OFFICIAL TITLE:

"Efficacy of Oral Supplementation with Magnesium to Reduce Febrile Neutropenia in Pediatric Oncology Patients treated with Cisplatin-Based Chemotherapy: Randomized Clinical Trial"

Responsible Party:

Dr. Osvaldo Daniel Castelán Martínez, Facultad de Estudios Superiores Zaragoza, Universidad Nacional Autónoma de México

Collaborators:

Dr. Miguel Ángel Palomo Colli, Departamento de HematoOncología, Hospital Infantil de México Federico Gómez

Dr. Luis Enrique Juárez Villegas, Departamento de HematoOncología, Hospital Infantil de México Federico

Central Contact Person: QFB. Victoria Elena Barrios López, Departamento de Farmacología, CINVESTAV

1.   Abstract

Background. Febrile neutropenia (FN) is a worrying outcome in children receiving chemotherapy because it increments the risk of major complications, reduces quality of life and increments treatment costs. Moreover, it is the most common diagnosis in pediatric oncology patients admitted into emergency rooms and represents the second cause of hospitalization, just behind hospitalization for administration of chemotherapy.

Problem statement: In Mexico, incidence of FN is of 62% of children with solid tumors treated with cisplatin-based chemotherapy (CBC). Cisplatin is one of the most nephrotoxic drugs being used in clinical setting. Nephrotoxicity is usually manifested by tubular damage that causes electrolyte losses, specially of magnesium. Recently, an association of hypomagnesemia and FN apparition. This association has a biologic explanation in the fact that magnesium is a necessary cofactor for the neutrophil's diapedesis and complement activation. To our knowledge, the role of magnesium supplementation in reducing FN episodes has not been explored. With this evidence in mind, we wondered if oral supplementation with magnesium will reduce FN episodes in pediatric oncology patients treated with CBC.

Objective. Determine the efficacy of oral supplementation with magnesium to reduce FN episodes in pediatric oncology patients treated with CBC.

Hypothesis. Previous clinical trials made in adult population had report that supplementation with magnesium salts reduce episodes of hypomagnesemia between 13 to 50%. Thus, oral supplementation with magnesium oxide will reduce in 20% FN episodes in pediatric oncology patients treated with CBC.

Materials and Methods. Randomized Clinical Trial, open-label, parallel groups of children over nine years old with solid tumors treated with CBC at the Haemato-Oncology Department of the Hospital Infantil de México. To prove the hypothesis, it is required to randomize 107 CBC cycles to the intervention group and 107 CBC cycles to the control group. The sample size calculation was made by using the two proportions formula. Randomization of children will be performed when they receive CBC indication. Patients assigned to the intervention group will receive institutional attention protocol plus a magnesium oxide, at the moment of hospitalization discharge. Patients assigned to the control group will receive only institutional attention protocol. The follow-up of patients will be made until an episode of FN appears or until the patient comes back for another CBC cycle. FN assessment will be measured with a unique temperature >38.3°C or a sustained temperature >38°C over the course of an hour plus a count of neutrophils under 1000 cells/mm^3. The efficacy of oral supplementation with magnesium oxide will be determined by a Relative Risks calculation with IC 95%. Moreover, Absolute Risk Reduction will be calculated, as well as Necessary Number to Treat. To adjust the principal variable a multivariate analysis will be made with a multiple logistic regression. The analysis will be made by protocol and by intention to treat.

2.   Background

Cancer in pediatric patients

Cancer it's a major health problem on Mexican pediatric population. The incidence of cancer cases in our country has been estimated in 126 cases/million/year and it's estimated that there are between 5000 and 6000 new cancer cases per year in children, whereas the incidence ratio is about 9 cases per 100 000 children for non-insured population. [1,2] Approximately, 40% of all neoplasms presented in Mexican childhood are solid tumors. [1,3] The age of apparition of cancer in Mexican pediatric population fluctuates between 2 and 14 years old.[4]

Secondary to the improvement of diagnosis methods and treatments, the survival of children with cancer has been incremented to 80% to 5 years. [5,6] In our country, efforts made in the last year have created a tendency to upward survival.

Cancer treatment

Cancer treatment options depends on cancer type, stage, and other factor such as age, and general health status of each patient. Treatment is founded in three major strategies: surgery, radiotherapy and chemotherapy. Chemotherapeutic drugs work causing cellular death in diverse ways. Genotoxic agents are drugs that damage DNA, interfere with DNA replication, stop cellular division or induce cellular apoptosis. [7] However, chemotherapeutic drugs also affect non-cancerous cells, contributing to their toxicity. Fast regenerating cells, like the ones from the bone marrow and the walls of the intestines, tend to be more affected, causing neutropenia and mucositis, respectively. Thus, the death of non-cancerous cells constitutes the most frequent adverse reaction of chemotherapy. About 75% of pediatric patients with cancer had suffered at least one adverse reaction associated to chemotherapy,

and 36% had suffered a severe adverse reaction that threatens their life or permanently incapacitates them.[8]

Cisplatin is an irreplaceable drug in the treatment of diverse solid tumors in both adults and children. At the Hospital Infantil de México Federico Gómez, chemotherapeutic schemes that include cisplatin as a first line treatment for solid tumors like osteosarcomas, hepatoblastomas and germ cells tumors.

Febrile Neutropenia

Neutropenia is a common adverse reaction associated to cytotoxic chemotherapy. Diminish of neutrophils count increases the risk of opportunistic infections that manifests with fever. Therefore, ambulatory patients with cancer come to emergency rooms with febrile neutropenia (FN) induced by chemotherapy, an emergency that requires immediate evaluation and treatment.[9] In the US, more than 60000 patients with cancer (7.38 cases/1000 patients with cancer) are hospitalized annually for febrile neutropenia and related infections, with a mortality that rises to the 6.8%. Nonetheless, it's been reported that FN mortality can fluctuate between 2.3 and 14% depending on the type of tumor, the age of the patient and the studied population.[11-13]

In pediatric population with cancer, the FN is an important adverse reaction because it increments the risk of major complications, it reduces the quality of life and it increments the treatment costs.[14] Moreover, FN is the most common diagnosis in children with cancer admitted into emergency room and the second cause of hospitalization, just behind hospitalization for chemotherapy. [15,16] In Mexico, incidence of FN is about 62% of children with solid tumors treated with cisplatin-based chemotherapy (CBC). [17] Likewise, hospital stay is around 6 and 9 days with an approximated cost of $100,000 MXN per episode. [18]

Magnesium

Magnesium is the fourth most abundant cation in organisms and has a role as a cofactor of 300 enzymatic systems, especially in reactions where ATP (adenosine triphosphate) intervenes, since it stabilizes negative charges of triphosphates.[19] Magnesium is necessary for generation of energy in glycolysis, it forms part of the ATP-Mg complex, and is an important enzymatic cofactor.[20] In mitochondria, enzymes use ATP and ADP-magnesium chelate as substrates for phosphate transference.[19]

Magnesium's presence is important to maintain an adequate supply of necessary nucleotides for the synthesis of DNA and RNA that produces in cellular proliferation. Likewise, cellular replication needs protein synthesis, that diminishes with the depletion of magnesium supply. [21,22]

Magnesium is most abundant in the bones (50-60%) and in minor proportion in muscles. Just 1-2% is found in extracellular liquid, and the rest is localized in the inside of cells, where is the second most abundant cation, after Potassium. Magnesium corporal deficiency appears with concentrations minor to 1 mg/dL. Approximately, 25% of serum magnesium is bonded to proteins, most to albumin; 15% forming other complexes; and 60% is free; the ionized form of magnesium is the one with physiological activity. [23,24]

With an average diet people ingests about 300 mg/day of elemental magnesium. Near 30-40% of ingested magnesium is absorbed long in the gastrointestinal tract, mainly in the jejunum and ileum. Before a deficient magnesium ingest on the diet, non-saturable passive mechanisms of absorption and saturable active transport increase intestinal absorption around 70-80%. [24-26]

Kidney is the main organ involved in magnesium homeostasis. [27] Renal management of magnesium is a filtration-reabsorption process. No description of tubular secretion of

magnesium has been described. Approximately, 65% of filtered magnesium is reabsorbed on Henle's loop, and between 20-30% on proximal convoluted tubule.[27] Magnesium reabsorption in the proximal convoluted tubule seems to be passive and follows changes in water and sodium reabsorption, moreover is associated to the fluid flux rate. On Henle's circuit, it seems to be an additional active transport: there is decrease in magnesium's reabsorption on this segment independently of the sodium chloride transport in hypermagnesemia or hypercalcemia.[28] Magnesium's renal excretion is around 100 mg/day, representing less than 3% of magnesium's glomerular filtration.[24]

Magnesium imbalance can be found in type 2 diabetes, chronic renal failure, nephrolithiasis, osteoporosis, aplastic osteopathy, migraine, cardiac disease and hypertension. There are three described physiological mechanisms of magnesium deficiency: poor intestinal absorption, increased urinary lost or intracellular changes of this cation.[29]

Cisplatin-induced hypomagnesemia

Cisplatin is one of the most nephrotoxic drug used in clinical setting. Cisplatin-induced hypomagnesemia has an origin in the direct damage on magnesium reabsorption mechanisms at Henle's loop and distal tubule.[30] The incidence of hypomagnesemia in children that receive cisplatin is around 40%.[31]

Due to the importance of maintenance of adequate magnesium levels different strategies have been proposed. Studies done on guinea pigs have shown that a rich magnesium diet can prevent severe cisplatin-induced hypomagnesemia.[32]

Most of clinical studies conducted on this manner have focused on intravenous administration of magnesium to prevent and treat cisplatin-induced hypomagnesemia. Nevertheless, there is evidence showing that oral supplementation with magnesium salts can be effective to prevent hypomagnesemia. Willox et al., reported that oral supplementation

with magnesium citrate, between chemotherapy cycles in patients with testicular cancer receiving cisplatin, increases significantly magnesium concentration in comparative with a group of patients that didn't receive the supplement.[33] Martin et al., demonstrated that prophylactic oral supplementation with magnesium pidolate reduced in 50% the episodes of hypomagnesemia in patients treated with four cycles of cisplatin.[34] In Iran, oral supplementation with magnesium oxide reduced in 13% the prevalence of hypomagnesemia in adult patients with cancer treated with cisplatin.[35]

Magnesium's role in infectious process

Magnesium plays an important role on immune response in different ways: it is a necessary cofactor for immunoglobulin and C3 convertase synthesis, it participates in immune cell adherence, antibody-dependent cytolysis, lymphocytes union, macrophage response to lymphokines, adherence between T lymphocytes and B lymphocytes, adherence of P substance to lymphoblast, and antigen to RNA binding of macrophages.[36]

Low serum concentration of magnesium had been associated with acute bacterial infections, although low association had been made with viral acute infections.[37] In the same sense, hypomagnesemia has been associated with development of sepsis in critically ill patients at Intensive Care Units. [38] Moreover, it has been demonstrated that low intake of magnesium in the diet alters the morphology and the immune response of gut mucosae in mice.[39]

Recently, our team has reported an independent association between hypomagnesemia and FN in pediatric patients with solid tumors treated with cisplatin-based chemotherapy (RR = 8.20, CI95% [1.81-37.14]).[17] This evidence suggests that if reduction of serum concentrations of magnesium is prevented, the incidence of FN can be diminished. Supporting this hypothesis, Willox et al., showed that supplementation with magnesium

citrate presents a tendency to reduce FN episodes (about 15%) in adult patients with testicular cancer treated with cisplatin.[33] However, the small number of patients included in the study, and the fact that the study wasn't designing to prove reduction of apparition of FN limited the statistical power of these findings.

Safety of magnesium supplementation

Adverse effects of magnesium caused by ingestion of food hadn't been identified since kidneys have mechanisms for the elimination of magnesium surplus.[29] Nonetheless, adverse effects of magnesium secondary to the ingestion of supplements had been showed.[40] The first symptoms of magnesium surplus are diarrhea and laxative effects that originates on the osmotic activity of non-absorbed salts in the intestine and colon, as well as gastric motility stimulation (these adverse effects are the reason why magnesium salts are used as laxative therapy). Magnesium salts that were reported for diarrhea are carbonate, chloride, gluconate and magnesium oxide.[41]

Toxicity symptoms of magnesium surplus manifests when serum concentrations are above 4.2 mg/dL; and can include hypotension, nausea, vomit, facial blush, urine retention, ileus, depression and lethargy before it progresses to muscular weakness, dyspnea, extreme hypotension, irregular heart rhythm and cardiac arrest.[29]

Individuals with renal impair are in major risks to present adverse effects secondary to magnesium supplementation. Symptoms of toxicity induced by magnesium had been observed in patients with renal impair that consumed moderate doses of magnesium laxatives or antacids.[42]

Within clinical trials designed specifically to reduce incidence of hypomagnesemia induced by cisplatin using any magnesium salt it has been described the presence of vomit and diarrhea.[34, 35] However, one of the trials showed no gastrointestinal toxicity.

The Food and Nutrition Board of the US (FNB) stablished a maximum daily limit for magnesium supplementation in children: from 1 to 3 years, 65mg per day; from 4 to 8 years, 110 mg per day; and in children >9 years, 350 mg per day. [43]

Interactions between magnesium supplements and drugs

Various types of medicines have potential to interact with magnesium supplements or alter magnesium status. Medicines or supplements rich in magnesium can diminish the absorption of oral bisphosphonates, like alendronate (used for osteoporosis treatment). The administration between magnesium supplements and oral bisphosphonates must be separated by at least 2 hours.[44]

Magnesium can form insoluble complexes with tetracyclines, like demeclocycline and doxycycline, as well as quinolones, like ciprofloxacin and levofloxacin. These antibiotics must be taken at least 2 hours before or 4 to 6 hours after a magnesium supplement. [45]

Chronic treatment with loop diuretics (like furosemide and bumetanide), thiazide diuretics (like hydrochlorothiazide and ethacrynic acid), can augment the magnesium loss in urine. On the contrary, potassium-sparing diuretics (like amiloride and spironolactone) reduce magnesium excretion.[46]

Inhibitors of proton-pump like esomeprazole and lansoprazole when taken for long periods (more than a year) can cause hypomagnesemia that originates with the impair of magnesium absorption in the intestine.[47-49]

3.   **Problem statement**

Febrile Neutropenia (FN) is an important and serious health problem in children that receive chemotherapy because it increments the risk of major complications, it reduces the patient's quality of life, and increments treatment costs. Moreover, it is the most common diagnosis in children with cancer admitted into emergency rooms and the second cause of hospitalization, just after hospitalization for chemotherapy. In Mexico, FN incidence is 62% in children with solid tumors treated with cisplatin-based chemotherapy (CBC). Cisplatin is one of the most nephrotoxic drugs used in the clinic, this nephrotoxicity is showed by tubular damage that has electrolyte losses as a consequence, specially magnesium loss. Recently, an association between hypomagnesemia and the apparition of FN has been demonstrated. This finding can be explained based on the participation of magnesium as a cofactor in immune responses. Previous clinical trials, made in adult population, have showed that oral supplementation with magnesium in between chemotherapy cycles increment the serum concentration of magnesium and reduce hypomagnesemia episodes. With these evidences put together, we hypothesize that oral supplementation with magnesium oxide in between CBC cycles in children with solid tumors will maintain serum concentrations of magnesium in physiological parameters and in consequence this electrolyte will exercise its function in the immune system, contributing to the reduction of FN episodes. Therefore, the purpose of this protocol is to determine the efficacy of oral supplementation with magnesium to reduce incidence of febrile neutropenia in pediatric patients treated with cisplatin-based chemotherapy.

4.   Hypothesis

Clinical evidence obtained in Mexican pediatric patients suggests that hypomagnesemia is associated to apparition of febrile neutropenia in patients that receive cisplatin-based chemotherapy. Previous clinical trials have reported that supplementation with magnesium salts reduce hypomagnesemia episodes in between 13 and 50%. With this in mind, we allow us to stablish the hypothesis that oral supplementation with magnesium oxide will reduce incidence of neutropenia febrile in 20% in pediatric patients treated with cisplatin-based chemotherapy.

5.   Objectives

General:

- Determine the efficacy of oral supplementation with magnesium to reduce febrile neutropenia episodes in pediatric patients treated with cisplatin-based chemotherapy

Specific:

- Recruit patients for the clinical trial until completion of the sample size
- Monitor clinical accomplish of patients to magnesium supplementation
- Build and analyze the data base

Secondary:

- Determine if supplementation with magnesium oxide modifies the time of apparition of febrile neutropenia in pediatric patients treated with cisplatin-based chemotherapy
- Evaluate the safety of supplementation with magnesium oxide
- Determine the efficacy of oral supplementation with magnesium oxide to reduce incidence of hypomagnesemia in pediatric patients treated with cisplatin-based chemotherapy

6. Methodology

Study Design

Randomized clinical trial, open-label, parallel groups.

Participants

Pediatric patients with solid tumors that receive cisplatin-based chemotherapy.

Inclusion Criteria

- Pediatric patients with sloid tumors treated with cisplatin-base chemotherapy

- Both sexes

- Patients over 9 years old

- Informed consent signed by the parents

- Informed assent signed by the patient

Non-inclusion Criteria

- Patients whose parents don't accept to participate

- Patients with magnesium loss tubulopathy diagnosed previous to CBC

- Patients with hypomagnesemia previous to CBC

Exclusion Criteria

- Patients whose parents retire informed consent during trial

Procedure

Basal status of trial will be integrated at the moment the attending physician indicates that the patient will be treated with cisplatin-based chemotherapy (CBC). The clinical monitor will establish contact with the parent of the patient and explain the purpose of the trial and will invite them to participate through signing the informed consent. Once the informed consent is signed the clinical monitor will explain the patient the purpose of the trial in order to obtain the informed assent.

To prove the hypothesis, it is required to randomize 107 CBC cycles to the intervention group and 107 CBC cycles to the control group. To determine whether the patient will receive supplementation or not in that CBC cycle, the clinical monitor will notify the principal investigator that a patient will commence treatment. In response the investigator will communicate the clinical monitor where to allocate the patient´s CBC cycle. Randomize will be made by generating non-repeated random numbers with the program available at: http://randomnumbergenerator.intemodino.com/es/generador-de-numeros-aleatorios.html. Patients assigned to the supplementation group will receive institutional care protocol plus a bottle with magnesium oxide tablets and will be explained that they should take a tablet daily. In the case that the patients were assigned to the control group they will receive institutional care protocol only.

Oral supplementation with magnesium consists on a daily tablet (245 mg magnesium oxide and 5mg magnesium gluconate, GNC, US). Supplementation will be interrupted when the patients returns for the administration of another cisplatin cycle or with the appearance of a febrile neutropenia episode. In the same sense, patients on control group will be monitored until an FN episode appears or until they return for the next cisplatin cycle.

The main outcome of this study is the apparition of febrile neutropenia that is defined as a neutrophils total count below 1000/mm^3 together with a unique temperature >38.3 °C or a sustained temperature of ≥38 °C for over an hour. Patients with a neutrophils total count <100/mm^3 will be considerate as a profound neutropenia. [50] Clinical monitor will visit the emergency department every day to identify if one of the enrolled patients has been hospitalized due febrile neutropenia diagnosis.

To evaluate if oral supplementation with magnesium reduces secondary to CBC hypomagnesemia's, serum magnesium will be quantified before CBC and it will be measured again after the apparition of febrile neutropenia or at the moment the patients returns to another CBC cycle. Serum concentrations of magnesium below 1.6 mg/dL will be considered as hypomagnesemia.[29,50]

Daily maximum intake of magnesium supplements recommended for children over 9 years is 350 mg.[51] Nevertheless, the dose that will be used on this protocol is less that the recommended, it is necessary to evaluate safety of supplementation with magnesium in pediatric patients with cancer. To fulfill this purpose, each patient will be given a binnacle where they will register adverse effects that could be presented, such as diarrhea, nausea, vomit, etc.; binnacle is showed in Appendix 1. Moreover, clinical studies like hematic biometry, and other biochemical tests will be performed to determine if there is hepatotoxicity (ALT, AST and alkaline phosphatase), nephrotoxicity (creatinine) and cardiotoxicity (LDH). Biochemical determination will be made on both groups at the basal status and before every CBC cycle. Oral supplementation with magnesium will be interrupted in patients that present severe adverse reactions. All adverse reactions will be registered according NOM-220-SSA1-2015. [52]

7.   Analysis data plan

Continuous variables with normal distribution will present as means and standard deviation. If variable have free distribution they will be presented as median and interquartile ranges. Categoric variables will be presented as frequencies and percentages. Operability of variables is showed at Appendix 3. Statistic differences at basal status will be calculated through t-Student test for continuous variables, whilst qualitative variables will be contrasted by X^2 test. A $p<0.05$ will be considered as statistical significance.

Proportion of patients with febrile neutropenia will be calculated in both groups means the division of number of cases with febrile neutropenia between the total of CBC cycles assigned to each group (experimental or control). Efficacy of supplementation with magnesium will be determined through calculation of Relative Risks with Confidence Interval of 95% (CI 95%). Relative Risks will be considered significative when the value of CI95% don't cross the unit. Furthermore, Absolute Risk Reduction and Number Needed to Treat will be calculated. To adjust principal confusing variables, a Multivariate Analysis will be made with a Multiple Logistic Regression. Analysis by protocol (just patients that finish protocol) and by intention to treat (including all patients) will be made. Statistical analysis will be made performed with SPPS software v.21 (Chicago, IL, US).

Sample Size Calculation

Necessary number of patients was estimated considering a normal distribution means two proportions formula, using alpha = 0.05 (two tails), beta = 0.20, 1 on1 proportion of assignation to each group. For calculus it was considered that non-exposed group will have a proportion of 62%, while supplemented group will have a proportion of 42% (delta

20%).[17,35] With the previous conditions and considering a continuity correction, to perform the study it is required to randomize 214 cycles and assign 107 to control group and 107 to supplemented group. Calculus was done with Sample Size Calculator for Designing Clinical Research by University of California San Francisco, available at http://www.sample-size.net/sample-size-proportions/.

8.   Ethical considerations

The present protocol is classified as a minimum risk trial since is a clinical trial that involves the use of a common dietary supplement and has authorization for sale. Moreover, doses that will be used do not exceed recommended dose for children over 9 years.

Design and execution of the present protocol will be performed in observance of Declaration of Helsinki, and following guides E6 (Good Clinical Practices), E9 (Statistical Principles for Clinical Research) and E11 (Clinical Research on Pediatric Population) of the International Council of Harmonisation (ICH). [53-55]

Protocol has been summited and accepted by Investigation, Ethics and Biosafety Committees of the Hospital Infantil de Mexico Federico Gómez with the ID HIM-2015-085. This protocol has been registered on Postgraduate and Investigation Division of the Facultad de Estudios Superiores Zaragoza UNAM with the number FESZ-RP/17-117-004.

To participate on this clinical trial parents will be asked to sign informed consent, where it is explained the purpose, procedures, benefits and risks that this study implies. Also, children will be asked to sign informed assent. This protocol has no cost for the patients. Invitation to enter this protocol will be responsibility of the clinical monitor in independence of the attending physician.

Personal information of patients will be codified with an alphanumeric folio in both

registry and database to assure confidentiality.

9.   References

1.   Fajardo-Gutierrez A, Rendon-Macias ME, Mejia-Arangure JM. Cancer epidemiology in Mexican children. Overall results. *Rev Med Inst Mex Seguro Soc*. 2011;49 Suppl 1:S43-70.
2.   CeNSIA. Cáncer Infantil en México. 2015 [citado en abril 2017]; Available at: censia.salud.gob.mx/contenidos/cancer/cancer_infantil.html.
3.   Subsecretaria de Prevención y Promoción de la Salud. Dirección General de Epidemiología. Perfil epidemiológico de cáncer en niños y adolescentes en México. Secretaria de Salud. 2011.
4.   Mejia Arangure JM, Flores Aguilar H, Juarez Munoz I, Vazquez Langle J, Games Eternod J, Perez Saldivar ML, et al. Age of onset of different malignant tumors in childhood. *Rev Med Inst Mex Seguro Soc*. 2005;43(1):25-37.
5.   Mertens AC, Yasui Y, Neglia JP, Potter JD, Nesbit ME, Jr., Ruccione K, et al. Late mortality experience in five-year survivors of childhood and adolescent cancer: the Childhood Cancer Survivor Study. *J Clin Oncol*. 2001;19(13):3163-72.
6.   Howlader N, Noone A, Krapcho M, Neyman N, Aminou R, Altekruse S, et al. SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations), National Cancer Institute. Bethesda, MD. 2011 [citado en abril 2017]; Available at: http://seer.cancer.gov/csr/1975_2009_pops09/.
7.   Hurley L. DNA and its associated processes as targets for cancer therapy. *Nat Rev Cancer*. 2002;2(3):188-200.
8.   Geenen MM, Cardous-Ubbink MC, Kremer LC, van den Bos C, van der Pal HJ, Heinen RC, et al. Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. *JAMA*. 2007;297(24):2705-15.
9.   Freifeld AG, Pizzo PA. The outpatient management of febrile neutropenia in cancer patients. *Oncology (Williston Park)*. 1996;10(4):599-606.
10.   Caggiano V, Weiss RV, Rickert TS, Linde-Zwirble WT. Incidence, cost, and mortality of neutropenia hospitalization associated with chemotherapy. *Cancer*. 2005;103(9):1916-24.
11.   Chindaprasirt J, Wanitpongpun C, Limpawattana P, Thepsuthammarat K, Sripakdee W, Sookprasert A, et al. Mortality, length of stay, and cost associated with hospitalized adult cancer patients with febrile neutropenia. *Asian Pac J Cancer Prev*. 2013;14(2):1115-9.
12.   Schelenz S, Giles D, Abdallah S. Epidemiology, management and economic impact of febrile neutropenia in oncology patients receiving routine care at a regional UK cancer centre. *Ann Oncol*. 2012;23(7):1889-93.
13.   Pathak R, Giri S, Aryal MR, Karmacharya P, Bhatt VR, Martin MG. Mortality, length of stay, and health care costs of febrile neutropenia-related hospitalizations among patients with breast cancer in the United States. *Support Care Cancer*. 2015;23(3):615-7.
14.   Castagnola E, Paola D, Giacchino R, Rossi R, Viscoli C. Economic aspects of empiric antibiotic therapy for febrile neutropenia in children with cancer. *Support Care Cancer*. 1998;6(6):524-8.

15.	Mueller EL, Sabbatini A, Gebremariam A, Mody R, Sung L, Macy ML. Why pediatric patients with cancer visit the emergency department: United States, 2006-2010. *Pediatr Blood Cancer*. 2015;62(3):490-5.

16.	Klaassen RJ, Goodman TR, Pham B, Doyle JJ. "Low-risk" prediction rule for pediatric oncology patients presenting with fever and neutropenia. *J Clin Oncol*. 2000;18(5):1012-9.

17.	Castelan-Martinez OD, Rodriguez-Islas F, Vargas-Neri JL, Palomo-Colli MA, Lopez-Aguilar E, Clark P, et al. Risk Factors for Febrile Neutropenia in Children With Solid Tumors Treated With Cisplatin-based Chemotherapy. *J Pediatr Hematol Oncol*. 2016;38(3):191-6.

18.	Oncología.mx. La neutropenia febril: un grave riesgo. 2012 [citado en abril 2017]; Available at: http://oncologia.mx/permalink/3102.html.

19.	Wacker WE, Parisi AF. Magnesium metabolism. *N Engl J Med*. 1968;278(13):712-7.

20.	Garfinkel L, Garfinkel D. Magnesium regulation of the glycolytic pathway and the enzymes involved. *Magnesium*. 1985;4(2-3):60-72.

21.	Rubin H. Central role for magnesium in coordinate control of metabolism and growth in animal cells. *Proc Natl Acad Sci U S A*. 1975;72(9):3551-5.

22.	Switzer RL. Regulation and mechanism of phosphoribosylpyrophosphate synthetase. 3. Kinetic studies of the reaction mechanism. *J Biol Chem*. 1971;246(8):2447-58.

23.	Whang R. Magnesium deficiency: pathogenesis, prevalence, and clinical implications. *Am J Med*. 1987;82(3A):24-9.

24.	Gonzalez EP, Santos F, Coto E. Magnesium homeostasis. Etiopathogeny, clinical diagnosis and treatment of hypomagnesaemia. A case study. *Nefrologia*. 2009;29(6):518-24. 25.

25.	Kayne LH, Lee DB. Intestinal magnesium absorption. *Miner Electrolyte Metab*. 1993;19(4-5):210-7.

26.	Fine KD, Santa Ana CA, Porter JL, Fordtran JS. Intestinal absorption of magnesium from food and supplements. *J Clin Invest*. 1991;88(2):396-402.

27.	Quamme GA, Dirks JH. The physiology of renal magnesium handling. *Ren Physiol*. 1986;9(5):257-69.

28.	Quamme GA. Control of magnesium transport in the thick ascending limb. *Am J Physiol*. 1989;256(2 Pt 2):F197-210.

29.	Musso CG. Magnesium metabolism in health and disease. *Int Urol Nephrol*. 2009;41(2):357-62.

30.	Lajer H, Daugaard G. Cisplatin and hypomagnesemia. *Cancer Treat Rev*. 1999;25(1):47-58.

31.	Knijnenburg SL, Mulder RL, Schouten-Van Meeteren AY, Bokenkamp A, Blufpand H, van Dulmen-den Broeder E, et al. Early and late renal adverse effects after potentially nephrotoxic treatment for childhood cancer. *Cochrane Database Syst Rev*. 2013(10):CD008944.

32.	Sahin AA, Oysu C, Yilmaz HB, Topak M, Kulekci M, Okar I. Effect of oral magnesium supplementation on cisplatin ototoxicity. *J Otolaryngol*. 2006;35(2):112-6.

33.	Willox JC, McAllister EJ, Sangster G, Kaye SB. Effects of magnesium supplementation in testicular cancer patients receiving cis-platin: a randomised trial. *Br J Cancer*. 1986;54(1):19-23.

34.   Martin M, Diaz-Rubio E, Casado A, Lopez Vega JM, Sastre J, Almenarez J. Intravenous and oral magnesium supplementations in the prophylaxis of cisplatin-induced hypomagnesemia. Results of a controlled trial. *Am J Clin Oncol*. 1992;15(4):348-51.

35.   Zarif Yeganeh M, Vakili M, Shahriari-Ahmadi A, Nojomi M. Effect of Oral Magnesium Oxide Supplementation on Cisplatin-Induced Hypomagnesemia in Cancer Patients: A Randomized Controlled Trial. *Iran J Public Health*. 2016;45(1):54-62.

36.   Galland L. Magnesium and immune function: an overview. *Magnesium*. 1988;7(5-6):290-9.

37.   Cojocaru IM, Cojocaru M, Tanasescu R, Iacob SA, Iliescu I. Changes of magnesium serum levels in patients with acute ischemic stroke and acute infections. Rom J Intern Med. 2009;47(2):169-71.

38.   Limaye CS, Londhey VA, Nadkart MY, Borges NE. Hypomagnesemia in critically ill medical patients. *J Assoc Physicians India*. 2011;59:19-22.

39.   Zimowska W, Girardeau JP, Kuryszko J, Bayle D, Rayssiguier Y, Mazur A. Morphological and immune response alterations in the intestinal mucosa of the mouse after short periods on a low-magnesium diet. *Br J Nutr*. 2002;88(5):515-22.

40.   Navarro-Gonzalez JF, Mora-Fernandez C, Garcia-Perez J. Clinical implications of disordered magnesium homeostasis in chronic renal failure and dialysis. *Semin Dial*. 2009;22(1):37-44.

41.   Ranade VV, Somberg JC. Bioavailability and pharmacokinetics of magnesium after administration of magnesium salts to humans. *Am J Ther*. 2001;8(5):345-57.

42.   Linus Pauling Institute. Magnesio. Oregon Sate University; 2016 [citado abril 2017]; Available at: http://lpi.oregonstate.edu/es/mic/minerales/magnesio.

43.   Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition, Board, Institute of Medicine. Magnesium. Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. Washington, D.C.: THE NATIONAL ACADEMIES PRESS; 1997. p. 190-248.

44.   Dunn CJ, Goa KL. Risedronate: a review of its pharmacological properties and clinical use in resorptive bone disease. *Drugs*. 2001;61(5):685-712.

45.   Arayne MS, Sultana N, Hussain F. Interactions between ciprofloxacin and antacids--dissolution and adsorption studies. *Drug Metabol Drug Interact*. 2005;21(2):117-29.

46.   Sarafidis PA, Georgianos PI, Lasaridis AN. Diuretics in clinical practice. Part II: electrolyte and acid-base disorders complicating diuretic therapy. *Expert Opin Drug Saf*. 2010;9(2):259-73.

47.   Epstein M, McGrath S, Law F. Proton-pump inhibitors and hypomagnesemic hypoparathyroidism. *N Engl J Med*. 2006;355(17):1834-6.

48.   Famularo G, Gasbarrone L, Minisola G. Hypomagnesemia and proton-pump inhibitors. *Expert Opin Drug Saf*. 2013;12(5):709-16.

49.   Thongon N, Penguy J, Kulwong S, Khongmueang K, Thongma M. Omeprazole suppressed plasma magnesium level and duodenal magnesium absorption in male Sprague-Dawley rats. *Pflugers Arch*. 2016;468(11-12):1809-21.

50.   Nacional Cancer Institute. Common Terminology Criteria for Adverse Events v4.0 (CTCAE). 2010 [citado enero 2017]; Available at:
https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

51.   National Institues of Health. Magnesium. 2016 [citado abril 2017]; Available at:
https://ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/#h2.

52.   Secretaris de Salud. PROY-NOM-220-SSA1-2015, Instalación y operación de la farmacovigilancia. 2016 [citado en abril 2017]; Available at:
http://www.dof.gob.mx/nota_detalle.php?codigo=5453679&fecha=23/09/2016.
53.   The International Council for Harmonisation. Statistical Principles For Clinical Trials E9. 1998 [citado en abril 2017]; Available at:
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step 4/E9_Guideline.pdf.
54.   The International Council for Harmonisation. Guideline For Good Clinical Practice E6(R1). 1996 [citado en abril 2017]; Available at:
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf.
55.   The International Council for Harmonisation. Clinical Investigation of Medicinal Products in the Pediatric Population. 2000 [citado abril 2017]; Available at:
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E11/Step4/E11_Guideline.pdf.

Appendix 1

HOSPITAL INFANTIL DE MÉXICO FEDERICO GÓMEZ

FACULTAD DE ESTUDIOS SUPERIORES ZARAGOZA

Daily binnacle of symptoms

Folio_____ Delivery of binnacle_____

Symptoms	Start Date	Due Date
Constipation		
Diarrhea		
Gas or abdominal distension		
Dizziness		
Nervousness		
Abdominal pain		
Blisters		
Rash		
Itchiness		
Urticaria		
Swelling of eyes, face, lips, tongue, throat, arms, hands, legs, feet, ankles or calfs		
Difficulty breathing or swallowing		
Indigestion		
Excessive fatigue		
Pain on the upper right abdomen		
Nausea		
Loss of appetite		
Yellowing on the skin and eyes		
Flu symptoms		
Paleness		
Fast heartbeat		
Weightloss		
Back pain		
Difficulty or pain to urinate		
Blurry vision, changes on color perception and other visual problems		
Red eyes		
Neck stiffness		
Headache		
Confussion		
Other		

Reception: _____

Appendix 2

HOSPITAL INFANTIL DE MÉXICO FEDERICO GÓMEZ

FACULTAD DE ESTUDIOS SUPERIORES ZARAGOZA

Capture Sheet

"Efficacy of Oral Supplementation with Magnesium to Reduce Febrile Neutropenia in

Pediatric Patients treated with Cisplatin-Based Chemotherapy: Clinical Trial"

Folio | E | M | | | |

Date _____

Date of birth (dd/mm/yy) _____ CBC start date (dd/mm/yy) _____

Gender (M/F) _____ Weight (kg) _____ Height (cm) _____ CS (m^2) _____

Diagnosis_____

Chemotherapy scheme_____

Number of hemotherapy cycles received _____

Other schemes received _____ Which one? _____

Previous febrile neutropenia episodes_____ How many? _____

Dates_____

Treatment_ _____

Previous hypomagnesemias_____ How many?_____

Dates _____

Treatment_____

Pharmacotherapy

Chemotherapeutic drug	Dose	Dose number	Acummulated Dose, mg/m^2	Administration Dates
Cisplatin				
Anthracycline				
Cyclophosphamide				
Etoposide				
Iphosphamide				
Vincristine				
Other				

Concomitant Drugs

Concomitant Drug	Drug	Dose	Dose Number	Administration Dates
G-CSF				
Inhibitors of the protom pump				
Loop Diuretic				
Thiazide Diuretic				
Potassium-sparing Diuretic				
Tetracycline				

Quinolone				
Bisphosphonate				
Other				

Biochemical Tests

Parameter	Measure before supplementation	Date	Measure after supplementation	Date
Leukocytes/mm^3				
Neutrophils/mm^3				
Platelets/mm^3				
Hb (g/dL)				
Hto (%)				
Magnesium (mg/dL)				
Calcium (mg/dL)				
ALT (U/L)				
AST (U/L)				
Alkaline phosphatase (U/L)				
Creatinine (mg/dL)				
LDH (U/L)				

Febrile neutropenia

Apparition Date_____ Hospitalization (S/N) _____

Hospitalization Days_____ Discharge Date_____

Microbiology results_____

Treatment_ _____

Complications_ _____

Febrile neutropenia prophylaxis received_____

Other adverse effects to chemotherapy

Adverse effect	Apparition and remission date	Evidence	Treatment	Complications

Comments:

Done by: _____

Appendix 3

Operability of variables

Variable	Definitions
Fever and neutropenia Units: With or without febrile neutropenia	**Conceptual Definition:** adverse reaction to chemotherapy that manifests with fever and neutrophil count below normal limits. **Operative Definition:** count < 1000 neutrophils/mm^3 and a temperature > 38.3 °C or a sustained temperature ≥ 38 °C over the course of an hour. **Variable type:** Dichotomous qualitative.
Hypomagnesemia Units: With or without hypomagnesemia	**Conceptual Definition:** adverse reaction to chemotherapy characterized by low serum magnesium levels. **Operative Definition:** Serum concentrations of magnesium ≤ 1.6 mg/dL. **Variable type:** Dichotomous qualitative.
Serum magnesium levels Units: mg/dL	**Conceptual Definition:** Quantity of magnesium in serum. **Operative Definition:** Quantity will be measured on patient's serum before and after supplementation with magnesium. **Variable type:** Continuous quantitative.
Age Units: years old	**Conceptual Definition:** Time passed since birth until start date of supplementation with magnesium. **Operative Definition:** Calculated with birthdate and start date of supplementation with magnesium. **Variable type:** Discrete quantitative.
Gender Units: male or female	**Conceptual Definition:** Biological conditions distinguishing between males and females. **Operative Definition:** Gender registered on capture sheets. **Variable type:** Dichotomous qualitative.
Diagnosis Units: type of solid tumor.	**Conceptual Definition:** Procedures performed by attending oncology physicians to determine type of tumor. **Operative Definition:** Diagnosis registered on capture sheets. **Variable type:** Ordinal qualitative.
Height Units: centimeters.	**Conceptual Definition**: Human height. **Operative Definition:** Height registered according to nursery sheets before any CBC cycle **Variable type:** Continuous quantitative.
Weight Units: kilograms.	**Conceptual Definition:** Corporal mass measure. **Operative Definition:** Weight registred according to nursery sheets before any CBC cycle. **Variable type:** Continuous quantitative.
Corporal Surface Units: m^2	**Conceptual Definition**: Calculus of corporal surface. **Operative Definition:** Corporal surface will be calculated through Haycock's formula $CS = 0.024265 \times \text{weight (kg)}^{0.5378} \times \text{height (cm)}^{0.3964}$ **Variable type:** Continuous quantitative.

Acummulated cisplatin dose Units: mg/m^2	**Conceptual Definition**: Total dose that accumulates since exposure to cisplatine. **Operative Definition:** It will be calculated multiplying the dose times the number of cycles of cisplatine received until the start of supplementation with magnesium. **Variable type:** Continuous quantitative.
Acummulated anthracycline dose Units: mg/m^2	**Conceptual Definition**: Total dose that accumulates since exposure to anthracycline. **Operative Definition:** It will be calculated multiplying the dose times the number of cycles of anthracyclines received until the start of supplementation with magnesium. **Variable type:** Continuous quantitative.
Acummulated vincristine dose Units: mg/m^2	**Conceptual Definition**: Total dose that accumulates since exposure to vincristine. **Operative Definition:** It will be calculated multiplying the dose times the number of cycles of vincristine received until the start of supplementation with magnesium. **Variable type:** Continuous quantitative.
Acummulated cyclophosphamide dose Units: mg/m^2	**Conceptual Definition**: Total dose that accumulates since exposure to cyclophosphamide. **Operative Definition:** It will be calculated multiplying the dose times the number of cycles of cyclophosphamide received until the start of supplementation with magnesium. **Variable type:** Continuous quantitative.
Acummulated etoposide dose Units: mg/m^2	**Conceptual Definition**: Total dose that accumulates since exposure to etoposide. **Operative Definition:** It will be calculated multiplying the dose times the number of cycles of etoposide received until the start of supplementation with magnesium. **Variable type:** Continuous quantitative.
Concomitant use of G-CSF Units: receives or not G-CSF	**Conceptual Definition:** Glycoprotein produced by different tissues, and that promotes maturation of precursor cells in the bone marrow to neutrophils. **Operative Definition:** Registry of if the patient receives or nor G-CSF. **Variable type:** Dichotomous qualitative.
G-CSF Dose Units: Dose number.	**Conceptual Definition:** Glycoprotein produced by different tissues, and that promotes maturation of precursor cells in the bone marrow to neutrophils. **Operative Definition:** Registry of the dose number that the patient receives. **Variable type:** Discrete quantitative.
Concomitant use of tetracyclines	**Conceptual Definition:** Antibiotic group holding a tetracycline nucleus that confers a broad spectrum of antimicrobial activity.

Units: receives or not any tetracycline	**Operative Definition:** Registry of if the patient receives any tetracycline. **Variable type:** Dichotomous qualitative
Concomitant use of proton pump inhibitors Units: receives or not any proton pump inhibitor	**Conceptual Definition:** Drugs whose main activity is to reduce acid production on gastric juice. **Operative Definition:** Registry of if the patient receives any proton pump inhibitor. **Variable type:** Dichotomous qualitative
Concomitant use of diuretics Units: receives or not any diuretic	**Conceptual Definition:** Drugs whose main activity is to induce water and electrolyte elimination through urine. **Operative Definition:** Registry of if the patient receives any diuretics. **Variable type:** Dichotomous qualitative