

76438_Auto_Edited.docx

Name of Journal: *World Journal of Clinical Oncology*

Manuscript NO: 76438

Manuscript Type: ORIGINAL ARTICLE

Clinical Trials Study

Clinical relevance of the use of Dentoxol® for oral mucositis induced by radiotherapy: A phase II clinical trial

2

Sebastián Solé, Sergio Becerra, Claudia Carvajal, Piero Bettolli, Hernán Letelier, Alejandro Santini, Lorena Vargas, Alexander Cifuentes, Francisco Larsen, Natalia Jara, Jorge Oyarzun, Eva Bustamante, Benjamín Martínez, David Rosenberg, Tomás Galván

Abstract

BACKGROUND

Severe oral mucositis associated with cancer therapy is a frequent complication that may affect a patient's systemic condition, resulting in interruption and/or prolongation of cancer therapy.

Dentoxol® is a medical solution in the form of a mouthwash that has been shown to result in statistically significant improvement in the prevention of severe oral mucositis. However, knowing the measures of the clinical significance of this therapy is important for accurate decision-making.

AIM

The aim of this article is to describe the clinical impact of Dentoxol® use in severe oral mucositis.

METHODS

Clinical significance was measured using the results obtained in a randomized controlled clinical trial previously conducted by the same group of researchers.

The measures of clinical significance evaluated were the absolute risk (AR) or incidence, relative risk (RR), absolute risk reduction (ARR), relative risk reduction (RRR), number needed to treat (NNT), and odds ratio (OR).

RESULTS

The data obtained show that the impact of DentoxolÒ on reducing the severity of oral mucositis has important clinical relevance.

CONCLUSION

The results of this study justify the incorporation of DentoxolÒ mouth rinse into clinical protocols as a complement to cancer therapy to prevent and/or treat oral mucositis secondary to radiotherapy.

INTRODUCTION

Oral mucositis is a complication that arises from cancer treatment (chemotherapy and/or radiotherapy) and manifests as erythematous and ulcerative lesions of the oral mucosa. These lesions cause considerable pain and functional impairment that can compromise nutritional status and prevent adequate oral hygiene in patients, increasing the risk of local infection and systemic spread. Additionally, in some cases, it can limit the dose or continuity of cancer therapy^[1-3].

The available scientific evidence indicates that between 94-96% of patients treated with head and neck radiotherapy develop some degree of oral mucositis, while 66% present with severe oral mucositis^[4,5].

The pain caused by lesions often compromises a patient's ability to eat, frequently leading to the need for *via* nasogastric or gastrostomy tubes, which can impact the general condition of the patient due to weight loss ^{35%}^[6] as well as the overall cost of therapy by requiring hospitalization. Approximately 16% of patients with head and neck radiotherapy require hospitalization due to oral mucositis. In addition, 11% of

patients who received radiotherapy for head and neck cancer had unplanned interruptions in radiotherapy due to severe oral mucositis^[7].

The pathogenesis of oral mucositis is complex and involves different pathways. One of the events involved in the development of mucositis is the inflammatory response of tissues to cancer therapy^[8,9]. Within these tissues, the participation of proinflammatory cytokines such as TNF- α and IL-1 β plays key roles in both the onset of tissue damage and acceleration of the process^[10-13]. Likewise, these cytokines induce the expression of cyclooxygenase-2 (COX-2), which is responsible for the production of proinflammatory prostanooids such as prostaglandin E2 (PGE2) and prostacyclin I2 (PGI2) and for tissue injury and pain at the inflammation site^[14-16].

Additionally, ulcers caused by oral mucositis can be colonized by bacteria from the patient's own oral flora. This secondary colonization may aggravate the clinical picture of mucositis through the release of bacterial products (lipopolysaccharides) capable of generating greater tissue damage and inhibiting the healing process^[13]. Sobue *et al.*^[17] evaluated the growth of and inflammatory responses against *Candida albicans*, *Candida glabrata*, and 2 streptococcal species of the mitis group (*S. oralis* and *S. mitis*), which are frequently associated with oral mucositis, in an organotypic model to represent chemotherapy-induced mucositis. Although a nonsignificant increase in growth was observed for the species studied, the authors reported an exacerbated proinflammatory response to *C. albicans*, *C. glabrata*, and *S. oralis*^[17]. Recently, a positive correlation was found between \geq grade 2 oral mucositis and the presence of *Bacteroidales* G2, *Capnocytophaga*, *Eikenella*, *Mycoplasma*, *Sneathia*, and the periodontopathogens *Porphyromonas* and *Tannerella*. Additionally, a large amount of *Fusobacterium*, *Haemophilus*, *Tannerella*, *Porphyromonas*, and *Eikenella* on buccal mucosa influenced oral mucositis susceptibility^[18]. Bacteriome disturbance has been shown to have a strong and independent association with oral mucositis severity through decreases in commensal organisms such as those belonging to the *Streptococcus*, *Actinomyces*, *Gemella*,

Granulicatella, and *Veillonella* genera and increases ingram-negative bacteria such as *Fusobacterium nucleatum* and *Prevotella oris*^[19].

The complex nature of oral mucositis requires a comprehensive preventive and therapeutic approach that can address the different pathways involved to achieve a successful outcome^[20]. Managing only inflammation or overinfection is not sufficient for efficient and adequate control.

In this context, DentoxolÒ, an aqueous solution used as a mouthwash, whose main mode of action is mechanical sloughing of the superficial epithelial cell layer of the oral mucosa, thus stimulating local regeneration of the epithelium, was developed. The interaction of its components (purified water, xylitol, sodium bicarbonate, eugenol, camphor, parachlorophenol, and peppermint essence) in specific concentrations sloughs and eliminates cells damaged by radio/chemotherapy as well as particles and detritus present in the oral cavity, such as bacteria and organic debris. The clinical effect observed is a result of the interaction of its components acting on the different aspects of the physiopathogenesis of oral mucositis (antioxidant, bacteriostatic, bactericidal, anti-inflammatory, and moisturizing properties and mucosal regenerative stimulation). As a result, DentoxolÒ can prevent oral mucositis by physically moisturizing and lubricating the oral mucosa to provide flexibility and resistance. Accordingly, it affects several pathways that influence the severity of oral mucositis^[21].

Recently, a randomized controlled clinical trial conducted by this research team evaluated the effect of DentoxolÒ mouthwash on the prevalence of severe oral mucositis and found statistically significant results regarding the prevention and reduction in the severity of oral mucositis^[21]. Many clinical studies present their results based on statistical significance. However, clinical measures of significance are essential for evaluating the relevance and usefulness of a therapy in daily clinical practice^[22].

Considering the high incidence of oral mucositis in patients undergoing head and neck cancer therapy as well as the relevant impact of this pathology on patient morbidity and quality of life, in addition to the associated economic costs, the clinical significance of an agent that can successfully treat oral mucositis needs to be analyzed.

The aim of the present study is to objectively and clearly present the clinical impact of DentoxolÒ on affected tissues based on statistical results obtained in a previously conducted clinical trial, with the aim of providing a clearer picture of the impact that clinicians responsible for managing this pathology should expect in their daily work when using this preventive and therapeutic tool to manage and control oral mucositis.

MATERIALS AND METHODS

Definition

Severe oral mucositis: grade 3 or 4 mucositis based on the scale described by the World Health Organization (WHO) (Table 1).

A descriptive study was conducted on the clinical significance of DentoxolÒ in treating oral mucositis based on results obtained in a randomized controlled clinical trial with a parallel arm design (1:1) evaluating the effect of DentoxolÒ mouthwash (test group) *vs* a placebo mouthwash (control group) on the incidence of severe oral mucositis associated with cancer therapy. The full methodology of the clinical trial was previously published by Lalla *et al*^[21].

A total of 108 patients older than 18 years (DentoxolÒ group = 55 and control group = 53) participated in the study.

Once the statistical results of the clinical trial were obtained, clinical significance measures such as the absolute risk (AR), relative risk (RR), absolute risk reduction (ARR), relative risk reduction (RRR), number necessary to treat (NNT), and odds ratio (OR) were calculated using a contingency table (Table 2).

RESULTS

RESULTS

Patient selection

A total of 108 patients were considered for the analysis of the outcomes of the randomized controlled clinical trial evaluating the use of DentoxolÒ.

Oral mucositis severity

Table 1 shows the number and percentage of patients who presented with severe oral mucositis in each treatment group. The Dentoxol[®] and control groups showed a progressive increase in the frequency of severe oral mucositis, with a peak at seven weeks.

Compared with the control group, the Dentoxol[®] group presented a lower number of patients with severe oral mucositis every week except for the first week, with a statistically significant difference observed at weeks 3 and 4 of the follow-up (see Table 1).

Clinical relevance

Table 2 shows the measures of clinical significance. The ARs of severe oral mucositis in the Dentoxol[®] group were 0.04 and 0.09 or 4% and 9% for weeks 3 and 4, respectively, vs 0.23 and 0.29 or 23% and 29%, respectively, in the control group. Additionally, from week 2 onward, the relative risk of severe oral mucositis in the Dentoxol[®] group was less than 1, indicating that Dentoxol[®] use acted as a protective factor.

Dentoxol[®] use was positively associated with a reduction in severe oral mucositis from week 2 onward, showing ARR values greater than 0. The values at weeks 3 and 4, ARR= 0.19 or 19% and 0.21 or 21%, respectively, indicate that if 100 patients were treated with Dentoxol[®], 19 and 21, respectively, fewer cases of severe mucositis would occur compared to the control group. Likewise, during weeks 3 and 4, when statistically significant differences between the groups were noted, 5 patients (NNT) would need to be treated with Dentoxol[®] to prevent 1 additional case of severe oral mucositis (Table 3).

DISCUSSION

DISCUSSION

Measures of clinical significance allow making well-founded decisions when evaluating a therapy and can be applied in daily clinical practice and especially in

recommendations for massive clinical protocols because through these measures, expected results with a real impact on the population can be obtained.

In the present study, the group that used DentoxolÒ showed a lower incidence (AR) of severe oral mucositis than the control group (Figure 1) from the 2nd week of evaluation to the 4th week, representing the greatest difference between the groups (see Table 2). The results shown in Table 2 demonstrate the strong potential of DentoxolÒ to lower treatment complications. Treating 5 patients with DentoxolÒ will prevent 1 additional case of severe oral mucositis that may need percutaneous endoscopic gastrostomy (PEG) tubes, liquid diet supplements, pain medications, *etc.* Moreover, the results in Table 1 show that DentoxolÒ delayed the onset of severe mucositis such that even patients with a severe grade who received it had the complication for a shorter period, with benefits on cost and quality of life.

Another important conclusion of the clinical trial was that the most beneficial effects of therapy with DentoxolÒ are observed in patients who follow the instructions to rinse 4 times a day. Therefore, following the recommended instructions specifying that more frequent rinses yield better clinical results is important. Furthermore, the rinsing time should be longer than 1 minute to allow the product to exert its effects on the oral mucosa. This is not a minor point because cancer patients very often have nausea and vomiting, which should be controlled to allow rinses at the appropriate frequency and time. A clinically recognized effective strategy is to begin with rinses days or ideally weeks before starting cancer therapy to prepare the mucosa for toxic effects and their consequences and thus more effectively prevent the onset of mucositis. Therefore, continuing to study different clinical protocols based on the experience of clinicians regarding this aspect through well-designed controlled clinical trials is essential.

With respect to the latter, the literature contains multiple studies evaluating different products and protocols to reduce the onset and severity of oral mucositis^[23-25]. Properly designed studies allow their results to be comparable in terms of clinical effectiveness for correct decision-making. In this sense, 1 multicenter clinical trial evaluated the ability of CaphosolÒ, an electrolyte solution with concentrated calcium phosphate, to

reduce oral mucositis in patients who received radiotherapy for head and neck cancer^[26]. When observing the percentages of severe oral mucositis, 29.3% and 42.4% of grade 3 mucositis occurred during the 3rd and 4th weeks, respectively, and 8.6% and 18.6% of grade 4 mucositis occurred during the same weeks. If we compare these results with those obtained in the Dentoxol[®] trial, at the 3rd and 4th weeks, only 4.1% and 8.7% of patients who rinsed with Dentoxol[®] had severe oral mucositis, respectively (grades 3 and 4, respectively). Another more recent clinical trial showed no reduction in the incidence or duration of severe oral mucositis with Caphosol[®] use in patients with head and neck cancer *vs* the control group (64.1% *vs.* 65.4%)^[24]. Given the results obtained in these studies, the benefit of Caphosol[®] is not clear. On the other hand, Dentoxol[®] showed a statistically significant clinical benefit for patients undergoing radiotherapy for head and neck cancer.

Systematic reviews are also useful for comparing the different applications and clinical effectiveness of multiple therapeutic alternatives. Accordingly, a 2017 Cochrane Library review evaluated the effect of cytokines and growth factors in the prevention of oral mucositis^[25]. The main agent evaluated was keratinocyte growth factor (KGF). The results indicated that KGF decreased the risk of severe oral mucositis in patients undergoing head and neck cancer therapy, with an RR = 0.79 and a 95% confidence interval (CI) = 0.69-0.90 (obtained from 3 studies), and that 7 patients (95%CI = 5-15) would need to be treated to prevent 1 case of severe mucositis^[25]. If we compare those findings with the results for Dentoxol[®], the latter agent had a lower RR from the 3rd week of follow-up, with RR values = 0.18 to 0.75, and between 5 and 7 patients (depending on the week of follow-up) would be required to prevent an additional case of severe oral mucositis. Although these results may seem similar, notably, KGF is a drug with important limitations: it is not indicated for solid tumors because it may enhance their growth; the cost is much higher; and it must be administered by IV infusion. Other products used for similar clinical conditions could be considered for comparative evaluations^[27].

To better present the results of the DentoxolÒ study and to facilitate comparisons with other results, we must note that the placebo used in the clinical trial from which the analysis of the present study was performed was not a totally inactive agent. Due to ethical reasons, the control group could not be deprived of minimum protection; therefore, the placebo used was a mouthwash composed of an aqueous solution of sodium bicarbonate and xylitol, thus reducing the actual difference between the DentoxolÒ group and the control group. Therefore, the benefit provided by rinses with DentoxolÒ is even greater in reality.

In conclusion, more well-designed controlled clinical trials are needed to increase scientific evidence and test different clinical protocols and therapeutic strategies to offer patients effective solutions based on scientific evidence. To facilitate comparisons with other interventions, the type of cancer presented by the patients, the type of therapy (chemo- and/or radiotherapy), the frequency, dose, starting point, and duration of therapy for oral mucositis, *etc.*, should be considered. Additionally, the timing of evaluation considering the pathogenesis of mucositis is also an important factor.

CONCLUSION

CONCLUSION

In this study, the safety and clinical efficacy of DentoxolÒ were demonstrated for the prevention and treatment of severe oral mucositis, an unwanted pathology that is a complication of treatments for much more serious diseases, including cancer. However, this complication can impact the costs and continuity of cancer treatment and, above all, the quality of life of patients. In this study, the effects of DentoxolÒ were clinically evident and detectable in a small number of treated patients; therefore, the inclusion of DentoxolÒ in clinical protocols is highly recommended for the management and control of the side effects of cancer treatments, which is as important as the other components of the therapeutic arsenal for cancer.

ARTICLE HIGHLIGHTS

Research background

Severe oral mucositis associated with cancer therapy is a frequent complication that may affect a patient's systemic condition, resulting in interruption and/or prolongation of cancer therapy.

Dentoxol[®] is a medical solution in the form of a mouthwash that has been shown to result in statistically significant improvement in the prevention of severe oral mucositis. However, knowing the measures of the clinical significance of this therapy is important for accurate decision-making.

Research motivation

The main motivation of the group of researchers is to be able to visualize one of the most serious side effects of cancer treatments, which is often undervalued by professionals who are focused on fighting the disease, but we neglect the quality of life of our patients, assuming that the secondary effects will have to be endured as part of a whole and it will be a situation that will inevitably have to be experienced and accepted. However, there are biotechnological developments such as Dentoxol, which allows us to provide our patients with an alternative for prevention and treatment of oral mucositis, improving their quality of life when undergoing oncological treatments.

Research objectives

The aim of the present study is to objectively and clearly present the clinical impact of Dentoxol[®] on affected tissues based on statistical results obtained in a previously conducted clinical trial, with the aim of providing a clearer picture of the impact that clinicians responsible for managing this pathology should expect in their daily work when using this preventive and therapeutic tool to manage and control oral mucositis.

Research methods

Definition

Severe oral mucositis: grade 3 or 4 mucositis based on the scale described by the World Health Organization (WHO) (Table 1).

A descriptive study was conducted on the clinical significance of DentoxolÒ in treating oral mucositis based on results obtained in a randomized controlled clinical trial with a parallel arm design (1:1) evaluating the effect of DentoxolÒ mouthwash (test group) *vs* a placebo mouthwash (control group) on the incidence of severe oral mucositis associated with cancer therapy. The full methodology of the clinical trial was previously published by Lalla *et al*^[21].

A total of 108 patients older than 18 years (DentoxolÒ group = 55 and control group = 53) participated in the study.

Once the statistical results of the clinical trial were obtained, clinical significance measures such as the absolute risk (AR), relative risk (RR), absolute risk reduction (ARR), relative risk reduction (RRR), number necessary to treat (NNT), and odds ratio (OR) were calculated using a contingency table (Table 2).

Research results

RESULTS

Patient selection

A total of 108 patients were considered for the analysis of the outcomes of the randomized controlled clinical trial evaluating the use of DentoxolÒ.

Oral mucositis severity

Table 1 shows the number and percentage of patients who presented with severe oral mucositis in each treatment group. The DentoxolÒ and control groups showed a progressive increase in the frequency of severe oral mucositis, with a peak at seven weeks.

Compared with the control group, the DentoxolÒ group presented a lower number of patients with severe oral mucositis every week except for the first week, with a

statistically significant difference observed at weeks 3 and 4 of the follow-up (see Table 1).

Clinical relevance

Table 2 shows the measures of clinical significance. The ARs of severe oral mucositis in the Dentoxol[®] group were 0.04 and 0.09 or 4% and 9% for weeks 3 and 4, respectively, vs 0.23 and 0.29 or 23% and 29%, respectively, in the control group. Additionally, from week 2 onward, the relative risk of severe oral mucositis in the Dentoxol[®] group was less than 1, indicating that Dentoxol[®] use acted as a protective factor.

Dentoxol[®] use was positively associated with a reduction in severe oral mucositis from week 2 onward, showing ARR values greater than 0. The values at weeks 3 and 4, ARR= 0.19 or 19% and 0.21 or 21%, respectively, indicate that if 100 patients were treated with Dentoxol[®], 19 and 21, respectively, fewer cases of severe mucositis would occur compared to the control group. Likewise, during weeks 3 and 4, when statistically significant differences between the groups were noted, 5 patients (NNT) would need to be treated with Dentoxol[®] to prevent 1 additional case of severe oral mucositis (Table 3).

Research conclusions

In this study, the safety and clinical efficacy of Dentoxol[®] were demonstrated for the prevention and treatment of severe oral mucositis, an unwanted pathology that is a complication of treatments for much more serious diseases, including cancer. However, this complication can impact the costs and continuity of cancer treatment and, above all, the quality of life of patients. In this study, the effects of Dentoxol[®] were clinically evident and detectable in a small number of treated patients; therefore, the inclusion of Dentoxol[®] in clinical protocols is highly recommended for the management and control of the side effects of cancer treatments, which is as important as the other components of the therapeutic arsenal for cancer.

Research perspectives

The continuous and persistent biotechnological development, especially of products to prevent and treat diseases or side effects, which have been successfully and effectively tackled, are an enormous need. We must concentrate on the development and application of new and innovative technologies to maintain the health of our patients and not allow treatments to generate damage that causes a detriment to the quality of life of patients and their families who care for and support them during the oncology therapies. Thus, it is also necessary to design and conduct serious studies and then publish the results of scientific studies that support them, in order to offer patients solutions based on scientific evidence, with data that demonstrate not only statistical significance, but also clinical relevance, which will finally be used by medical teams and health systems to build and recommend effective guidelines in clinical therapeutics.

ACKNOWLEDGEMENTS

ACKNOWLEDGEMENTS

We extend our most sincere gratitude to Felipe Galván and Dr. Rajesh Lalla for their constant support in the study.

ORIGINALITY REPORT

4%

SIMILARITY INDEX

PRIMARY SOURCES

- | | | |
|--|---|-----------------|
| <div style="background-color: red; color: white; padding: 5px; display: inline-block; width: 30px; height: 30px; text-align: center; line-height: 30px;">1</div> | www.scielo.cl
<small>Internet</small> | 99 words — 3% |
| <hr/> | | |
| <div style="background-color: magenta; color: white; padding: 5px; display: inline-block; width: 30px; height: 30px; text-align: center; line-height: 30px;">2</div> | www.pubfacts.com
<small>Internet</small> | 28 words — 1% |
| <hr/> | | |
| <div style="background-color: purple; color: white; padding: 5px; display: inline-block; width: 30px; height: 30px; text-align: center; line-height: 30px;">3</div> | Yan Wang, Xinyi Zeng, Xue Yang, Jiajia Que, Qin Du, Qiong Zhang, Jing Zou. "Oral health, caries risk profiles, and oral microbiome of pediatric patients with leukemia submitted to chemotherapy", Research Square Platform LLC, 2020
<small>Crossref Posted Content</small> | 18 words — < 1% |
| <hr/> | | |
| <div style="background-color: teal; color: white; padding: 5px; display: inline-block; width: 30px; height: 30px; text-align: center; line-height: 30px;">4</div> | ebm.vghtc.gov.tw
<small>Internet</small> | 18 words — < 1% |

EXCLUDE QUOTES ON
EXCLUDE BIBLIOGRAPHY ON

EXCLUDE SOURCES OFF
EXCLUDE MATCHES < 12 WORDS