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The impact of hyperbaric oxygen therapy on the rate of wound healing in Fournier's gangrene

Wpływ tlenoterapii hiperbarycznej na szybkość gojenia ran w zgorzeli Fourniera

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Abstract

Aim: The aim of the study was to assess the impact of hyperbaric oxygen therapy on the rate of wound healing in Fournier's gangrene. **Materials and methods:** This was a retrospective analysis of 13 patients treated for Fournier's gangrene at the Military Institute of Medicine from October 2017 to November 2020. The study group consisted of males ($n = 13$) aged 24 to 83 years. Two groups of patients were distinguished: group 1 – patients who underwent hyperbaric oxygen therapy as an adjuvant treatment, group 2 – patients who did not undergo hyperbaric oxygen therapy. **Results:** In the first group, hyperbaric oxygen therapy was used as an adjuvant treatment of wound healing in 8/13 patients (62%) with Fournier's gangrene. In this group, significant acceleration of this process and shorter hospital stay were observed (mean = 29 days). In the second group, the hospitalisation time was significantly longer (mean = 51 days) in 5 out of 13 patients (38%). There were no deaths in either group 1 or group 2. **Conclusions:** Hyperbaric oxygen therapy is an effective adjuvant therapy in the treatment of Fournier's gangrene. It has an impact on the rate of wound healing and shorter hospitalisation time.

Keywords: Fournier's gangrene, hyperbaric oxygen therapy, treatment

Streszczenie

Cel: Celem badania było określenie wpływu tlenoterapii hiperbarycznej na proces gojenia ran w zgorzeli Fourniera. **Materiał i metoda:** Badania przeprowadzono, poddając analizie retrospektywnej przypadki 13 chorych, których leczono z powodu zgorzeli Fourniera w Wojskowym Instytucie Medycznym w okresie od października 2017 do listopada 2020 roku. Badaną grupę stanowiły wyłącznie osoby płci męskiej ($n = 13$) w wieku 24–83 lat. Wyodrębniono 2 podgrupy: grupa 1 – 8 pacjentów, u których zastosowano tlenoterapię hiperbaryczną jako leczenie wspomagające, grupa 2 – 5 pacjentów, u których ta terapia nie została zastosowana. **Wyniki:** W grupie 1 (62% grupy badanej) u 8 z 13 pacjentów zastosowano tlenoterapię hiperbaryczną jako leczenie wspomagające gojenie ran w zespole Fourniera. W grupie tej stwierdzono zdecydowane przyspieszenie tego procesu i skrócenie czasu trwania hospitalizacji (średnio 29 dni). W grupie 2 (38% grupy badanej) u 5 z 13 pacjentów czas trwania hospitalizacji był dłuższy i wynosił średnio 51 dni. Zarówno w grupie 1, jak i w grupie 2 nie odnotowano przypadków śmiertelnych. **Wnioski:** Uzyskane wyniki badań wykazują, że tlenoterapia hiperbaryczna wpływa korzystnie na szybkość gojenia ran w zgorzeli Fourniera, powoduje znaczne skrócenie czasu hospitalizacji chorych, a także zmniejszenie liczby wykonywanych procedur chirurgicznych.

Słowa kluczowe: zgorzel Fourniera, tlenoterapia hiperbaryczna, leczenie

INTRODUCTION

Fournier's gangrene (FG) is an aggressive and often fatal multi-microbial form of necrotising fasciitis involving the soft tissues of the perineum, rectum and external genital organs. It was first described by Jean Alfred Fournier, who reported 5 cases of young men with FG. Fournier's gangrene can develop at any age and is ten times more common in men than in women⁽¹⁾. It usually causes painful scrotal or perineal swelling accompanied by sepsis. Physical examination shows small areas of necrotic skin with erythema and swelling. At a more advanced stage of the disease, foul-smelling, purulent discharge appears (Fig. 1).

Fever, chills, tachycardia and malaise are common systemic symptoms of FG⁽²⁾. Risk factors for increased mortality include immunosuppression, diabetes mellitus, alcoholism, atherosclerosis, malnutrition, recent urethral or perineal surgery, human immunodeficiency virus (HIV) infection, liver disease, leukaemia and obesity⁽³⁾. About 40% of patients present with an insidious onset of the disease, which manifests with mild scrotal, perineal and anal pain. The symptom is often ignored and therefore causes treatment delays. Fournier's gangrene can be caused by trauma, an insect bite, or unsafe sexual practices⁽⁴⁾. Computed tomography (CT) or magnetic resonance imaging (MRI) can be helpful in assessing rectal, perineal and scrotal involvement⁽⁴⁾. The degree of internal necrosis is usually higher than indicated by external symptoms. Surgical debridement should be performed within 24 hours as delay in the procedure increases the risk of death (Fig. 2)⁽⁵⁾. Immediate initiation of empiric broad-spectrum antibiotic therapy is recommended. The suggested regimen usually includes vancomycin or linezolid and piperacillin with tazobactam, optionally carbapenems or ceftriaxone and metronidazole⁽⁶⁾.

Hyperbaric oxygen therapy (HBOT) is a method that is increasingly used in the treatment of severe infections of soft tissues, FG in particular. It involves patient exposure to increased ambient pressure while breathing 100% oxygen. Under HBOT conditions, oxygen is transported to cells both by haemoglobin and in the plasma. Research data show that 1 L of blood serum provides 3 mL of physically dissolved oxygen. Breathing

Fig. 1. Necrotic skin lesion of the penis and scrotum with subcutaneous tissue oedema

with 100% oxygen under normobaric conditions ensures oxygen blood saturation at the level of 20 mL/L⁽⁷⁾. The physiological effects of HBOT include increased ability of leukocytes to neutralise aerobic bacteria, stimulation of collagen formation and increased levels of superoxide dismutase, resulting in improved tissue vitality. Hyperbaric oxygen therapy is used as an adjuvant treatment, i.e. to support surgical interventions and broad-spectrum antibiotic therapy^(5,8).

Interdisciplinary treatment of FG involves a combination of surgical and urological interventions, antibiotic therapy, VAC dressing, HBOT and surgical reconstruction (Fig. 3).

AIM OF THE STUDY

The aim of the study was to assess the effects of hyperbaric oxygen therapy on the rate of wound healing in FG.

MATERIALS AND METHODS

This was a retrospective analysis of 13 patients treated for FG at the Military Institute of Medicine from October 2017 to November 2020. The study was approved by the Bioethics Committee of the Military Institute of Medicine. The study group consisted only of male subjects ($n = 13$) aged 24–83 years (Tab. 1). Two groups of patients were distinguished: group 1 – patients who underwent HBOT as an adjuvant treatment, group 2 – patients who did not undergo HBOT. Hyperbaric oxygen therapy procedures were performed at the

Fig. 2. Wide excision of the necrotic tissues of the lower abdomen, perineum, scrotum and buttock

Fig. 3. Interdisciplinary treatment of FG⁽⁹⁾ (modified by the authors)

Clinical Department of Hyperbaric Medicine of the Military Institute of Medicine in Warsaw. The standard treatment protocol uses pure oxygen in a hyperbaric chamber at 2.5 atmospheres absolute (ATA). Standard HBOT programme consists of 3 20-minute sessions with 5-minute intervals when the patient breathes air. Additionally, the treatment includes 2 10-minute periods of compression and decompression at the beginning and at the end of the procedure, respectively. During these periods, patients also breathe air⁽¹⁰⁾.

Diagnosis of FG, i.e. necrotising soft tissue infection, and age >18 years were inclusion criteria. Failure to meet the inclusion criteria and contraindications to HBOT were the exclusion criteria. We assessed the following parameters: gender, age, comorbidities, laboratory tests on admission (C-reactive protein, CRP; white blood cells, WBC; haematocrit, HCT; platelets, PLT; sodium; potassium; creatinine; procalcitonin; international normalised ratio, INR), gangrene culture, antibiotic therapy used, length of hospital stay, number of surgical interventions and HBOT procedures.

Furthermore, comparative analyses of 2 groups of patients were performed to assess the impact of HBOT on the rate of wound healing in FG.

RESULTS

In group 1, which consisted of 8 patients (62% of the study group), HBOT was used as an adjuvant treatment for FG wounds. In this group, the process of wound healing was significantly accelerated, and the length of hospital stay shorter (7–60 days, average 29 days). The mean age of patients in this group was 54 years. Laboratory findings were as follows: CRP 13.4–399.6 mg/dL (reference: 0–0.8 mg/dL; mean: 147.0 mg/dL), WBC 4.56–29.2 × 10⁹/L (mean: 14.0 × 10⁹/L), HCT 24.0–43.0% (mean: 36.0%), PLT 170.0–405.0 × 10⁹/L (mean: 283.2 × 10⁹/L), sodium 133.0–141.4 mmol/L (mean: 136.0 mmol/L), potassium 3.1–5.5 mmol/L (mean: 4.0 mmol/L), creatinine 0.4–4.75 mg/dL (mean: 2.0 mg/dL), procalcitonin 0.88–340.6 ng/mL (mean: 109.0 ng/mL), INR 1.06–1.77 (mean: 1.0).

No.	HBOT	Age [years]	CRP [mg/dL]	WBC [×10 ⁹ /L]	HCT [%]	PLT [×10 ⁹ /L]	Sodium [mmol/L]	Potassium [mmol/L]	Creatinine [mg/dL]	Procalcitonin [ng/mL]	INR
1	Yes	50	399.6	28.2	36.8	170	139.2	3.87	1.33	–	1.06
2	Yes	60	61.4	13.11	42.0	289	137	5.0	4.3	8.53	1.31
3	Yes	24	46.6	7.11	43.0	280	133	3.9	1.9	85.92	1.35
4	Yes	66	25.2	4.56	35.0	–	134	3.7	1.4	–	–
5	Yes	69	166.4	13.69	36.7	–	141.4	3.1	1.0	0.88	1.36
6	Yes	83	320.0	29.2	39.8	177	137	5.5	4.75	340.60	1.77
7	Yes	43	13.4	8.76	24.0	378	134	4.6	0.8	–	1.26
8	Yes	34	–	6.68	31.0	405	133	4.4	0.4	–	1.39
9	No	73	38.1	20.50	34.0	119	138	4.7	1.6	21.10	1.54
10	No	31	4.22	10.05	38.0	293	142	4.5	0.8	–	0.95
11	No	42	0.1	10.12	38.0	244	143	4.7	1.3	–	1.01
12	No	43	15.7	19.98	25.0	594	137	3.0	1.1	0.60	1.95
13	No	55	23.1	16.65	35.0	378	116	7.3	1.2	1.16	1.12

CRP – C-reactive protein; WBC – white blood cells; HCT – haematocrit; PLT – platelets; INR – international normalised ratio.

Tab. 1. Demographic and laboratory data of patients before treatment by division into group 1 (HBOT; blue) and group 2 (no HBOT; gray)

No.	HBOT [number of sessions]	Hospital stay [days]	Antibiotic therapy [days]	Number of surgical procedures
1	2	22	11	2
2	2	46	22	3
3	2	25	12	2
4	6	7	7	2
5	2	29	15	1
6	2	60	31	1
7	19	26	17	1
8	3	22	13	2
9	0	55	22	2
10	0	23	14	2
11	0	7	7	4
12	0	64	32	3
13	0	106	33	6

Tab. 2. An analysis of both groups for the length of hospital stay, antibiotic therapy and the number of surgical procedures

In group 2, which consisted of 5 patients (38%), the hospital stay was longer and ranged from 7–106 days (mean 51 days). The mean age of patients in this group was 49 years. Laboratory findings were as follows: CRP 0.1–38.1 mg/dL (reference: 0–0.8 mg/dL; mean: 16.0 mg/dL), WBC $16.65\text{--}20.5 \times 10^9/\text{L}$ (mean: $16.0 \times 10^9/\text{L}$), HCT 25.0–38.0% (mean: 34.0%), PLT $119.0\text{--}594.0 \times 10^9/\text{L}$ (mean: $326.0 \times 10^9/\text{L}$), sodium 116.0–143.0 mmol/L (mean: 135.0 mmol/L), potassium 3.0–7.3 mmol/L (mean: 5.0 mmol/L), creatinine 0.8–1, 6 mg/dL (mean: 1.2 mg/dL), procalcitonin 0.6–21.1 ng/mL (mean: 7.62 ng/mL), INR 0.95–1.95 (mean: 1.4) (Tab. 1).

There were no mortal cases in any of the groups.

Two patients (1 in each group) had diabetes mellitus. A history of cancer was reported in 4 patients (2 in each group). The following bacteria were obtained from gangrene cultures in group 1: *Escherichia coli* in 4, *Pseudomonas aeruginosa* in 2 and *Enterococcus faecalis* in 2 patients. *Escherichia coli* (1 patient), *Enterococcus faecalis* (1 patient), and *Pseudomonas aeruginosa* (3 patients) were detected in group 2. The targeted antibiotic therapy primarily included metronidazole, vancomycin, clindamycin, carbapenems, piperacillin with tazobactam or linezolid. No correlation was found between the efficacy of HBOT, and the type of bacterial strain detected, or between the efficacy of HBOT and the type of antibiotic used. Between 1 and 6 surgical procedures (a mean of 2 procedures in group 1 and 3 procedures in group 2) were performed in the study group. The length of antibiotic therapy was 7–33 days (mean: 16 days in group 1 and 22 days in group 2). Furthermore, 2–19 HBOT sessions were performed in group 1 (a mean of 5 procedures) (Tab. 2).

DISCUSSION

Fournier's gangrene is a rare, severe disease. Despite advances in understanding its aetiology and pathophysiology, mortality rates in FG are still high, ranging from 3 and 45%⁽¹¹⁾. If implemented early enough, HBOT contributes to effective treatment of severe diseases. Furthermore, immediate transport of the patient to a specialised centre, ideally

within 3–5 hours of symptom onset, is crucial⁽¹²⁾. Many conditions, such as diabetes, alcoholism, immunodeficiency, injuries and genitourinary infections, predispose to FG^(12,13). A 1980–2017 literature review covering prospective and retrospective randomised clinical trials showed a 5–10% mortality in FG^(14–16). The higher risk of mortality correlates with advanced age, obesity and diabetes⁽¹⁷⁾.

In the study group, 2 patients (1 in each subgroup) had diabetes. A history of cancer was reported for 4 patients; however, no fatal cases were reported.

Lauerma et al. conducted a retrospective study on the duration of antibiotic therapy and the outcomes of FG treatment. The authors found no significant difference in mortality rates between patients who received parenteral antibiotics for ≤ 10 days ($n = 80$) and those who received parenteral antibiotics > 10 days ($n = 88$)⁽¹⁸⁾. A literature review on wound closure has shown that primary or secondary wound closure is recommended when the scrotal defect is $\leq 50\%$, with advancement flap or skin graft needed for scrotal defects $> 50\%$ or extending beyond the scrotum⁽¹⁹⁾.

In our study, the duration of antibiotic therapy was shorter in the HBOT group (mean of 16 days) than in non-HBOT group (mean of 22 days).

Li et al. demonstrated benefits of HBOT in 16 patients compared with 12 patients who did not receive this therapy, with reduced mortality and the need for fewer surgeries in the first group⁽¹⁹⁾. Anheuser et al. conducted a multicentre retrospective study in a group of 62 FG patients. HBOT was used in 17 patients and no fatalities were reported. HBOT was not used in 45 patients, and the mortality rate was 4.5%⁽²⁰⁾. This points to the benefits of using HBOT in patients with FG.

Creta et al. also showed that HBOT accelerates wound healing and improves survival rates in patients with FG. No deaths were reported in the HBOT group compared to 33.3% mortality in the non-HBOT group⁽²¹⁾.

In the current epidemiological situation caused by the outbreak of the COVID-19 pandemic, it is recommended that each hyperbaric medical facility reassess the risk associated

with the use of HBOT in specific indications as an extension of the standard risk analysis and compliance with hospital recommendations. In severe cases of directly life-threatening diseases, which are an indication for HBOT (e.g. gas embolism, necrotizing soft tissue infections, gas gangrene, severe carbon monoxide poisoning) in a patient with a confirmed diagnosis or suspicion of COVID-19, HBOT should be performed only after careful evaluation of all risks associated with the primary disease, comorbidities, transport options, as well as safe implementation of HBOT sessions⁽²²⁾.

CONCLUSIONS

Hyperbaric oxygen therapy has a positive effect on the rate of wound healing in FG, as well as significantly reduces both the hospitalisation time and the number of surgical procedures performed.

Conflict of interest

The authors do not declare any financial or personal links to other persons or organisations that could adversely affect the content of this publication or claim rights thereto.

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