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Local Cutaneous Effects Associated with Chlorhexidine-Impregnated Gel Dressing in Hematopoietic Stem Cell Transplantation Patients

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Abstract

Introduction: Hematopoietic stem cell transplantation (HSCT) often requires a central venous catheter (CVC) for quick and safe vascular access. Currently, new technologies are available to protect the catheter insertion site, such as chlorhexidine-impregnated gel dressings (CIGD). **Objectives:** To evaluate local cutaneous effects associated with CIGD in patients undergoing HSCT. **Methods:** In this cross-sectional, prospective study, we evaluated 25 HSCT patients who had a CVC inserted. Patients were visited daily to monitor the CIGD changing procedures and evaluate abnormalities of the underlying skin after dressing removal. **Findings:** Local erythema was the most frequently detected abnormality, although usually transient and considered secondary to the mechanical trauma of dressing removal. The most severe lesions, consisting of areas of skin loss, erythematous plaques and/or vesicles were classified as skin irritation and presented in 11 (44%) of the 25 patients. An association test showed that skin irritation was more frequent in patients who underwent allogeneic HSCT ($p = 0.03$). Skin irritation was most frequently observed in areas of contact with the non-woven polyester adhesive tape ($n = 22$; 88%), which made up the adhesive margins of the dressing. The CIGD was discontinued in 6 (54%) of the 11 patients who presented severe skin injuries. **Conclusion:** In this study, we detected that skin irritation was more frequent in patients who underwent allogeneic HSCT. The most common skin manifestation was skin loss.

Keywords

Bandages, Catheterization, Central Venous Catheters, Hematopoietic Stem Cell Transplantation, Skin Abnormalities

1. Introduction

Hematopoietic Stem Cell Transplantation (HSCT) refers to a procedure where normal hematopoietic stem cells are given to a recipient to reconstitute hematopoiesis. It is a potentially curative therapy for many life-threatening cancers, and onco-hematologic, genetic, and autoimmune diseases [1] [2] [3]. HSCT using the patient's own hematopoietic cells is called autologous HSCT, and when the hematopoietic cells derive from a donor (family members, volunteer donors, or umbilical cord blood banks), it is called allogeneic HSCT. Stem cells can be derived from bone marrow, peripheral blood, or umbilical cord blood [1] [2] [3]. Before infusion of stem cells, patients are treated with a conditioning regimen, which may include high dose chemotherapy, immunotherapy and/or radiotherapy, aiming to decrease the function of the hematopoietic system and treat the underlying disease [2]. Central Venous Catheters (CVC) are commonly used in patients with hematological malignancies to enable HSCT therapy [4] as they are useful for infusion of drugs, including chemotherapy; infusion of blood products and total parenteral nutrition; blood withdrawal; and hemodynamic monitoring [4] [5] [6]. There are two different types of long-term CVC used for prolonged treatments (more than 14 days) in HSCT: surgically implanted tunneled CVC (e.g., Hickman catheter) with a tunneled portion exiting the skin and a cuff inside the exit site, and non-tunneled CVC which is percutaneously inserted into central veins [5]. One harmful effect caused by the use of CVC is the risk of central line-associated bloodstream infection (CLABSI). In non-tunneled CVC, this occurs through migration of microorganisms from the skin to the catheter tip, direct contamination of the catheter by hand contact or infusion of contaminated fluids [4] [7] [8]. In tunneled catheters, the hub is the major source of contamination [9]. Dressings used to protect the catheter exit site provide a protective barrier to prevent migration of skin microorganisms into the cutaneous catheter tract, as well as preventing direct contamination of the catheter through contact with hands and other materials, allowing catheter stabilization by reducing movement and preventing accidental removal or partial dislodgment of the catheter [4] [7] [10] [11]. Recently, new technologies have become available such as medication-impregnated dressings, and of these, chlorhexidine-impregnated gel dressings are the most commonly used [11] [12]. A metanalysis and a systematic review showed that chlorhexidine-impregnated gel dressings prevented CLABSI when compared to other dressings without medication [11] [13]. Chlorhexidine-impregnated gel dressings are changed every seven days or earlier if the integrity of the dressing is compromised, or it becomes soiled or

wet [7] [14] [15]. Repeated applications and removals of the dressing impact on the skin integrity, causing inflammatory skin reactions and increasing rates of central line-associated bloodstream infection [4] [16] [17]. Although the dressing prevents catheter related infections, there is concern regarding the risk of skin irritation caused by the use of the chlorhexidine-impregnated gel dressings. The most commonly reported adverse effect is contact dermatitis [4] [11] [13]. Studies on chlorhexidine-impregnated gel dressings mainly report the incidence of catheter related infections and do not evaluate the impact of this dressing on the skin as a primary outcome [4] [15] [18] [19] [20]. This study aims to evaluate local cutaneous effects associated with CIGD in patients undergoing HSCT. These patients present extreme immunosuppression due to the treatment they are submitted to, which is aggressive to the skin itself. We believe our results will aid nurses to identify and prevent the development of dressing related skin injuries that may increase the risk of infections to which the patient is already exposed.

2. Methods

2.1. Study Design and Sample

This was a prospective cross-sectional study conducted at the Bone Marrow Transplantation, Immunotherapy, and Hematology units and at the Outpatient Clinic of a School Hospital in Brazil. Patients with autoimmune or onco-hematological diseases of any age, admitted to the units where the study was conducted, and having a CVC inserted for HSCT were eligible for the study. Exclusion criteria were: patients who had the catheter inserted before hospital admission for HSCT and with a known allergic/hypersensitivity reaction to chlorhexidine. Acute and chronic leukemias, lymphomas, multiple myelomas and bone marrow failures were diagnosed according to World Health Organization (WHO) 2016 criteria [21], the hemoglobinopathies according to the National Institutes of Health (NIH) 2013 Classification of the Disorders of Hemoglobin [22] and systemic sclerosis was according to the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2013 criteria [23].

2.2. Ethical Considerations

This study was approved by the Ethics Committee (CAAE-21162213.7.0000.5393). Written informed consent was obtained from adult patients. Patients younger than 18 years old had the family contacted by the investigator who asked for permission to include the patient in the study.

2.3. Recruitment

Data were collected from November 2013 to June 2014. Patients were approached by the investigator of the study after receiving CVC and were invited to participate in the study. Inclusion criteria were checked and, if eligible, the study was explained to the participant or his/her family.

2.4. Dressing Description

All included patients received Chlorhexidine-Impregnated Gel Dressings (CIGD) (3M™ Tegaderm™ CHG) to cover the catheter exit site while undergoing HSCT. The dressing is composed of a transparent polyurethane film that contains a continuous-release hydrogel with 2% chlorhexidine (by weight) and a non-woven polyester adhesive tape on the edges [15] [18] [24].

2.5. Procedure

Patients who met the inclusion criteria were approached by the researcher after receiving CVC. Non-tunneled CVCs were inserted bedside and tunneled CVCs were surgically inserted, both with maximal sterile barrier precautions. At the beginning of the study, registered nurses responsible for patient care at each participating unit were invited to participate in the study; those who agreed completed a training session to standardize the CIGD application and dressing change procedure. CIGD was applied on the CVC exit site as soon as it stopped bleeding and changed every seven days; unscheduled dressing changes occurred when the dressing was damp, loose, or visibly soiled [7]. Daily, the researcher assessed the patients with CIGD to follow the dressing change procedure performed by registered nurses. The investigator evaluated local cutaneous effects on the skin in contact with the CIGD; assessed through skin evaluation immediately after each dressing removal to detect skin integrity, color abnormalities, or the presence of skin lesions. A retrospective cross-sectional study conducted at the same hospital and care unit in 2011 analyzed patients submitted to allogeneic HSCT that used tunneled catheters and showed that the mean permanence of the catheter was 45 days [25]. Based on this study, we followed the patients for 45 days. If the catheter was removed before this period, data was collected until catheter removal, starting from the day of CVC insertion. Sociodemographic and clinical variables collected were age, length of hospital stay, sex, baseline disease, type of HSCT, chemotherapy conditioning regimens. The catheter variables were type of catheter, insertion vein, catheter time in place, and reasons for catheter removal.

2.6. Outcomes

The primary outcome was the occurrence of skin irritation defined as skin loss, erythematous plaques, or vesicles. Secondary outcomes were: -Occurrence of skin erythema which was considered a color abnormality secondary to the mechanical trauma caused by the removal of the dressing; -Discontinuation of the use of the CIGD. In cases that the patient present skin irritation, it was decided if the CIGD should be discontinued or not; -Occurrence of central line-associated bloodstream infection, classified according to the Clinical Practice Guidelines for the Diagnosis and Management of Intravascular Catheter-Related Infection and American Society of Clinical Oncology Clinical Practice Guidelines [9] [26]. In cancer patients, most bloodstream infections are treated without catheter

withdrawal. The criteria for central line-associated bloodstream infection is differential time to positivity, which is when a blood culture drawn from the catheter hub becomes positive at least two hours earlier than simultaneously drawn peripheral vein blood of equal volume [9] [26]. -Association between skin irritation and the following variables: type of HSCT, type of catheter, catheter time in place and type of chemotherapy conditioning regimens. The type of chemotherapy conditioning regimens were classified according to its intensity: high intensity (Melphalan; association of Bussulfan and Fludarabine; association of Busulfan, Fludarabine and Cyclophosphamide; association of Busulfan, Fludarabine and Immunoglobulin Antithymocyte; association of Busulfan and Cyclophosphamide); medium intensity (association of Carmustine, Etoposide, Cytarabine and Melphalan); and low intensity (Cyclophosphamide; association of Cyclophosphamide and Immunoglobulin Antithymocyte; association of Cyclophosphamide, Immunoglobulin Antithymocyte and Fludarabine; association of Fludarabine, Melphalan and Immunoglobulin Antithymocyte; association of Cyclophosphamide, Fludarabine and total body irradiation) [27].

2.7. Statistical Analysis

For statistical analysis, IBM Statistical Package for the Social Sciences (SPSS) software version 24.0 was used. Descriptive simple frequency analysis was developed for nominal and categorical variables. Central trend (mean) and dispersion (standard deviation) measures were developed for continuous variables. The Fisher's exact chi-square test was used to verify possible associations between skin irritation and the following variables: central line-associated bloodstream infection, type of HSCT, type of catheter, catheter time in place, and type of chemotherapy conditioning regimens. Significance was set at 5%.

3. Results

A total of 26 patients fulfilled the inclusion criteria. One patient was excluded as the catheter was inserted prior to hospital admission for HSCT. Thus, 25 patients were prospectively evaluated. All patients completed the study follow-up.

Distribution of clinical and sociodemographic characteristics are shown in Table 1.

Most subjects were male 52% (n = 13) and mean age was 34 years (SD = 18). The mean length of hospital stay was 36 days (SD = 19.4). The mean time of the conditioning regimens was 4.8 days (SD = 1.8) and each patient was transplanted only once. Catheter characteristics are shown in Table 2. All patients who underwent allogeneic HSCT (n = 12) had tunneled catheters inserted. Twelve patients who were treated with autologous HSCT received non-tunneled catheters and only one patient submitted to autologous HSCT had a tunneled catheter inserted. Seven of 13 (52%) patients with tunneled catheters had a remaining catheter for more than 45 days which was the time of the study follow up. According to the local institutional protocol, tunneled catheters can be

Table 1. Patient clinical and sociodemographic characteristics.

Characteristics	
Age in years, mean (SD*) copy	34 (18.0)
Length of stay in days, mean (SD)	36.0 (19.4)
Sex, % male (n)	52.0 (13)
Baseline disease, % (n)	
Leukemia[a]	32.0 (8)
Bone marrow failure and hemoglobinopathies[b]	28.0 (7)
Multiple myeloma	20.0 (5)
Lymphoma	12.0 (3)
Systemic sclerosis	8.0 (2)
Type of HSCT, % (n)	
Autologous for onco-hematological disease	44.0 (11)
Autologous for autoimmune disease	8.0 (2)
Related allogeneic HLA-matched	36.0 (9)
Related allogeneic haploidentical	12.0 (3)
Type of chemotherapy conditioning regimens, % (n)	
Low intensity[b]	32.0 (8)
Medium intensity[c]	12.0 (3)
High intensity[d]	56.0 (14)

*SD = Standard Deviation [a]Myeloid or lymphoid acute leukemia, chronic myeloid leukemia; [b]sickle cell disease, Fanconi anemia, thalassemia, myelofibrosis, severe aplastic anemia. [b]conditioning regimen which cannot be classified as medium or high intensity. [c]non myeloablative conditioning regimen with minimal cytopenia. [d]myeloablative conditioning regimen with irreversible pancytopenia.

Table 2. Overview of catheter characteristics.

Catheter characteristics	
Type of CVC, % (n)	
Tunneled	52.0 (13)
Non-tunneled	48.0 (12)
Insertion vein, % (n)	
Jugular	80.0 (20)
Subclavian	20.0 (5)
Time in place in days, mean (SD)	
Tunneled catheters removed during the study follow up	27 (7.6)
Non-tunneled catheters	15 (3.6)
Reason for tunneled catheter removal, % (n)	
Tunneled catheters that remained more than 45 days	54.0 (7)
Suspected infection	23.0 (3)
Diagnosed infection	8.0 (1)
Catheter was no longer needed	8.0 (1)
Catheter breakage	8.0 (1)
Reason for non-tunneled catheter removal, % (n)	
Hospital discharge	42.0 (5)
Catheter was no longer needed	25.0 (3)
Diagnosed infection	25.0 (3)
Catheter breakage	8.0 (1)

*P-value from Fisher's exact chi-square test. [a]Hematopoietic stem cell transplantation.

maintained until 100 days after HSCT and non-tunneled catheters must be removed when they are no longer needed or at hospital discharge. Tunneled catheters removed during the study follow up remained for a mean of 27 days (SD = 7.6) and non-tunneled catheters remained for a mean of 15 days (SD = 3.6). Patients with tunneled catheters had a mean of 5.2 (SD = 1.7) dressing changes per patient, while in those with non-tunneled catheters the mean was 2.7 (SD = 1.1). Eleven (44%) of 25 patients presented with skin irritation with one or more skin lesions at the same evaluation time point, such as skin loss, erythematous plaques and vesicles. In four (37%) of these patients we observed skin loss after dressing removal.

Three (27%) patients presented with skin loss and vesicles, two (18%) patients presented with skin loss and erythematous plaques and two (18%) patients presented with skin loss, erythematous plaques and vesicles. Some examples of these skin lesions are shown in Figure 1. Eight (73%) of eleven patients that presented with skin irritation were submitted to allogeneic HSCT and had a tunneled catheter inserted. Three (27%) patients who presented with skin irritation were treated with autologous HSCT and received a non-tunneled catheter. The association test between the variables: type of HSCT and skin irritation was statistically significant (p = 0.03). Skin irritation was more frequent in patients who underwent allogeneic HSCT (32%) and less frequent in autologous HSCT (40%). Statistical Analysis are shown in Table 3. Considering the three different materials that constituted the CIGD, these lesions were predominantly detected on the skin in contact with the non-woven polyester adhesive tape (n = 22; 88%). The dressings were discontinued in 6 of the 11 patients who presented skin irritation. In two of them, however, it was possible to resume dressing applications, as the injuries were small and easily healed. While the CIGDs were discontinued,

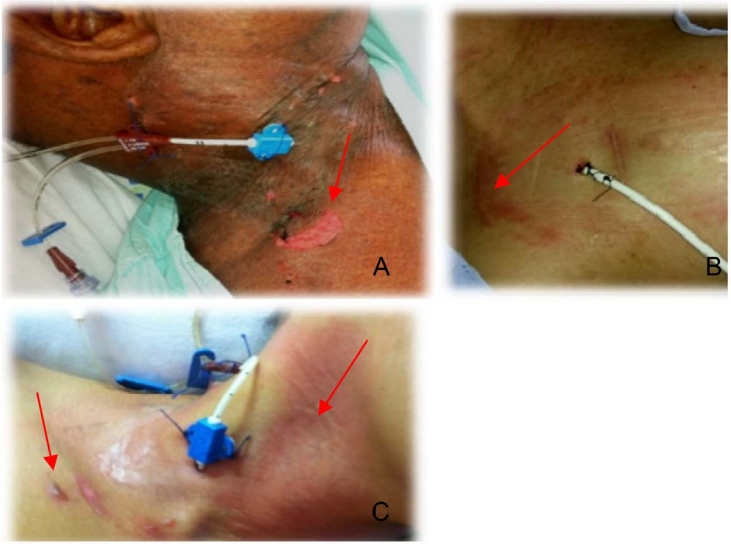

Figure 1. Images of different skin lesions observed in subjects with skin irritation. (A): Areas of skin loss. (B): Erythematous plaque. (C): Presence of vesicle and erythema.

Table 3. Associations between skin irritation and the following variables: central line-associated bloodstream infection, type of HSCT[a], catheter time in place, and type of chemotherapy conditioning regimens.

Variables	Skin irritation		
	Yes N = 11	No N = 14	P-value*
Central line-associated bloodstream infection, % (n)			0.68
Catheter present infection occurrence	16.0 (4)	16.0 (4)	
Catheter absent infection occurrence	28.0 (7)	40.0 (10)	
Type of HSCT, % (n)			0.03
Allogenic	32.0 (8)	16.0 (4)	
Autologous	12.0 (3)	40.0 (10)	
Type of catheter, % (n)			0.67
Tunneled CVC	32.0 (8)	20.0 (5)	
Non-tunneled CVC	12.0 (3)	36.0 (9)	
Catheter time in place, % (n)			0.67
Less than 20 days	12.0 (3)	36.0 (9)	
More than 20 days	32.0 (8)	20.0 (5)	
Type of chemotherapy conditioning regimens, % (n)			0.88
Low intensity	16.0 (4)	16.0 (4)	
Medium intensity	4.0 (1)	8.0 (2)	
High intensity	24.0 (6)	32.0 (8)	

*P-value from Fisher's exact chi-square test. [a]Hematopoietic stem cell transplantation.

the catheter sites were protected with gauze and adhesive tape or transparent polyurethane film.

Among the 11 patients with skin irritation, three (27%) developed central line-associated bloodstream infection and the microorganisms found were Corynebacterium sp, carbapenem-resistant Klebsiella pneumonia and Acinetobacter lwoffii. Two patients underwent allogeneic HSCT and one patient underwent autologous HSCT. Conversely, 4 (28%) of the 14 patients who did not develop skin irritation presented central line-associated bloodstream infection. The microorganisms found were Klebsiella pneumoniae, isolated in two patients, and Comamonas testosterone and Acinetobacter baumannii isolated in the other two patients, respectively. Three subjects underwent autologous and one allogeneic HSCT. The association tests between the variables central line-associated bloodstream infection, type of catheter, catheter time in place, type of chemotherapy conditioning regimens and skin irritation showed no statistical significance. P-values are shown in Table 3. Skin erythema was detected in 100% of the 25 patients after at least one dressing change procedure. This manifestation was considered a color abnormality secondary to mechanical trauma caused by the

removal of the dressing. The distribution of the outcomes is shown in Table 4.

4. Discussion

The present study evaluated the local cutaneous effects of chlorhexidine-impregnated gel dressings used to cover the central venous catheter exit site of patients undergoing HSCT. Chemotherapy conditioning regimens used in this study didn't have any statistically significant association with skin irritation after CIGD removal. However, studies show that chemotherapy and radiotherapy used in transplant procedures are associated with numerous adverse events affecting skin, mucous membranes, hair, and nails [28]. As examples, melphalan, busulfan, and cyclophosphamide can cause skin or mucosal hyperpigmentation while melphalan is also associated with alopecia and maculopapular rash [28]. A study with children undergoing autologous or allogeneic HSCT showed that approximately 50% of patients developed some degree of skin damage. Among the different conditioning regimens, this complication was more frequent (80%) in patients treated with busulfan and thiotepa, presenting as burnlike lesions [29]. Busulfan causes general darkening of the skin secondary to a toxic effect on melanocytes. This effect may be potentiated by other factors, such as the presence of sweat with secreted chemotherapy in areas of skin occluded by adhesive bandages [28]. Skin injured by chemotherapy may strongly adhere to the bandage, being removed along with the dressing characterizing skin loss, which was presented in all the patients of this study who had skin irritation. Skin injuries are usually noticed when adhesive dressings are used for long periods, with numerous dressing change procedures and when the adhesive strength exceeds the skin cell-to-cell interactions leading to dermo-epidermal detachment [29] [30] [31]. Most of our patients with skin irritation and skin loss were submitted to allogeneic HSCT, which usually includes high intensity chemotherapy conditioning regimens. Adhesive dressings have a maximum recommended time in place, according to which changing intervals should be programmed. Additional unscheduled changes may cause skin irritation or worsen effects of radiation and chemotherapy due to damage caused by the adhesive tape [32]. Patients with tunneled catheters were submitted to more dressing change procedures than patients with non-tunneled catheters. This finding was expected due to the time in place of each type of catheter which is longer in tunneled catheters. In addition, skin irritation was more frequent among allogeneic HSCT that used tunneled

Table 4. Overview of the outcomes.

Outcomes	N = 25
Skin irritation, % (n)	44.0 (11)
Skin Erythema, % (n)	100.0 (25)
Catheter absent infection occurrence	28.0 (7)
Discontinuation of the CIGD, % (n)	24.0 (6)
Central-line associated bloodstream infection, % (n)	32.0 (8)

catheters. A randomized clinical trial evaluated children undergoing high dose chemotherapy followed by HSCT and detected a 70% reduction in the incidence of local skin toxicity when dressings were changed every 15 days instead of every four days without increasing rates of catheter-related infections [29]. Therefore, it has been emphasized that changes scheduled at longer intervals may prevent the onset of skin irritation. On the other hand, extended intervals may increase the rate of unscheduled changes due to detachment or other mechanical events affecting adhesiveness. Nurses and other health professionals should be aware of possible skin irritation when adhesive dressings, including CIGD, are used. CIGD should be maintained for its maximum recommended time in place, which is seven days, avoiding unscheduled changes of the dressing, trying to prevent the onset of skin irritation. However, patients with CIGD should be daily evaluated to detect dressing detachment or mechanical events that require unscheduled dressing change and be aware of higher risk of skin irritation [29] [31]. A multicenter randomized trial [15] carried out in intensive care units, found that of 817 patients who used the CIGD, eight (1%) presented severe contact dermatitis. This complication was generally observed in severely ill patients with multiple organ failure, subcutaneous edema, and fragile skin. In a different study, these same authors compared different types of transparent dressings in intensive care unit patients and found that skin injury scores were higher in patients using dressings containing chlorhexidine compared to patients using the transparent film without chlorhexidine [19]. A report of seven cases of erosive contact dermatitis due to the CIGD [33] showed that four out of the seven patients were immunosuppressed, and the majority of catheters had been inserted into the femoral vein. Six cases occurred in children from four months to two years of age. In the seven cases described, the dressing was discontinued. This study suggests that children are more susceptible to the irritating effects of dressings with chlorhexidine in their composition. The erosive lesions were attributed to prolonged occlusion of the skin, exposure to components of the dressings, and local concentrations of chlorhexidine. Interestingly, the authors observed a higher incidence of dermatitis on the skin in contact with the chlorhexidine gel. In contrast, in the present study, 88% of the most severe lesions, classified as skin irritation, were detected predominantly in the areas of contact with the adhesive parts of the dressing. A multicenter randomized trial on chlorhexidine dressings in neutropenic patients detected cutaneous abnormalities in 12.4% of patients using the dressing. Symptoms observed were erythema, pruritus, vesicles, and skin defects [16]. Thus, in accordance with the literature, our study demonstrates that CIGD is associated with a degree of injury to the skin in contact with it as we also observed some of these symptoms. In our patients, we were able to identify specific predisposing factors, which have been previously described in the literature, such as skin sensitivity due to the toxic effects of chemotherapy, high rate of cell renewal, and use of corticosteroids and secondary immunosuppression to treat the underlying disease, along with che-

motherapeutic agents in the transplant conditioning regimen. Other factors, such as age, infections, malnutrition, and dehydration may also contribute to the development of skin lesions [31]. Studies on CIGD that evaluated its potential for infection reduction as the first endpoint also evaluated possible skin reactions associated to the dressing. They reported episodes of necrotic lesions, redness, irritation, skin macerations and mild erythema after dressing removal. These lesions are usually self-healing with no need of further intervention [34] [35] [36] [37] [38]. Manifestations of cutaneous effects, such as erythema were observed in 100% of our patients. However, this manifestation is considered transient and not harmful to the patient, being mostly secondary to the mechanical trauma caused by the removal of the dressing [31] [35]. In our patients, we did not observe an impact of CIGD-derived skin injuries on the incidence of bloodstream infections, whether catheter-related or not. Similar studies have also not confirmed this association [11] [15] [16] [19] [33]. In fact, in the report of seven cases of erosive contact dermatitis due to the CIGD, all cultures and microbiological evaluations from the sites presented negative results [33]. A large study that compared chlorhexidine-containing and non-containing CVC dressings demonstrated a significant reduction in local contamination in patients using the chlorhexidine-impregnated dressings. However, the authors were not able to correlate these findings with catheter-related infections [35]. The limitations of the present study were that we were not always able to identify which lesions were directly due to the dressings and which were associated with other local or systemic factors, such as allergic rashes, graft versus host disease, and viral infections, among other conditions. The majority of HSCT studies have small sample sizes due to the restricted number of transplants. Therefore, a large sample is only possible in a multicenter trial. Further studies, under more controlled conditions, with a larger number of participants, are still warranted. Nevertheless, our findings are clinically relevant and should contribute to patient assistance and health care professional education.

5. Conclusion

In this study, we detected that skin irritation was more frequent in patients who underwent allogeneic HSCT. The most common skin manifestation was skin loss. Lesions such as skin loss, erythematous plaques, or vesicles were classified as skin irritation, potentially leading to discontinuation of the dressing. We also observed that most skin irritation events occurred in areas in contact with the adhesive bandage of the dressing. This study indicates that health professionals should carefully evaluate each patient individually for use of CIGD, considering the risk of local lesions and ideal changing intervals.

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