidradenitis suppurativa is an inflammatory disease of the apocrine glands. The mechanism underlying combinatory HBOT and oral rifampicin and clindamycin treatment for hidradenitis suppurativa is still undetermined.[59] However, previous studies have suggested that HBOT may be used at higher pressures to facilitate bactericidal action by providing a substrate for the formation of oxygen free radicals and augmenting the respiratory tract.[60] Furthermore, during the healing process, HBOT-driven formation of capillaries leads to increased antibiotic action in the high-oxygen environment; in a recent prospective randomized control trial, HBOT supplemented antibiotic administration for hidradenitis suppurativa with a 100% resolution rate in 22 patients and no reported adverse effects.[61]

Conclusion

HBOT is becoming an increasingly attractive treatment option in genitourinary medicine as it promotes tissue repair and healing, facilitates angiogenesis and fibroblast growth, and stimulates anti-inflammatory activity. Though initially prominent for treatment of Fournier's gangrene, radiation-induced cystitis, and interstitial cystitis, HBOT is gaining traction as a sustainable, low-risk option. While HBOT has demonstrated promise in most indications mentioned in this review, future research is required to determine the viability of HBOT for treatment of autoimmune diseases, uremic osteodystrophy, and neuropathy due to chronic renal diseases amongst a host of others. It is also crucial to continue investigating the utility of HBOT in all indications discussed heretofore to survey and prevent the common side effects associated with HBOT, including sinus barotrauma and claustrophobia. Through multicenter studies, conventional treatments should be used to gauge the efficacy of HBOT for each indication.

Acknowledgements
The authors are thankful to Drs. Kelly Warren, Inefta Reid, Todd Miller, and Peter Brink (Department of Physiology and Biophysics, Stony Brook University School of Medicine, Stony Brook, NY, USA) for departmental support, as well as Mrs. Wendy Isser and Ms. Grace Garey (Northport VA Medical Center Library, Northport, NY, USA) for literature retrieval.

Author contributions
JG: Designed, organized, and wrote the review article; designed the outline; solved queries related to scientific publications from the journals. OS: Performed Medline searches, aided in writing the review article and critiqued the literature. GJ: Critiqued and applied logical reasoning to the literature. SV: Critiqued and applied logical reasoning to the literature. SAK: Revised the article to add logical reasoning and corrected the literature. SAK: Formulated clinical concepts, reviewed the article, and corrected the references. NS: Reviewed the article and updated basic science references. All authors have read and approved the manuscript provided.

Conflicts of interest
The authors have no conflicts of interest to declare.

Financial support
None.

Plagiarism check
Checked twice by iThenticate.

Peer review
Externally peer reviewed.

Open peer reviewers
Qin Hu, Shanghai Jiao Tong University School of Medicine, China; Nemoto Edwin, University of New Mexico Health Sciences Center, USA.

References

1. Al-Waili NS, Butler GJ. Effects of hyperbaric oxygen on inflammatory response to wound and trauma: possible mechanism of action. *Scientific World Journal*. 2006;6:425-441.
2. Stern KL, Humphreys MR. Hyperbaric oxygen for refractory dystrophic calcifications of the prostate: a case series and review of the literature. *J Urol Res*. 2016;3:1058.
3. Aşçi R, Sarikaya S, Büyükalpelli R, Yilmaz AF, Yildiz S. Fournier's gangrene: risk assessment and enzymatic debridement with lyophilized collagenase application. *Eur Urol*. 1998;34:411-418.
4. Paty R, Smith AD. Gangrene and Fournier's gangrene. *Urol Clin North Am*. 1992;19:149-162.
5. Li C, Zhou X, Liu LF, Qi F, Chen JB, Zu XB. Hyperbaric oxygen therapy as an adjuvant therapy for comprehensive treatment of Fournier's gangrene. *Urol Int*. 2015;94:453-458.
6. Kobayashi S. Fournier's gangrene. *Am J Surg*. 2008;195:257-258.
7. Hung MC, Chou CL, Cheng LC, et al. The role of hyperbaric oxygen therapy in treating extensive Fournier's gangrene. *Urol Sci*. 2016;27:148-153.
8. Shaw JJ, Psoinos C, Emhoff TA, Shah SA, Santry HP. Not just full of hot air: hyperbaric oxygen therapy increases survival in cases of necrotizing soft tissue infections. *Surg Infect (Larchmt)*. 2014;15:328-335.
9. Pizzorno R, Bonini F, Donelli A, Stubinski R, Medica M, Carmignani G. Hyperbaric oxygen therapy in the treatment of Fournier's disease in 11 male patients. *J Urol*. 1997;158:837-840.
10. Rosa I, Guerreiro F. Hyperbaric oxygen therapy for the treatment of Fournier's gangrene: a review of 34 cases. *Acta Med Port*. 2015;28:619-623.
11. Korhonen K, Hirn M, Niinikoski J. Hyperbaric oxygen in the treatment of Fournier's gangrene. *Eur J Surg*. 1998;164:251-255.
12. Liberman D, Mehus B, Elliott SP. Urinary adverse effects of pelvic radiotherapy. *Transl Androl Urol*. 2014;3:186-195.

13. Del Pizzo JJ, Chew BH, Jacobs SC, Sklar GN. Treatment of radiation induced hemorrhagic cystitis with hyperbaric oxygen: long-term followup. *J Urol*. 1998;160:731-733.
14. Passavanti G. The use of the hyperbaric oxygenation therapy in urology. *Arch Ital Urol Androl*. 2010;82:173-176.
15. Degener S, Pohle A, Strelow H, et al. Long-term experience of hyperbaric oxygen therapy for refractory radio- or chemotherapy-induced haemorrhagic cystitis. *BMC Urol.* 2015;15:38.
16. Norkool DM, Hampson NB, Gibbons RP, Weissman RM. Hyperbaric oxygen therapy for radiation-induced hemorrhagic cystitis. *J Urol*. 1993;150:332-334.
17. Mougin J, Souday V, Martin F, Azzouzi AR, Bigot P. Evaluation of hyperbaric oxygen therapy in the treatment of radiation-induced hemorrhagic cystitis. *Urology*. 2016;94:42-46.
18. Corman JM, McClure D, Pritchett R, Kozlowski P, Hampson NB. Treatment of radiation induced hemorrhagic cystitis with hyperbaric oxygen. *J Urol*. 2003;169:2200-2202.
19. Rose D. Hyperbaric oxygen therapy for radiation cystitis. *Am Fam Physician*. 2016;94:418.
20. Chong KT, Hampson NB, Bostwick DG, Vessella RL, Corman JM. Hyperbaric oxygen does not accelerate latent in vivo prostate cancer: implications for the treatment of radiation-induced haemorrhagic cystitis. *BJU Int*. 2004;94:1275-1278.
21. Oliai C, Fisher B, Jani A, et al. Hyperbaric oxygen therapy for radiation-induced cystitis and proctitis. *Int J Radiat Oncol Biol Phys*. 2012;84:733-740.
22. Urbaniak-Kujda D, Kapelko-Slowik K, Biernat M, Dybko J, Laszkowska M, Kuliczkowski K. The use of hyperbaric oxygen therapy in the treatment of hemorrhagic cystitis after allogeneic stem cell transplantation from an unrelated donor. *Int J Hematol*. 2015;102:364-367.
23. Matz EL, Hsieh MH. Review of advances in uroprotective agents for cyclophosphamide- and ifosfamide-induced hemorrhagic cystitis. *Urology*. 2017;100:16-19.
24. Ajith Kumar S, Prasanth P, Tripathi K, Ghosh P. Hyperbaric oxygen-A new horizon in treating cyclophosphamide-induced hemorrhagic cystitis. *Indian J Urol.* 2011;27:272-273.
25. Davis M, MacDonald H, Sames C, Nand K. Severe cyclophosphamide-induced haemorrhagic cystitis treated with hyperbaric oxygen. *N Z Med J*. 2011;124:48-54.
26. Jou YC, Lien FC, Cheng MC, Shen CH, Lin CT, Chen PC. Hyperbaric oxygen therapy for cyclophosphamide-induced intractable refractory hemorrhagic cystitis in a systemic lupus erythematosus patient. *J Chin Med Assoc*. 2008;71:218-220.
27. van Ophoven A, Rossbach G, Pajonk F, Hertle L. Safety and efficacy of hyperbaric oxygen therapy for the treatment of interstitial cystitis: a randomized, sham controlled, double-blind trial. *J Urol*. 2006;176:1442-1446.
28. Tanaka T, Nitta Y, Morimoto K, et al. Hyperbaric oxygen therapy for painful bladder syndrome/interstitial cystitis resistant to conventional treatments: long-term results of a case series in Japan. *BMC Urol*. 2011;11:11.
29. Parker SG, Miakhil I, Kommu SS. Hyperbaric oxygen therapy in interstitial cystitis/painful bladder syndrome. *Open J Urol*. 2013:189-193.
30. Sadek AR, Blake H, Mehta A. Emphysematous cystitis with clinical subcutaneous emphysema. *Int J Emerg Med*. 2011;4:26.
31. Dhingra KR. A case of complicated urinary tract infection: Klebsiella pneumoniae emphysematous cystitis presenting as abdominal pain in the emergency department. *West J Emerg Med*. 2008;9:171-173.
32. McCabe JB, Mc-Ginn Merritt W, Olsson D, Wright V, Camporesi EM. Emphysematous cystitis: rapid resolution of symptoms with hyperbaric treatment: a case report. *Undersea Hyperb Med*. 2004;31:281-284.
33. Fuccio L, Frazzoni L, Guido A. Prevention of pelvic radiation disease. *World J Gastrointest Pharmacol Ther*. 2015;6:1-9.
34. Ouaïssi M, Tran S, Mege D, et al. Pelvic radiation disease management by hyperbaric oxygen therapy: prospective study of 44 patients. *Gastroenterol Res Pract*. 2014;2014:108073.
35. Morris KA, Haboubi NY. Pelvic radiation therapy: Between delight and disaster. *World J Gastrointest Surg*. 2015;7:279-288.
36. Dall'Era MA, Hampson NB, Hsi RA, Madsen B, Corman JM. Hyperbaric oxygen therapy for radiation induced proctopathy in men treated for prostate cancer. *J Urol*. 2006;176:87-90.
37. Grodsky MB, Sidani SM. Radiation proctopathy. *Clin Colon Rectal Surg*. 2015;28:103-111.
38. Kitta T, Shinohara N, Shirato H, Otsuka H, Koyanagi T. The treatment of chronic radiation proctitis with hyperbaric oxygen in patients with prostate cancer. *BJU Int*. 2000;85:372-374.
39. Jones K, Evans AW, Bristow RG, Levin W. Treatment of radiation proctitis with hyperbaric oxygen. *Radiother Oncol*. 2006;78:91-94.
40. Hong JJ, Park W, Ehrenpreis ED. Review article: current therapeutic options for radiation proctopathy. *Aliment Pharmacol Ther*. 2001;15:1253-1262.
41. Jeon SW, Park YK, Chang SG. Dystrophic calcification and stone formation on the entire bladder neck after potassium-titanyl phosphate laser vaporization for the prostate: a case report. *J Korean Med Sci*. 2009;24:741-743.
42. Walsh JS, Fairley JA. Calcifying disorders of the skin. *J Am Acad Dermatol*. 1995;33:693-706; quiz 707-710.
43. Blaschko SD, Sanford MT, Cinman NM, McAninch JW, Breyer BN. De novo erectile dysfunction after anterior urethroplasty: a systematic review and meta-analysis. BJU Int. 2013;112:655-663.
44. Vilela DS, Lazarini PR, Da Silva CF. Effects of hyperbaric oxygen therapy on facial nerve regeneration. *Acta Otolaryngo*l. 2008;128:1048-1052.
45. Yuan JB, Yang LY, Wang YH, Ding T, Chen TD, Lu Q. Hyperbaric oxygen therapy for recovery of erectile function after posterior urethral reconstruction. *Int Urol Nephrol*. 2011;43:755-761.
46. Paick JS, Donatucci CF, Lue TF. Anatomy of cavernous nerves distal to prostate: microdissection study in adult male cadavers. *Urology*. 1993;42:145-149.
47. Sander AL, Henrich D, Muth CM, Marzi I, Barker JH, Frank JM. In vivo effect of hyperbaric oxygen on wound angiogenesis and epithelialization. *Wound Repair Regen*. 2009;17:179-184.
48. Broderick GA. Priapism and sickle-cell anemia: diagnosis and nonsurgical therapy. *J Sex Med.* 2012;9:88-103.
49. Levey HR, Segal RL, Bivalacqua TJ. Management of priapism: an update for clinicians. *Ther Adv Urol*. 2014;6:230-244.
50. Azik FM, Atay A, Kürekçi AE, Ay H, Kibar Y, Ozcan O. Treatment of priapism with automated red cell exchange and hyperbaric oxygen in an 11-year-old patient with sickle cell disease. *Turk J Haematol*. 2012;29:270-273.
51. Ballas SK, Kesen MR, Goldberg MF, et al. Beyond the definitions of the phenotypic complications of sickle cell disease: an update on management. *Scientific World Journal*. 2012;2012:949535.
52. Tezcan O, Caliskan A, Demirtas S, et al. Effects of hyperbaric oxygen treatment on renal system. *Iran J Kidney Dis*. 2017;11:18-22.
53. Cebi G, Yildiz Ş, Uzun G, et al. The effect of hyperbaric oxygen therapy on rhabdomyolysis-induced myoglobinuric acute renal failure in rats. *Ren Fail.* 2016;38:1554-1559.
54. Mitrović A, Nikolić B, Dragojević S, Brkić P, Ljubić A, Jovanović T. Hyperbaric oxygenation as a possible therapy of choice for infertility treatment. *Bosn J Basic Med Sci*. 2006;6:21-24.
55. Passavanti G, Tanasi P, Brauzzi M, Pagni MR, Aloisi AM. Can hyperbaric oxygenation therapy (HOT) modify the blood testosterone concentration? *Urologia*. 2010;77:52-56.
56. Nasole E, Nicoletti C, Yang ZJ, et al. Effects of alpha lipoic acid and its R+ enantiomer supplemented to hyperbaric oxygen therapy on interleukin-6, TNF-alpha and EGF production in chronic leg wound healing. *J Enzyme Inhib Med Chem*. 2014;29:297-302.
57. An J, Devaney B, Ooi KY, Ford S, Frawley G, Menahem S. Hyperbaric oxygen in the treatment of calciphylaxis: A case series and literature review. *Nephrology (Carlton)*. 2015;20:444-450.
58. McCulloch N, Wojcik SM, Heyboer M 3rd. Patient outcomes and factors associated with healing in calciphylaxis patients undergoing adjunctive hyperbaric oxygen therapy. *J Am Coll Clin Wound Spec*. 2015;7:8-12.
59. Uzun G, Özdemir Y, Mutluoğlu M, Güleç B. Hyperbaric oxygen therapy as an adjunct to surgical treatment of extensive hidradenitis suppurativa. *World J Surg*. 2010;34:861-862; author reply 863.
60. Cimşit M, Uzun G, Yildiz S. Hyperbaric oxygen therapy as an antiinfective agent. *Expert Rev Anti Infect Ther*. 2009;7:1015-1026.
61. Yildiz H, Senol L, Ercan E, Bilgili ME, Karabudak Abuaf O. A prospective randomized controlled trial assessing the efficacy of adjunctive hyperbaric oxygen therapy in the treatment of hidradenitis suppurativa. *Int J Dermatol*. 2016;55:232-237.