Hyperbaric oxygen therapy as an adjuvant to source control in necrotizing soft tissue infections

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ABSTRACT

Introduction: Necrotizing soft tissue infections (NSTI) are rare but potentially lethal disorders, and adequate management is time- and resource-demanding. This study aims to assess whether variations in the treatment modalities – surgery, hyperbaric oxygen (HBO_2)therapy and negative pressure wound therapy – had an impact on the length to definitive source control in NSTI patients who underwent HBO_2.

Methods: This is a retrospective study of all NSTI patients treated with hyperbaric oxygen therapy between March 2007 and May 2015 at Unidade Local de Saúde de Matosinhos (ULSM) Hyperbaric Unit. A multiple linear regression model was used to assess the impact of different treatment modalities in the post-diagnosis time until source control.

Results: 58 patients were included; overall mortality was 13.8%. Mean time until source control was 10.4 days (±5.4). All patients were under empiric and broad-spectrum antibiotics on the day of diagnosis. Patients underwent an average of 0.62 (±0.29) surgical interventions and 1.06 (±0.52) HBO_2 sessions per day. The regression model (R^2=0.86) showed that after adjusting for other covariates, doubling the number of HBO_2 sessions per day shortened source control by five days (β= -5.25; 95% CI -6.49 to -4.01), and for each day that HBO_2 was delayed, source control was achieved one day later (β = 1.03; 95% CI 0.82 to 1.24).

Conclusion: More intensive HBO_2 protocols with earlier and more frequent sessions shorten the time until definitive source control in necrotizing soft tissue infections, potentially lowering the impact of systemic effects of infection and complications associated with organ dysfunction.

INTRODUCTION

Necrotizing soft tissue infections (NSTI) are a group of severe diseases that affect soft tissue compartments. They are rare, with a global prevalence of four cases per million, but with a potentially devastating outcome due to major local tissue destruction and systemic manifestations [1]. NSTI include a number of diseases differentiated by location, pathogens involved and clinical course (e.g., necrotizing fasciitis, Fournier's gangrene, gas gangrene, and other less frequently used terms). More recently the term "necrotizing soft tissue infections" has been used as an umbrella term for all of these conditions, encouraging the use of the same diagnostic and treatment strategies [2].

Clinically, patients usually present with pain, swelling and erythema that are frequently attributed to other causes. The appearance of bullae, skin necrosis and crepitus are late signs that reflects the invasive nature and subcutaneous progression of the infection [3]. Laboratory measurements are non-specific and imaging studies have low sensitivity. Because of this, the diagnosis remains clinically based [2,3].

Adequate treatment of NSTI is time- and resource-demanding, aiming for a rapid control of infection spread. The mainstay of successful management consists of early, thorough and repeated surgical debridement with appropriate antibacterial therapy and wound care [1]. Hyperbaric oxygen (HBO_2) therapy is considered an

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adjunctive treatment for NSTI by the European Committee for Hyperbaric Medicine and the Undersea and Hyperbaric Medical Society, even though high-quality evidence from randomized clinical trials is lacking [4].

Hospital Pedro Hispano (HPH), in Matosinhos, Portugal, provides advanced surgical care, HBO_2 and intensive care support in the same facility, with 'round-the-clock availability, a setting that is unique in continental Portugal. It has been recognized as a referral center in the country for almost 10 years.

We hypothesize that more aggressive treatment protocols may be associated with faster control of infection. The aim of this study is to assess whether variations in the treatment modalities – surgery, HBO_2 and negative pressure wound therapy – had an impact on the time to definitive source control in NSTI patients who underwent HBO_2 therapy.

METHODS

We performed a retrospective observational study that included all patients with a diagnosis of NSTI treated with HBO_2 in the period between March 2007 and May 2015. Data were collected using medical chart review, with approval from Institutional Review Board and Ethics Committee (approval number 09/CE/JAS).

Study population

Age, gender and the presence of the following comorbidities were recorded: diabetes, obesity, arterial hypertension, chronic heart failure, coronary disease, cerebrovascular disease, anticoagulation status, smoking, chronic obstructive pulmonary disease, chronic renal failure, ethanol abuse, illicit drug abuse, malignancy, chemotherapy and chronic corticosteroid therapy [1, 5]. An acute physiology and chronic health evaluation (APACHE) II score of patients in intensive care was also recorded.

The presence of an NSTI was determined by the intraoperative finding of infection and necrosis of the deep layers of skin, fascia and/or muscle. The type, site and microbiology of the infection were recorded.

Treatment interventions

As for the main treatment interventions – surgery, antibiotics and HBO_2 therapy – we recorded the timing in days and number of procedures/sessions performed since diagnosis until definitive source control was achieved. These data were retrospectively analyzed and quantify the actual treatment plan these patients received regardless of surgical or HBO_2 protocol. Source control was established when no new areas of necrotic or inflammatory tissue were found intraoperatively, which prompted interruption of HBO_2 therapy. Complications attributed to HBO_2 treatment were recorded. We also investigated whether negative pressure wound therapy was used. HBO_2 was conducted in a multiplace chamber (Haux Starmed 2200), with maintenance of the level of monitoring and organ support required, such as mechanical ventilation and hemodynamic support, attended by a team of critical care-trained physician and nurse during transport and HBO_2. A standard protocol was used – 3.0 ATA, 100% O_2, 60 minutes – with two daily sessions in the first 72 hours and one session thereafter until source control.

Outcomes and statistical analysis

The main objective of this study was to determine the 30-day mortality of NSTI patients treated in our institution and secondly to investigate the impact of the different treatment modalities on the number of days required to achieve source control. For every surviving patient we retrospectively analyzed, we used a multiple linear regression model with five different treatment variables:

- number of HBO_2 sessions per day after beginning of treatment;
- delay in initiating HBO_2 after diagnosis of NSTI;
- use of negative pressure wound therapy;
- number of surgical debridement interventions per day;
- delay in first debridement after diagnosis of NSTI.

The multiple linear regression model was performed to determine the association between the secondary outcome and these covariates, related to the main treatment modalities used in the management of these patients. "Number of HBO_2 sessions per day," "delay in initiating HBO_2", "number of surgical debridement interventions per day" and "delay in first debridement" were introduced in the model as continuous variables, while "use of negative pressure wound therapy" was coded as a binary categorical variable. We attributed statistical significance to a two-sided P-value of less than 0.01. Statistical analysis was performed using IBM® SPSS Statistics software version 22.0.

RESULTS

Patient characteristics

The study included 58 patients diagnosed with necrotizing soft tissue infections. Thirty-four (59%) of them were referred from other institutions. Median age was 58 (range 16-82), and 40 (69%) were male. Patient-related comorbidities are presented in Table 1. Arterial hypertension (48.3%) and diabetes mellitus (39.7%) were the most prevalent comorbidities, and 21% of patients had no associated risk factors. The most frequently affected sites were the perineum (40%) and lower extremities (38%), as described in Table 2.

NSTI are usually classified I-IV according to the microbial agents isolated from the wound, which relates to the clinical presentation and epidemiology (Type I, polymicrobial, more indolent; Type II, monomicrobial skin- and throat-derived agents, aggressive; Type III, gram-negative monomicrobial, seafood ingestion or water contamination; Type IV, fungal). Table 3 shows the number of cases of each type (3). Thirty cases (52%) were classified as a type I NSTI, 23 (32%) as type II and one case of type IV. In 3 cases (5%), no microbial pathogen was isolated. Forty-seven patients (81%) were admitted in the intensive care unit with multiple organ dysfunction. All patients were under empiric and broad-spectrum antibiotic therapy on the day of diagnosis of NSTI as per local protocol guidance (complying with standard practice), and subsequently adjusted to microbiological findings.

Four patients had complications during treatment that required its interruption. This was due to severe bronchospasm, growing dyspnea that required endotracheal intubation, ear barotrauma and oxygen toxicity with seizures.

Table 1: NSTI patient-related comorbidities

risk factor	number	percent
hypertension	28	48.3
diabetes	23	39.7
obesity	15	25.9
ethanol abuse	12	20.7
smoking	10	17.2
coronary disease	3	5.2
other	17	29.1
healthy	12	20.7

Patient-related comorbidities in our population of NSTI patients. About 80% of cases had an associated comorbidity.

Table 2 – Extent of infection

site of infection	number	percent
perineum	23	40
lower extremity	22	38
upper extremity	10	17
abdomen	7	12
neck	3	5
thorax	1	2

Extent of infection based on anatomic areas. Some patients had involvement of multiple body regions.

Table 3 – Classification of NSTI

type	number	percent
1	30	51.7
2	23	39.7
3	0	0
4	1	1.7
no isolate	3	5.2
unknown	1	1.7

Classification of NSTI necrotizing soft tissue infection according to the microbiological findings, based on a classification described by Morgan (Morgan MS. J Hosp Infect. 2010;75:249-57).

Primary outcome – mortality

Overall mortality was 13.8% (eight patients), with a mean time until death of 9.3 days after diagnostic (minimum <24 hours, maximum Day 22). Mortality in the subgroup of patients with multiple organ dysfunction was 19%.

Secondary outcome – time to source control

Surviving patients were managed with a daily average number of 0.62 (±0.29) surgical interventions and 1.06 (±0.52) HBO_2 sessions. Negative pressure wound therapy was used in 24 (41.4%) patients.

A multiple regression was performed to assess the relation between time until source control and the different treatment variables such as number of HBO_2 sessions per day after beginning of treatment; delay in initiating HBO_2 after diagnosis of NSTI; use of negative pressure wound therapy; number of surgical debridement interventions per day and delay in first debridement after diagnosis of NSTI. Number of HBO_2 sessions per day after beginning of treatment and delay in initiating HBO_2 after diagnosis of NSTI statistically significantly predicted time until source control ($R^2 = 0.86$, $P < .001$). The other three variables did not

add statistical significance to the prediction, P > .01 (Table 4). According to our model, time until source control is determined by the following equation:

Time (number of days) = 14.8 + 1 (delay in initiating HBO_2 in days) – 5.2 (number of HBO_2 sessions per day)

Thus, a delay in initiating HBO_2 therapy was correlated with delayed source control (P<0.01) (Figure 1), and a higher number of HBO_2 sessions per day was correlated with earlier source control (P<0.01) (Figure 2). The other covariates analyzed do not contribute to the multiple regression model, after adjustment.

The patients' clinical severity may influence the time until source control. To evaluate this effect we calculated a model including the APACHE II score of our ICU patients (n=35) and found it had no significant effect on this outcome (regression ANOVA: P<0.001; adjusted R^2 0.82; APACHE II P=0.154).

DISCUSSION

Necrotizing soft tissue infections are highly lethal. Even though their incidence is relatively rare, several factors contribute to their being a significant public health problem. Historically, mortality has been very high, reaching 76% [6]. Contemporary reports of mortality are highly variable, having recently been determined at 21.4% [2,7]. There is a growing prevalence of factors that increase the susceptibility to the development of soft tissue infections, and its clinical presentation in initial stages may be subtle. This leads to patients presenting to the emergency department with substantial progression of the infection and severe systemic involvement [3,5]. It is well accepted that these patients benefit greatly from early recognition and intervention, despite the fact that it represents a major diagnostic and therapeutic challenge.

Surgical debridement is the primary treatment modality for NSTI. This should be done promptly and radically, including necrosectomy and fasciotomy in cases presenting with compartment syndrome [1,8]. The Infectious Diseases Societies of America (IDSA) recommends that most patients with necrotizing fasciitis be operated upon daily until there is no need for further debridement [9].

Negative pressure wound therapy has been used increasingly in the management of complicated wounds. Nevertheless its applicability in NSTI has not been as extensively studied. This treatment modality is thought to improve local conditions, namely by improving blood flow, increasing the migration of inflammatory cells, accelerating the formation of granulation tissue and removing bacterial contamination, exudate and necrotic debris [10-12].

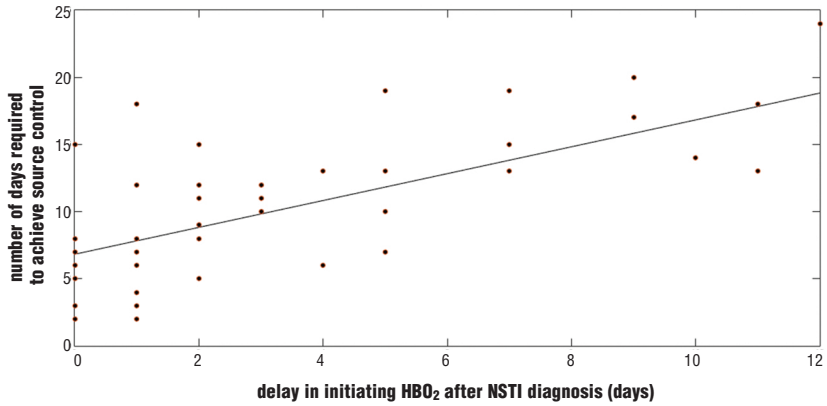
HBO_2 exerts an antimicrobial effect through several mechanisms: bacteriostatic and bactericidal effect on agents involved in NSTI (Clostridia, *Escherichia coli*, *Pseudomonas*) [13]; inhibition of clostridial α-toxin production [14]; optimization of local microcirculatory conditions of infected areas [15]; enhanced activity of granulocytes and macrophages (increased phagocytic capacity and oxidative burst) [16]. Additionally, a synergistic effect of HBO_2 and a number of antibiotics used against bacteria isolated in NSTI has been demonstrated [15,17].

The utility of HBO_2 therapy in NSTI was initially demonstrated in clostridial gas gangrene [14,18,19]. Its role in the treatment of NSTI is defined as an adjuvant to surgical treatment and antibiotic therapy. There are no randomized clinical trials demonstrating its effectiveness, as reported in a recent Cochrane review [20]. Nevertheless, a number of case series and retrospective reports have studied the impact of HBO_2 on the mortality of patients with NSTI [21-28]. From this evidence, it seems that HBO_2 has a beneficial effect when used as a complementary treatment [4,29-33]. However, two studies state that patients treated with HBO_2 in addition to surgery and antibiotics had higher morbidity and mortality, but they can arguably be attributed to a selection bias, as these patients were more severely ill [34,35]. In fact, other authors state that the sickest patients benefit the most from HBO_2 [32].

The existing protocols for application of HBO_2 in NSTI patients are variable and supported by limited data. Due to the absence of studies, not much has changed since the pioneer studies of gas gangrene models on rats, and most centers use a protocol of 253-304 kPa (2.5-3.0 atmospheres absolute/ATA) during 60 to 90 minutes [36]. In our hyperbaric medicine unit, the standard protocol is 3.0 ATA100% oxygen for 60 minutes, with two daily sessions in the first 72 hours and one session thereafter until source control.

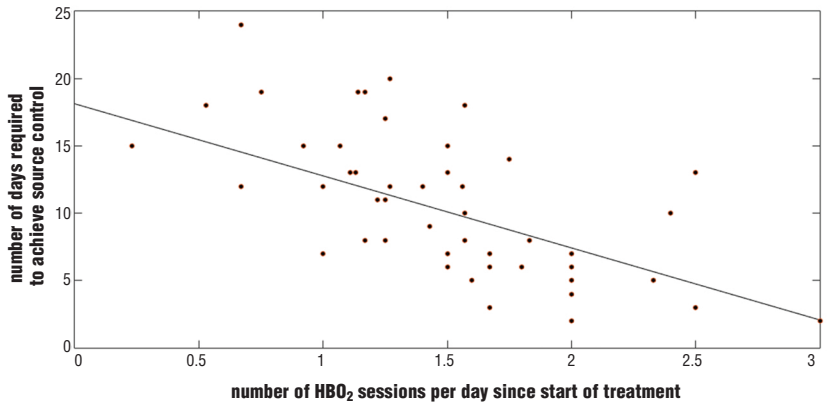
A number of factors, however, may interfere with patient treatment plans, such as the need for further operative debridement, cardiovascular or respiratory instability, logistical problems, or medical decision to increase or decrease the number of sessions ac-

Figure 1: Impact of delay in initiating HBO_2



Impact of the delay in initiating HBO_2 in the number of days required to achieve source control. Each patient is represented by a point; the line represents the regression based on the multivariate regression model.

Figure 2: Impact of the number of HBO_2 sessions per day



Impact of the number of HBO_2 sessions per day in the number of days required to achieve source control. Each patient is represented by a point; the line represents the regression based on the multivariate regression model

cording to disease progress. For example, less severe infections with little systemic derangement may be treated with one daily sessions, and in the most severe cases we may continue with two daily sessions until the patient responds favorably, even after the first 72 hours. Similarly, the surgical debridement strategy is not the same for every patient, due to a variety of factors, and the utilization of negative pressure wound therapy in the presence of an active infection is controversial [1,37]. Therefore, we hypothesized that all these different criteria can influence patient outcomes, which was the objective of this study: to determine whether control of the infection was more effective in the patients who had either more aggressive surgical or HBO_2 protocols. Our patients' mortality results compare favorably with recently published literature [27,31,32,38].

Data suggest that the period of acute disease and initial management is the time when mortality is greater, mostly due to the systemic effects of infection, with consequently higher demand for intensive care support and complications associated with organ dysfunction. Source control is a fundamental step in the management of septic patients, and patients with NSTI need multiple surgical interventions to achieve it [39]. Therefore, halting the progression of infection in a shorter period of time may result in a decreased incidence of mortality-related complications such as refractory septic shock, acute respiratory distress syndrome and in a decreased requirement for mechanical ventilation, which are major contributors to the morbidity and mortality associated with NSTI [37].

To the best of our knowledge, this is the first study that compares treatment interventions with time to source control. Our results demonstrate that HBO_2 treatment influences the time it takes to achieve complete source control. Objectively, as described in Table 4, our

Table 4

variables	adjusted β (95% CI)	P-value
number of HBO_2 sessions per day after beginning of treatment	-5.25 (-6.49 to -4.014)	<0.01
delay in initiating HBO_2 after diagnosis	1.03 (0.82 to 1.24)	<0.01
negative pressure wound therapy	0.52 (-0.79 to 1.82)	0.430
delay in first debridement after diagnosis	0.29 (-0.36 to 0.94)	0.373
number of surgical interventions per day	-0.08 (-3.54 to 3.38)	0.963

The adjusted β coefficient reports the independent effects of each treatment variable on the number of days until source control, based on our regression model. Delay in initiating HBO_2 and the number of HBO_2 sessions have a statistically significant effect.

analysis shows that for every day that we anticipate the initiation of HBO_2 treatment, source control was achieved one 1.03 days earlier (0.82 to 1.24, 95% confidence interval, P<0.01), and increasing the number of daily sessions of HBO_2 by one reduces by 5.25 days the time until source control (4.01 to 6.49, 95% confidence interval, P<0.01). Therefore, early initiation of HBO_2 therapy with multiple daily sessions are statistically significant independent predictors of earlier achievement of source control. We believe that, as with antibiotics, HBO_2 therapy must be initiated early and in a sufficient "dosage" (i.e., more frequent treatment sessions).

Neither the utilization of negative pressure therapy, timing of first operative intervention, or number of debridement procedures caused a statistically significant difference in the time of source control. Regarding surgical aggressiveness, indicated by the number of debridement interventions per day, the statistical model demonstrated that before adjustment for the other covariables there was an inverse association between the number of interventions per day and time to source control. However, this effect was lost after adjustment for the other covariables.

These findings are not consistent with the available literature [6,9,40]. We attributed this to the fact that this study is underpowered to detect differences that result from the surgical strategy, since all but nine patients were operated upon in the first 24 hours after diagnosis, as supported by current best evidence.

We understand from our experience that, due to the persisting controversy regarding the applicability of HBO_2 therapy, some patients are transferred following several days of standard operative and antibacterial therapy and failure of infection control. This constitutes a bias on outcomes, either because patients die prior to transport to our institution or because they are referred in a later phase of the disease progression.

Additionally, interhospital transfer exposes patients to an increased risk of complications, and this risk must be balanced against the potential benefit [41]. In NSTI patients, the existing evidence suggests that patients benefit from an initial operative debridement at the original hospital, with subsequent transport to a referral center with more adequate resources, as opposed to transferring patients before the initial surgical debridement [27].

LIMITATIONS

A limitation of our study is that due to its retrospective design, the timing of interventions could be determined in days only, not hours. Additionally, this is a single-center study with a limited number of patients. Finally, the data collection spans a nine-year period, sufficient for medical practice to change significantly, particularly in the multidisciplinary management of critical care patients.

CONCLUSION

In summary, our data demonstrate that a more aggressive HBO_2 protocol with earlier and more frequent sessions shortens the time until definitive source control in necrotizing soft tissue infections, potentially lowering the impact of systemic effects of infection and complications associated with organ dysfunction. Further multicenter research is necessary to determine the clinical significance of our findings and the ideal treatment protocol for patients with NSTI.

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