Hyperbaric Oxygen Therapy in Necrotizing Soft Tissue Infections: A Retrospective Study

Tina Steiner, Annett Seiffart, Julia Schumann, and Michael Bucher

Abstract

Necrotizing soft tissue infection is a severe life-threatening disease correlated with high mortality. Until now, therapeutic concepts include antimicrobial, intensive care and surgical interventions, as well as the application of hyperbaric oxygenation (HBO), which still has a controversial status. Evidence of the therapeutic concept of HBO is, so far, limited to positive experiences in case studies and physiological benefits in animal studies. That is why the HBO therapy method is not yet fully established. In this light, a retrospective data analysis was conducted. The analysis involved 91 intensive care patients in the Clinic for Anesthesiology and Surgical Intensive Care at the University Hospital Halle (Saale) who, because of a necrotizing soft tissue infection, were treated with HBO therapy (period of observation from 2008 to second quarter 2017). Treatment outcome was examined with regard to mortality, complications, time spent in the intensive care unit, and functional limitations. The criteria of therapy relevance, therapy management, and conclusions drawn from the treatment results were evaluated. By examining the result of combining all four categories of treatment, we aim to investigate established guidelines and their practicability. We expect treatment with HBO to have no disadvantages compared with acknowledged treatment concepts. This study considers the success of treatment as a result of complying with optimal therapy. In a contribution to establish coverage use and an inventory of hyperbaric chambers, we also aim to create a national case register, so that patients do not have to depend on long and risky transportations.

1 Introduction

Necrotizing soft tissue infections (NSTI) can be described as a variety of infections of any of the layers within the soft tissue compartment (dermis, subcutaneous tissue, superficial fascia, deep fascia, or muscle) that are associated with necrotizing changes [1]. Early manifestations of these infections include swelling, erythema, fever and tachycardia [1–3]. Additionally, pain is specified as ‘pain out of proportion’, meaning a strong pain in contrast to an inconspicuous skin appearance. With progression of the infection, typical ‘hard’ signs occur including hemorrhagic bullae, necrosis of skin and crepitus with subcutaneous gas, and skin anesthesia, often associated with

T. Steiner · A. Seiffart · J. Schumann (✉) · M. Bucher
Clinic for Anesthesiology and Surgical Intensive Care, University Hospital Halle (Saale), Halle (Saale), Germany
e-mail: julia.schumann@uk-halle.de

© Springer International Publishing AG, part of Springer Nature 2018

O. Thews et al. (eds.), *Oxygen Transport to Tissue XL*, Advances in Experimental Medicine and Biology 1072, https://doi.org/10.1007/978-3-319-91287-5_42

severe sepsis and organ failure [2–4]. Due to the unspecific symptoms at the onset of infection, establishing an early diagnosis is difficult and depends on the experience and knowledge of the surgeon [1, 5].

Current therapy concepts involve early and aggressive debridement, intensive medical care, and pathogen-specific antibiotic therapy [6]. Additionally, adjuvant hyperbaric oxygen therapy (HBO) may be applied. HBO is a form of therapy in which the patient is placed in a chamber with increased ambient pressure >1 atmosphere absolute while breathing 100% oxygen. The rationale for this concept is justified in increasing tissue oxygen tension, potentially leading to beneficial effects in NSTI such as bacterial killing, potentiation of antibiotics (aminoglycosides), and wound healing [6]. The mechanism of bacterial killing may be twofold: First, strict anaerobic bacteria cannot grow in an oxygen-rich environment. Second, the ability of leukocyte to phagocytose bacteria is increased by enhanced oxygen supply in the infected tissue [7]. In addition, HBO may enhance wound healing by stimulation of fibroblasts/endothelial cells and promotion of angiogenesis [8]. To date, application of HBO therapy is based on level III evidence only [7, 9]. The present studies are retrospective, uncontrolled, with insufficient numbers of cases, and have conflicting results [7, 9]. Therefore, HBO treatment of NSTI remains highly controversial [5].

Against this background we aimed to examine the existing data of patients who have undergone HBO therapy due to NSTI in our university clinic. The aim is to evaluate and optimize present therapy concepts. With the aim to establish an approach to the reasoned care of patients suffering from NSTI, this study might pave the way to a national case register.

2 Methods

A retrospective, descriptive analysis was performed based on the Integrated Care Manager Database (ICM), which provides a complete and progressive medical record of a patient's data. The analysis involved 91 intensive care patients in the Clinic for Anesthesiology and Surgical Intensive Care at the University Hospital Halle (Saale) who, because of a necrotizing soft tissue infection, were treated with HBO therapy (period of observation from 2008 to second quarter 2017). Data were extracted at four defined dates: date of admission, day 5 of the stay in the intensive care unit (ICU), day 10 of the stay in the ICU, and date of discharge. Each patient record was viewed with respect to demographic information, diagnosis, and pre-existing comorbidities. The localization of infection was also examined. Treatment outcome was analyzed with regard to mortality, functional limitations, complications, time spent on the ICU, and overall duration of stay at the hospital. Furthermore, we investigated vital parameters, laboratory findings, and use of supportive medicine including antimicrobial therapy, pain and catecholamine management. Additionally, we inspected treatment-related data such as microbiological findings and surgical interventions, as well as the total number and the procedure of the HBO therapy. The use of organ replacement modalities (such as dialysis, mechanical ventilation, and blood product transfusions) was also extracted. Finally, we plan to evaluate (i) the period of time from diagnosis until the first surgical and hyperbaric intervention, and (ii) the hospital's catchment area. Data were collected and documented by means of Microsoft Excel software; statistical analysis was performed with SPSS software and the chi-square test. The study protocol was approved by the local ethics committee of the University Clinic Halle (Saale), reference number 2017-47.

3 Results

The study group consisted of 62 males (68.1%) and 29 females (31.9%). We treated transferred patients from seven federal states; of these, the majority (51 patients; 56.0%) came from Saxony-Anhalt. With 20 registered deaths, the intensive care mortality was 22.0%. Overall, 23 patients died resulting in a hospital mortality of 25.3%.

Table 1 Descriptive parameters of patients with necrotizing soft tissue infections

Descriptive parameters	Total (N = 91)	Survivors (N = 71)	Non-survivors (N = 20)	p-value
Male	62	49 [79.0%]	13 [21.0%]	0.734
Female	29	22 [75.9%]	7 [24.1%]	
Age <70 years	57	50 [87.7%]	7 [12.3%]	0.004
Age ≥70 years	34	21 [61.8%]	13 [38.2%]	
Single localization of infection	61	50 [82.0%]	11 [18.0%]	0.195
Multiple localization of infection	30	21 [70.0%]	9 [30.0%]	
Amputation	35	26 [74.3%]	9 [25.7%]	0.604
No amputation	56	45 [80.4%]	11 [19.6%]	
HBO ≤2 treatments	24	14 [58.3%]	10 [41.7%]	0.007
HBO >2 treatments	67	57 [85.1%]	10 [14.9%]	

Table 2 Pre-existing medical conditions of patients with necrotizing soft tissue infections

Comorbidities	All patients (n = 91)	Survivors (n = 71)	Non-survivors (n = 20)	p-value
Myocardial infarction	8	3 [37.5%]	5 [62.5%]	0.004
Kidney disease	44	29 [65.9%]	15 [34.1%]	0.007
Cardiovascular disease	49	33 [67.3%]	16 [32.7%]	0.008
Immunosuppression	4	1 [25.0%]	3 [75.0%]	0.009
Hypertension	55	39 [71.0%]	16 [29.0%]	0.043
Hepatic disease	8	4 [50.0%]	4 [50.0%]	0.045
Organ failure	46	32 [69.6%]	14 [30.4%]	0.049
Peripheral vascular disease	44	37 [84.1%]	7 [15.9%]	0.176
Intravenous drug abuse	2	2 [100.0%]	0 [0.0%]	0.448
Respiratory insufficiency	24	20 [83.3%]	4 [16.7%]	0.464
Cancer	10	7 [70.0%]	3 [30.0%]	0.516
Diabetes mellitus	43	34 [79.1%]	9 [20.9%]	0.819
Alcohol abuse	10	8 [80.0%]	2 [20.0%]	0.873

The average stay in the ICU was 19.6 days, with a minimum of 0.2 h and a maximum of 110.5 days.

The average age of the group was 64.7 (range 27.0–92.5) years. The average age of patients who died in the ICU was 72.1 years; the average age of the survivors was 62.6 years. As shown in Table 1 patients aged ≥70 years were more likely to die than younger persons (p-value 0.004).

Amputations had to be performed in 35 (38.5%) cases; of these, 12 (34.3%) were performed in our university hospital and 23 (65.7%) were performed previously in another hospital. Of the 23 latter amputations, five patients had to be amputated for a second time in our university hospital due to the spread of infection or to complications.

HBO treatments were performed in all cases with an average of 5.4 treatments per patient. The mean number of HBO treatments was 5.8 for survivors and 3.9 for non-survivors. According to Table 1 patients receiving more than two HBO treatments were more likely to survive than patients receiving one or two HBO treatments (p-value 0.007).

The patient's characteristics with respect to comorbidities are shown in Table 2. There was a high incidence of accompanying illnesses. Hypertension was significantly associated with mortality. Additional frequently occurring comorbidities significantly associated with mortality include: kidney disease, cardiovascular disease, and organ failure. Whereas no association was found between diabetes mellitus and mortality.

In total, 72 patients (79.1%) were treated for severe sepsis or septic shock; of this group, organ failure was documented in 45 patients. Additional reasons for necrotizing soft tissue infection included trauma, skin infections or ulcers, medical interventions such as injections

or operations, and idiopathic settings. In one-third of the patients only one area was affected by infection, whereas in the other patients two or more areas were infected. Survival rate of patients with one infected area was 82.0%; survival rate of patients with several infected areas was 70.0%. The source of infection could be determined for only 47 patients (51.6%); of this group, postoperative wound infections were most frequently detected (27.5%). However, the origin of infection seemed to have no impact on patients' rate of survival.

4 Discussion

NSTI are rare but severe and rapidly progressive, resulting in high mortality. In previous studies, death rates are reported to range from 16% to 34% [3]; our results are comparable to these data. We observed a large scale of comorbidities, namely hypertension and diabetes mellitus, which is in line with previous reports [5]. This is of importance, since hypertension is correlated with higher mortality. Another identified risk factor was the patient's age.

In this study, non-survivors received fewer HBO treatments than survivors. This might at least in part be explained by the fact that non-survivors were generally characterized by a more severe and progressive infection. The resulting hemodynamic instabilities are opposed to the patient management necessary for HBO therapy. This aspect makes it difficult to rule out the benefit of additional HBO treatment. Other weaknesses of our study include the retrospective study design and the absence of a control group not receiving HBO therapy. However, with respect to the severity of necrotizing soft tissue infections, withholding HBO therapy would be medically inappropriate in these patients. Thus, the establishment of a randomized prospective trial is not feasible for ethical reasons.

Remarkably, 56% of the study population originated from Saxony-Anhalt, which means that almost half of the seriously ill persons had to be transferred from different federal states to receive HBO therapy. Bearing in mind that a delay in the start of appropriate therapy is associated with increased mortality [10] this represents an alarming situation. There is a need to increase the awareness of HBO therapy of NSTI and to intensify research in this respect. The current study is intended to contribute to the establishment of a case register, which would be the first in Saxony-Anhalt. In addition, we have invited other HBO centers to jointly examine their patient database in order to implement a multicenter study. We are convinced that a sound scientific basis will support the work of the existing HBO centers and may even facilitate the set-up of new ones.

Based on the study's preliminary results it can be indicated that the use of the HBO approach as therapy method in NSTI merit further research. Until now we were able to identify only a few parameters with a positive correlation to a low mortality rate. Therefore, further investigations concerning the effect of certain parameters still need to be done in order to optimize the survival rate of patients suffering from NSTI.

Acknowledgments We are grateful to Mrs. Annett Christel from our clinic for her assistance in data mining and Mr. Dr. Daniel Tiller for statistical support.

References

1. Anaya DA, Dellinger EP (2007) Necrotizing soft-tissue infection: diagnosis and management. Clin Infect Dis 44(5):705–710. https://doi.org/10.1086/511638
2. Hakkarainen TW, Kopari NM, Pham TN et al (2014) Necrotizing soft tissue infections: review and current concepts in treatment, systems of care, and outcomes. Curr Probl Surg 51(8):344–362. https://doi.org/10.1067/j.cpsurg.2014.06.001
3. Krieg A, Dizdar L, Verde PE et al (2014) Predictors of mortality for necrotizing soft-tissue infections: a retrospective analysis of 64 cases. Langenbeck's Arch Surg 399(3):333–341. https://doi.org/10.1007/s00423-014-1162-1
4. Phan HH, Cocanour CS (2010) Necrotizing soft tissue infections in the intensive care unit. Crit Care Med 38(9):S460–S468. https://doi.org/10.1097/CCM.0b013e3181ec667f
5. Mills MK, Faraklas I, Davis C et al (2010) Outcomes from treatment of necrotizing soft-tissue infections: results from the National Surgical

Quality Improvement Program database. Am J Surg 200(6):790–796. https://doi.org/10.1016/j.amjsurg.2010.06.008
6. Wilkinson D, Doolette D (2004) Hyperbaric oxygen treatment and survival from necrotizing soft tissue infection. Arch Surg 139(12):1339–1345. https://doi.org/10.1001/archsurg.139.12.1339
7. Shaw JJ, Psoinos C, Emhoff TA et al (2014) Not just full of hot air: hyperbaric oxygen therapy increases survival in cases of necrotizing soft tissue infections. Surg Infect 15(3):328–335. https://doi.org/10.1089/sur.2012.135
8. Sander AL, Henrich D, Muth CM et al (2009) In vivo effect of hyperbaric oxygen on wound angiogenesis and epithelialization. Wound Repair Regen 17(2):179–184. https://doi.org/10.1111/j.1524-475X.2009.00455.x
9. Mathieu D, Marroni A, Kot J (2017) Tenth European Consensus Conference on hyperbaric medicine: recommendations for accepted and non-accepted clinical indications and practice of hyperbaric oxygen treatment. Diving Hyperb Med 47(1):24–32
10. Martinschek A, Evers B, Lampl L et al (2012) Prognostic aspects, survival rate, and predisposing risk factors in patients with Fournier's gangrene and necrotizing soft tissue infections: evaluation of clinical outcome of 55 patients. Urol Int 89(2):173–179. https://doi.org/10.1159/000339161