Topical Treatment for Bleeding from Tumor Wounds: An Integrative Review

ABSTRACT
Objective: to carry out an integrative literature review, focused on the identification and evaluation of primary studies aiming at the topical control of bleeding in tumor wounds. Methods: bibliographic research was carried out from December 2020 to January 2021 in the Scopus, Cinahl, PubMed and Web of Science databases and used the keywords wounds and injuries, hemorrhage, neoplasms and nursing and the keywords symptom management, bleeding and therapeutics. Results: The final sample consisted of 06 studies. The most frequent designs were case series / case report, with five studies (83.3%), and one cohort study (16.7%). Therefore, five studies (83.3%) presented evidence level 6 (weak) and one (16.7%), evidence level 4 (moderate). Conclusion: it is recommended that further studies with a better methodological design be conducted in order to produce more concrete evidence.

Descriptors: Bleeding; Oncology; Wounds; Palliative care.

RESUMEN
Objetivo: realizar una revisión integradora de la literatura, enfocada a la identificación y evaluación de estudios primarios orientados al control tópico del sangrado en heridas tumorales. Métodos: se realizó una investigación bibliográfica de diciembre de 2020 a enero de 2021 en las bases de datos Scopus, Cinahl, PubMed y Web of Science y se utilizaron las palabras clave heridas y lesiones, hemorragia, neoplasias y enfermería y las palabras clave manejo de síntomas, sangrado y terapéutica. Resultados: La muestra final constó de 06 estudios. Los diseños más frecuentes fueron series de casos / relatos de caso, con cinco estudios (83,3%) y un estudio de coorte (16,7%). Por tanto, cinco estudios (83,3%) presentaron nivel de evidencia 6 (débil) y uno (16,7%), nivel de evidencia 4 (moderado). Conclusión: se recomienda que se realicen más estudios con un mejor diseño metodológico para producir evidencia más concreta.

Descriptors: Sangrado; Oncología; Heridas; Cuidados paliativos.

RESUMO
Objetivo: realizar uma revisão integrativa da literatura, focada na identificação e avaliação de estudos primários objetivando o controle tópico do sangramento em feridas tumorais. Métodos: foi feita pesquisa bibliográfica no período de dezembro de 2020 a janeiro de 2021 nas bases de dados Scopus, Cinahl, PubMed e Web of Science e usados os descritores wounds and injuries, hemorrhage, neoplasms e nursing e as palavras chaves symptom management, bleeding e therapeutics. Resultados: A amostra final foi composta por 06 estudos. Os delineamentos mais frequentes foram série de casos/relato de caso, com cinco estudios (83,3%), e um estudo de coorte (16,7%). Portanto, cinco estudios (83,3%) apresentaram nível de evidência 6 (fraca) e um (16,7%), nível de evidência 4 (moderada). Conclusão: recomenda-se que estudos posteriores com melhor delineamento metodológico sejam conduzidos a fim de produzir evidências mais concretas.

Descriptors: Sangramento; Oncologia; Feridas; Cuidados Paliativos.
**INTRODUCTION**

Tumor wounds originate from the infiltration of neoplastic cells in the structures of the skin, leading to disruption of tissue integrity and causing vascular disorders that generate tissue necrosis. The process of carcinogenesis, characterized by uncontrolled cell proliferation, leads to the appearance of ulcerative lesions. The literature shows that 5% to 10% of patients with advanced cancer are affected by these lesions and among its main symptoms, pain, foul odor, intense exudation and friability stand out. Among these, bleeding is described in the literature as a poorly studied symptom due to the fact that it is unpredictable and has different intensity.

Tumor wounds are a source of great psychological and social suffering because they cause a major change in the body image of patients, mainly due to their physical symptoms such as odor, pain, itching, excessive exudate and bleeding. Patients report feeling psychological distress, shame, loss of confidence, fear, guilt, depression and social isolation. As for bleeding, this symptom is described as distressing and a source of stress for patients, families and caregivers.

Bleeding from tumor wounds is associated with damage to blood vessels by cancer cells, which can be intensified by impaired platelet function and local stimulation of vascular endothelial growth factor. In addition, some procedures, such as dressing changes, when not performed cautiously, can cause trauma to the wound bed or blood vessels close to the tumor, triggering hemorrhagic processes.

Tumor wounds are generally associated with poor prognosis, with advanced disease. In this context, although therapeutic approaches such as radiotherapy, chemotherapy, hormonal therapies and surgery can promote symptom relief, these approaches may not be recommended depending on the patient’s clinical status and, in most cases, do not represent curative approaches. Thus, the most recommended approach in the treatment of tumor wounds is based on palliative care. These are based on the control of symptoms and the guarantee of the patient’s quality of life.

The most widespread way of controlling the symptoms of tumor wounds is topically. The use of this route stands out in the control of the classic symptoms of these wounds, such as pain, odor, secretion and bleeding, where the off-label use of medications and dressings is frequently made. With regard to bleeding specifically, the literature has a series of recommendations based largely on the application of topical agents, among which calcium alginate, surgical hemostatics and silver nitrate stand out.

However, there is a scarcity of primary studies with methodological designs with a high level of evidence that demonstrate the best approaches and coverage aimed at the management of bleeding in tumor wounds. It is noteworthy that the importance of preparing these studies represents not only a scientific gain, especially for evidence-based nursing practice, but also reflects on the quality of life of patients who will have their symptoms controlled, providing them with greater comfort and safety. In this sense, this study aims to carry out an integrative review of the literature, focused on the identification and evaluation of primary studies aiming at the topical control of bleeding in tumor wounds.

**METHOD**

It is an integrative literature review based on the synthesis of the knowledge produced on the subject in different methodological approaches, built through systematic and broad analysis of the studies available in the scientific community. The integrative literature review method consists of six steps: establishment of the review hypothesis or question; selection of the sample to be reviewed; categorization and evaluation of studies; interpretation of results; and presentation of the knowledge review or synthesis.

The guiding question of this integrative review was structured based on the PICOD system, that is, after considering:
the target population (P), the interest of the area (I), types of intervention or care (C), obtaining results and considering the effects to be achieved (O) and study design (D) resulting in the expression: what are the conducts adopted to control bleeding in tumor wounds. In it, the first element of the strategy (P) consists of patients with tumor wounds; the second (I), the conducts adopted for the topical control of bleeding in tumor wounds; the fourth element (O) synthesizes a set of evidence regarding the conducts adopted for the topical control of bleeding in tumor wounds and the sixth element (D) selection of primary studies.

The literature search was carried out between December 2020 and January 2021 in the following databases: Scopus Info Site (SCOPUS), Cumulative Index to Nursing & Allied Health Literature (CINAHL), National Library of Medicine (PubMed) and Web of Science. Descriptors were selected from the international vocabulary used in the health field - the Medical Subject Heading (MeSH), created by the National Library of Medicine for literature indexed in Medline and the descriptors in health sciences (DeCS), combined with Boolean operators and keywords. Both terms were combined in different ways to ensure a broad search (Chart 1). There were two manual inclusions of articles that were already known by the researchers.

The inclusion criteria for pre-selection of studies were: primary articles, published in journals and indexed, available electronically in full, in English, Spanish or Portuguese, regardless of the year of publication. According to the exclusion criteria, articles that did not answer the research question, literature reviews, duplications and those that were not found in full were excluded. The articles found in duplicate were counted in the database with the highest number of references.

The process of identification, selection and inclusion of the studies was carried out by two reviewers independently. Disagreements between reviewers were resolved with a third reviewer. The process took place in three stages. In the first stage, duplicate articles were removed; thus, of the total of 243 articles, 52 were removed. In the second stage, the titles and abstracts of the 191 articles were read, based on the inclusion criteria. Thus, 99 articles were selected. In the third stage, 99 articles were read in full, 93 articles were removed because they did not meet the inclusion criteria and did not answer the guiding question of this review, so that the final sample consisted of 06 articles. Figure 1 illustrates the selection process for the articles in this integrative review.

For the level of evidence, the classification suggested by Melnyk and Fineout-Overholt (2005) was used, which classifies the studies into seven levels: 1 - evidence from systematic review or meta-analysis of randomized controlled clinical trials or clinical guidelines based on reviews systematic randomized controlled clinical trials; 2 - evidence from at least one well-designed randomized controlled clinical trial; 3 - evidence obtained from well-designed clinical trials without randomization; 4 - evi-
Evidence that originated from well-designed cohort and case-control studies; 5 - evidence originating from a systematic review of descriptive and qualitative studies; 6 - evidence derived from a single descriptive or qualitative study; 7 - evidence from the opinion of authorities and/or the report of expert committees. According to this classification, levels 1 and 2 are considered strong evidence, 3 and 4 moderate and 5 to 7 weak.

RESULTS

The final sample consisted of 06 studies, the oldest published in 2000 and the most recent in 2015, of which one (16.7%) was published in 2000, one (16.7%) in 2010, two (33.3%) in 2012, one (16.7%) in 2014 and one (16.7%) in 2015. Regarding the origin of the studies, five (83.3%) were published in the English language and one (16.7%) was published in the Spanish language. All studies were published in international journals. As for the location of the study, one (16.7%) was carried out in France, one (16.7%) in Spain, two (33.3%) in Japan, one (16.7%) in the USA and one in Nigeria (16.7%). The most frequent designs were case series/case report, with five studies (83.3%), and one cohort study (16.7%). Therefore, five studies (83.3%) presented evidence level 6 (weak) and one (16.7%), evidence level 4 (moderate).

The synopsis of the articles included in this study is shown in Chart 1, containing the authorship, the title of the article and the year of publication, the level of evidence, the objective, method and the recommendations/conclusions of the study. Regarding the level of evidence, most studies (83.3%) presented level 6, which corresponds to evidence derived from a single descriptive or qualitative study, and the predominant method in these studies was a case study/case series. One study (16.7%) presented evidence level 4, which corresponds to evidence that originated from well-designed cohort and case-control studies, being a cohort study.

DISCUSSION

Half of the studies were conducted with patients with tumor wounds caused by breast cancer. 16,17,18 This result is in line with the literature that reports that approximately 50% of such wounds are associated with this diagnosis. 19,20 Two studies reported the use of Mosh paste as a topical treatment for bleeding from tumor wounds. The Mosh paste is made up of a combination of zinc chloride, distilled water, zinc powder and glycerin in varying concentrations. It was initially developed for the purpose of chemical fixation of a cutaneous tumor during micrographic excision and currently, the literature has demonstrated that it is effective in the hemostasis of bleeding from tumor wounds through direct application. 17

Although both studies reported favorable outcomes in containing bleeding, they presented poorly robust methodological designs, with little representative samples and without describing a careful control in relation to the use of treatments concomitant with the studied therapy and its possible interferences in the results, producing, thus, weak evidence.

In addition, it was observed that although the respective studies have described similar compositions in the Mosh Paste making process, there was no standardization in relation to the concentrations of the components. This lack of consensus represents a major problem in the use of this substance for therapeutic purposes, since it does not offer basic safety principles, representing risks to patients’ health. This aspect becomes even more worrying when one takes into account the high toxicity of the Mosh paste described in the literature. 21

A similar methodological limitation was identified in the study by Adeba-
<table>
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<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Study Design</th>
<th>Description</th>
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<tr>
<td>Ladas EJ, Karlik JB, Rooney D, Taronmina Nd, Gra-nowetter L, Kelly KM</td>
<td>2012</td>
<td>Case series with four patients with tumor wounds resulting from: synovial sarcoma in the mandible and oral cavity; Right axillary synovial sarcoma and chest wall; Burkitt’s lymphoma and recurrent alveolar rhabdomyosarcoma. YNB usage protocol: Patient 1: topical application of YNB capsules, crushed and dipped in a sterile sponge. No specific time of use was mentioned. Patient 2: Application of YNB in a sponge directly on the bleeding surface as many times as necessary to dry it. Patient 3: topical application of YNB associated with petroleum jelly. The frequency of application was not mentioned. The use of the herb with a cotton swab topically twice a day for 1 week was recommended as prophylactic use. Patient 4: Topical YNB associated with vaseline tablets and aminocaproic acid in the presence of a hemorrhagic episode.</td>
<td>To describe the use of a medicinal powder based on Chinese herbs called Yunnan Baiyao (YNB) for the control of bleeding in adolescents with cancer.</td>
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<td>Kakimoto M, Tokita H, Okamura T, Yoshino Koji</td>
<td>2010</td>
<td>Case series with five breast cancer patients. Hemostatic chemical treatment was carried out with Mohs paste. Topical application of Mohs paste on the tumor surface with the aid of wooden sticks or application of the paste on the gauze and compression of it directly on the active bleeding sites in the tumor. An application time of 5 to 10 min was mentioned to stop the bleeding.</td>
<td>Perform hemostatic chemical treatment with zinc chloride paste (Mohs’ paste) on bleeding breast tumor wounds.</td>
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<td>Fromantin I, Watson S, Baffie A, Rivat A, Falcou M-C, Kriegel I, Ingenior YR</td>
<td>2014</td>
<td>Prospective cohort for 20 months (May 2010 to January 2011), conducted with 32 patients with breast cancer. Inclusion and exclusion criteria were listed. Assessments were made over a period of 42 days, with an assessment every 21 days (day 0, day 21 and day 42). Infection, pain, odor, exudate and bleeding were investigated. Bleeding was considered spontaneous when it occurred between two dressing changes, or induced when it occurred during dressing change. Dressings: alginates, hemostats and local adrenaline for spontaneous bleeding and application of a non-adherent dressing of the interface type or impregnated with silicone as a routine.</td>
<td>Evaluate the use of topical therapies and characteristics of tumor wounds.</td>
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All patients in the study obtained control of bleeding. However, it was not possible to assess the exact contribution of YNB to hemostasis of tumor wounds, since the powder was used as adjuvant therapy.

Hemostatic treatment was successful on the first application in all five patients. Bleeding control was maintained from 3 weeks to more than 3 months.

The bleeding was controlled by local wound care. The number of patients included in the study was too small to draw any robust conclusions about care guidelines. The study’s evaluation period was considered relatively short to assess the evolution of a chronic wound.
mowo (2000) 22, that sought to evaluate the use of topical formalin in a series of cases. The use of formalin was initially reported to control bleeding from hemorrhagic cystitis 23, and was subsequently used to treat bleeding from radiation retnitis 24,25, in addition it is a tissue fixative, preservative, disinfectant and embalming agent.

The study demonstrated that only one application of topical formalin was effective in controlling bleeding in 77.3% of patients, in addition there was a certain standardization of the procedure for applying it and duration, however the authors emphasized that the volume of absorption of substance in the body is not known and that although formalin was administered in the study at an average concentration of 10 ml, considered safe by the authors, other studies do not corroborate this information.

Other study 17 of this sample described the use of a medicinal powder based on Chinese herbs called Yunnan Baiyao (YNB) for the control of bleeding in a series of cases composed of five patients with tumor wounds derived from recurrent synovial sarcoma in the left jaw and oral cavity, sarcoma right axillary synovial and chest wall, Burkitt’s lymphoma and recurrent alveolar rhabdomyosarcoma. Yunnan Baiyao (YNB) is characterized by a medicinal powder based on Chinese herbs (Panax notoginseng, Ajuga forrestii Diels, Dioscoreae Parvi-flora Ting, Herba Inulae Cappae, Herba Geranii and Herba Erodii, Rhizoma Dioscoreae and Rhizoma Dioscoreae and 40% of Dose of Dioscoreae of dry root extract of P. notoginseng) formulated initially in 1902.

Regarding the effectiveness of YNB as hemostatic, a small double-blind, placebo-controlled trial was conducted to investigate the hemostatic properties of YNB in preventing blood loss in adults undergoing orthopedic maxillary surgery. For this, YNB was administered orally for 3 days before surgery. The study identified significantly less blood loss in the treated group compared to the control group, in addition, no thromboembolic events or other side effects were identified. 26 Two other Chinese studies reported that oral YNB administration decreased intraoperative bleeding during a laminoplasty procedure and during transurethral resection of the prostate, demonstrating similar side effect rates between the treated and control groups. 27

Although the aforementioned studies have methodological designs more consistent with randomization and double-blinding, they were performed in surgical patients and the same evidence cannot be inferred for bleeding from tumor wounds, since the pathophysiology of bleeding in these wounds is specific and associated with the oncogenesis process.

Although the study by Ladas et al (2012) 28 has proposed to provide this scientific evidence for the oncological context and has presented a favorable outcome in terms of bleeding control, it has shown low evidence. Its greatest weaknesses were identified in relation to the lack of standardization regarding the YNB application protocol, the varied presentation of the substance and the concomitant use of other topical treatments for bleeding, such as amino-
caproic acid, which was configured as a major confounding factor for the investigation of the therapeutic effects of the substance.

Two studies of the sample did not investigate a specific topical substance for the control of bleeding, but addressed as therapeutic strategies the use of coverings and dressing techniques specific to the management of friable oncological wounds. The study by Monleón-Just et al (2012) 16, sought to describe the use of a hydrocellular triaminate dressing, with soft gel adhesive in a patient with a tumoral wound in the breast, aiming to control exudate, odor and bleeding, in addition to evaluating the psychological effects of the treatment.

The evaluated coverage promoted a delicate adhesion to the wound bed, avoiding trauma during the dressing changes and performed the effective control of the wound exudate, allowing more spaced changes of the dressing, avoiding the manipulation of the wound and consequently reducing the risk of bleeding. As limiting factors, the article presented low evidence due to its unsatisfactory sample size and limited experimental design.

A similar result was identified in the study by Fromantin et al (2014), the only study in the sample in this review that presented moderate evidence. The study evaluated the use of topical therapies to control the symptoms of tumor wounds, including bleeding. To this end, a prospective cohort study was carried out for 20 months (May 2010 to January 2011), conducted with 32 patients with tumor wounds resulting from breast cancer. The study presented a more robust methodological design, describing the inclusion and exclusion criteria, a detailed description of the materials and procedures performed, and definition of the criteria for evaluating the control of symptoms.

The main gaps evidenced in the study were in relation to a small number of the sample of patients, which does not allow to establish robust conclusions about the care guidelines. In addition, the study’s evaluation period was 42 days, a period considered relatively short to assess the evolution of a chronic wound. Both studies showed, respectively, the importance of the use of adequate technique by the professionals during the dressing of tumor wounds, and the effectiveness of the bleeding control of these wounds through the use of dressings based on alginates, hemostats and adrenaline, in case of spontaneous local bleeding and application of non-adherent dressing of the interface type or impregnated with silicone as a routine.

It is important to highlight that the topical and more conservative approach to bleeding from tumor wounds performed by means of dressings is preferable for most of these patients, especially because they do not have satisfactory clinical conditions to undergo more aggressive anti-hemorrhagic procedures, such as surgical dryness or anti-hemorrhagic radiation therapy, in addition to these more conservative procedures provide greater comfort and better quality of life for these patients. It is known that in some cases, the topical approach is not sufficient to control bleeding, especially in case of rupture of large vessels that cause profuse bleeding, in these cases, procedures such as embolization or suture of the vessel are highly recommended. 6,8

CONCLUSION

The present study sought to gather the evidence available in the literature regarding the best practices and recommendations associated with the control of bleeding in tumor wounds. Although the evidence presented here is not high, the studies described a series of substances, coverings and procedures that have been used by professionals in the practical management of this symptom with satisfactory results. Even if it is not configured as robust evidence and it is not possible to generalize the results,
REFERENCES


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