

Which Role for Hyperbaric Oxygen Therapy in the treatment of Fournier's gangrene? A Retrospective Study.

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Abstract

Background: In Fournier's gangrene the surgical debridement plus broad-spectrum antimicrobial therapy is the mainstay treatment but can cause a great loss of tissue. Moreover, the local poor blood supply, the infection and the damage to the vessels can delay the healing. Consequently, the disease needs long hospital stays and, despite all, has high mortality rate. The aim of our study is to investigate the improvement offered by hyperbaric therapy in Fournier's gangrene.

Methods: We retrospectively evaluated data on 23 consecutive patients admitted for Fournier's gangrene at the University hospital "P.Giaccone" of Palermo from 2011 to 2018. The relation between hyperbaric therapy, hospital stay and mortality was evaluated. Factors related to mortality were also examined.

Results: The use of hyperbaric therapy was offered to 13(56.5%) patients. Hospital stay was longer in patients treated with HBOT[mean11(C.I.0.50-21,89)vs25(C.I.18.02-31.97); $p=0.02$]. Mortality occurred in three patients(13.1%), two of whom treated with HBOT.

Mortality was not statistically related to sex($p=0.20$), BMI($p=0.53$), renal failure ($p=1.00$), diabetes($p=0.49$), age>65 years old($p=0.55$), simplified FGSI>2($p=0.05$), higher ASA scores(>=4)($p=0.47$), symptoms at admission lasting since more than 72 hours ($p=0.28$), HBOT($p=1.00$), need of colostomy($p=0.06$), several operations($p=1.00$), several operations plus HBOT($P=1.00$). Conversely, the delay between admission and surgical operation was statistically related to mortality, 1.7 days(C.I.0.9-3.5) in survivors vs 6.8 days(C.I.3.5-13.4) in death patients($p=0.001$).

Conclusions: Our study proves that a delay in the treatment of patients with Fournier's gangrene has a correlation with the mortality rate, while the use of HBOT seems to not improve the survival rate, increasing the hospital stay instead.

Background

Fournier's gangrene (FG) comprises all necrotizing fasciitis of the perineum, including the genitalia in both sexes and at all ages, regardless of the etiology, with or without proven infection.¹ The etiopathogenesis is debated between primary ischemic process and infection because it is unclear if the disease represents an ischemic process complicated by infection from commensals or an infection finally causing a thrombosis of small subcutaneous vessels.¹

The most frequent microbiological samples are often polimicrobic and include clostridia, klebsiella, streptococci, coliforma, staphylococci, bacteroides and corynebacteria while controversial is the role of the clostridium perfringens, only occasionally isolated.¹ The related mortality arises from 3 to 45 per cent with an overall rate of 16 per cent proposed by a recent review.² Deaths are due to severe sepsis, coagulopathy, acute renal failure, diabetic ketoacidosis and multiple organ failure.

The Fournier's gangrene severity index score (FGSIS) that evaluates serum creatinine, hematocrit, potassium, body temperature, heart rate, respiratory rate, white blood cell count, serum sodium and serum bicarbonate has been proposed by Laor to stratify the disease with a cutoff point of 9 so that when FGSIS is > 9, the probability of death is 75%, and when it is < 9, the probability of survival is 78%.³ To improve scores-use Lin proposes a simplified score (LRINEC) that includes only creatinine, hematocrit and potassium.⁴

The surgical debridement associated with broad spectrum antimicrobial therapy is the main treatment. The common proposed treatment includes penicillin for streptococci, metronidazole for anaerobic organisms, and a third-generation cephalosporin with or without gentamicin for coliform organisms and staphylococci. However, during recent years a monotherapy with imipenem/cilastatin demonstrates adequate antibiotic coverage.⁵ This broad-spectrum therapy is suggested regardless the gram's stain and the culture results and can be reassessed when results are obtained.¹

In FG the poor local blood supply, the infection and the damage to the blood vessels or a combination of these factors can delay the healing.⁶ An adequate debridement can cause a great loss of tissue whose healing process can take longer time confirmed by the long hospital stays and high mortality rate.

In this scenario hyperbaric oxygen therapy (HBOT) could potentially be a therapeutic option enabling to speed the wound healing as it increases tissue oxygen tension to a level that inhibits and kills anaerobic bacteria, reduces systemic toxicity, limits the necrotizing fasciitis and enhances the demarcation of gangrene.

The aim of HBOT is to bathe all fluids, tissues and cells of the body in a high concentration of oxygen placing the patient in an airtight chamber and administering 100% oxygen for respiration at a pressure greater than 1 atmosphere.⁵

Thus, HBOT acts enhancing the transportation of oxygen by increasing the oxygen saturation in blood. The elevation of the partial arterial oxygen pressures greater than 1000 mm Hg causes an up-regulation of growth factors, a down-regulation of inflammatory cytokines, an increasing of fibroblast activation, angiogenesis, antibacterial effects and an enhanced antibiotic action.⁷

To investigate the role of HBOT in the treatment of Fournier's gangrene we retrospectively evaluated the patients admitted at the O.U. of General surgery and emergency of the University hospital "P. Giaccone" of Palermo from January 2011 to November 2018.

Methods

Data on 23 consecutive patients admitted at the Urgent and General surgery O.U. of the Policlinico "P. Giaccone" of Palermo and undergoing surgical operations for Fournier's gangrene were retrospectively collected. The patients were identified by the diagnostic code on admission of International Classification of Diseases-9: 608.83. For each patient we collected demographic data, admission characteristics,

management and treatment results from patients' charts. Demographic data collected include age, sex, body mass index (BMI), comorbidities, American Society of Anesthesiologists (ASA) score, delay before admission.

Admission characteristics included laboratory values, radiological findings, and microbiological stains results. The LRINEC score was calculated for each patient. Data on perioperative management included time until first operation, number and type of operative procedures, need of colostomy, type of anesthesia, type of antibiotic therapy and HBOT. Were also recorded length of hospital stay (HS) and 30-days mortality.

Statistical analysis:

We conducted this statistical analysis to examine the potential relationship between the use of HBOT, the length of hospital-stay and mortality.

Descriptive data are presented as parametric and non-parametric data.

To evaluate the gravity of the disease the relationship between the LRINEC score, age and ASA was analyzed using the Fisher's exact test.

The influence on the length of hospital stay offered by the severity of the disease calculated with the LRINEC score, the use of HBOT, the need of a diverting stoma (colostomy) was evaluated using the independent-sample t-test or the Welch-test when appropriate.

Factors influencing mortality and specifically sex, age, BMI, comorbidity, ASA score, duration of symptoms, LRINEC score, the use of HBOT, the need of colostomy and the need of several operations or both were evaluated using the independent-sample t-test, the Welch-test or the Fisher's exact test.

Statistical analysis was conducted using MedCalc Statistical Software (MedCalc Software, Ostend, Belgium).

Results

Twenty-three patients [(16 M, 7 F) (mean age 62.7, sd 13.1, C.I. 37–84)] were admitted between 2011 and 2018 for Fournier's Gangrene and underwent a surgical operation.

Patients' characteristics showed tobacco consumption in 50% of patients, alcoholic abuse in 15%, diabetes in 55%, BPCO in 13.1%, cardiovascular diseases in 34.8%, inflammatory bowel diseases in 13.1%, arthritis in 8.7%, renal failure in 13.1%, liver diseases in 8.7%, oncological disease on chemotherapy in 13%. Average BMI was 29.4 (sd. 6.5, C.I. 20.5-47.75).

The average duration of symptoms before admission was 11 days (sd 7.9, C.I. 3–30).

First location of symptoms was gluteal in five patients (21.7%), inguinal in four (17.4%), perineal in 8 (34.8%) and scrotal in 6 (26.1%). Average white blood count at admission was 21.000 (sd. 10.300), and

average neutrophils count 80.1% (sd.17.9). C-reactive protein was >1.25 mg/dL in 47% of patients. Fever was present in only three patients (18.8%) and bulging in seven patients (43.8%).

The diagnosis was supported by an ultrasound examination in 8 patients (34.8%), and a CT scan in 21 patients (91.3%). Air bubbles were found at CT scan in the 69.5% of patients, fluid collections in 52.2%, and soft tissue edema in 43.5%.

The average delay between admission and surgery was 4 days (sd 4.4; C.I. 0.1–17); less than 24 hours in 30%, 24–48 hours in 22%, 48–72 hours in one patient and more than 72 hours in 43.5% of patients.

The ASA score was I [0 patients], II [2], III [5], IV [8], V [1], ASA score was unreported in six of the patients managed only with local anesthesia.

Empiric broad spectrum antibiotic therapy was always administered and successively modified accordingly to the results of the samples (Table 1). Data on samples are not available for some patients; the ones collected are showed in Table 1. The used antibiotic regimens are reported in table n.2. The average length of antibiotic therapy was 22 days (sd 11, C.I. 10–60).

General anesthesia was used in 12 patients (52%), and local anesthesia in 11 (47.8%).

A colostomy was performed in 4 patients (17.4%). Ten patients (43.5%) needed more than one surgical procedure. HBOT was offered to 13 (56.5%) patients using a scheduled session of 60 minutes daily, one patient wasn't suitable for HBOT; we have no data regarding four patients. An adverse event represented by dyspnoea, sweating and agitation during HBOT was reported and the treatment in this patient was suspended.

The average length of hospital stay was 26 days (sd. 17.9; C.I. 3–72).

Mortality occurred in three patients (13.1%), two being treated with HBOT.

A LRINEC score at admission > 2 was not statistically related to ASA score ($p = 0.28$), age > 65 years old ($p = 0.30$), need of several operations ($p = 1.000$).

Repeated operations and the need of colostomy were not related ($p = 0.58$). Hospital stay was not related to the need of colostomy ($p = 0.21$) nor to LRINEC score > 2 ($p = 0.68$). The use of HBOT was not related to need of colostomy ($P = 0.50$), need of several operations ($p = 1.00$), LRINEC score > 2 ($p = 0.13$). Hospital stay was longer in patients treated with HBOT [mean 11(CI 0.50–21,89) vs 25(CI 18.02–31.97); $p = 0.024$].

Mortality was not statistically related to sex ($p = 0.20$), BMI ($p = 0.53$), renal failure ($p = 1.00$), diabetes ($p = 0.49$), age > 65 years old ($p = 0.55$), LRINEC score > 2 ($p = 0.05$), higher ASA scores ($> = 4$) ($p = 0.47$), symptoms lasting since more than 72 hours ($p = 0.28$), HBOT ($p = 1.00$), need of colostomy ($p = 0.06$), several operations ($p = 1.00$), several operations plus HBOT ($P = 1.00$). The time between admission and

operation was statistically related to mortality being 1.7 days (C.I. 0.9–3.5) in survivors vs 6.8 days (C.I. 3.5–13.4) in death patients ($p = 0.001$).

Discussion

FG is a disabling disease that causes high mortality rates reported in literature to be up to 21% in the analyzed studies, so an effort to improve these results is necessary.

The aim of our study was to analyze the possible improvements offered by the use of HBOT in the management of Fournier's gangrene in terms of loss of tissue, its related time to heal, and in term of mortality, since the studies in literature have reported mixed results of improvement.

In this disease the infection and edema reduce local blood circulation and tissue oxygenation which increase the progression of necrosis, impair host defenses, and permit invasion of micro-organisms. Bacterial seeding can occur if aerobic bacteria get access to hypoxic tissues, which tends to likely happen during instrumentation in presence of certain pathologies as such genitourinary and colorectal. Once the bacteria have seeded, the production of exotoxins by the infecting aerobic bacteria cause the interaction between immunologically competent cells and chemical mediators of inflammation.

Tissue hypoxia is determined by two main factors: the reduction of blood flow in the amiated tissues and the concomitant proliferation of aerobic bacteria. Thus, this decrease in local oxygen concentration facilitates the seeding and spread of anaerobic bacteria, while causing thrombosis and tissue ischemia.

The rationale of the HBOT treatment is to increase the amount of oxygen that reaches hypoxic tissue and brings oxygen levels back to normal or even hyper oxygenates them.

It is important to note that as far as the regeneration of the amiated tissues is concerned, hyperbaric oxygen therapy stimulates fibroblast activity and angiogenesis. Consequently, there is an increased rate of collagen deposition which rises the time needed for wound healing. This comes from the fact that hyperbaric oxygen therapy has a direct toxic effect on anaerobic bacteria as it generates an increased concentration of free radicals (peroxide and superoxide) delivered from increased oxygen concentrations in the previously hypoxic tissues. Majority of these free radicals are not capable of producing the necessary degrading enzymes (catalase for the peroxide radical and superoxide dismutase for the superoxide radical), that's why they generate direct toxic effect.

The optimization of tissue oxygenation, which can be obtained with repeated hyperbaric oxygen therapy, is fundamental for the body's regenerative and bactericidal mechanism.⁷ On the other hand, oxygen in high doses can be toxic particularly in rich perfused tissue such as the brain and lungs. The acute cerebral oxygen toxicity is reversible whilst the chronic pulmonary oxygen toxicity is dose related and reversible at the used doses. Other risks include barotrauma to the ears, sinuses and lungs and the psychological effect of confinement.

There are different opinions and studies on the use of HBOT in this type of patients (Table 3).^{5;8–19} In a series of 11 patients, Pizzorno *et al.* attributed a 0% mortality rate to the adoption of HBOT.⁸ Accordingly, none of the patients who underwent HBO therapy died in the series proposed by Ayan *et al.*¹⁷ Another positive outcome comes from a study done by Mehl *et al.* where patients with FG who were given HBOT with routine surgical treatment had a mortality rate of 11.5%, whereas the rate was 35.7% for those who underwent only to conventional surgical treatment. Thus, the study concluded that patients who were treated with HBOT had a lower mortality rate compared to conventional therapy alone.²⁰ Interestingly, Hollanbaugh *et al.* observed that the use of HBOT is statistically significant in 26 cases of FG where mortality rate was 7%, and the index increased 5 times in patients without HBOT.¹⁸

In contrast, recently Rosa and Guerreiro reported a mortality rate of 20.8% in a series of 34 patients treated with HBOT.²¹

In a larger retrospective study, Mindrup *et al.* found no difference in length of stay or mortality in relation to HBOT and the authors cautioned against routinely use of HBOT based on the cost associated with the therapy, \$600–\$1,300 per treatment at their center.⁹

Shupak *et al.* pointed out through their study that HBOT when used as a complementary treatment for necrotizing fasciitis, does not offer advantage in decreasing the morbidity and mortality. The outcome in their study among patients treated with HBTO showed a mortality rate of 36% for the treated group while 25% for the untreated one, also founding that the average number of surgical debridement per patient was also lower in the untreated group.²²

Similar outcomes came from Tharakaram and Keckes who also observed a lower number of surgical debridement in the untreated group. On the contrary, in their study the mortality is lower in the HBOT treated group versus the untreated one (12.5% – 2/16 – and 33.3% – 4/12 respectively).²³

In a study proposed by Stanley, analyzing 636 patients, mortality rate is reported in 10.1% of patients and was related to older age, higher BMI and WBCs and lower platelet counts in a multivariate analysis. No data on the HBOT use was reported from their analysis.²⁴

Differing from the high mortality rate found by Rosa and Guerreiro's recent study, as well as from the no difference in length of stay with the use of HBOT stated by Mindrup *et al.* our study shows an increase in hospital stay in patients treated with HBOT [mean 11(CI 0.50–21,89) vs 25(CI 18.02–31.97); p = 0.02] and no statistical significant relation between HBOT and mortality, assessed in 15.4% in the HBOT group and 10% in the not HBOT one (p > 0.05).

Indeed, in our study the mortality was unrelated to the adjunction of HBOT to the surgical debridement plus antibiotic therapy and the only factors that adverse the prognosis was a delay between the admission and the surgical debridement.

When approaching patients, we have to remember that tenderness, erythema and swelling can mimic less severe infections such as cellulitis and erysipelas; however, pain out of proportion to clinical examination should alert the clinician to the strong possibility of necrotizing fasciitis. Cellulitis and erysipelas can present with well-demarcated areas of erythema or inflammation, whereas necrotizing fasciitis is characterized by poorly demarcated erythema. In addition, cellulitis and erysipelas commonly present with generalized signs of infection (ie, fever, lethargy), whereas necrotizing fasciitis can result in systemic toxicity with associated multiorgan dysfunction.²⁵

Yeniyol et al. in a study on 25 patients report that mortality was related to FGSI and to the difference in the duration of symptoms before admission being 1.9+0.7 days in survivors and 4.1+1.4 days in patients who died.²⁶

The progression of the disease is described from Horta as a four steps process with a first phase of 24–48 hours of non-specific symptoms associated with local hardening, edema and erythema, a second phase that is considered invasive and presents with local and regional inflammatory manifestations, a third necrotic phase with a rapid worsening of the general state evolving in a septic shock in 50% of the cases and a fourth phase of healing or spontaneous restoration.²⁷ The rapidity of progression of the gangrenous area is considered a 2–3 cm/h.²⁸

Our data are supported by many studies presents in literature showing a greater elapse of the disease in non-survivors patients in respect to survivors, however these data were often not statistically significant.

Altarac reported that the median duration of symptoms before admission was a day longer in non-survivors (4 days compared to 3), but this was not associated with higher mortality ($p = 0.11$).²⁹

Similar data are reported by Basoglu et al., in their study the duration of the symptoms prior to gangrene in the survivors was 6.2 days (range 2–20 days) in comparison to 7.5 days (range 5–10 days; $P > 0.05$) for the non-survivors.³⁰

Ersay et al. state that the median duration of symptoms at presentation was 7.00 days in survivors, but 8 days in non-survivors. The time from the onset of symptoms to presentation was not significantly different in survivors and non-survivors ($P > 0.05$).³¹

In contrast, to these reports our study focused the problem on the prompt surgical treatment when patients are admitted, thus in our series mortality was related to the delay of in-hospital treatment whether than on the delay between symptoms and admission. Of course, both delays are important for the cure rate even one of them not statistically significant in our series.

These data should stress the concept of the urgent situation when approaching a suspected FG and encourage to an aggressive treatment each time a suspicion arise in a patient admitted in the urgency surgical department.

The current study has several limitations. It was retrospective and the number of patients was quite small but this can arise on the rarity of the disease. The gravity of the disease was evaluated with the LRINEC score instead of the FGSI cause not all data to calculate this score were presents and no data on the extension of the disease are reported.

Conclusions

In our study patients treated with HBOT showed an increase in hospital stay and the HBOT did not offer an improvement in mortality when added to the surgical debridement plus antibiotic therapy.

We cannot confirm the advantages offered by the use of HBOT, moreover its role is not clear by the current literatures and more studies are probably needed.

As previously suggested the incoming necrosis have to be promptly stopped when the first suspicious income because the delay in treatment seems the most important factor in cause an increase in mortality and the only factor in our study that disadvantaged the prognosis of patients.

Abbreviations

FG

Fournier's gangrene

FGSI

Fournier's gangrene severity index score

LRINEC

simplified score by Lin

HBOT

hyperbaric oxygen therapy

BMI

body mass index

ASA

American Society of Anesthesiologists score

HS

Hospital stay

Declarations

Ethics approval and consent to participate: This retrospective study was approved by the local ethics committee of the Azienda Opedaliera Universitaria Policlinico "Paolo Giaccone" di Palermo and is in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patients. Used data were anonymised before its use.

Consent for Publication: Written informed consent was obtained from the patients. Used data were anonymised before its use.

Availability of data and material: The datasets generated and analyzed during the current study are available from the corresponding author repository on reasonable request.

Competing interests: Authors declare that they have no competing interest.

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Authors' contributions: All authors contributed to the conception and design of this study. Material preparation, data collection and analysis were performed by FC and GR. The first draft of the manuscript was written by RT, all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Tables

Microbiological samples
ESCHERICHIA COLI
ESCHERICHIA COLI
ENTEROCOCCUS FECALIS
STAFILOCOCO AUREO,ENTEROCOCCUS FECALIS,
ESCHERICHIA COLI
STREPTOCOCCUS SPECIES
PROTEUS MIRABILIS,ESCHERICHIA COLI
STAFILOCOCO AUREUS
PSEUDOMONAS AERUGINOSA,ESCHERICHIA COLI
ESCHERICHIA COLI,CANDIDA ALBICANS
CANDIDA GLABRATA,STERPTOCOCCUS SPECIES
STREPTOCOCCUS ANGINOSUS
ESCHERICHIA COLI, STREPTOCOCCUS SANGUINIS,
ENTEROCOCCUS FECALIS

Table n.1 Microbiological samples

Antibiotic Regimens
Daptomycin, Metronidazole, Levofloxacin, Meropenem
Clindamycin, Imipenem, Daptomycin, Vancomycin, Meropenem, Metronidazole
Metronidazole, Cubicin, Meropenem
Clindamycin, Piperacillin-Tazobactam, Daptomycin
Ceftazidime, Metronidazole
Daptomycin, Piperacillin-Tazobactam, Metronidazole
Levofloxacin
Clindamycin, Piperacillin-Tazobactam, <i>Anidulafungin</i> , Linezolid
Teicoplanin, Metronidazole, Colimicine, Nistatin
<i>Amoxicillin/ Clavulanate</i>
Clindamycin, Ceftazidime, Imipenem, Vancomycin
Cefixime, Metronidazole
Cefixime
Linezolid, Cefotaxime, Clindamycin, Ampicillin/Sulbactam
Clindamycin, Daptomycin, Tigecycline, Meropenem

Table n. 2 The used antibiotic regimens

Authors (year)	N. of patients	Days of hospital stay		Mortality		Total
		HBOT	Without HBOT	HBOT	Without HBOT	
Pizzorno et al. (1997)	11	NR	-	0	-	0
Korhonen et al. (1998)	33	36	-	9.1%	-	9%
Mindrup et al. (2005)	42	21	25	26.9% (7/26)	12.5% (2/16)	21.4%
Wagner et al. (2011)	41	23	-	0	-	0
Janane et al. (2011)	70	6	-	11.4%	-	11.4%
Martinschek et al. (2012)	8	NR	-	12.5%	-	12.5%
Li et al. (2015)	28	31	31	12.5% (2/16)	33.3% (4/12)	21.43%
Hung et al. (2015)	60			0	66.7% (32/48)	32/60
Milanese et al. (2015)	6	NR	-	0	-	0
Ferretti et al. (2017)	20	22	34	0 (0/4)	18.75% (3/16)	15%
Ayan et al.	41			0 (0/18)	39% (9/23)	
Hollabaugh et al.				7%	42%	
Baraket et al. (2018)	20	NR	NR	0 (0/4)	25% (4/16)	20%
Our study	23	25	11	15.4% (2/13)	10% (1/10)	13%

Table n. 3 Literature reports on the use of HBOT in Fournier's gangrene