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Evaluation of the effect of ozone therapy with ozonized water in oral mucositis of pediatric cancer patients

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Abstract

Introduction: Mucositis will be produced as a side effect of antineoplastic treatments, being a multifactorial pathology that begins on the third or tenth day after the start of antineoplastic treatment, lasting 2 to 4 weeks, signs and symptoms are burning in the mouth , erythema, ulcers and inflammation in the non-keratinized tissues of the oral cavity bringing problems in the individual such as dehydration, growth of immunosuppression and malnutrition, triggering fungal, bacterial and septic events. There are a variety of treatments for both prevention and treatment, however they have not shown great success. Ozone therapy consists of the administration of a mixture of oxygen (95%) and ozone (5%) to the organism by topical and systemic routes as a therapeutic means, within its properties we can find that it is oxygenating, revitalizing, antioxidant, modulating, regenerative, anti-allergic, anti-inflammatory and germicidal.

Objective: To evaluate the effect of ozonated water on oral mucositis of pediatric cancer patients.

Materials and methods: This was a quasi-experimental study with a chronological series design in a single group of repeat therapy, longitudinal and prospective. The universe was formed by all the patients who were hospitalized in the oncology area of the Dr. Rodolfo Nieto Padrón Children's Hospital, the sample was of 15 patients between 1 and 15 years of age who presented various degrees of oral mucositis (criteria established by the WHO).

Results: The data obtained were through 15 patients with Acute Lymphoblastic Leukemia, distributed by age and sex; the decrease in days of the OM was obtained in a range less than 7 days, the most severe cases of the OM being grade 4 its total involution was on the seventh day; Regarding the tolerance of food, patients with grade 1, 2 and 3 showed painless intake from the first day of application with W3O, a single patient with grade three showed improvement on the second day and patients with grade 4 between the third and fourth day of administration with W3O.

Conclusions: The total remission of mucositis with ozone therapy through W3O was achieved at 7 days, in the most severe cases. Compared with the average of 22 days documented by other studies, recovery was achieved in a third of the average time with other treatments.

Introduction

The cancer will be an uncontrolled multiplication or division, abnormal, rapid, autonomously and disorderly of abnormal cells that will not only be its invasion locally but can spread to other regions of the body or spread throughout the body taking nutrition from the organism, causing in the organism a physiological failure.[1,2] Globally in 2018 it was estimated that 18 million cancer patients were diagnosed, mentioning that 200,000 of that figure refers to the child and adolescent population. In Mexico until 2017 it was reported that childhood cancer has an incidence rate per million in infants of 111.4 between 0 to 9 years and 68.1 from 10 to 19 years.[3]

Acute lymphoblastic leukemia (ALL) a malignant and chronic neoplasm, which affects 25% of the bone marrow, as a "consequence of malignant transformation of an immature lymphoid progenitor cell that has the ability to spread forming a clone of identical progenitor cells blocked in a point of its differentiation", being considered as the most frequent type of leukemia in the child population, being the most affected male sex. With an incidence in the state of Tabasco of 42.5% of cases reported.[4–6]

The treatments of choice is chemotherapy and radiotherapy, many times Antineoplastic treatments will have side effects, because they not only focus on diseased cells, but also healthy ones. The toxicity that occurs will be due to several factors, such as functional status, age, previously administered antineoplastic treatments, liver or kidney failure and the type of pathology; exerting problems to the hematopoietic system. Odontologically, the side effects produced by chemotherapeutic drugs are: taste disturbance, less salivation secretion and mucositis.[7,8]

Oral mucositis (OM) a pathology of complex multifactorial etiology beginning on the third or seventh day of the antineoplastic treatment and with a recovery approximately 2 or 4 weeks after the end of the treatment, which gastrointestinal tract damages (from the mouth to the anus) manifesting as severe and acute diffuse ulcer injury, with the presence of severe pain, ulceration and inflammation in the oral mucosa (soft palate, jugular mucosa, tongue belly, floor of mouth and labial mucosa) and redness of the tongue, such as result of the decrease of the basal renewal epithelium, therefore this will be very thin. The manifestations that occur in mucositis will bring problems in the individual such as dehydration, growth in the state of immunosuppression and malnutrition, leading to fungal, bacterial and sepsis problems.[9–12] As shown in Table 1, there are several classifications for mucositis, however one of the most prominent is by WHO.[14]

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The variety of therapeutics for both prevention and treatment can be classified by general oral care protocols, interventions for the reduction of mucosal toxicity caused by chemotherapy drugs, mouthwashes of mixed action, immunomodulatory agents, topical anesthetics, antiseptics, agents, antibacterials, antifungals and antivirals, barriers in the mucous membranes and protective agents, cytoprotectors, stimulants of the mucous cells, psychotherapy and analgesics, despite the many therapies it has not been possible to obtain very successful results.[14,15]

Table 1 WHO Classification for mucositis.[13]

Grade	Characteristics
0	No presence of symptoms
1	Pain and erythema
2	Erythema, ulcer, with ability to eat solid diet
3	Ulcer, external erythema and accurate liquid diet
4	Ulcers that prevent food intake and requires tube or intravenous feeding

Currently, the use of ozone therapy has been implemented in a therapeutic way, which consists in the administration of ozone (5%) - oxygen (95%) which is achieved through generators. The properties offered by ozone therapy are the oxygenation of cells providing a better blood supply, revitalization through the stimulation of ATP to the cells, antioxidant as it will stimulate the body's antioxidant cellular enzymes by eliminating free radicals, immune by increasing of humoral and cellular immunity, regenerative by stimulating tissue regeneration and healing wounds that are difficult to cure, anti-allergic and anti-inflammatory through neurochemical mediators and a potent germicide eliminating bacteria, fungi and viruses.[16,17] One of the presentations for the administration of ozone therapy is through ozonated water (O3W),wich have been widely used in the medical area for ulcers, traumatic injuries, burns, fungal infections, for the elimination of pus and necrotic áreas.[18]

Material and method

This was a quasi-experimental study type with a chronological series design in a single group with repeated therapy, prospective and longitudinal, with a sample of 15 patients between 1 and 15 years of age of both sexes, who were hospitalized in the area of oncology at Dr Rodolfo Nieto Padron Children Hospital and presented oral mucositis in the various degrees specified by the WHO and was collected in the period from February 2018 to August 2019. The criteria for sample selection were patients who are undergoing chemotherapy treatment, patients presenting with oral mucositis and tutors who accept the treatment, at Dr. Rodolfo Nieto Padrón Children Hospital.

With the objective of evaluating the effect of ozonated water on oral mucositis of pediatric cancer patients. Mucositis grade: eight patients presented grade 1 mucositis, three manifested grade 2, two patients with grade 3 and two patients with grade 4. Once the mucositis was diagnosed, the patient meet the inclusion criteria and the parent or caregiver gave his authorization , the distilled water in the Bio3 domestic ozone generator was ozonized for 5 minutes, then it was administered in syringes of 10 ml to patients 1 to 6 years and 150 to 200 ml to patients between 7 and 15 years, the administration of the O3W was in a period of 5 minutes, then it was requested that it be discarded or swallowed, and this action was performed one to three times, through the help of parents in patients 1 to 6 years and patients 7 to 15 years old was administered by the researcher. The administration of O3W was carried out twice a day with each of the patients, with intervals of 4 hours during the afternoon from Monday to Friday and if required on Saturdays and Sundays, until the complete involution of the OM.

Variables of personal data of the patients (age and sex) were registered, also evaluating the variables of type of diagnosis of patients and type of chemotherapy used, as well as degree of mucositis according to the parameters established by the WHO as information was also collected. It relates to the evolution of recovery with the use of ozone therapy with O3W and recovery day in food intake. The inspection and registration of the information was taken daily by the investigator, as the correct verification of the application of the therapy.

The data obtained in a dump sheet were emptied, for the statistical analysis electronic information processing was done in the SPSS® version 22 program.

To carry out the study, it was approved by the Ethics Committee of the Academic Division of Health Sciences of the Universidad Juárez Autónoma de Tabasco. The data were collected by the researcher himself and the commitment was made that the assessments and information provided were only used for research purposes. According to the ethical considerations of Helsinki and articles 100 and 101 of the General Health Law of Mexico and through an informed consent given by the patient's parents or caregivers.

Results

Personal data of the patients

The data obtained from the 15 patients with Acute Lymphoblastic Leukemia, were grouped by age and sex. Table 2 shows the distribution by sex of the sample, showing that female had a greater predominance (60%). (n=9).As Table 3 shows, the ages of the patients in the study ranged from 1 to 15 years.

Table 2 Gender

Gender			
		Frequency	Percentage
Age	Female	9	60
	Male	6	40
	Total	15	100

Table 3 Age

Age in years	Frequency	Percentage
1	1	6.7
2	1	6.7
3	3	20
6	1	6.7
7	3	20
10	1	6.7
12	1	6.7
13	1	6.7
14	1	6.7
15	2	13.3
Total	15	100

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Decrease in days of the OM

As you can see in Figure 1, the decrease of mucositis was achieved in a range of less than 7 days. Obtaining a recovery in 20% (n=3) of the patients on the first day, there was also a 33% (n=5) decrease in the OM on the second day, on the other hand on the third day there was a 20% (n=3)that manifested the decrease in the OM, during on the fourth and fifth day, 6.67% (n=1)of the patients were observed involution of the OM and as a last data obtained a total remission of the OM was observed in 13% (n=2)of the patients.

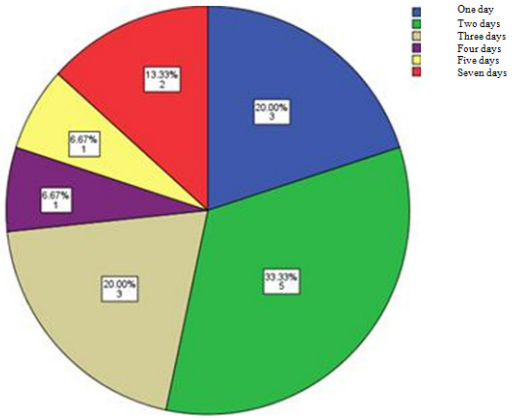

Figure 1 Evolution of recovery in days.

Reduction of the OM in days according to the degree of oral mucositis

Table 4 shows that 37,5% (n=3) of the patients with grade 1 presented a total recovery of OM on the third and fifth day, as well as the 100% (n=3) of grade 2, the involution of the OM was observed on the third day, instead the patients with a grade 3 it was reported that the total involution was the fourth and fifth days, as a last record it was found that in the most severe cases of the OM being Grade 4 its total involution was on the seventh day.

Tolerance to the oral route

Table 5 shows that patients with grade 1 (n=8), grade 2 (n=3) and grade 3 obtained intake tolerance from the first day of application with O3W, it was reported that a single patient with grade three showed improvement on the second day, instead patients with Grade 4 between the third and fourth day of administration with O3W.

Discussion

According to the total remission of OM, in 2009 Smajbegovic and Cols conducted a study with application of the clear gel, resulting in the total decrease of the OM in grades 2,3 and 4 over a period of 14 days, in contrast to the study by Sheibani and Cols in 2015 with the use of benzidamine in mouthwash, a total remission was obtained in grades 2.3 and 4 of OM up to 28 days, this research contrasts with the two previous studies, due to that the total involution of the OM was achieved at 7 days in grade 4 which is the most severe.

In 2017, Villordo and Cols, in their study on cryotherapy applied to oral pain in patients with OM, found that oral pain decreased instantly, however this analgesia was only a period of time, making morphine mouthwashes as adjuvants, on the other hand, with our study, the response of analgesia exerted by ozone therapy with O3W was from the first application, without the help of another analgesia therapeutic.

Barbosa et al. In 2017 used Triticum vulgare as a mouthwash, demonstrating that at 21 days they presented a decrease in oral pain for food intake, in this study the patients manifested improvement between the first and fourth day.

Bayer and cols in 2017 conducted a study in rats that were induced mucositis, comparing the laser and ozone through gas, it was found that both therapies were beneficial on oral mucositis, indicating that the laser seemed more effective, proposing it could be due to the duration and dose used, however they think that by changing the dose and time the results may change, the present study has similarity with the results of the previous study, since it was observed that the use of ozone therapy with O3W provided positive results in the administration for the feeding and swallowing of liquids and involution of oral mucositis in less than 2 or 4 weeks that the literature marks.

Table 4 Degree of mucositis and its evolution in days

				Day of tolerance to intake with ozone therapy				
				Day 1	**Day 2**	**Day 3**	**Day 4**	**Total**
Degree of mucositis present	Grade 1	Count		8	0	0	0	8
		Expect count	6.4		0.5	0.5	0.5	8
		% within Degree of mucositis present	100.00%		0.00%	0.00%	0.00%	100.00%
		% within Day of tolerance to intake with ozone therapy	66.70%		0.00%	0.00%	0.00%	53.30%
		% of the total	53.30%		0.00%	0.00%	0.00%	53.30%
	Grade 2	Count	3		0	0	0	3
		Expect count	2.4		0.2	0.2	0.2	3
		% within Degree of mucositis present	100.00%		0.00%	0.00%	0.00%	100.00%

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Table Continued

		% within Day of tolerance to intake with ozone therapy	25.00%	0.00%	0.00%	0.00%	20.00%
		% of the total	20.00%	0.00%	0.00%	0.00%	20.00%
	Grade 3	Count	1	1	0	0	2
		Expect count	1.6	0.1	0.1	0.1	2
		% within Degree of mucositis present	50.00%	50.00%	0.00%	0.00%	100.00%
		% within Day if tolerance to intake with ozone therapy	8.30%	100.00%	0.00%	0.00%	13.30%
		% of the total	6.70%	6.70%	0.00%	0.00%	13.30%
	Grade 4	Count	0	0	1	1	2
		Expect count	1.6	0.1	0.1	0.1	2
		% within Degree if mucositis present	0.00%	0.00%	50.00%	50.00%	100.00%
		% within Day if tolerance to intake with ozone therapy	0.00%	0.00%	100.00%	100.00%	13.30%
		% of the total	0.00%	0.00%	6.70%	6.70%	13.30%

Table 5 Degree of mucositis and the relationship between food intake and the administration of ozone therapy with O

			Evolution if recovery in days						
			First day	**Second day**	**Third day**	**Fourth day**	**Fifth day**	**Seventh day**	**Total**
Degree of mucositis present	Grade 1	Count	3	5	0	0	0	0	8
		Expect count	1.6	2.7	1.6	0.5	0.5	1.1	8
		% within Degree of mucositis present	37.50%	62.50%	0.00%	0.00%	0.00%	0.00%	100.00%
		% within Recovery evolution in days	100.00%	100.00%	0.00%	0.00%	0.00%	0.00%	53.30%
		% of the total	20.00%	33.30%	0.00%	0.00%	0.00%	0.00%	53.30%
	Grade 2	Count	0	0	3	0	0	0	3
		Expect count	0.6	1	0.6	0.2	0.2	0.4	3
		% within degree of mucositis present	0.00%	0.00%	100.00%	0.00%	0.00%	0.00%	100.00%
		% within Recovery evolution in days	0.00%	0.00%	100.00%	0.00%	0.00%	0.00%	20.00%
		% of the total	0.00%	0.00%	20.00%	0.00%	0.00%	0.00%	20.00%
	Grade 3	Count	0	0	0	1	1	0	2
		Expect count	0.4	0.7	0.4	0.1	0.1	0.3	2
		% within Degree of mucositis present	0.00%	0.00%	0.00%	50.00%	50.00%	0.00%	100.00%
		% within Recovery evolution in days	0.00%	0.00%	0.00%	100.00%	100.00%	0.00%	13.30%
		% of the total	0.00%	0.00%	0.00%	6.70%	6.70%	0.00%	13.30%
	Grade 4	Count	0	0	0	0	0	2	2
		Expect count	0.4	0.7	0.4	0.1	0.1	0.3	2
		% within Degree of mucositis present	0.00%	0.00%	0.00%	0.00%	0.00%	100.00%	100.00%
		% within Recovery evolution in days	0.00%	0.00%	0.00%	0.00%	0.00%	100.00%	13.30%
		% of the total	0.00%	0.00%	0.00%	0.00%	0.00%	13.30%	13.30%

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Conclusion

This study showed that ozone therapy can be an effective alternative treatment in this highly susceptible population, since the total remission of mucositis with ozone therapy through O3W was achieved at 7 days, in the most severe cases. Compared with the average of 22 days documented by other studies, recovery was achieved in a third of the average time with other treatments, due to its regeneration properties offering a reepitelization in a short period of time.

It was also possible to verify through this study that ozoneteherapy with ozonated water is a practical therapeutic to use with pediatric patients without being toxic or harmless, with a tolerable taste compared to other therapies that may make them uncomfortable in their taste or texture and also provides tissue hydration.

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Conflicts of interest

The authors declare no conflicts of interest.

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