REVIEW

The use of the hyperbaric oxygenation therapy in urology.

Giandomenico Passavanti

Department of Urology Misericordia Hospital Grosseto; Department of Physiology University of Siena, Italy

Summary

The basic principle of the hyperbaric oxygenation therapy (HOT) is to increase the dissolved oxygen in the blood when it is administered at high pressure. Then O_2 will be distributed to the tissues through the pressure gradient, in this way obtaining an hyper-oxygenation of the tissue that has anti-inflammatory and pain-killing effects and induces augmentation of bacterial permeability to the antibiotics, neo-angiogenesis, enhancement of lymphocytes and macrophages function, augmentation of the testosterone secretion (in male), and healing of wound.

These positive effects can be used in urology in several conditions: Scroto-perineal fascitis; Radiation-induced cystitis (and proctitis); Interstitial cystitis (urgency-frequency syndrome); Chronic pelvic pain.

Our experience and the specific literature on this subject, suggest that HOT, sometimes associated with other medical and surgical therapies, can be a useful tool for treating such urologic diseases; in some cases this use is codified (Fournier's gangrene and Radiation-induced cystitis) in others (urgency-frequency syndrome and chronic pelvic pain) it represents a promising technique and needs further research.

KEY WORDS: *Hyperbaric oxygenation therapy; Necrotizing fascitis, Radiation-induced cystitis.*

Submitted 25 April 2010; Accepted 30 October 2010

INTRODUCTION

The hyperbaric oxigenation therapy is used in some urological diseases. The basic principle of this therapy is the tissue hyperoxigenation obtained by the increase of the diluted oxygen in the blood. Normally the haemoglobin is saturated by oxygen up to 98% and this level of saturation can't be increased; to improve the amount of diluted oxygen in the blood it is necessary to administer it at high pressure. Oxygen increases by 10-13 times (1) and this high amount of oxygen is distributed to the tissues with a pressure gradient (2).

The hyperoxygenation has an anti-inflammatory effect and favors tissue regeneration, recovery and healing (3, 4).

The hyperoxygenation moreover improves local synthesis of the growth factors, particularly *fibroblastic growth factor* (FGF) and *vascular endotelial growth factor* (VEGF) (5) which improves the neoangiogenetic process (3, 6). Furthermore hyperoxigenation regulates production of *tumor necrosis factor* (TNFa), reduces synthesis of PGE2 and COX-mRNA (2), enhances the limphocytic and macrophagic functions (2, 7, 8) and, finally, increases bacterial permeability to antibiotics (2, 4, 9, 10). The use of the hyperbaric oxygenation therapy in urology is definitely accepted in the treatment of the *Fournier's gangrene* and radio-induced cystitis and rectal bleeding (2).

For interstitial cystitis, urge-frequency syndrome and chronic pelvic pain this therapy is still experimental.

FOURNIER'S GANGRENE

This disease is a necrotizing fasciitis which affects the fascial plains of the scrotum and perineum, but it can affect also groins until the flank and ischiatic regions (11).

It presents in patients with immuno-deficienct conditions (diabetes, ethilisms chronic degenerative diseases) and develops from urethral, anal or dermatologic diseases (12).

The isthology shows an inflammation of the fatty subcutaneous tissue, with oedema, endo-arteritis and thrombosis creating necrosis of tissues (12).

Near the necrotic areas appears an extended panniculitis

which secretes an exudate, which contains toxic cytokines. The microbiologic ethiology is complex and multimicrobial: *Staphylococcus, Streptococcus, Clostridium etc.* (11, 13).
The mortality rate ranges between 7 to 60% (14, 15).
Necrosis and panniculitis extension and numerous metabolic parameters (most importantly renal function) are the prognostic factors (16).
Early treatment improves the prognosis (12)and reduces the extension of surgical demolition (13).
The therapy of the *Fournier's gangrene* includes multiple methodologies such as surgery, advanced dressings and hyperbaric oxygenation therapy with daily 90 min long sessions, for 30-40 sessions at 2,5 ATA (atmospheres absolute). General and metabolic therapy are associated and also antibiotics (12, 13, 17).
When the acute phase is resolved, it is possibile to cover the destroyed regions with cutaneous flaps (18, 19).
The hyperbaric oxigenation therapy supports the therapy of the *Fournier's gangrene* during the initial therapeutic phases and during the reconstructive therapeutic period, because it reduces inflammation and has an antimicrobial action, promoting the tissues regeneration and rooting of the flaps (2, 6). The use of the hyperoxigenation in this syndrome isn't proven with statistical evidence, but the efficiency is confirmed by numerous empirical data obtained from frequent clinical use.

Radiation induced cystitis

Radio-therapy in urology is mainly used to treat prostate cancer as a radical therapy as well as after a radical prostatectomy (20). Actually it is performed with conformational methodology to reduce exposed areas to radiation, nevertheless radio-induced inflammation of the bladder and rectum can occur.
The radio induced cystitis can appear during radiotherapy or a long time after therapy (21).
The histology presents the oedema of the mucosa of the bladder with inflammation of the lamina propria. This kind of cystitis can be healed or can evolve into subacute or chronic disease (21).
In this case the histology shows occlusive arterial thrombosis with epithelial necrosis and mucosal bleeding and fibrosis of the smooth muscle cells (21). The most important clinical aspect is the persistent and recurrent hematuria with urge, frequency and disurya (21). This cystitis is staged with a scale (2). The epidemiology is not well defined because numerous mild cases are not even reported but actually the clinically manifested cases are reduced from 20% to 5% of the patients treated with conformational radiotherapy (2).
In these cases the hyperbaric oxygenations is largely used and commonly 40-60 sessions 90 min long at 2,5ATA are carried out.
It causes a reduction of the tissue inflammation (4), reduces the capillary pressure with reduction of the oedema, promotes the healing process and amplifies fibroblastic activity and neoangiogenesis (2, 22).
Several Authors report the hyperbaric oxygenation therapy as beneficial in the recovery of long-term hematuria (2, 22-25) and irritative micturitional symptoms (23). As in cystitis, the radioinduced proctopathy is treated with hyperbaric oxygenation that reduces tenesmus and rectal bleeding (26, 27).
Generally it is suggested an early start of the hyperbaric oxygenation after radiotherapy, but this topic is still debated (28).
Finally it is important to note that neo-angiogenesis caused from the HOT doesn't induce the recurrence of the prostate cancer (8, 29).

The interstitial cystitis and urgency/frequency syndrome

These two conditions present a clinical pattern with pelvic and urethral pain, micturitional urgency/frequency, negative microbiological urinary culture, negative urine citology, haematuria; the morphological aspects are less defined, in fact the classic interstitial cystitis with Hunner's ulcer, is rare (30), and often the diagnosis is based on the association of clinical, endoscopic (glomerulations) and urodynamics aspects (31).
The therapy aims to reduce the inflammation of the bladder and therefore the symptoms (30, 31); in the case of the Hunner's ulcer a surgical procedure with augmentation ileocystoplasty is needed (30).
The interstitial cystitis and the urgency/frequency syndrome have some clinical and morphological analogy with radioinduced cystitis and so some Authors have tried to treat also it with hyperbaric oxygenation therapy.
In fact hyperbaric oxygenation due to its antinflammatory effect and the activation of the angiogenesis and healing processes can improve the symptoms, in particular in cases presenting with glomerulations (7, 32).
The therapy consists of 30-40 sessions 90 min long at 2,5 ATA.
The series are limited in number but the results are interesting with improvement of frequency, urgency and pain for 15-24 months (7, 32); these results are based on self-evaluation from the patients and therefore could be related to both placebo or therapeutic effect (placebo is effective in this syndrome up to 30% of cases) (33). On the contrary it is almost impossible to evaluate the changes of the histological aspects.
For this reason the use of hyperbaric oxygenation in these syndromes should be validated by further research.

Chronic pelvic pain syndrome

The clinical analogy between the chronic pelvic pain syndromes and interstitial or radioinduced cystitis, suggests to propose the hyperbaric oxygenation also for the treatment of this disease.
The chronic pelvic pain is a condition of pelvic, perineal, testicular or hypogastric, chronic or relapsing pain (34).
The ethiology and physio-pathology are unknown
The EAU guidelines identifies two groups of patients with chronic pelvic pain: one includes patients with defined diseases (such as prostatitis) or with a morpho-anatomic equivalent (endometriosis, anal diseases etc.) and another including the patients with the idiopathic forms which have the same sites of pain in common (34).

Regarding the first group the hyperbaric oxygenation can operate against the inflammation and also promote the reduction of the symptomatology. To explain the effect of the hyperbaric oxygenation in the second group is more difficult; we can hypothesize that hyperbaric oxygenation modulates the synthesis of the growth factors and PGE promoting some local and central pain-killing effects.
Hyperbaric oxygenation is used to treat chronic pain syndromes affecting different somatic tracts, with encouraging results (10, 35), therefore extensive research including urologists, gynecologists and hyperbaric specialised physicians, should be promoted in order to integrate this therapy with the other numerous treatments for chronic pelvic pain syndromes.

Conclusion

Our experience with the use of the hyperbaric oxygenation therapy in urology is based on 22 patients treated for *Fournier's gangrene*, 8 patients treated for radiation induced cystitis and 4 patients treated for urgency/frequency syndrome (after approval of ethical committee). In consideration of our promising preliminary results, we can conclude that the hyperbaric oxygenation therapy interferes in the tissue metabolism, has an anti-inflammatory effect, and also promotes neo-angiogenesis, tissue repair and healing; in urology this therapy seems to offer promising prospectives and in fact its use is confirmed for radio-induced cystitis and rectal bleeding and for necrotizing fasciitis.
In other fields of the urology – such as urgency/frequency syndromes and chronic pelvic pain syndromes – it would be interesting to extend the research to better understand if this therapy can reduce the symptoms and can improve the efficacy of multimodal therapies and promote the hyperbaric oxygenation therapy on the basis of more solid findings.

References

1. Hammarlund C. "The physiologic effects of hyperbaric oxigenation". In Kindwall and Whelan (eds.) "Hyperbaric medicine practice" 1999; BPC ed., pp. 37-68.

2. Pires C, Irani J, Ouaki F, et al. "Oxygénothérapy hyperbare et cystite hémorragique post-radique". Prog Urol 2002; 12:1188-1193.

3. Bilic I, Petri NM, Bezic J, et al. "Effects of hyperbaric oxygen therapy on experimental burn wound healing in rats: a randomized controlled study". Undersea Hyper Med 2005; 32:1-9.

4. Al Waili NS, Butler GJ. "Effects of hyperbaric oxygen on inflammatory response to wound and trauma: possible mechanism of action" Scientific world journal 2006; 3:425-441.

5. Kang TS, Gorti GK, Quan SY, et al. "Effect of hyperbaric oxygen on the growth factor profile of fibroblasts". Arch Facial Plast Surg 2004; 6:31-35.

6. Marx RE, Ehler WJ, Tayapongsak P, et al. "Relationship of oxygen dose to angiogenensis induction in irradiated tissue". Am J Surg 1990; 151:1514-1517.

7. Van Ophoven A, Rossbach G, Oberpenning F, et al. "Hyperbaric oxygen for the treatment of interstitial cystitis: long-term results of a prospective pilot study". Eur Urol 2004; 46:108-113.

8. Conconi MT, Baiguera S, Guidolin D, et al. "Effects of hyperbaric oxygen on proliferative and apoptotic activities and reactive oxygen species generation in mouse fibroblast 3T3/J2 cell line". J Investig.Med 2003; 51:227-232.

9. Sumen G, Cimsit M, Eroglu L. "Hyperbaric oxygen treatment reduces carrageenan-induced acute inflammation in rats". Eur J Pharmacol 2001; 431:265-268.

10. Yildiz S, Uzun G, Kiralp MZ. "Hyperbaric oxygen therapy in chronic pain management". Curr Pain Headache Rep 2006; 10:95-100.

11. Margolis DJ. "Malattie cutanee dei genitali esterni maschili" In "Urologia di Campbell". Verduci Ed. 1999; 2:705-720.

12. Asci R, Sarikaya S, Buyukalpalli R, et al. "Fournier's gangrene: risk assessment and enzymatic debridement with lyophilized collagenase application". Eur Urol 1998; 34:411-418.

13. Corman JM, Moody JA, Aronson WJ. "Fournier's gangrene in a modem surgical setting: improved survival with aggressive management". BJU Int 1999; 84:85-88.

14. Lauks SS. "Fournier's gangrene". Surg Clin North Am 1994; 74:1339-1352.

15. Sorensen MD, Krieger JN, Rivara FP, et al. "Fournier's gangrene: population based epidemiology". J Urol 2009; 181:2120-2126.

16. Jeong HJ, Park SC, Seo IY, et al. "Prognostic factors in Fournier gangrene". Int J Urol 2005; 12:1041-1044.

17. Passavanti G, Pizzuti V, Costantini FM, et al. "Traitment par une thérapie multidisciplinaire et reconstruction chirurgicale avec l'utilisation d'un expanseur cutané, dans un cas de gangrène de Fournier". Andrologie 11; 2002; 12:402-403.

18. Al-Shaham AA. "Prepucial skin flap for reconstruction of the scrotum in Fournier's gangrene". Ann Chir Plast Esthet 2001; 46:637-639.

19. Passavanti G, Bragaglia A, Costantini FM, et al. "Hyperbaric oxigen therapy, surgery and advanced dressings, in the treatment of Fournier's gangrene". Urology 2007; S3A:45.

20. Porter A, Littrup P, Grignon D, et al. "Radioterapia e crioterapia del carcinoma prostatico" in "Urologia di Campbell", Verduci ed. 1999; pp. 2637-2660.

21. Sant GR. "Inflammatory disease of the bladder". In Gillenwater, Grayhack, Howards, Duckett (eds.) "Adult and pediatric Urology" Mosby ed. 1996; pp. 1327-1354.

22. Neheman A, Nativ O, Moskovitz B, et al. "Hyperbaric oxygen therapy for radiation-induced haemorrhagic cystitis". BJU Int 2005; 96:107-109.

23. Corman JM, McClure D, Pritchett R, et al. "Treatment of radiation induced hemorrhagic cystitis with hyperbaric oxygen". J Urol 2003; 169:2200-2202.

24. Mayer R, Klemen H, Quehenberger F, et al. "Hyperbaric oxygen therapy an effective tool to treat radiation morbidity in prostate cancer". Radiother Oncol 2001; 61:151-156.

25. Yoshida T, Kawashima A, Ujike T, et al. "Hyperbaric oxygenation therapy for radiation-induced hemorrhagic cystitis". Int J Urol 2008; 15:639-641.

26. Dall'Era MA, Hampson NB, His RA, et al. "Hyperbaric oxygen

therapy for radiation induced proctopathy in men treated for prostate cancer". J Urol 2006; 176:87-90.

27. Schultheiss TE, Lee WR, Hunt MA, et al. "Late GI and GU complications in the treatment of prostate cancer". Int J Radiat Oncol Biol Phys 1997; 37:3-11.

28. Crew JP, Jephcott CR, Reynard JM. "Radiation-induced haemorragic cystitis". Eur Urol 2001; 40:111-123.

29. Chong KT, Hampson NB, Bostwick DG, et al. "Hyperbaric oxygen does not accelerate latent in vivo prostate cancer: implication for the treatment of radiation-induced haemorrhagic cystitis". BJU Int 2004; 94:1275-1278.

30. Hanno P. "Cistite interstiziale e malattie correlate" in "Urologia di Campbell". Verduci ed. 1999; 2:617-649.

31. Ferchaud J, Deval B. "Cystyte interstitielle". Pelv Perineol 2006; 1:117-124.

32. van Ophoven A, Rossbach G, Pajonk F, et al. "Safety and efficacy of hyperbaric oxygen therapy for treatment of interstitial cystitis: a randomised, sham controlled, double-blind trial". J Urol 2006; 176:1442-1446.

33. Propert KJ, Payne C, Kusek JW, et al. "Pitfalls in the design of clinical trials for interstitial cystitis". Urology 2002; 60:742-748.

34. Fall M, Baranowski AP, Fowler CJ, et al. "EAU guidelines on Chronic Pelvic Pain". Eur Urol 2004; 46:681-689.

35. Kiralp MZ, Yildiz S, Vural D, et al. "Effectiveness of hyperbaric oxygen therapy in the treatment of complex regional pain syndrome". J Int Med Rse 2004; 32:258-262.

Correspondence

Giandomenico Passavanti, MD
Via Oberdan 44
58100 Grosseto
mpeppina@infinito.it