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Prospective Pilot study of Quality of Life in patients with severe late-radiation-toxicity treated by Low hyperbaric-oxigen-therapy

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ABSTRACT

Background/purpose: The aim of this study is to assess for the first time the immediate and long term impact on quality-of-life of HBO treatments(HBOT) at 1.45 ATA (Absolute Atmospheric Pressure) Medical Hyperbaric chamber.

Methods: Patients over 18 years-old, suffering of grade 3 Common Terminology Criteria for Adverse Events (CTCAE) 4.0 radiation induced late toxicity and progressing to standard support therapy were included in this prospective study. HBOT was given daily, sixty minutes per session by a Medical Hyperbaric Chamber Biobarica System at 1.45 ATA at 100% O2. Forty sessions were prescribed for all patients given in 8 weeks. Patients reported outcomes (PROs) was assessed by the QLQ-C30 questionnaire, before starting, in the last week of the treatment, as well as during follow up.

Results: Between February-2018/June-2021, 48 patients fulfilled the inclusion criteria. A total of 37 patients (77%) completed the treatment prescribed HBOT sessions. Patients with anal fibrosis (9/37) and brain necrosis (7/37) were the most frequently treated. The most common symptoms were pain (65%) and bleeding (54%). In addition, thirty out of the 37 patients who completed the pre- and post-treatment Patients Reported Outcomes (PROs) assessment also completed the follow up European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire C30 (EORTC-QLQ-C30), and were evaluated in the present study. Mean follow up was 22,10 (6–39) months.

The Median score of the EORTC-QLQ-C30, at the end of HBOT and during follow-up, was improved in all assessed domains, except in the cognitive aspect ($p = 0.106$).

Conclusions: HBOT at 1.45 ATA is a feasible and well tolerated treatment, improving long term quality of life in terms of physical function, daily activities and general health subjective state of patients suffering severe late radiation-induced toxicity.

Introduction

Radiotherapy is a major treatment for cancer patients. Late radiation-induced toxicity is a complex process involving fibroblasts and endothelial cells that evolves to poor oxygenation in tissues, atrophy and hypoplasia in the connective tissue. As a consequence, fibrosis and tissue necrosis cause a permanent damage [1]. These complications bring symptoms such as pain, bleeding, neurological dysfunction, tenesmus and incontinence that would be detrimental to the patient's quality of life (QoL) [2].

Treatment of these complications is usually unsuccessful due to the difficulty in supplying oxygen and nutrients to the devascularized areas [3]. Hyperbaric oxygen therapy (HBOT) consists of breathing 100% oxygen in a pressurized chamber at a pressure higher than the ambient atmospheric pressure (>1ATA) [2,4,5]. Thus, the oxygenation of the tissues is improved by increasing the arterial oxygen pressure and

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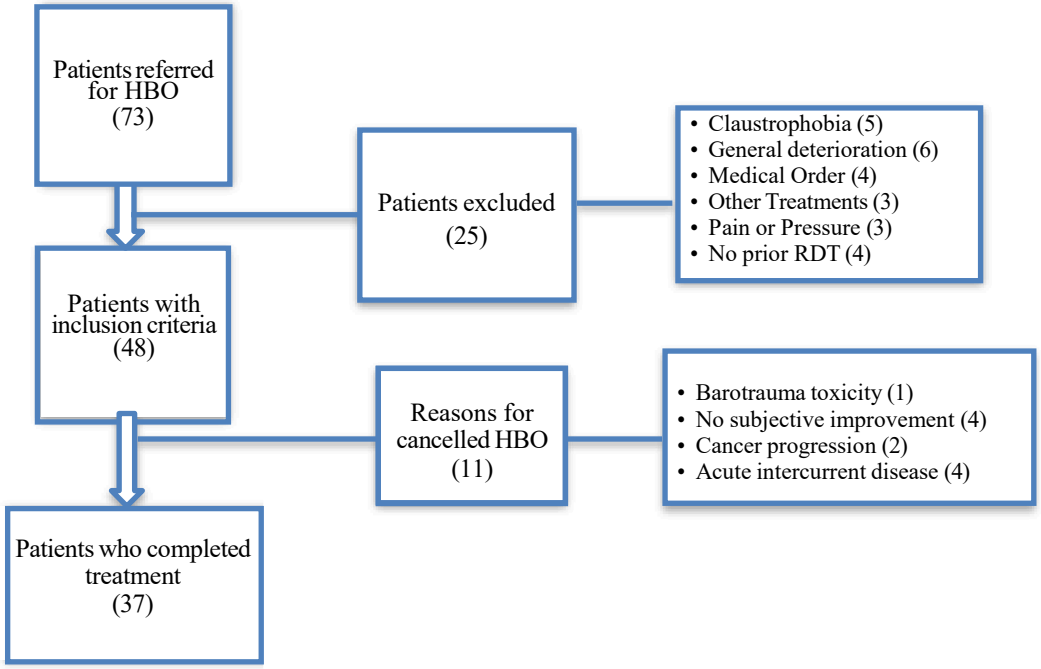

Fig. 1. Patients referred for hyperbaric treatment and criteria for exclusion or no completed treatment.

the dissolved oxygen content in the plasma. HBOT effects in irradiated tissues are related to its ability to induce vascular proliferation by promoting angiogenesis, fibroblasts proliferation and collagen synthesis favoring the healing of these tissues. HBOT can compensate tissue hypoxia by reducing tissue oedema, promoting healing and preventing infection by stimulating leukocytes and regulating the immune system function by promoting blood flow within ischemic tissues [3].

HBOT is already indicated in severe late radiation-induced toxicities, like soft tissue/bone necrosis, proctitis, cystitis and brain necrosis [5]. All of these studies have been performed with the available multi-seat hyperbaric subaquatic chambers at $\geq$ 2 ATA [2]. However, one of the main drawbacks of using HBOT at high pressures ($\geq$2 ATA) is toxicity, mainly middle ear and sinus/paranasal barotrauma, described in about 2–46% of patients that lead to premature discontinuation of treatment [6–9]. Another side effect of high-pressure chambers is the risk of neurotoxicity, associated with high oxygen concentrations. Among other limitations, such as access difficulties, cost of treatments and the need of treating several patients at the same time. Besides that, patients cannot use their electronic devices inside the chamber, limiting adherence to treatment [10].

The use of low-pressure hyperbaric chambers, allow the administration of O2 at a concentration close to 100% in an environment at least to 1.45 ATA, where the penetration radius of O2 from the capillaries to the tissues is ~ 75 μm allowing to reach an arteriolar oxygen pressure gradient (PpO2) of approximately 950 mmHg, exceeding the minimum physiological requirements of PpO2 (PpO2 20 mmHg), without exceeding a concentration that causes toxicity or an excessive production of reactive oxygen species [10].

The role of low-pressure hyperbaric chambers (e.g. 1.45 ATA), have already been evaluated in a randomized study, with encouraging better results in terms of pain control, fatigue, and functional capacity compared to standard therapy [11].

The major concerns of patients suffering from late radiation induced toxicity is their limited quality of life in terms of reduced functional capabilities, pain or other symptoms and limitations in their ability to cope with daily activities among others. Therefore, the treatment of these radiation-induced severe toxicities, should be devoted to improve the patient́s perceived QoL and evaluated by PROs [12–13].

We hypothesized that HBOT administered in an individual medical hyperbaric chamber at 1.45 ATA breathing 100% O2, would improve the quality of life of severe late radiation-induced toxicity patients.

The aim of this study is to assess for the first time both the immediate and long term impact of HBOT administered in an individual medical hyperbaric chamber at 1.45 ATA breathing 100% O2, on the quality of life of severe late radiation-induced toxicity patients.

Method

From February 1st, 2018 to June 30th, 2021, patients were enrolled if they were over 18 years old suffering of severe late radiation induced toxicity (grade 3 CTCAE 4.0) and progressing to standard support therapy were included in this prospective study. Exclusion criteria were: patients with general state severe deterioration, claustrophobia, uncontrolled seizures, previous barotraumas or medical criteria as well as other complications non related to radiotherapy treatment. All patients provided written informed consent. This study was done in accordance with the Helsinki Declaration and the International Conference on Harmonization: Harmonized Tripartite Guideline: Guideline for Good Clinical Practice. The study was approved by the Ethic Committee of our Institution.

HBO treatment

The treatment is performed in a mono-place chamber, breathing 100 %O2 at 10 l/m. Hyperbaric treatment consists in daily sessions, 60 min per session. Forty sessions were prescribed to all patients. Briefly, the patient is introduced into the chamber lying on a stretcher, the hatch is closed and the internal pressure begins to increase until it reaches 1.45 ATA. At that moment the patient puts on the mask and begins to breathe the enriched air for 60 min. The patient is provided with an assistive listening device and the use of electronic devices was allowed inside the chamber during HBOT [10].

Patients reported Outcomes (PROs)

PROs was assessed using the Spanish version of the European

Table 1
Patients characteristics to completed HBO treatment.

CharacteristicsTreatment HBO N° of patients	37
Age (years)	59,81 ± 10.31 (37–80)
Sex	
Male	23 (62,2%)
Female	14 (37,8%)
Primary tumor	
Rectal cancer	11 (29,7%)
Anal cancer	10 (27,0%)
Bladder and prostate cancer	5 (13,5%)
H&N cancer	4 (10,8%)
Breast cancer	3 (8,1 %)
Lung cancer	3 (8,1 %)
Pelvic Sarcoma	1 (2,7%)
Toxic Symdroms	
Proctitis and rectal ulcer	5 (13,5%)
Osteonecrosis of de Jaw	2 (5,4%)
Fibrosis and anal ulcer	9 (24,3%)
Cutaneus Fistula	4 (10,8%)
Flap	2 (5,4%)
Cistitis and bladder ulcer	6 (16,2%)
Fibrosis and H&N ulcer	1 (2,7%)
Gastric ulcer	1 (2,7%)
Brain necrosis	7 (18,9%)

* H&N: head and neck.

Organization for Research and Treatment of Cancer Quality of Life Questionnaire(EORTC-QLQ-C30)[12]. This questionnaire contains 30 items, grouped into 8 domains. The scores obtained are standardized for different domains. In domains 1–7, higher values indicate a decrease in QoL, while high values in the global health domain (8) indicate a better QoL. The QoL questionnaires were given to the patients previous to start the HBOT, the last week of treatment sessions and at least 6 months after the end of HBOT. The QoL score was analyzed in each of the 8 different domains comparing the pretreatment assessment, the one carried out in the last week of treatment with HBOT, as well as the one carried out in the last follow-up visit.

Statistical analysis

Means, standard deviation and quartiles have been calculated so as to describe quantitative variables. Quantitative variable's normality has been tested through Shapiro Wilks test. Qualitative variables have been described through absolute and relative frequencies. Friedman test has been used to compare the scores in every one of the 3 moments of time. Dichotomous variables in the 3 stages have been compared using Cochran's Q test. Fisher's exact test has been used to check the association between qualitative variables. P- value lower than 0.05 is considered significant. R Core Team 2022 (v4.2) has been the statistical program for this study [14].

Role of the funding source

This is an independent academic study. Protocol design, data analysis, interpretation, and preparation of this report was done by authors. Data analysis was performed by an independent statistician (JMGM). All authors had access to the study data. All decisions relating to the manuscript writing and content were made jointly by the authors, including the final decision to submit for publication.

Results

Feasibility and acute toxicity

Between February 2018 and June 2021, 73 patients were referred for HBO treatment, 25 of which did not fulfill the inclusion criteria (Fig. 1). Eleven of the 48 selected patients (23%) did not complete the prescribed 40 sessions of HBOT due to: patient́s refusal to treatment after no subjective improvement (4 patients), intercurrent acute disease (4 patients), death due to cancer progression (2 patient) and one patient (2%) showed bilateral toxicity grade 4 barotrauma, of the middle ear (hemotympanum without alteration of the tympanic membrane) after the third HBO session (Fig. 1). Therefore, 37/48 (77%) patients completed the whole prescribed treatment.

The mean age was 59,81 ± 10,31 years (37–80) and 23 were men (62%). The most common radiation-induced toxicity treated were: 9 anal fibrosis (24%), 7 brain necrosis (19%), 6 late radiation cystitis (16%) and 5 proctitis (14%) (Table 1). The most common symptoms were pain (65%) and bleeding (54%) (Fig. 2).

The mean follow-up was 22.10(6–39) months. Seven patients did not complete the follow up questionnaires due to early death due to cancer progression (2) and follow up loss (5). Therefore, 30 patients have completed the three questionnaires required for the analysis.

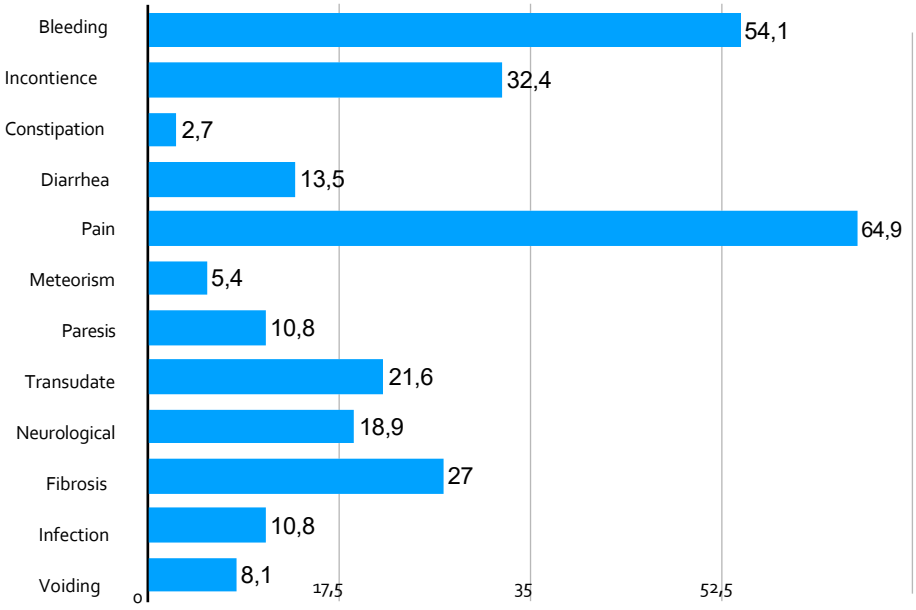

Fig. 2. Percentage of symptoms whit patients to completed HBO treatment.

Table 2
Comparative Patients Reported Outcomes according to specific EORTC-QLQ-C30 domains.

Domains	Item Number	Mean score Initial	Final	Follow up	p Value comparative
1. Physical function	1–5	9.29 ± 3.68 (5–19)	8.19 ± 3.24 (5–16)	8.00 ± 4.04 (5–19)	P = 0.002
2. Daily activities	6–7	4.58 ± 2.08 (2–8)	4.13 ± 1.71 (2–8)	3,52 ± 2.01 (2–8)	p = 0.008
3. Symptoms	8–19	23.71 ± 7.64 (12–41)	20.19 ± 6.61 (12–38)	19.23 ± 6.31 (12–34)	p < 0.001
4. Cognitive function	20,25	3.71 ± 1.40 (2–6)	3.26 ± 1.39 (2–6)	3.26 ± 1.84 (2–8)	p = 0.106
5. Emotional function	21–24	8.42 ± 3.34 (4–16)	7.26 ± 3.13 (4–16)	7.55 ± 3.62 (4–16)	p = 0.029
6. Social function	26,27	5.71 ± 2.65 (2–12)	4.48 ± 2.11 (2–10)	5.26 ± 2.61 (2–12)	p = 0.016
7. Economic impact *	28	38.71 %	25.81 %	19.35%	p = 0.022
8. General health subjetive state	29,30	6.87 ± 3.07 (2–14)	9.52 ± 2.49 (4–14)	9.61 ± 3.23 (2–14)	p < 0.001

* Items in 'Economic Impact' is divided in two categories, 'Nothing at all and A bit' versus 'Considerably and A lot', only the percentage of the latter was taken into account to compare and assess improvement at every single stage of the follow-up.

Patients reported Outcomes. (PROs)

Assessment of the different EORTC-QLQ-C30 domain at the end of HBO treatment and at the maximum follow-up assessment performed, showed a significant improvement of the perceived self-wellbeing, in all the domains evaluated, except domain related to the cognitive function ($p = 0.106$) (Table 2). Major improvements were observed in physical function ($p = 0.002$), daily activities ($p = 0.008$), symptoms ($p < 0.001$) and general health subjective state ($p < 0.001$). These PROs improvements seems to last during patients follow-up (Fig. 3).

Discussion

HBOT is an evidence-based treatment for severe late radiation-induced toxicity [3]. Most published studies have used hyperbaric multi-seat subacuate-treatment chambers at a pressure ≥ 2ATA [2,3]. However, no data is available in relation to feasibility, toxicity and efficacy in terms of quality of life for HBOT treatment administered with a Medical Hyperbaric Chamber at 1.45 ATA in patients with severe late radiation induced toxicity. The simplicity of use, privacy, availability to general population and low expected side-effects of this medical chambers would deserve further investigation in this setting.

Patients seeking treatment for their severe late radiation-induced toxicity usually show poor quality of life scores. Symptoms progression, social limitations and emotional distress are often found in these patients[2,13,15]. Unfortunately, the amount of publications about patients reported outcomes, assessed by QoL scales in HBOT treatments are few. Data in breast and head and neck cancers patients, evaluated through EORTC-validated questionnaires, showed that treatment at ≥ 2 ATA HBO improved the quality of life at the end of the treatment in 67%-71% of patients [13,15]. Other studies showed improvement of scores related to evaluation of pain, depression [16] or in non-standardized patient/clinical evaluations [17].

We must emphasize that PROs should be the main endpoint for studies in this clinical situation, where the relief of the universe of symptoms and feelings that limits the patient well-being, must be a priority [13].

Our results confirm an improvement in all (except cognitive

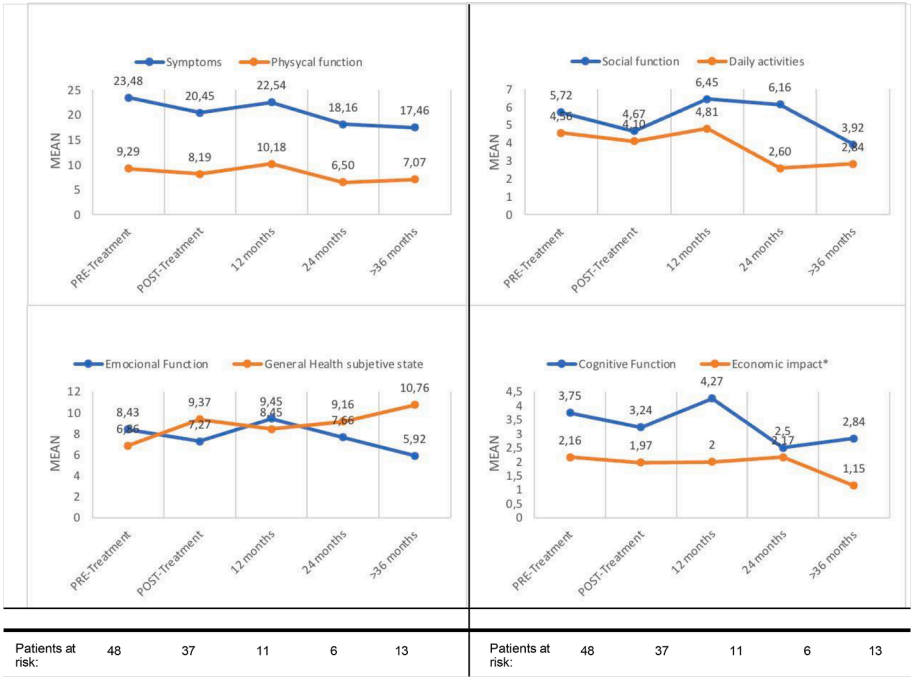

Fig. 3. Evolution of *Patients Reported Outcomes according to specific EORTC-QLQ-C30 domains.*

function) domains assessed. Moreover, the statistically significant improvement in these domains observed immediately after the end of HBOT, also last during patients follow-up. In our patients, symptoms are the domain that probably is the one that most impact the quality of life, influencing other domains, as the social function and the general condition of the patients [11,13,15,16].

Patients also presented an objective recovery of their physical function, daily activity and economic situation. This last domain, maybe due to the decrease in medical requirements needed after symptomatic control and an improvement in the possibility to get back to work [18].

Cognitive function did not improved after HBOT. A detailed analysis of a larger series of patients with brain necrosis and perhaps, a more accurate assessment criteria and tools should be used to get to know the real impact HBOT in this domain specifically. [19–21].

The most important result in our study is that General Health Subjective State significantly improve both at the end of the treatment and during the follow up. It is also worth considering the difficulty that patients might find in answering questionnaires accurately. In our opinion, General Health Subjective State was the domain describing the patients' feelings in a better way. Furthermore, it should be the most considered domain to validate the effectiveness of HBOT, mostly in our series that has a great heterogeneity of toxic syndromes evaluated.

Our proposed HBOT treatment was feasible and safe. Only 5 patients (13.5%) did not completed the HBOT due to personal decision (4) or barotrauma (One case in a 81-y old patient not following physicians indications to prevent ear pressure damage). As expected, our barotrauma rate (1/37) compares favorably with up to 46% reported in HBOT(>2 ATA) studies [6,7,22].

One of limitations of this series, it is the small number of patients included in each category. Future studies with a greater number of patients would enabled an stratification in terms of types of Severe Late Toxicity Syndrome which would help determining which groups would take more advantage of HBOT.

Conclusion

We show for the first time that HBOT by medical hyperbaric chamber at 1.45 ATA breathing 100 %O2 at 10 l/m is feasible, effective, simple and well-tolerated. In our study, HBOT improves the immediate and long-term quality of life of patients, suffering from severe late radiation-induced toxicity syndrome. Major improvements were observed in terms of physical function, daily activities and general health subjective state of patients suffering severe late radiation-induced toxicity.

Other studies including larger sample size are needed in to best draw more comprehensive conclusions.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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