Original Article

Topical oxygen therapy can reduce related symptoms of malignant fungating wounds in breast cancer: a retrospective observational case series study

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Abstract: Purpose: Malignant fungating wounds (MFWs) are particularly difficult to treat, so we carried out an observational, retrospective study to determine the effect of topical oxygen therapy (TOT) on malignant fungating wounds in patients with breast cancer. Methods: From January 2014 to June 2018, 53 patients with breast cancer who had MFWs were enrolled in this study from the Department of Breast Internal Medicine. The patients received non-TOT routine treatment in the first three days, including wound cleaning with hydrogen peroxide and iodophor and wound bandaging and then received TOT in the next three days, mainly including routine wound cleaning, oxygen provided through a catheter, and wound bandaging. A retrospective analysis was carried out to compare the wound length, odour, exudate weight, serum inflammatory indexes (C-reactive protein (CRP), interleukin-6 (IL-6), and interleukin-10 (IL-10)), oxidative stress indexes (malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione peroxidase (GSHPx)), hemorrhage, tissue bacteriology, pain degree (VAS), and life quality score (QLQ-C30) between two groups before and after the TOT of MFWs. Results: Compared with non-TOT, TOT significantly alleviated the odour, exudation, hemorrhage, and anaerobic infection of the wound surface in malignant breast tumors, and also greatly decreased the levels of serum CRP, IL-6, and MDA and increased the levels of IL-10, SOD, and GSHPx. In addition, there was no significant difference between patients treated with non-TOT and those treated with TOT, and patients treated with TOT obtained significantly higher QLQ-C30 scores. Conclusion: Our research suggests that TOT may be a safe and effective approach to treat MFWs in patients with breast cancer.

Keywords: Breast cancer, malignant fungating wounds, topical oxygen therapy, exudation, odour, pain, anaerobic infections

Introduction

The incidence of breast cancer is increasing annually worldwide, and it is a primary cancer among women. Breast cancer may metastasise to the lung, liver, bone, brain, and skin, with especially high rates of metastasis to skin sites [1]. These skin metastases are called malignant fungating wounds (MFWs) [2, 3]. MFWs are caused by rapid proliferative growth and hypergranulation producing an unmistakable fungoid, cauliflower-like appearance; hence, the word fungating [4]. Patients with such wounds may have numerous related symptoms, including exudate, bleeding, pain, and odour [5, 6]. The healing of MFWs is difficult and even impossible in many cases. The treatment and care of malignant wounds is primarily palliative focusing on alleviating pain, controlling infection and odour from the wound, managing exudate, and protecting the surrounding skin from further deterioration. Usually, it is an advanced and incurable condition with poor prognosis and limited treatment options for patients [7-9]. Since the treatment for MFWs was introduced ten years ago, no modification has been made, which indicates a stagnant understanding of this disease [10]. Therefore, finding a new treatment method for MFWs in breast cancer for ameliorating the symptoms of MFWs and improving the quality of life of patients is of great significance.
A chronic wound is an interruption in the continuity of the body’s surface that requires a prolonged time to heal, does not heal, or recurs [11]. Both MFWs and diabetic foot ulcers (DFU) are chronic wounds. Although the exact mechanisms are still under investigation, various factors have been found to be responsible for the abnormal blood supply in MFWs and DFU, and the large amount of tissue death and exudate becomes an ideal breeding ground for wound pathogens [7, 12]. Topical oxygen therapy (TOT) is a new modality in the treatment of DFU [12-14], and its underlying mechanism is to enhance the oxygenation of tissues around the wound, promote the immune killing ability of local tissue leukocytes, promote angiogenesis, enhance the viability of fibroblasts and strengthen collagen synthesis. Finally, the wound contracts, and the new tissue is filled to achieve healing [14, 15]. MFWs are similar to diabetic foot ulcers in that the tissues lose nourishment due to poor blood flow and eventually die. They are mixed infections with bacteria and they have a foul smell. TOT may inhibit the growth of anaerobic bacteria and reduce the bad smell of the wounds. However, TOT has not been reported in the treatment of MFWs. In this study, a retrospective analysis was carried out to compare the weight of wound exudate, odour changes, pain score, and tissue bacteriological analysis before and after TOT of MFWs.

Materials and methods

Patient selection

This retrospective study was carried out in accordance with the principles of the Declaration of Helsinki. Approval to perform the study was obtained from the ethics committee of the Affiliated Tumor Hospital of Guangxi Medical University. All participants signed informed consent forms before implementation of the study, and the study was registered in June 2018. From January 2014 to June 2018, 53 patients with breast cancer who had malignant fungating wounds were enrolled from the Department of Breast Internal Medicine. The patients accepted the TOT. Management measures included treating the wound bed and TOT.

The inclusion criteria for the study were as follows: (1) Patient aged 18 to 70, male or female; (2) Patient with histologically or cytologically confirmed breast tumour; (3) Patient with malignant fungating wounds; (4) Patient willing to receive TOT; (5) Patient who was willing to join this study, signed the informed consent, had good adherence, and cooperated with the follow-up.

The exclusion criteria were: (1) Patients with a scheduled change in concurrent cancer therapy during the study period; (2) Those with malodourous fungating wounds not in contact with tumour tissue or those with fungating tumours invading bone tissue; (3) Serious cardiovascular diseases, haemodyscrasia, or central or peripheral neurological disorders.

All eligible patients were required to have complete clinical data, demographic data, clinical characteristics, and radiographic parameters. The patients with data missing were excluded.

Treatment

On d 1, d 2, and d 3, the wounds were treated according to non-TOT methods. The steps were as follows: 1. Clean the wound with hydrogen peroxide and iodophor. 2. Wrap the wound until the wound exudate appears again and then change the dressing according to the above steps. 3. Record and measure the number and weight of gauze.

On d 4, d 5, and d 6, the wounds were treated according to TOT three times a day, one hour each time. The steps were as follows: 1. Clean the wound with hydrogen peroxide and iodophor. 2. Use a catheter to continuously generate pure, humidified oxygen at flow rates of 3-15 ml/hr and deliver it directly to the wound bed via tubing, typically 90-minute exposures once a day. 3. Wrap the wound until the wound exudate appears again, and then change the dressing according to the above steps. 4. Record and measure the number and weight of gauze.

Odour score

On d 1 and d 6, the patients were required to evaluate the odour of the fungating wound over the last 24 h using a 100 mm visual analogue
The weight of the exudate

The weight of the exudate (g) = the weight of the square gauze (g) - the number of gauze pads * 1.5 g. During the treatment period, no anti-tumour treatment was used because the patient’s pathological results and immunohistochemical results had not been reported.

Detection of serum inflammatory indexes and oxidative stress indexes

The levels of C-reactive protein (CRP), interleukin-6 (IL-6), and interleukin-10 (IL-10) in the serum of patients were determined using a corresponding enzyme-linked immuno-sorbent assay (ELISA) kits (QN-PS0135, QN-PS0049, and QY-MB10156, Joe Feather Biotechnology Co., Ltd., Shanghai, China) in strict accordance with kit instructions, and the absorbance was measured at 450 nm by a microplate reader (21261000, Image Trading Co., Ltd., Beijing, China).

The levels of malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione peroxidase (GSHPx) in the serum of patients were also determined using corresponding kits (JK-(a)-2197, JK-(a)-2293, and JK-(a)-2396, Jingkang Bioengineering Co., Ltd., Shanghai, China) in strict accordance with kit instructions.

Bacteriological testing

Samples were collected from the wound area with the most severe inflammation and exudate (usually around the centre) for identification and transported to the laboratory on ice. The samples were stored at -80°C until extraction. Bacterial DNA was extracted from the samples using the QIAampDNA Stool MiniKit (Qiagen, Hilden, Germany) according to the manufacturer’s instructions.

Pain assessment

At the time of screening, we used painkillers to stabilize patients’ pain. On days 3 and 6, the patients were required to evaluate the pain of the MFWs over the last 24 h using a 100-mm visual analogue scale (VAS) [17] (0 mm, no pain; 100 mm, worst imaginable pain).

Life quality assessment

On days 3 and 6, the life quality of the patients was scored using the EORTC Quality of Life Questionnaire (QLQ-C30) [18], with a score of 0-100 points, and the score was positively correlated with life quality.

Statistical analyses

The patient demographics, maximum diameter of the tumour collapse surface, wound scar area, nature of the exudate, and post-treatment situation were reviewed. Normally distributed data were expressed as the mean ± standard deviation. Non-normally distributed data were expressed as the median and interquartile range, and a t-test was used to analyze difference between groups. Count data were expressed as rates, and compared between groups by the χ² test. The data analysis was performed using SPSS version 22.0 (SPSS, Inc, Chicago, IL). The tests were carried out were two-tailed, and the statistical significance level was set at P<0.05.

Results

Demographic and clinical characteristics

A total of 53 patients (average age of (50.38±11.9) years) who received continuous diffusion of oxygen therapy treatment between January 2014 and June 2019 were included in the study. The patients consisted of patients at ECOG grade 1 (40%), patients at ECOG grade 2 (30%), patients at ECOG grade 3 (21%), and patients at ECOG grade 0 (7%). The wound duration of the patients ranged from 1 to 20 months, with a median time of (7.11±5.37) months, and the wound size was mainly 0.80-20.00 cm, with a median size of (8.11±4.46) cm. The average pain score of the patients was (32.28±13.30) points. The histological type of the tumor was mainly ductal invasive carcinoma (96.00%), and only 9 patients had spontaneous bleeding (17.00%). In addition, patients at Grade III were the most common (57.00%), followed by patients at grade II (28.00%) and patients at grade I (15.00%). Positive PgR was found in 34 patients (64.00%), positive ER in 30 patients (57.00%), and positive Her-2 in 19 patients (36.00%). The proportion of TN was less (15.00%). The patients mainly suffered from ductal invasive breast cancer (96.00%),
and their wound was mainly caused by a primary tumor (55.00%) and skin metastasis (45.00%) Table 1.

Effects of TOT on the wound of patients

Compared with non-TOT, TOT significantly alleviated the odor of the wound of patients and decreased exudation of it (P<0.05), but caused no difference in wound length (P>0.05) Figure 1.

Effects of TOT on the hemorrhage and bacteriological testing of the patients

After intervention with TOT, the number of cases of hemorrhage was significantly reduced to 10 (P<0.05) Facultative Anaerobe bacteria include Escherichia coli, Staphylococcus aureus, ß-Streptococcus, Gram-negative anaerobic bacteria; Obligate anaerobic bacteria include Bacteroides fragilis, Fusobacterium sp. Peptostreptococcus magnus, Peptostreptococcus micros, and Streptococcus intermedius; Aerobic bacteria include Acinetobacter baumanii complex, Pseudomonas aeruginosa, and Gram-negative aerobic bacteria. The number of infections with facultative anaerobic bacteria, obligate anaerobic bacteria and aerobic bacteria before TOT were higher than that after TOT, but this result was not significant (P>0.05). Of the 53 patients, 31 were infected with anaerobic bacteria after TOT, and the number of anaerobic bacteria infections was significantly reduced to 19 cases (P<0.05) Table 2.

Effects of TOT on the serum inflammatory indexes of patients

Compared with non-TOT, TOT caused a significant decrease in the levels of serum CRP and IL-6 and a significant increase in IL-10 level (all P<0.05) Figure 2.

Effects of TOT on serum oxidative stress indexes of the patients

Compared with non-TOT, TOT led to a significant decrease in the levels of serum MDA and a significant increase in SOD and GSHPx levels (all P<0.05) Figure 3.

Effects of TOT on the pain degree and life quality score of the patients

There was no significant difference in VAS pain score between patients treated with TOT and
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Figure 1. Effects of TOT on the wound length, odour, and exudate weight of the patients. A. There was no significant difference in wound length between patients treated with TOT and those treated with non-TOT. B. The wound odour score of patients under TOT was significantly lower than that of those under non-TOT. C. The weight of wound exudate of patients under TOT was significantly lower than that of those under non-TOT. Note: ***indicates P<0.001 vs. non-TOT.

Table 2. Effects of TOT on wound hemorrhage and bacterial infection of patients

<table>
<thead>
<tr>
<th>variable</th>
<th>Non-TOT (%)</th>
<th>TOT (%)</th>
<th>χ²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding</td>
<td>46 (86.79)</td>
<td>10 (18.87)</td>
<td>49.063</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Facultative Anaerobe bacteria</td>
<td>19 (35.85)</td>
<td>17 (32.08)</td>
<td>0.168</td>
<td>0.682</td>
</tr>
<tr>
<td>Obligate Anaerobic bacteria</td>
<td>14 (26.42)</td>
<td>10 (18.87)</td>
<td>0.862</td>
<td>0.353</td>
</tr>
<tr>
<td>Aerobic bacteria</td>
<td>26 (49.06)</td>
<td>25 (47.17)</td>
<td>0.038</td>
<td>0.846</td>
</tr>
<tr>
<td>Anaerobic bacteria</td>
<td>31 (58.49)</td>
<td>19 (35.85)</td>
<td>5.451</td>
<td>0.020</td>
</tr>
</tbody>
</table>

those treated with non-TOT (P>0.05), and compared with patients treated with non-TOT, those treated with TOT had a significantly higher QLQ-C30 score (P<0.05) Figure 4.

Discussion

Having MFW is a source of distress to patients who are suffering from breast cancer, reminding them of the disintegration of their bodies [19-21]. Unless the underlying malignancy can be treated effectively, medically or surgically, the fungation in a malignant wound will continue to grow and lead to further damage to the surrounding skin, through a loss of vascularity, proliferative growth and ulceration [8]. Healed malignant wounds are very rare [22, 23]. In addition, the commonly associated symptoms of pain, copious exudate, and malodour and the risk of haemorrhage are extremely distressing for people with advanced cancer. To alleviate the suffering of patients with MFWs, it is essential to explore an effective, convenient and innovative treatment to reduce the related symptoms of MFWs.

In this study, the efficacy of 3-day consecutive use of TOT on MFWs was investigated in 53 female patients with breast cancer. The subjects of this study were patients with a fungating tumour and malodour from infection, and other types of malodourous fungating tumours were not evaluated. We found that TOT significantly reduced odour and exudates over a period of 3 days. This finding has several clinical implications. Odour management is one of the most challenging aspects in the care of patients with MFW. Patients repeatedly describe the “bad smell” in wounds as a primary source of their misery. The odour that accompanies MFWs is associated with the anaerobic bacteria that thrive in necrotic tissue. It is known that TOT, as an oxygen therapy, can reduce the viability of anaerobic bacteria under normal oxygen pressure, which may partly explain the inhibitory effect of TOT on MFW malodour [24]. In our research, we found that the MFWs after TOT presented reduced odour. However, the reason why TOT can reduce wound odour remains unclear. In addition, excessive exudate of MFWs, which can amount to over 1 L per day in some individuals, results from a combination of vascular, bacterial and lymphatic factors [8]. The skin-to-wound exudates may cause wound moisture-associated dermatitis (MAD), giving rise to pain or itching [23]. These symptoms compromise the quality of life. More effective exudate management could prevent the development of MAD and thus improve patient well-being [25]. In our research, we found that the MFWs after TOT presented reduced exudate. We speculate that TOT accelerates the circulation of...
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air on the surface of the wound, causing the exudate to air dry. However, the theory is not clear.

The bleeding from MFWs can be spontaneous or provoked by events such as dressing changes [26]. The constant possibility of a spontaneous fatal haemorrhage due to extreme swelling has been described as “living with a time bomb” [27]. In our research, we found that the

MFWs after TOT showed reduced bleeding, and we speculated that the reason was that TOT reduces the frequency of wound dressing provoked by events. Fromantin et al. reported that the bacterial concentration in wounds is associated with odour and exudates [28]. Due to the strong connection between the severity of symptoms and bacterial concentration in MFWs, a potential therapeutic route could be developed to reduce the microbial concentration. Although our research did not measure the bacterial concentration in wounds, we found that anaerobic bacterial infections were no longer detectable in twelve patients after TOT, suggesting that TOT effectively reduced the anaerobic bacteria in the wounds. We speculated that it may also be related to the ability of TOT to effectively reduce the odour and exudate in the wounds. Studies have revealed that serum CRP and IL-6 in wound exudate are closely

Figure 2. Effects of TOT on the serum inflammatory indexes of the patients. A. TOT significantly lowered the serum CRP in the patients. B. TOT significantly lowered the serum IL-6 in the patients. C. TOT significantly increased the serum IL-10 in the patients. Note: ***indicates P<0.001 vs. non-TOT.

Figure 3. Effects of TOT on serum oxidative stress indexes of the patients. A. TOT significantly lowered serum MDA in the patients. B. TOT significantly increased serum SOD in the patients. C. TOT significantly increased serum GSHPx in the patients. Note: ***indicates P<0.001 vs. non-TOT.

Figure 4. Effects of TOT on the pain degree and life quality score of the patients. A. There was no significant difference in pain degree between patients treated with TOT and those treated with non-TOT. B. There was no significant difference in life quality score between patients treated with TOT and those treated with non-TOT. Note: ***indicates P<0.001 vs. non-TOT.
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related to inflammation of chronic wounds, while IL-10 is related to alleviation of body inflammation [29, 30]. In addition, wound healing is also related to oxidative stress. Increasing the activities of antioxidant enzymes such as SOD and GSHPx and decreasing MDA are beneficial to restoring the balance between oxidation and antioxidant, which is of great significance for wound healing [31]. Therefore, we further analyzed inflammatory response indexes and oxidative stress indexes in the serum of patients, finding that TOT significantly decreased the levels of serum CRP, IL-6, and MDA, and significantly increased the levels of IL-10, SOD, and GSHPx, implying that TOT may improve the body’s anti-inflammatory and antioxidant capabilities by inhibiting the patient’s inflammatory reaction and oxidative stress, thus alleviating wound odour and exudate. One study by Rao et al. [32] has pointed out that TOT can inhibit wound inflammation and promote wound healing by increasing the oxygen pressure in the wound, which is helpful to explain the anti-inflammatory effect of TOT and improvement of TOT on wound hypoxia.

Half of the patients with malignant wounds needed to manage their pain. The causes of pain in patients with breast cancer with malignant wounds are assumed to be the progression of cancer, infection, and peri-wound dermatitis caused by wound exudate [33]. In our research, we used VAS as a tool to assess pain, and it is one of the commonly used measurements in many countries to evaluate pain multilaterally. We found that after we used painkillers to stabilize patients’ pain, the TOT did not increase the pain in patients’ wounds even though pain is a most subjective experience and the expression of pain varies widely. Moreover, we also evaluated the patients’ life quality through QLQ-C30, finding that TOT was beneficial to improving their life quality. We believe that the ability of TOT in ameliorating the pain and quality of life of patients can be attributed to the relief of MFW odour and exudate.

In this study, TOT was intermittent (typically 90-minute exposures once a day) and the subject had to remain immobile during the treatment. TOT is desirable for its lower cost, low risk of bacterial resistance, and easy accessibility without a prescription. TOT can be used by nurses and patients whenever MFWs are present without causing any discomfort or pain. A limitation of our study is that the sample population was small, and generalization was restricted. Further prospective investigations would be useful to examine the effects of TOT for MWFs.

Conclusions

Our research suggests that TOT may be a safe and effective approach to treat MWFs in patients with breast cancer, because it may effectively reduce wound odour, exudate, hemorrhage, and anaerobic infection, and can also inhibit inflammation and oxidative stress, which not only alleviates the pain of patients, but also improves the quality of life.

Disclosure of conflict of interest

None.

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