

Hyperbaric oxygen therapy as adjuvant treatment for surgical site infections after male-to-female gender affirmation surgery: A 10-year experience

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Abstract

Introduction: Several urological conditions that share an impairment of tissue oxygenation can benefit from hyperbaric oxygen therapy; limited evidence is available of its impact on patients undergoing male-to-female gender affirmation surgery.

Aim: To evaluate the efficacy and safety of hyperbaric oxygen therapy as adjuvant treatment for surgical site infections in patients undergoing male-to-female gender affirmation surgery.

Methods: This research was conducted as an observational retrospective study. Patients undergoing male-to-female gender affirmation surgery at the principal investigators' institution from January 2009 to September 2019, with a discharge diagnosis of complicated superficial or deep wound infections, were included. All patients underwent standard management of wound infection. Subjects received/not-received hyperbaric oxygen therapy at the surgeon's discretion and were assigned to the hyperbaric oxygen therapy versus non-hyperbaric oxygen therapy group accordingly. Complete wound healing rate (primary outcome), duration of antibiotic therapy, perineal drain time, bladder catheter time, and hospital stay were recorded. All adverse events that occurred during the study period were described.

Results: A total of 156 patients underwent male-to-female gender affirmation surgery in the study period. Thirty-three patients were enrolled. Fifteen subjects belonged to the hyperbaric oxygen therapy group, the other 18 to the non-hyperbaric oxygen therapy group. No statistically significant differences were found between the two groups at baseline. Penile inversion vaginoplasty and intestinal vaginoplasty were performed in nine (60%) and six (40%) patients of the hyperbaric oxygen therapy group. Only

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penile inversion vaginoplasty was performed in subjects of the non-hyperbaric oxygen therapy group. Complete wound healing was obtained in 15 patients (100%) of the hyperbaric oxygen therapy group and 17 patients (94.4%) of the non-hyperbaric oxygen therapy group ($p = 0.35$). Duration of antibiotic therapy, perineal drain time, bladder catheter time, and hospital stay were significantly lower in the hyperbaric oxygen therapy group ($p < 0.05$).

Conclusion: Our preliminary data suggest a role of hyperbaric oxygen therapy as adjuvant treatment for surgical site infection in patients undergoing male-to-female gender affirmation surgery. Randomized controlled trials properly powered are needed to confirm our findings.

KEYWORDS

gender affirmation surgery, hyperbaric oxygen therapy, infection, male-to-female, transgender, vaginoplasty

1 | INTRODUCTION

Hyperbaric oxygen therapy (HBO) has gained increasing clinical recognition in the last few decades. The patient is placed in a special treatment chamber that is pressurized at higher than at sea level (between 1.4 and 3.0 atm) and breathes in 100% oxygen.¹ During the treatment of different types of infections and post-operative open wounds, increased oxygen concentrations can lead to a direct toxic effect on some anaerobic bacteria by inducing free radical formation.² Although oxygen has no significant direct antibacterial effects on aerobes and facultative anaerobes organisms, neutrophils need the support of oxygen in the process of phagocytosis of all bacteria.³ In infected or traumatized tissues, leukocytes frequently function poorly because of inadequate oxygen levels secondary to reduced perfusion, bacterial overgrowth, and increased phagocytosis.^{4,5} Furthermore, HBO can improve the demarcation between viable and necrotic tissues, permitting more accurate debridement and less extensive loss of healthy tissue.⁶

Several urological conditions that share an impairment of tissue oxygenation can benefit from HBO. Iatrogenic hemorrhagic cystitis and Fournier's gangrene are among the main urological indications for HBO.⁷⁻⁹ Testicular torsion, priapism, and preparation for pelvic surgery of patients with previous pelvic irradiation are further urological applications proposed for HBO, although there is limited evidence in these settings.¹⁰ To the best of our knowledge, no study has investigated the impact of HBO in patients undergoing male-to-female (MtF) gender affirmation surgery (GAS) so far. We hypothesized a possible role of HBO as an adjuvant therapy of wound infections in this setting.

GAS is a series of complex surgical procedures (genital and non-genital) performed for the treatment of gender dysphoria,¹¹ which can be associated with significant sexual dissatisfaction and sexual pain.¹² The outcomes of GAS involving the genitals (i.e., vaginoplasty) strictly depend on the quality of the surgical wound healing process.¹³ A

wound infection, resulting in a delayed and inappropriate healing process, can lead to inadequate aesthetic results often requiring a second corrective intervention, with consequent poor patient satisfaction.¹⁴ The most fearful infections are sustained by mixed aerobic and anaerobic pathogens, which are frequently detected in case of predisposing factors such as non-perfused tissues and low tissue oxygen tension, and are clinically characterized by acute onset and rapid progression with abundant and often bad-smelling purulent secretions.¹⁵ Infection-related post-operative complications have a high prevalence and include generic wound infection (4.0%–16.8%), wound healing disorders (33%), and tissue necrosis (4.2%–33.0%).¹⁶⁻¹⁸

The aim of the present study was to evaluate the efficacy and safety of HBO as adjuvant treatment for surgical site infections in patients undergoing MtF GAS.

2 | MATERIALS AND METHODS

2.1 | Study design and patient enrollment

We designed an observational retrospective study conducted on consecutive patients who had undergone MtF GAS at our institution (University Hospital of Naples, Naples, Italy) from January 2009 to September 2019. A prospectively maintained database was used to collect all data.

Transgender female patients with diagnosis of gender dysphoria according to DSM-5 criteria and discharge diagnosis of complicated superficial or deep wound infections following MtF GAS were included in the study. Subjects younger than 18 years of age, immunosuppressed, or under chemotherapy regimen, or with a history of previous GAS or genital traumas were excluded.

The study was conducted in accordance with the Declaration of Helsinki on ethical principles for medical research involving human subjects. All patients provided written informed consent for the

inclusion of their data in a database and their use for scientific research purposes.

2.2 | Peri-operative details and HBO protocol

All surgical procedures were performed by a single experienced surgeon after thorough disinfection of the surgical site with povidone-iodine 10% solution. All patients received peri-operative antibiotic prophylaxis based on intravenous administration of 6 g (2 g every 8 hours) of a third-generation cephalosporin on the day of surgery. Patients undergoing enterovaginoplasty received an additional 15 mg/kg loading dose infused over 1 hour and then a 7.5 mg/kg maintenance dose infused over 1 hour every 8 hours of metronidazole, starting the day before surgery and ending the day of procedure. A perineal drain was placed in all patients at the end of the surgical procedure. After surgery, cleaning of the surgical wound and dressing change were performed once a day.

All patients underwent standard management of wound infection consisting of conservative antibiotic treatment, disinfection of wound with povidone-iodine 10% solution, and dressing change on a daily basis. Antibiotic therapy was chosen on the basis of our institution's surgical wound infection management protocol. Subjects were divided into an HBO and a non-HBO group. The assignment of patients to the HBO group was not randomized but at the surgeon's discretion based on the cultural test, clinical presentation of infection, appearance of the surgical wound, and patient characteristics. Positive wound culture for anaerobic bacteria, history of chronic vascular disease, presence of necrosis, and significant purulent discharge were criteria for inclusion in the HBO group. Exclusion criteria for HBO were untreated pneumothorax, claustrophobia, chronic obstructive pulmonary disease, upper respiratory infection, chronic sinusitis, uncontrolled high fever ($\geq 39^{\circ}\text{C}$), seizure disorder, recent chest or ear surgery, untreated cancer, and any other contraindications to HBO.¹⁹ The number, duration, and characteristics of HBO sessions varied according to the severity of the wound infection and were established together with HBO unit (one session per day, 5 days per week from 1 to 3 weeks, between 30 and 90 minutes per session, from 2.2 to 3.0 atm per session).²⁰

2.3 | Patient assessment and data collection

Age, body mass index (BMI), comorbidities, and cardiovascular risk factors of patients were recorded before surgery. Complete wound healing was chosen as the primary outcome and defined as wound healing without necrotic tissue requiring surgical excision. It was evaluated once a week for a month. The peri-operative data collected were type of surgery, operative time, antibiotic therapy (type and duration), perineal drain time, bladder catheter time, and hospital stay. All adverse events (intraoperative, postoperative, and post-HBO) that occurred during the study period were recorded. Post-operative adverse events included the complications that occurred between

TABLE 1 Surgical site infections (SSI) criteria³³

Superficial incisional SSI

- Occurs within 30 days after any operative procedure (where day 1 = the procedure date)
- Involves only skin and subcutaneous tissue of the incision

and at least one of the following criteria:

- Purulent drainage from the superficial incision
- Organisms identified from an aseptically obtained specimen from the superficial incision or subcutaneous tissue by a culture or non-culture-based microbiologic testing method, which is performed for purposes of clinical diagnosis or treatment
- Superficial incision that is deliberately opened by a surgeon, physician, or physician designee and culture or non-culture-based testing of the superficial incision or subcutaneous tissue is not performed and at least one of the following signs or symptoms: localized pain or tenderness, localized swelling, erythema, or heat.
- Diagnosis of superficial incisional SSI by a surgeon or physician designee

Deep incisional SSI

- Occurs within 30 or 90 days after the operative procedure (where day 1 = the procedure date)
- Involves deep soft tissues of the incision (e.g., fascial and muscle layers)

and at least one of the following criteria:

- Purulent drainage from the deep incision
- A deep incision that spontaneously dehisces, or is deliberately opened or aspirated by a surgeon, physician or physician designee and organisms identified from the deep soft tissues of the incision by a culture or non-culture-based microbiologic testing method that is performed for purposes of clinical diagnosis or treatment or culture or non-culture-based microbiologic testing method is not performed and patient has at least one of the following signs or symptoms: fever ($>38^{\circ}\text{C}$), localized pain, or tenderness
- An abscess or other evidence of infection involving the deep incision that is detected on gross anatomical or histopathologic exam, or imaging test

the end of surgery and discharge and were categorized according to Clavien–Dindo classification.²¹ All patients were diagnosed with surgical site infection according to Centers for Disease Control and Prevention (CDC) criteria (Table 1).²² In each subject, a deep wound swab test was performed with the maximum possible sterility to detect the presence of both aerobic and anaerobic pathogens before starting therapy.

2.4 | Statistics

The categorical variables were described as frequencies and percentages, whereas for the quantitative variables, medians and interquartile ranges (IQRs) were used as a measure of central tendency and statistical dispersion, respectively. The Shapiro–Wilk test was applied as normality test. The Mann–Whitney test and chi-square test were used to compare the medians and percentages, respectively. *p*-Value threshold was arbitrarily set at 0.05. IBM SPSS Statistics (IBM Corp Released

TABLE 2 Baseline characteristics of patients

	HBO (n = 15)	Non-HBO (n = 18)	p-Value
Age, median (IQR), years	30.0 (25–34)	31.5 (24–36)	0.39
BMI, median (IQR), kg/m ²	22.0 (18–29)	21 (17–31)	0.17
Diabetes mellitus, n (%)	3 (20.0)	2 (11.1)	0.30
Smoking, n (%)	11 (73.3)	13 (72.2)	0.94 ^a
Alcoholism, n (%)	2 (13.3)	3 (16.7)	0.79
Coronary artery disease, n (%)	1 (6.7)	0 (0)	0.92
Peripheral vascular disease, n (%)	0 (0)	1 (5.6)	0.35
CCI, n (%)			0.08
0–1	12 (80)	15 (83.3)	
2–3	3 (20)	3 (16.7)	
ASA score, n (%)			0.21
I	6 (40)	9 (50)	
II	8 (53.3)	7 (38.9)	
III	1 (6.7)	2 (11.1)	

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; CCI, Charlson comorbidity index; HBO, hyperbaric oxygen therapy; IQR, interquartile range.

^aThere was also no significant difference ($p = 0.21$) in the number of cigarettes smoked between the two groups.

2015 IBM SPSS Statistics for Windows, Version 23.0, Armonk, NY) was used for the statistical analyses.

3 | RESULTS

A total of 156 patients underwent MtF GAS in the study period. Thirty-three patients were enrolled (wound infection rate: 21.1%). Fifteen subjects were assigned to the HBO group, the other 18 to the non-HBO group. No statistically significant differences were found between the two groups according to baseline variables. The characteristics of patients are summarized in Table 2.

Penile inversion vaginoplasty and intestinal vaginoplasty were performed in nine (60%) and six (40%) patients of HBO group, respectively. Only penile inversion vaginoplasty was performed in subjects of non-HBO group. The most common pathogens detected with wound swab test were coagulase-negative staphylococci (30.3%) and *Staphylococcus aureus* (21.2%), followed by *Pseudomonas* spp. (18.1%), *Escherichia coli* (15.1%), *Enterobacter* spp. (9.2%), and anaerobic bacteria (6.1%). All patients underwent antibiotic therapy with a third-generation cephalosporin plus gentamicin. The therapeutic scheme was modified in three (16.7%) patients of the non-HBO group and one (6.7%) patient of the HBO group because of the lack of clinical improvement, by replacing the cephalosporin with intravenous vancomycin. Data concerning surgical procedures and antibiotic treatments were reported in Table 3. Patients in the HBO group underwent

TABLE 3 Surgical procedures and antibiotic treatments

	HBO	Non-HBO	p-Value
Type of surgery, n (%)			
• Penile inversion vaginoplasty	9 (60.0)	18 (100)	0.02
• Intestinal vaginoplasty	6 (40.0)	0 (0)	
Operative time, median (IQR), minutes	181 (160–232)	143 (131–206)	<0.001
Antibiotic therapy, n (%)			
• Third-generation cephalosporin plus gentamicin	15 (100)	18 (100)	0.32
• Vancomycin plus gentamicin	1 (6.7)	3 (16.7)	

Abbreviations: HBO, hyperbaric oxygen therapy; IQR, interquartile range.

TABLE 4 Peri-operative outcomes of MtF GAS

	HBO	Non-HBO	p-Value
Complete wound healing ^a , n (%)	15 (100)	17 (94.4)	0.35
Duration of antibiotic therapy, median (IQR), days	8.0 (6–12)	13.0 (11–16)	<0.031
Perineal drain time, median (IQR), days	9.0 (6–11)	12.0 (8–14)	<0.001
Bladder catheter time, median (IQR), days	11.0 (7–13)	14.0 (11–15)	<0.026
Hospital stay, median (IQR), days	9.0 (7–16)	18.0 (14–21)	<0.001

Abbreviations: GAS, gender affirmation surgery; HBO, hyperbaric oxygen therapy; IQR, interquartile range; MtF, male-to-female.

^aAt last follow-up visit.

a median of 10 sessions, with a median total treatment duration of 586 minutes.

Complete wound healing was obtained in 15 patients (100%) of the HBO group and 17 patients (94.4%) of the non-HBO group ($p = 0.35$) at last follow-up visit. One subject in the non-HBO group experienced a partial necrosis of the neovagina, requiring a surgical debridement of the necrotic tissue. Duration of antibiotic therapy, perineal drain time, bladder catheter time, and hospital stay were significantly lower in the HBO group ($p < 0.05$). The peri-operative outcomes are comprehensively reported in Table 4.

No intraoperative complications occurred. According to the inclusion criteria, a surgical wound infection (Clavien–Dindo grades II–III) was reported in all patients. No severe (Clavien–Dindo grades IV–V) post-operative adverse events were reported. Only two (13.3%) patients undergoing HBO experienced mild self-limiting side effects,

consisting of temporary myopia and fatigue. No severe post-HBO complications or discontinuation of the HBO protocol were recorded.

4 | DISCUSSION

In this study, we analyzed the data of 33 patients with surgical site infection after MtF GAS. In the study cohort, 15 underwent adjuvant HBO, while 18 received standard management only. Our results showed comparable complete wound healing rates in both groups (despite the likely inclusion of patients with more severe infections in the HBO group), and overall better peri-operative outcomes were achieved in the HBO group, in the face of negligible adverse effects.

Currently, there are only a few clear indications for HBO in the urological field and no studies have been conducted to explore its potential benefits in the setting of GAS.^{23,20} HBO is not indicated for any type of wound infection, and patient candidates for the procedure must be accurately selected according to multiple variables, including the appearance of the surgical wound, the clinical presentation of the infection, patient's medical history, and general clinical conditions as well as the availability of the treatment chamber.⁷ HBO is usually well tolerated, with only mild and self-limiting side effects (e.g., visual disturbances, fatigue) usually reported. More severe complications are rarely reported and include pneumothorax, oxygen toxicity seizures, eustachian tube dysfunction, claustrophobia, and hypoglycemia. These adverse events can be easily managed if recognized early, while the risk of occurrence can be minimized by carefully considering the most common predisposing risk factors and relative contraindications to HBO.^{7,24–26}

Some patients' characteristics (e.g., diabetes mellitus, obesity) can predict the risk and severity of wound infections, and guide clinicians to identify patients who can benefit from HBO. Prevalence of diabetes mellitus and obesity was similar between the two patient groups, although it must be noted that the only case of partial necrosis of neovagina requiring surgical debridement occurred in a diabetic obese patient included in the non-HBO group, this subject rejected HBO because of claustrophobia.

In the HBO group, the operative time was significantly longer, which was because of the inclusion in this group of all the cases of intestinal vaginoplasty. The subjects undergoing intestinal vaginoplasty were deemed unfit to penile inversion technique, several cases being surgical revisions of previous vaginoplasty (e.g., stenosis, necrosis). All surgical procedures were performed with an open approach. Operative time is considered as an important factor associated with increased risk of severe post-operative infections²⁷ and therefore it can be taken into account for patient selection. Longer exposure of the surgical field can increase tissue damage by reducing blood flow and cellular oxygenation,^{28,29} which is consistent with detection of anaerobic germs only in the swab tests of patients included in the HBO group of our study.

Also, we found a statistically significant reduction of duration of antibiotic therapy in the HBO group. This finding is not consistent with

the results published by Brown et al., who did not suggest that HBO affects duration of antibiotic therapy. In this regard, it must be noted that HBO may not only exert a direct effect on anaerobic bacteria and promote leukocyte phagocytosis, but it may favor the entry of some antimicrobial agents through the bacterial cell wall, with improved antibiotic effect.^{6,30} Antibiotic therapy was based on the empirical protocol of our institution rather than on the antibiograms. A lack of clinical improvement despite the antibiotic treatment was observed in four patients, resulting in the replacement of third-generation cephalosporin with vancomycin.

The development of a wound infection can complicate the post-operative management of transgender patients and generally lead to a longer hospital stay.³¹ We reported a statistically significant reduction in the hospital stay of subjects in the HBO group, which could be explained by the more rapid resolution of the infection and the consequent earlier healing of the surgical wound. Bouachour et al. reported a similar study in the management of crush injuries, although their results showed no statistical differences in term of hospital stay between patients treated and not treated with HBO.³² In the HBO group, faster improvement of post-operative wound allowed reduction of perineal drain and improved timing of bladder catheter removal.

A critical issue is with regards to the decision and timing to start HBO. This decision is entirely at the surgeon's discretion and is based on different clinical variables. At our institution, we currently use HBO as an adjuvant treatment to antibiotic therapy in patients undergoing MtF GAS presenting the following conditions: (a) surgical wound infection; (b) no contraindications to HBO; and (c) positive wound culture for anaerobic bacteria or significant purulent discharge. Prolonged surgery and rapid onset of infection are other features that may point toward HBO. Patients requiring a rescue intervention after stenosis or necrosis of neovagina are also considered for HBO.

The infections could have had a negative impact on the patency of the vaginal canal. During infections, the dilation is continued with a sterile sponge vaginal dilator soaked with povidone iodine changed daily to reduce the risk of vaginal canal stenosis. However, the available data did not allow us to perform any specific analysis of this outcome.

To the best of our knowledge, this is the first study evaluating the application of HBO to post-surgical infections after MtF GAS, and it could pave the way for a new line of investigation. However, our results should be read and interpreted carefully in view of the study limitations, which mainly include the retrospective design and the small sample size. Other relevant weaknesses are the absence of randomization, which may have led to a selection bias because of the assignment of patients with the most severe infections to the HBO group, and the lack of follow-up data, which did not allow evaluation of any long-term differences between the two treatment arms. The lack of a standardized HBO protocol and antibiotic therapy not based on the antibiograms are additional issues to be considered. Finally, although not included among the study objectives, functional outcomes and patient satisfaction were not evaluated.

In conclusion, our preliminary data suggest a role of HBO as adjuvant treatment for surgical site infection in selected patients

undergoing MtF GAS. Future randomized controlled trials properly powered are needed to confirm our findings.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: Davide Arcaniolo and Marco De Sio. Study design and manuscript writing: Marco Stizzo and Celeste Manfredi. Data collection: Lorenzo Spirito, Ciro Imbimbo, Felice Crocetto, and Carmine Sciorio. Scientific review: Javier Romero Otero, Juan Ignacio Martinez Salamanca, Paolo Verze, and Ferdinando Fusco. Supervision: Davide Arcaniolo and Marco De Sio

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