DOI: https://doi.org/10.36489/nursing.2020v23i271p4971-4978

Association of photobiomodulation and topical hyaluronidase in extravasation and infiltration of antineoplastics. Retrospective study

ABSTRACT | Objective: to evaluate the action of photobiomodulation associated with topical hyaluronidase on extravasations and infiltrations of antineoplastic agents, in preventing the formation of lesions. Method: Cross-sectional, retrospective, descriptive study that analyzed data referring to extravasation and infiltration of antineoplastic agents in an Oncology Outpatient Clinic of a Public Hospital in the interior of the State of São Paulo from January 2018 to October 2019. Results: The population the study consists of 15 participants, of which 53% (n = 8) had leakage and 47% (n = 7) infiltration, generating an incidence of 0.6% and 0.5% respectively. The most involved antineoplastic agents were paclitaxel and carboplatin. There was no lesion formation in the 15 studied patients. Only 02 sessions of FBM were performed in each patient with the exception of 01 patient who were performed 07 sessions, for being anthracycline leakage. Conclusion: The administered protocol was effective in preventing the formation of lesions during extravasation and infiltration of antineoplastic agents.
Keywords: Low-Level Light Therapy, Lasers; Extravasation of Diagnostic and Therapeutic Materials; Antineoplastic Agents.

RESUMEN | Objetivo: evaluar la acción de la fotobiomodulación asociada a la hialuronidasa tópica sobre extravasaciones e infiltraciones de agentes antineoplásicos, en la prevención de la formación de lesiones. Método: Estudio descriptivo, transversal, retrospectivo, que analizó datos referentes a extravasación e infiltración de agentes antineoplásicos en un Ambulatorio de Oncología de un Hospital Público del interior del Estado de São Paulo de enero de 2018 a octubre de 2019. Resultados: La población el estudio consta de 15 participantes, de los cuales el 53% (n = 8) presentaba fugas y el 47% (n = 7) infiltración, generando una incidencia de 0,6% y 0,5% respectivamente. Los agentes antineoplásicos más implicados fueron paclitaxel y carboplatino. No hubo formación de lesiones en los 15 pacientes estudiados. Solo se realizaron 02 sesiones de FBM en cada paciente con excepción de 01 paciente que se realizaron 07 sesiones, por ser fuga de antraciclinas. Conclusión: El protocolo administrado fue eficaz para prevenir la formación de lesiones durante la extravasación e infiltración de agentes antineoplásicos.
Palabras claves: Terapia por Luz de Baja Intensidad; Rayos Láser; Extravasación de Materiales Terapéuticos y Diagnósticos; Antineoplásicos.

RESUMO | Objetivo: avaliar a ação da fotobiomodulação associada a hialuronidase tópica nos extravasamentos e infiltrações de antineoplásicos, na prevenção de formação de lesões. Método: Estudo transversal, retrospectivo, descritivo que analisou os dados referentes a extravasamento e infiltração de antineoplásicos em um Ambulatório de Oncologia de um Hospital Público do interior do Estado de São Paulo no período de janeiro de 2018 a outubro de 2019. Resultados: A população do estudo constituise de 15 participantes, destes, 53% (n=8) apresentaram extravasamento e 47% (n=7) infiltração, gerando uma incidência de 0,6% e 0,5% respectivamente. Os antineoplásicos mais envolvidos foram paclitaxel e carboplatina. Não houve formação de lesões nos 15 pacientes estudados. Foram realizadas apenas 02 sessões de FBM em cada paciente com exceção de 01 paciente que foram realizadas 07 sessões, por ser extravasamento de antraciclina. Conclusão: O protocolo administrado foi efetivo na prevenção de formação de lesões durante extravasamento e infiltrações de antineoplásicos.
Palavras-chaves: Terapia com luz de baixa intensidade; Lasers; Extravasamento de materiais terapêuticos e diagnósticos; Antineoplásicos.

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Received on: 09/06/2020
Approved on: 09/23/2020

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INTRODUCTION

Antineoplastic chemotherapy is widely used in the treatment of cancer. Chemotherapy drugs are classified as vesicant, irritant and non-vesicant. Extravasation refers to the escape of the vesicant chemotherapist out of the vessel, presenting an incidence of 0,1 to 7% in peripheral infusion, whereas the infiltration is related to the escape of irritants and non-vesicants. Irritants can cause symptoms such as burning, phlebitis or pain even when properly infused and rarely cause necrosis or ulceration even when infiltrated in large quantities. [1,2] On the other hand, when vesicants leak, they cause great damage to the underlying tissue, causing pain and quickly leading to necrosis. [1,2,3] Unlike the aforementioned drugs, non-vesicants do not cause tissue damage. [3,4] In this sense, an important aspect to be investigated is how to avoid complications of leakage and infiltrations.

Hyaluronidase is an antidote used in the extravasation of chemotherapy drugs, however it is specific for vesicants that are not bound to DNA, although it is a potential antidote for anthracyclines. It modifies the permeability of the tissue by hydrolysis of hyaluronic acid and helps to disperse the vinca alkaloids of the tissue promoting resorption. [5] A maximum of ten minutes after application, it is already possible to observe the action of the enzyme, by increasing the diffusion of the leaked liquid in an area 3 to 5 times greater than an untreated area. The permeability of the tissue is restored 24 to 48 hours after the application of the antidote. [6]

Another recommended therapy to accelerate the healing process and in several pathologies, substantially improving the patient's quality of life, is photobiomodulation therapy (PBMT) or Low Intensity Laser (LLLT). [7],

It has anti-inflammatory, analgesic and healing actions, in addition to not causing side effects to the body, like many drugs of choice for different types of treatment, being characterized as a therapeutic resource often of first choice. [9]

Patients should be evaluated clinically for the application of FBM and some parameters for the success of therapy should be considered, such as wavelength, fluency, power density, pulse structure and applied light time. The choice of which parameter to use is very important and will depend on the specificity of each treatment. There is an ideal dose of light for any particular application and doses higher or lower than these optimum values may have no therapeutic effect. Therefore, a wrong choice of these parameters can mean reduced treatment effectiveness, or even a negative therapeutic result. PBMT is characterized by a biphasic dose-response, where lower doses of light are often more beneficial than high doses. [10]

This fact was confirmed in a study carried out to investigate the effects of PBMT in the repair of skin lesions in an animal model using a wavelength of 658, 830 and 904 nm. There was an increase in cellularity, neovascularization and type III collagen fibers in the group that used the 658 nm wavelength. The groups with longer wavelengths showed similar results to the control group that had not received PBMT. [11]

When applied to tissue, the stimulus is absorbed by cells that have photoreceptors, which may be enzymes, cell membrane molecules or any other structure that has an affinity for red (660nm) and infrared (880nm) wavelengths. [8]

The study is justified by the leakage/infiltration causing a decrease in quality of life, which may affect the continuity of antineoplastic treatment due to possible damage caused.

Its objective is to evaluate the action of PBMT associated with topical hyaluronidase in extravasations and infiltrations of antineoplastic agents, in preventing the formation of lesions.

METHOD

Cross-sectional, retrospective, descriptive study that analyzed data referring to extravasation and infiltration of antineoplastic agents in an Oncology Outpatient Clinic of a Public Hospital in the state of São Paulo.

Inclusion criteria were those patients who presented extravasation and infiltration of antineoplastic agents from January 2018 to October 2019, excluding extravasations and infiltrations of non-chemotherapy drugs.

The cases of extravasation and infiltration of antineoplastic agents were registered by the nurse daily in a spreadsheet of the Institution, recorded in the electronic medical record of the patient (EMR) and reported to the Sentinela Hospital. The Institution has a well-defined leakage and infiltration protocol, where all employees were trained. As an antidote, hyaluronidase cream (topical use) 65 RTU and PBMT.

Data collection and analysis were carried out from August to September 2020 after approval by the Research Ethics Committee, with the CAAE protocol: 31726620.5.0000.5411.

After filling out the Free and Informed Consent Form for patients with leakage and infiltration, data from the nursing notes inserted in the EMR and the Adverse Events Notification (fichas de Notificação de Eventos Adversos - FNEA) forms were analyzed.

Initially, all patients were identified using the FNEA. Afterwards, an EMR assessment was carried out to trace the profile of the patients (age range, sex, education, age, diagnosis), in addition to the antineoplastic protocol used, symptoms presented and whether all were treated according to the institution's protocol.

Descriptive statistical analysis was performed and simple measures were used, such as: frequency distribution, percentages and average. The discussion of the findings was made based on the literature produced on the topic. The incidence was calculated by dividing the number of leakage/infiltration cases by the number of chemotherapy performed in the period, multiplied by 100.

RESULTS

The study population consisted of 15 participants, of which 53% (n=8) had leakage and 47% (n=7) infiltration. Of the total sample, 50% were female. The predominant age group was 70 to 80 years (33%), with an average of 74,8 years. The predominant level of education was the complete elementary school 40% (n=6).

As for the diagnosis, breast cancer was the most prevalent (26,6%) followed by lung, lymphoma and esophagus with 13,3% each and rectum, acute lymphocytic leukemia, endometrium, larynx and prostate with 6,6%.

The chemotherapeutic drugs that showed a higher incidence of leakage and infiltration are described in tables 1 and 2 respectively. The most common signs and symptoms during the events were listed in Table 3. During the study period, 12,866 chemotherapies were administered, generating an incidence of 0,6% for leakage and 0,5% for infiltration.

All medical records contained care provided during the finding of overflow/infiltration, as well as the use of warm or cold compresses. Regarding the compresses, all were performed correctly according to the type of chemotherapy involved.

It was found that the conduct performed by the nurse in the face of extravasation was correctly described in the notification form and in the EMR of all patients. These precautions were described as: immediate stop of the infusion, maintenance of the device, aspiration of the residual drug, performance of PBMT with punctual technique using 1 red joule (J) with a distance of 1 cm at each application point, hot or cold compresses , limb elevation, hyaluronidase antidote application. Patients were instructed on the use of hyaluronidase 3 times a day, cold or warm compresses and return to the clinic to perform PBMT 3 times a week.

All patients (15) returned to the outpatient clinic for a new evaluation two days after the event and did not present the symptoms described above, being discharged after 2 sessions of PBMT. Only one patient was followed for 30 days because it was anthracycline extravasation (DNA-binding vesicant) receiving PBMT 3 x weeks in the first two weeks (totaling 7 sessions), with no lesion formation.

Table 1. Description of the chemotherapy drugs involved in the extravasation. Botucatu –SP, 2020

Quimioterápico	N	%
Paclitaxel	06	75
Docetaxel	01	12,5
Daunorrubicina	01	12,5
Total	08	100

Source: Database organized by the researcher

Table 2. Description of the chemotherapeutic agents involved in the infiltration. Botucatu –SP, 2020

Quimioterápico	N	%
Carboplatina	02	28,5
Gencitabina	01	14,3
Rituximabe	01	14,3
Oxaliplatina	01	14,3
Ifosfamida	01	14,3
Cisplatina	01	14,3
Total	07	100

Source: Database organized by the researcher

Table 3. Signs and symptoms presented during extravasation. Botucatu-SP. 2020

Sinais e Sintomas	N	%
Parada da infusão	15	100
Ausência de retorno venoso	15	100
Edema	15	100
Hiperemia	15	100
Dor	15	100
Calor	01	6,6

Source: Database organized by the researcher

DISCUSSION

The National Cancer Institute (INCA) estimates 66 thousand new cases of female breast cancer and 30 thousand cases of lung cancer per year for the 2020-2022 period. With the exception of non-melanoma skin cancer, breast cancer is the most prevalent in women. [12]

The incidence of leakage reported in the literature can vary from 0.01% to 7% 13, corroborating with our findings and diverging from a study also carried out in a University Hospital that observed a 23,6% rate of leakage. [2] The result of an overflow can lead to long-term complications, permanent disability of the limb, change in the patient's prognosis and decreased quality of life. [13]

The main signs and symptoms related to extravasation are: decreased serum flow or complete stop of the infusion, absence of venous return, burning, edema, redness, pain may or may not be present. [14]

We observed that all patients had the correct notes and documentation

regarding leakage and infiltration. In this sense, COFEN, through Resolution 429/2012, ensures that it is the responsibility of nursing professionals to record in appropriate documents the information relevant to all care provided to the patient. [15]. However, the literature points to a lack of registration of care in 15.9% of the forms and notification of leakage. [16]

Because it is considered an oncological emergency, extravasation requires rapid and assertive interventions. [16] For this, the extravasation protocol must be structured and based on scientific evidence, guaranteeing an agile and quality service. [17]

Therefore, it was found that the protocol used in the service was in accordance with that suggested by the international literature. The Infusion Nursing Society recommends that the infusion should initially be stopped, the device must not be disconnected, the maximum amount of drug should be aspirated, cold or warm compresses should be applied, and the standard antidote should be applied. [18]

The Institution has a PBMT device, incorporating this practice in its overflow protocol. There are no reports in the literature on PBMT in the extravasation of antineoplastic agents, however, it is already widely used in the prevention and treatment of injuries. An example of this therapy is its use in oral mucositis induced by cancer treatment (radiotherapy and/or chemotherapy), where analgesia and healing of oral lesions are promoted. To obtain an adequate response, PBMT must be performed at least 3 times a week. [19]

Regarding the hyaluronidase antidote, in a scoping review conducted by Melo, et al (2017) [20], it was found that several articles show that the enzyme degrades hyaluronic acid, improving the absorption of extravasated drugs, which can be effective in preventing skin necrosis by extravasation with vinca alkaloids and in taxanes.

It is also noteworthy that dexrazoxane is the only antidote whose effectiveness has been tested in clinical trials (through biopsy) for the treatment of anthracycline leakage and the only one approved by the FDA and the European Commission for this type of treatment [21], however, in Brazil there is no standardized antidote. It has a 98% effectiveness in the treatment of anthracycline extravasation, however, the use of this antidote is still unfeasible for the public sector, due to its high cost. [21]

CONCLUSION

Taking into account the severity of the leaks and infiltrations that occurred and the non-formation of lesions, it appears that the association of hyaluronidase with low-level laser is effective in the treatment of these events, and can be considered an adjunctive therapy combined with others practices already described.

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