

ORIGINAL ARTICLE

Intervention for symptom management in patients with malignant fungating wounds - a systematic review

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Summary

Purpose: To identify the latest data on interventions in the management of malignant fungating wounds (WFWs).

Methods: A systematic review has been conducted to explore the original research about symptom management of malignant fungating wounds. Keywords and time constraints were used for the period 2008-2017 using the online Medline database (NCBI) with combined inclusion and exclusion criteria.

Results: Eleven original research studies met the inclusion criteria. Nine of them referred to the use of materials and methods for managing the main symptoms which are malodour, exudate, pain and bleeding. An improvement in symptoms was observed in the involving intervention studies. According to the results, odor and exudates were significantly decreased by the use of honey and silver dressings. Wound

cleaning with saline or tap water and the use of metronidazole had also positive results. Pain management was performed by the systematic use of opioids and the administration of an additional dose prior to the dressing change.

Conclusion: Patients with MFWs need a holistic treatment approach. They often seek late for health services and professional help. The disease is already locally advanced and a variety of symptoms leads to suffering and low quality of life. The effective management of symptoms by health professionals is vital to support patients in advanced disease. The need for constant briefing and updating of knowledge is imperative.

Key words: fungating wounds, malignant wounds, malodorous wounds

Introduction

Malignant fungating wounds (MFWs) are chronic wounds that can be developed anywhere on the body. They occur when the skin, the supporting blood and the lymph supply are infiltrated by a local tumor or by the metastatic spread of a primary tumor to the area [1-4]. According to the National Cancer Institute (NCI), approximately 2.7 to 4.4% of cancer patients can develop MFWs. It is important to note that these rates are observed in developed countries where tumors are usually diagnosed in early stages. Therefore, data for developing countries may be quite different [5]. Life expectancy is averaged from 6 to 12 months, for 5% of patients with advanced cancers and 10% of

metastatic ones, afflicted by a chronic ulcer like a MFW [6].

In most cases these wounds are caused by tumor cells, metastasizing from local or distant primary tumors, primary cutaneous tumors and direct invasion of a primary tumor into the cutaneous structure [7]. The MFWs are commonly presented in the breast (49%), followed by the neck (21%), the chest (18%), the extremities (17%), genitals (17%), head (13%) and other areas (2%) [3,4,8].

Malodour, exudate, pain, bleeding, pruritus and local or systemic infection are the most frequent symptoms [4,9-12]. The MFW's treatment includes symptom management (controlling exudate

and odor, protecting surrounding skin, preventing infection, minimizing pain and bleeding) promotion of comfort and enhancement of quality of life [2,13].

The healing of MFWs is difficult and in many cases impossible, causing significant distress to patients, families and caregiving teams. Furthermore, these wounds are a constant and perceptible reminder (vision and smell) of disease progression [14]. Usually, it is an advanced and incurable condition with poor prognosis and limited treatment options for patients. As a result, MFWs are rarely healed and patients are referred to locally hospice care [15].

The aim of this study was to identify the latest data on intervention management of MFWs and to investigate the effectiveness of the materials and methods used to optimally manage their symptoms.

Methods

A systematic review has been conducted to find the original research about symptom management of MFWs, using the online Medline database (NCBI) for the period 2008-2017. All studies were evaluated according to the title and summary, while for the studies that met the criteria, a full text was searched and retrieved. The keywords were: *fungating wounds, malignant wounds and malodorous wounds* in all possible combinations.

The inclusion criteria for the study were defined as follows: original research studies [Randomized Controlled Trials (RCT), Controlled Clinical Trials (CCT), Multicenter Studies, Clinical Studies, Clinical Trials, Comparative Studies, Observational Studies, Case Reports and Meta-Analysis]. The articles were published in valid scientific journals in English or Greek language, with time frame from 2008 to 2017. The population studied were adult patients with MFW. The study excluded literature reviews, articles written in languages other than English, articles that did not concern MFWs' symptom management and those related to animals with no conceptual relation to this study.

Results

Of the 797 articles found from the initial search, 19 contained keywords in the title or summary and thus were selected for further evaluation. Eight articles were rejected, while 11 met the study criteria (Figure 1). Nine of them reported the use of materials and methods for effective symptom management. The other 2 were cross-sectional studies which investigated factors affecting dermatitis-related moisture (MAD) in patients with MFWs.

Tamai et al. [16] conducted a cross-sectional study to identify the relationship between MAD

surrounding MFWs and levels of various candidate irritating factors in their exudates. They measured the active acidity (pH) and metalloproteases (MMPs), as well as the polyamines present in the exudate that can contribute as ingredients to the development and maintenance of MAD. The results showed that there was no statistically significant difference in pH and MMP between patients with and without MAD. In the case of polyamines, the level of putrescine (PUT) was significantly higher in patients with MAD than in the non-MAD group ($p=0.008$) and cadaverine (CAD) was detected only in the MAD group ($p=0.016$) [16].

Tamai et al. [17] described the morphological characteristics of MAD in the qualitative descriptive part of the study and in the part of the cross-sectional study they investigate the associated factors. They classified the patients in two comparable groups: the MAD group (patients with MAD) and the group without MAD. The results showed that necrotic tissue was significantly more severe (thick and yellow or black) in the MAD group than in the non-MAD group ($p=0.048$). Wound exudate leakage was significantly more frequent in the MAD group than in the non-MAD group ($p=0.013$) [17].

The purpose of Drain and Fleming case study [18] was to investigate the efficacy of Manuka honey in the management of odor and inflammation in an 80-year-old patient with oral squamous cell carcinoma. Multiple ulcerations within the oral cavity were also observed along the mandible, with purulent secretion and intense odor. Calcium alginate impregnated with Manuka honey (Medihoney-Calcium Alginate) was applied to the external wound and Manuka honey paste (Medihoney) was applied twice daily with a swab in the oral cavity. After three months of using Medihoney products, pain and size of external wound was reduced, there was no odor and inflammation and the exudate was low-volume and serosanguineous in nature (Table 1) [18].

The purpose of Riot study [19] was to clarify whether the use of NPWT (Negative Pressure Wound Therapy) is legitimate in a palliative context for patients with malignant wounds. Patients ($n=5$) had metastatic cancer ($n=3$ sarcoma, $n=1$ breast carcinoma and $n=1$ melanoma) and were in palliative care. There was used KCI VAC device with a depression of 100-125 mmHg and continuous 24-h application. The patients reported a decrease in odor and exudates compared to the use of conventional wound dressings while the medical team reported no complications, such as bleeding. After a few days of treatment, the odor decreased and no exudate was observed in patient's wounds (Table 1) [19].

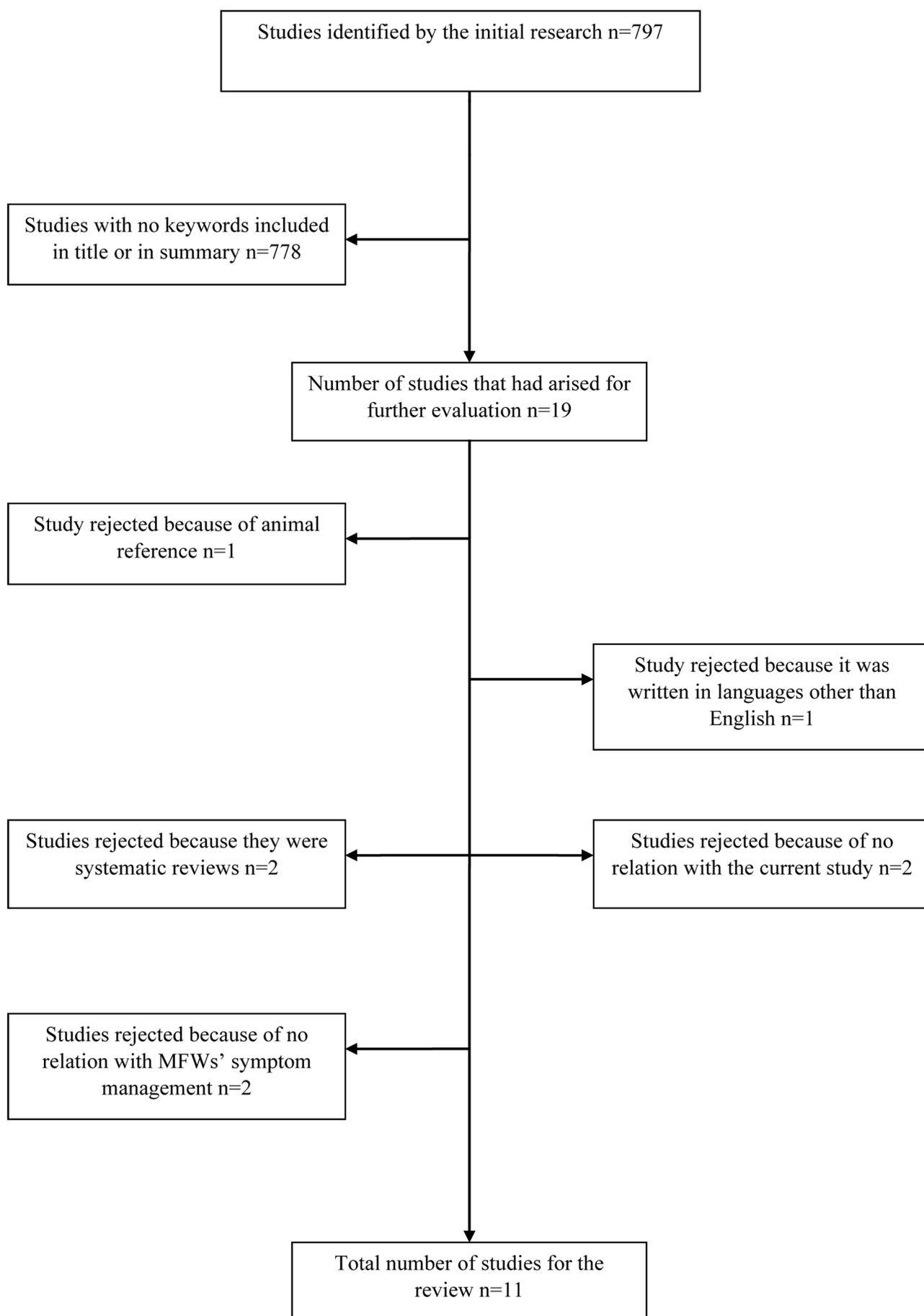


Figure 1. Flow chart. Criteria of studies' selection.

Table 1. Results of studies

Researcher / year	Type of study	Purpose	Sample size	Identification	Result
Tamai et al. 2016	Cross sectional design	Defined the relationship between Moisture-Associated-Dermatitis (MAD) (surrounding MFWs) and the levels of various candidate irritating factors in their exudates	n = 20	Breast	There was no statistically significant difference in PH and MMP between patients with and without MAD. In the case of polyamines, the level of putrescine (PUT) was significantly higher in patients with MAD than in the non-MAD group (p=0.008) and cadaverine (CAD) was detected only in the MAD group (p=0.016)
Drain & Fleming 2015	Case Study	Determined the effectiveness of Manuka honey in the management of odor and inflammation	n = 1	Oral Squamous Cell Carcinoma (SCC)	Manuka honey was proved to be safe, and effective in reducing the smell and inflammation of the wound
Riot et al. 2015	Patient group study	Clarified whether the use of NPWT (Negative Pressure Wound Therapy) is legitimate in a palliative context for patients with malignant wounds.	n = 5	1. Lowerlimb (melanoma) 1. Breast 1. Thigh (sarcoma) 2. Not reported (sarcoma)	NPWT application resulted a decrease in odor and exudates compared to the use of conventional wound dressings
Tamai et al. 2013	Qualitative descriptive study & Cross sectional study	Described the morphological characteristics of MAD and investigated the associated factors.	n = 24	Breast	The necrotic tissue was significantly more severe (thick and yellow or black) in the MAD group than in the non-MAD group (p=0.048). Wound exudate leakage was significantly more frequent in the MAD group than in the non-MAD group (p=0.013)
Kalemikerakis et al. 2012	Randomized controlled trial	Investigated the effectiveness of foam dressings with silver vs. foam dressings without silver in reducing malodorous and septic phenomena in MFWs.	n = 26	Breast, Head-Neck and other body points	A significant reduction of odor was observed in the group using foam dressings with silver (p= 0.049)
Recka et al. 2012	Case Study	The management of a bleeding symptom during the palliative care	n = 1	Neck Squamous Cell Carcinoma. (SCC)	Capillary bleeding was successfully treated by application of oxymetazoline spray, avasocontraction substance of local use.
O'Brien 2012	Case Study	The management of symptoms in a physical and psychological level during the palliative care	n = 1	Abdominal Squamous Cell Carcinoma (SCC)	Symptoms of odor were adequately controlled by using saline solution, absorbent hydrocolloid dressing, a charcoal dressing, metronidazole powder, and charcoal placed throughout the area
Lund-Nielsen et al. 2011(b)	Randomized Controlled Trial	Defined the effect of honey-coated bandages compared to silver-coated ones	n = 69	Breast, Head-Neck and other body points	No statistically significant differences were observed between the groups relative on wound size, cleanliness, malodour, exudation, and wound pain. A statistically significant reduction of malodour p= 0.007) and exudation (p< 0.0001) was noted, in both groups after the intervention. Additionally, a longer survival time was observed for patients with reduced wound size compared to those with no wound reduction (p= 0.003)

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Researcher / year	Type of study	Purpose	Sample size	Identification	Result
Lund-Nielsen et al. 2011(a)	Single-blind randomized controlled trial	Evaluated the bacteriology of malignant wounds and compared to the effect of a honey-coated to a silver-coated dressing on the qualitative bacteriology of malignant wounds	n = 67	Breast, Head-Neck and other body points	No statistically significant differences were found between the type and number (p=0.54) of different wound pathogens during the study between Group A and B. The anti-neoplastic and antibiotic treatment did not affect the presence of wound pathogens. There was no statistically significant difference regarding the wound size reduction and the prevalence of a particular group of pathogens after the intervention
Sesterhenn et al. 2009	Case Study	Presented a case study focusing on the treatment options of myiasis	n = 1	Oropharynx Squamous Cell Carcinoma	The current treatment, initially, involved mechanical removal of the maggots followed by the rinsing of hydrogen peroxide and metronidazole solution on wound, twice a day. In a further course the result was the macroscopically absence of maggots.
Maud 2008	Case Study	The improvement of quality of life through the management of symptoms of pain and odor, applying ActiFormCool ionic hydrogel dressings	n = 2	Shoulder, Arm and Thoracic Wall	The application of ActiFormCool dressing provided pain relief, exceptional fluid absorption, greater comfort and better quality of life
			Sum n = 217		

Kalemikerakis et al. [9] conducted a randomized clinical study to investigate the effectiveness of foam dressings with silver vs. foam dressings without silver to reduce malodorous and septic phenomena in MFWs. Patients were randomized in two groups. Foam dressings with silver content of 1 mg/cm² were used in the intervention group and foam dressings without silver in the control group. A significant reduction of odor was observed in 10 patients (76.9%) in the group using foam dressings with silver, while in the group using foam dressings without silver, odor was reduced to 4 patients (30.8%) (p=0.049) [9] (Table 1).

Only one study was found to address local hemorrhage of the wound in a palliative context. It concerned a case study of a 60-year-old patient with a bleeding malignant neck wound due to squamous cell carcinoma of the hypopharynx, in which capillary bleeding was successfully treated by the application of oxymetazoline spray and minimization of dressing changes (Table 1) [20].

O'Brien [21] presented as a case study a 66-year-old patient with an extensive abdominal malignant squamous cell carcinoma, in order to manage physical and psychological symptoms in palliative care. Symptoms of odor were adequately controlled using saline solution, absorbent hydrocolloid dressing, a charcoal dressing, metronidazole powder, and charcoal placed throughout the area. There were also used honey dressings but the effectiveness was limited given the size of the wound and the large amount of exudate. Pain was controlled with an opioid every 4 hours and an opioid every hour as needed to breakthrough pain, which was titrated according to his as-needed use. There was also subcutaneous administration of an additional dose prior to dressing changes (Table 1) [21].

Lund-Nielsen et al. [22] studied the effect of honey-coated bandages compared to silver-coated relative on wound size, cleanliness, malodour, exudation, and wound pain in patients with malignant wounds (MWs) and advanced-stage cancer. Patients were randomly selected in two groups. Manuka honey-coated bandages (Algivon/Activon Tulle), absorbent dressing (Sorbion/Drymax) and foam bandages (Allevyn Adhesive) were applied in Group A and nanocrystalline silver-coated bandages (Acticoat/Acticoat Absorbent) and foam bandages (Allevyn Adhesive) in Group B. In both groups after intervention it was observed a statistically significant difference in the reduction of odor (p=0.007) and exudate (p<0.0001). Also, longer survival time was observed for patients with reduced wound size compared to patients with no wound size reduction (p=0.003) (Table 1) [22].

The single blind randomized clinical trial of Lund-Nielsen et al. [23] was a part of a larger study, which was conducted to evaluate the bacteriology of malignant wounds. It compared the effect of a honey-coated (Group A) to a silver-coated (Group B) dressing on the qualitative bacteriology of malignant wounds [22]. No statistically significant differences were found between the type and number ($p=0.54$) of different wound pathogens during the study between Group A and B, whereas the anti-neoplastic and antibiotic treatment did not affect the presence of wound pathogens. Regarding the wound size reduction and the prevalence of a particular group of pathogens after the intervention, there was no statistically significant difference [23].

The study of Sesterhenn et al. [24] concerned a cutaneous manifestation of myiasis of a 61-year-old patient, with an extensive skin metastasis resulting from a recurrent oropharyngeal squamous cell carcinoma. The purpose of the study was to report the case and to review the literature with a focus on the treatment options of myiasis in malignant wounds. The intervention, initially, involved mechanical removal of the maggots followed by rinsing hydrogen peroxide and metronidazole solution on the wound twice a day. In a further course, the result was the macroscopically absence of maggots. After surgical removal of necrotic metastases, the patient was referred to the local hospice for the best supportive care [24].

Maund [25] presented two case studies involving two female patients with MFWs. Odor, high exudate and pain were wounds' characteristics. ActiFormCool ionic hydrogel dressing was used as the primary dressing in both cases. The hydrogel softened the necrotic tissue and slough and it was possible to mechanically remove it. Thus, it was observed reduction of necrotic tissue, septic phenomena and malodour. According to Maund the application of ActiFormCool dressing provided pain relief, exceptional fluid absorption, greater comfort and better quality of life (Table 1) [25].

Discussion

In the present study the most important symptoms of MFWs and the latest data concerning management interventions were identified. The main symptoms that researchers focus on the need of intervention are malodour and infection, exudate, pain and bleeding. Nine of the 11 studies reported the use of materials and methods to optimize symptom management and improve the quality of life of patients with MFWs.

Eighty percent of health professionals and 83% of the patients reported malodour as the main

symptom [8]. The variety of materials and methods used by researchers to manage malodour such as Manuka honey, silver, hydrogel, carbon, metronidazole and NPWT [9,18,19,21,22,25] evidence the significance and dimension of the problem. Manuka honey proved to be effective in reducing odor ($p=0.007$) in a randomized clinical study with a satisfactory sample [22] as in the case study of Drain & Fleming [18] indicating that Manuka honey dressings could be a solution to manage malodour.

Regarding the use of silver dressings, two randomized clinical trials have provided evidence that they significantly reduce odor and septic phenomena [9,22]. There are strong indications that silver can reduce odor in MFWs. The use of silver as an antimicrobial-antibiotic agent and wound cleansing with saline or tap water [9,22] is recommended by the European Nursing Oncology Society (EONS) [4]. The positive conclusions of Obrien study [21] on the use of metronidazole are consistent with the results of an earlier research by Bower et al. [26]. Despite the several methodological weaknesses the last one has, both of them refer the satisfactory reduction of the malodour. These indications are reinforced by a recent systematic review which states that the use of metronidazole is recommended in clinical practice. However, more randomized clinical studies are needed to support it [5]. Regarding the use of hydrogel (ActiFormCool dressing) for managing malodour [25], no reliable results can be derived because of the very small sample ($n=2$).

The management of local infection is referred in two studies which reported a reduction in wound inflammation and septic phenomena using topical antimicrobial antibiotics such as Manuka honey [18] and silver dressings [9].

The tendency of MFWs to produce moderate or high-volume exudates proves the severity that they should be treated. Manuka honey and silver have been proven effective in reducing exudate ($p<0.0001$) [22] providing significant evidence of their use. Regarding the management of exudate, the use of NPWT is a contraindication for malignant wounds [27-29]. Yet, the Riot study [19] reported a decrease in exudate as well as its elimination, while Adderley [30] cautions attention when using NPWT in abdominal wounds and suggests that NICE guidelines should be followed [30]. No safe conclusions can be drawn for the use of NPWT in MFWs due to the heterogeneity of the studies and the increased risk of bleeding of these injuries. Very good results on exudate management reported Maund in her study [25] where the application of the hydrogel dressing appears to offer excellent absorption of the exudate, but given the very small sample, further research is necessary.

Concerning pain, two studies have been found in which pain was effectively controlled by opioid administration [21]. This fact agrees with the WHO recommendations for the administration of opioids in treating pain from moderate to severe level [31]. The administration of analgesics of normal opiate treatment prior to dressing changing that Obrien had applied [21] accords with the EONS recommendations. WHO's pain management is recommended also by Naylor [32] in his study, who however suggests non-pharmaceutical methods, such as appropriate wound-cleaning techniques, use of wound dressings and complementary therapies. The magnitude of the problem of cancer pain is apparent from the researchers' attempt to test other alternative forms of treatment apart from the usual pharmaceutical methods. The use of medical cannabis (MC) seems to provide effective pain management [12,33] with researchers suggesting further investigation of its use. A bill that will allow the legitimate cultivation of pharmaceutical cannabis is expected in Greece, enabling studies to be carried out.

Only one study [20] reported intervention for bleeding management involving a case study (level of evidence IV) in which capillary bleeding was successfully treated by application of oxymetazoline spray. Although the first intervention is applying pressure to the wound for 10 to 15 min, EONS suggests the use of local hemostatic agents such as vasoconstrictors. Still, more studies are needed to confirm their effectiveness. The use of NPWT in

malignant wounds is controversial, although complications such as bleeding have not been reported in one study [19]. In addition, more reliable studies with bigger sample will be needed to indicate its use in palliative care. The management of bleeding appeared to be a lack of clinical studies with strong indications.

Intervention on human myiasis in malignant cutaneous wounds is reported only in one study [24]. According to the study the first intervention was the mechanical removal of the larvae and the rinse of wound with hydrogen peroxide solution and metronidazole, aiming to the absence of larvae, macroscopically. A surgical removal of necrotic metastases was performed later. Mechanical removal of the larvae, rinsing of the wound with hydrogen peroxide solution and surgical removal of the lesion seems to be consistent with another case study [34]. Pessoa and Galvao [35] argued the mechanical removal of the larvae with a different antiseptic substance (chlorhexidine solution 0.12%), in the case study they published. The scarcity of cutaneous manifestation of myiasis makes difficult the selection of a large sample size that a randomized clinical study needs. Therefore the results of case studies could be taken into account with an optimal systematic review for the management of MFWs myiasis.

Conflict of interests

The authors declare no conflict of interests.

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