Reviewer comments	Authors response
Reviewer #1: Scientific Quality: Grade C (Good) Language Quality: Grade A (Priority publishing) Conclusion: Accept (General priority) Specific Comments to Authors: The manuscript entitled "Clinical relevance of the use of Dentoxol for oral mucositis induced by radiotherapy: A phase II clinical trial." Has a title and abstract which reflect and summarize the manuscript. The background of the manuscript is adequately described. The Method of the manuscript is clear. The effect of Dentoxol mouthwash was tested in 55 patients and 53 patients were selected as the control group. The statistics are held properly. As a conclusion the researchers found that the Dentoxol group presented a lower number of patients with severe oral mucositis, with a statistically significant difference at weeks 3 and 4 of follow-up. In the discussion section the manuscript findings are compared and discussed in detail with the literature. Illustrations and tables are understandable and sufficient. Language is fine and statistical method is clear The manuscript has a conclusion that adds knowledge to the literature and has an impact on clinical practice. In my opinion the manuscript is acceptable for publication.	Dear reviewer #1, Thank you for your attention and interest in our research work. We appreciate your comments.

Reviewer #2: Scientific Quality: Grade B (Very good) Language Quality: Grade A (Priority publishing) Conclusion: Minor revision Specific Comments to Authors: 1. you wrote about mucositis bacterial colonization. Is there any other microorganisms that are able to colonize the lesion? what about candida albicans? 2. In the introduction, a big paragraph about Dentoxol is without any references. 3. For me, the results section in the text can be more elaborated 4. the references used are relatively old. only 3 out 23 references are from the last 5 years. Try to replace and/or add new references	Dear reviewer #2, 1. Regarding microorganisms that are able to colonize a lesion and the role of *Candida albicans*, the following paragraph (highlighted in yellow) was added to the introduction with the corresponding references. Sobue et al. 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*[1]. Recently, a positive correlation was found between ≥ 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[2]. 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 in gram-negative bacteria such as *Fusobacterium nucleatum* and *Prevotella oris*[3]. 2. In relation to the absence of references in a paragraph in the introduction, this was associated with the reference n°18: Lalla RV, Solé S, Becerra S, Carvajal C, Bettoli P, Letelier H, Santini A, Vargas L, Cifuentes A, Larsen F, Jara N, Oyarzún J, Feinn R, Bustamante E, Martínez B, Rosenberg D, Galván T. Efficacy and safety of Dentoxol® in the prevention of radiation-

	induced oral mucositis in head and neck cancer patients (ESDOM): a randomized, multicenter, double-blind, placebo-controlled, phase II trial. Support Care Cancer 2020; 28: 5871-5879 [PMID: 32266567 DOI: 10.1007/s00520-020-05358-4] 3. As requested, in the results section, the following text (highlighted in yellow) was modified. **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 Dentoxol®. **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 and Figure 3). **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, versus 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. Similarly, 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). 4. Regarding the incorporation of recent references into the introduction, at least 3 new references (2018, 2019, and 2020) have been added.
Reviewer #3: Scientific Quality: Grade D (Fair) Language Quality: Grade B (Minor language polishing) Conclusion: Major revision Specific Comments to Authors: Dear Authors, Thank you for this small phase 2 study. The authors have made very specific conclusions of "statistical efficacy" of this dentoxol. As usual, this is a very niche subject and there are many alternative agents in the market. 1) there is always a problem of selection bias The patients seem to be randomized to placebo versus treatment- were they blinded to the medication? Could I enquire if the clinicians assessing the mucositis grade were also equally blinded? This agent has list of ingredients "its components (purified water, xylitol, sodium bicarbonate, eugenol, camphor, parachlorophenol and peppermint essence)" that can taste, look, feel the same	Dear reviewer #3, thank you for your comments. According to your requests: 1. Patients and clinical evaluators were blinded to the group assignments. Both groups received similar mouth rinses in terms of color, flavor, and consistency, which were packed in identical bottles with the same labels (the control rinse contained purified water, xylitol, sodium bicarbonate, sucralose, and peppermint essence). 2. The frequency of severe mucositis in each week was considered independent, so the comparative analysis was only between both treatment groups, that is, it was only between two variables. The influence of the duration of radiotherapy was exactly the same for both groups in each week evaluated, so it was not considered an extra variable. Therefore, Bonferroni correction, which is recommended for multiple comparisons, was not necessary. Regarding the complete methodology, the study where it is explained in detail is cited in the materials and methods. The following sentence is added: See the full methodology of the clinical trial performed and published by Lalla et al. 2020[18].

and it can influence the grading of toxicities. 2) The statistical principle of Bonferroni correction https://en.wikipedia.org/wiki/Bonferroni_correction In the table 1- the authors have given a number of significant calculations. How do we know the significance is not due to repeatedly looking for correlations? The Table 1 and the methodology does not actually say how long is the radiotherapy course if for. The key is the dose and fractionation (plus/minus chemo or cetuximab + location/ volume of disease) will determine the time, duration of mucositis of these patients. Smoking status, alcohol status, p16 status are useful surrogate markers of compliance (heavy smoker, heavy alcohol consumption and p16 -ve status are usually marker of poorer compliance in Squamous cell carcinoma HN patients). I appreciate the hard work of authors but must stress that extensive care and effort must be taken to ensure the validity of said findings. Without understanding the rest of the methodology/ patients/ treatments, it is hard to comment if the conclusions are valid. I certainly hope so as - what is in the placebo? Is it just sterile water? You would hope there is a chance of reproducibility with this kind of intervention trials! Please can the authors address these concerns in order to improve reproducibility in clinical	

practice. BW	
Reviewer #4: Scientific Quality: Grade C (Good) Language Quality: Grade B (Minor language polishing) Conclusion: Minor revision Specific Comments to Authors: A review report of the manuscript titled “Clinical relevance of the use of Dentoxol for oral mucositis induced by radiotherapy: A phase II clinical trial”. Authors aimed to describe the clinical impact of the use of Dentoxol in severe oral mucositis. They concluded that the incorporation of Dentoxol mouth rinse in clinical protocols as a complement to cancer therapy to prevent and/or treat oral mucositis secondary to radiotherapy is justified. There are concerns that should be addressed: 1. In my view Introduction contains some unnecessary information. Introduction should be very specific and not include very general information (for example it is not clear in why authors included information regarding treatment costs; etc…). Authors should provide the background of the study, the scientific gap and based on this they should formulate the study aim. Thus I highly recommend to reduce Introduction keeping only very relevant information. 2. In the Materials and methods section authors should present the statistics information. 3. In the Discussion authors need to	Dear reviewer #4, thank you your comments. 1. According to the requests for the introduction, the following paragraph was deleted: “Because of the above, oral mucositis also has a significant economic impact due to the costs associated with pain management, secondary infections, hospitalizations, etc. It has been determined that the increase in treatment costs of patients with head and neck radiotherapy varies between US $1,700-6,000 per patient, depending on the severity of oral mucositis[6]”. 2. The study where the statistical analysis is explained in detail is cited in the materials and methods. In reference to the above, the following sentence was added: See the full methodology of the clinical trial performed and published by Lalla et al. 2020[18]. 3. According to the requests for the discussion, the following sentence with the respective reference (highlighted in yellow) was added: Other products used for similar clinical conditions could be considered for comparative evaluations[4].

present the effectiveness of other medicaments/adhesive films/mouthwashes for the treatment various oral ulcers/mucositis and compare with Dentoxol. I recommend this article: Heboyan A, Avetisyan A, Skallevold HE, Rokaya D, Marla V, Vardanyan A. Occurrence of Recurrent Aphthous Stomatitis (RAS) as a Rare Oral Manifestation in a Patient with Gilbert's Syndrome. Case Rep Dent. 2021 Apr 16;2021:6648729. doi: 10.1155/2021/6648729. PMID: 33953989; PMCID: PMC8068538.	
Reviewer #5: Scientific Quality: Grade C (Good) Language Quality: Grade B (Minor language polishing) Conclusion: Major revision Specific Comments to Authors: Dear authors Please find reviewer's comments- 1. Keywords need to be arranged alphabetically 2. Mention the study design 3. Sample size estimation should be included 4. references are too old. Kindly add recent references (preferably last two years) 5. et al. should be included after 6 authors. 7. Manuscript needs to be run on grammarly for spell and grammar check	Dear reviewer #5, thanks for your comments. 1. The key words were arranged alphabetically as follows (highlighted in yellow): Clinical trial, Dentoxol, Double blind, Oral mucositis, Prevention, Radiotherapy, Treatment. 2. The study design is mentioned at the beginning of the materials and methods: A descriptive study. 3. The sample size estimation is explained in the article cited in the materials and methods; the following sentence was added: See the full methodology of the clinical trial performed and published by Lalla et al. 2020[18]. 4. As requested, at least 3 new recent references were included in the introduction (2018, 2019, and 2020). 5. The expression “et al.” was checked and corrected when necessary. 6. The grammar was checked by language professionals.