Protocols for management of oral complications of chemotherapy and/or radiotherapy for oral cancer: Systematic review and meta-analysis current

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Abstract
Background and Objectives: Considering the high possibility of dentist consult a patient with oral complications of chemotherapy and/or radiotherapy for oral cancer because of the advances in this area, this study aims to systematically review the literature to identify and suggest effective and safe protocols for the managements of oral complications in oncology patients.

Material and Methods: The systematic review was designed by PICO and PRISMA including eligibility and exclusion criteria; the source of information and search strategy in PubMed according MeSH: “Mouth Neoplasms and Radiotherapy” and “Mouth Neoplasms and Drug Therapy” the period from 2010 to 2015; selection and data collection of study was carried form blind and independently by two researchers; risk of bias and methodological quality: ensured by the PEDro scale; synthesis of data: of oral complications were evaluated by adapted version of associative direction classification proposed by Costigan and collaborators; and data analysis was performed by the meta-analysis of BioEstat program (5.0) in the included studies.

Results: 2,700 articles found, 2,371 were selected after removal of duplicate and elected 40 full-text articles. Of
these, only 06 articles were included in the systematic review with exclusion of others, per obtain punctuation ≥ 7 with high methodological quality for synthesis of the managements of oral complications. Since 05 articles were associated with low risk of bias composing the protocols suggestive for managements and the meta-analysis in odds ratio (0.916) to cure and relative risk (1.049) for the development of oral mucositis and pain.

Conclusions: The protocols suggestive for managements of oral mucositis and pain with MuGard - mucoadhesive hydrogel; PerioAid Tratamiento® antiseptic mouthrinse with chlorhexidine and cetylpyridinium chloride; Episil® plus benzydamine - bioadhesive oromucosal gel; 0.03% of Triclosan mouthwash Colgate Plax; and Diode Laser Therapy of low-level are safe for oncology patients applied according to adopted clinical parameters.

Key words: Oral cancer, radiotherapy, chemotherapy, complications, management.

Introduction
Despite the recent increase in the incidence of Oral Squamous Cell Carcinoma (OSCC) in younger patients (1) and of gender female (2), yet the prevalence is in older males (2) between the 5th and 8th decade of life associated with high consumption of alcohol and tobacco. Since 4% of all oral malignancies are found in patients less than 40 years (3).

The OSCC is the most common malignancy of the oral cavity with high lethality when diagnosed in tongue and floor in advanced stages (3,4), representing 263,000 new cases and 127,700 deaths worldwide/year (2). The main modalities of contemporary treatments for oral cancer include surgical resection, chemotherapy (CT), radiotherapy (RT) and transplant immunotherapy of hematopoietic stem cells isolated or in combination (5). The modalities RT, CT and/or chemoradiotherapy (CRT) have a high potential of produce direct damage to tissues of the oral cavity or production of haematopoietic cells, because these have a high rate of cell turnover between 7 to 14 days (6). These oral complications are referred to as oral mucositis, dysgeusia, infectious diseases (5) and xerostomia associated with loss of glandular function. Together, these oral complications are called Oral Complications of Chemotherapy and/or Radiotherapy for Oral Cancer (OCCROC) (4). It is clear that high prevalence of oral cancer associated with advances in detection and application of new treatment modalities increase the possibility of the dentist come across, in his dental office, with patients presenting clinical condition of OCCROC (7). Thereby, we consider important to organize a study of systematic review of the topic in order for systematize and organize published data considering high methodological quality and low risk of bias and so identify and suggest effective and safe protocols for the managements of OCCROC in oncology patients.

Material and Methods
The systematic review was developed according to the recommendations of the PRISMA (8), except for protocol and registration, delimited you for the following PICO (patient, intervention, comparison and objective): “In patients with OCCROC, current protocols for management of the experimental group (EG) are safer and more effective than the control group (CG) to reduce/cure these oral complications?”. - Eligibility criteria
- Information sources and search strategy
- Study selection, collection process and data items
- Risk of bias and methodological quality

By means of research conducted in electronic databases of PubMed, with the following descriptor in English according to the MeSH (Medical Subject Headings): “Mouth Neoplasms” combined with “and” and qualifiers individually “Radiotherapy” and “Drug Therapy”, in the period 11 to 15 May 2015.

- Study selection, collection process and data items
- Risk of bias and methodological quality

The quality of the information collected in each selected article for the production of systematic literature review and protocols suggestive for managements of the thematic in question was ensured through the standardization of PEDro Scale, due to their effectiveness and practicability in the article validation (9).
The criteria of the PEDro Scale were originally developed to be used in experimental studies in humans, standardized on a 0-10 point score for quality of scientific evidence, with punctuation for the following criteria: 1) specification of the inclusion criteria (item not punctuated); 2) randomized allocation; 3) confidentiality allocation; 4) similarity of groups at baseline or the basal phase; 5) blinding subjects; 6) blinding therapist; 7) blinding evaluator; 8) measure of at least one primary outcome in 85% of subjects allocated; 9) analysis of intention to treat; 10) comparison between groups of at least one primary outcome and 11) reporting variability measures and estimation of the parameters of at least one primary variable (9).

For the criteria of exclusion and inclusion examiners proceeded the following rule: excluded from the review the articles with low [≤ 3 points] and moderate [4-6 points] methodological quality high and moderate risk of bias, respectively, including the others [≥ 7 points] of methodological quality high and low risk of bias in the systematic review.

- Synthesis of data
Regarding the association of OCCROCs with the management of EG, the studies included in the systematic review were evaluated by adapted version of associative direction classification proposed by Costigan et al. (10), through the association [positive, negative or no] of the outcome of management of EG with the indicator of oral complications. Pursuing with the codification of the results between studies equally associated by three simple rule of 0-33% as “0” (association without), of 34-59% as “?” (indeterminate association) and of 60-100% as “+” (positive association) or “-” (negative association). And posteriorly with the codification of the low risk of bias between four/more studies equally associated with the same previous parameter represented by “0 0” (association without), “? ?” (indeterminate association) and “+ +” (positive association) or “– –” (negative association) (11). This last quality of the studies combined to score 7-10 points of the PEDro Scale protocols suggestive for managements of patients with OCCROC.

- Data analysis
The meta-analysis was performed in BioEstat program (5.0) combining the data of the managements of EG and CG for oral mucositis and pain (OMP), considering the final values of degree and intensity OMP obtained in the clinical trials presented in the suggested protocols. The degree of homogeneity or heterogeneity of the studies was evaluated by statistical test Chi-square ($\chi^2$) resulting in the acceptance of the null hypothesis ($H_0$) in both tests, due the value of $P = 0.8985$ (homogeneity) and $P = 0.5299$ (heterogeneity) be ≥ to decision level α=0.01 and α=0.05, respectively. The $H_0$ of both tests applied to studies of this review confirm that the samples are heterogeneous, in this case, is indicated by the data analysis Random Effects Model of DerSimonian-Laird (12) for evaluation of the following Odds Ratio tests (OR) together with the Relative Risk Ratio (RR) to quantify the association between the presence of OMP and the effectiveness of managements of EG and CG with confidence interval of 95% (CI 95%) and decision value of OR ($P < 0.05$) and RR ($P < 0.01$) for statistical significance (13-15).

Results
1- Overview of studies
Were found, according to the eligibility criteria and search strategy of the articles in electronic databases of PubMed in the period from 11 to 15/05/2015, a total of 2,700 articles using three descriptors of the MeSH in the following association, “Mouth Neoplasms and Radiotherapy” and “Mouth Neoplasms and Drug Therapy”, of which we selected 2,371, removing duplicate articles. 40 articles were elected containing full text available at PubMed for qualification methodology and assessment of risk of bias by PEDro Scale. Only 06 articles obtained punctuation ≥ 7 with high methodological quality, criteria considered necessary for inclusion this systematic review (Fig. 1 and Table 1 and 1 continue).

Of the 06 articles included, five articles obtained punctuation 7 corresponding to RT treatment and an article obtained punctuation 9 related to the treatments CRT, respectively (Table 1 and 1 continue). These articles were submitted to the adapted version of associative direction classification (10), result of the following associations, in its most positive, between the index of oral complications and the management of EG, but with little positive coding the results of studies and low risk of bias (Table 2).

2- Risk of bias
The punctuation total of 40 selected articles varies between 4 and 9, moderate to low risk of bias. Specifically, 20 articles presented punctuation 4 (RT=11, CTR=02 and CRT=07), 06 articles punctuation 5 (RT=01, CTR=01 and CRT=04) and 08 articles punctuation 6 (RT=03, CTR=01 and CRT=04).

The 06 articles identified with low risk of bias demonstrated study design as clinical trial, prospective, retrospective, double-blind, randomized or controlled. And according to the direction associative classifications 05 articles were associated (+ +) with low risk of bias in only two indicators of oral complications so composing the protocols suggestive for managements of OCCROC (Table 3).

3- Synthesis of the managements of OCCROC
3.1- Oral mucositis
Of the four studies, all positively evaluated the association of oral mucositis with managements of EG with punctuation between 7 and 9 in the PEDro Scale (clinical trial, prospective, retrospective, double-blind, randomized or controlled). The results coding of 80%
(+ ) were checked in the reduction of the degree of oral mucositis as indicated in the protocol suggested in table 3 through managements with MuGard - mucoadhesive hydrogel (13), Diode Laser Therapy of low-level of InGaAlP (16), 0,03% of Triclosan mouthwash - Colgate Plax (6) and PerioAid Tratamiento® antiseptic mouthrinse combined with 0,12% of chlorhexidine and 0,05% of cetylpyridinium chloride (17).

3.2- Oral pain
Of the four studies, all positively evaluated the association of oral mucositis with managements of EG with punctuation between 7 and 9 in the PEDro Scale (clinical trial, retrospective, double-blind, randomized or controlled). The codification of studies was 80% (+) with positive results in the reducing of the intensity of oral pain as indicated by the protocol suggested in table 3 through managements with MuGard - mucoadhesive hydrogel (13), CAM2028 - Episil® plus benzydamine - bioadhesive oromucosal gel (14), Diode Laser Therapy of low-level of InGaAlP (16) and 0,03% of Triclosan mouthwash - Colgate Plax (6).

3.3- Dysphagia
Two studies with 7 and 9 points on the PEDro scale with statistical designs of clinical trial, double-blind, randomized or controlled, presented a positive association in control of dysphagia with managements of EG, coding 100% of your results (+) using the MuGard - mucoadhesive hydrogel (13) and 0,03% of Triclosan mouthwash - Colgate Plax (6) according to the protocol suggested in table 3.

3.4- Xerostomia
A study with 0% coding result (0) association without, punctuation 7 on the PEDro scale was related positively the association between xerostomia and the use of PerioAid Tratamiento® antiseptic mouthrinse combined with 0,12% of chlorhexidine and 0,05% of cetylpyridinium chloride (17) according to the protocol suggested in table 3.

3.5- Periodontal infections and fungal
Each oral compilation indicator is not coded by presenting only one study with the result of 0% (0). However, the study obtained scores 7 points on the PEDro Scale (clinical trial, double-blind, randomized and prospective). Associating yourself positively using PerioAid
Tratamiento® antiseptic mouthrinse combined with 0.12% of chlorhexidine and 0.05% of cetypyridinium chloride, in the reduction of Candida spp. colonies in the oral mucosa and tongue, as well as in samples of subgingival periodontal pathogens (P. gingivalis e E. corrodens) during the RT (15) according to the protocol.

### Table 1. Characteristics of the studies included in the systematic review (Continue).

| Primary author and year | Country   | Study design                              | Target population                                                                 | PEDro scale | Oncological treatment (therapy)                  |
|-------------------------|-----------|-------------------------------------------|----------------------------------------------------------------------------------|-------------|-------------------------------------------------|
| Allison et al. (13) 2014| EUA       | Clinical trial, double-blind, randomized and controlled | EG: 37 patients with OSCC treated surgically, most in stage III and IV with a mean age of 58 years; CG: 41 patients with OSCC treated surgically, most in stage III and IV with a mean age of 58 years. | 9           | CRT (50-72Gy cumulative + Cisplatin weekly every 3 weeks) |
| Hadjiev et al. (14) 2014| Bulgaria  | Clinical trial, double-blind, randomized and controlled | EG: 20 patients with OSCC treated surgically between 32-73 years; CG: 18 patients with OSCC treated surgically between 32-73 years. | 7           | RT (not indicated)                              |
| Lanzós et al. (15) 2011 | Spain     | Clinical trial, prospective, double-blind and randomized | EG: 18 patients with OSCC treated surgically between 24-72 years; CG: 18 patients with OSCC treated surgically between 24-75 years. Both with at least 10 teeth, smokers, chronically ill and without pathology of the oral mucosa. | 7           | RT (50-80Gy cumulative/5 periods)               |
| Carvalho et al. (16) 2011 | Brazil    | Clinical trial, double-blind, randomized and controlled between February 2008 to December 2009 | EG: 35 patients (25 male and 10 female) with OSCC treated surgically, most in stage III and IV between 22-94 years; CG: 35 patients (21 male and 14 female) with OSCC treated surgically, most in stage III and IV between 35-79 years. | 7           | RT/CRT (60-72Gy cumulative + Cisplatin 100mg every 21 days or 50mg/week) |
| Satheeshkumar et al. (6) 2010 | India    | Randomized clinical trial between January to June 2000 | EG: 12 patients (06 male and 06 women) with OSCC, mean age 63.7 years; CG: 12 patients (06 male and 06 women) with OSCC, mean age 65.9 years; Both groups without oral deleterious habits and not currently treated or with surgery earlier, CT or RT palliative. | 7           | RT (50-52Gy cumulative/15 fractions)            |
| Lanzós et al. (17) 2010 | Spain     | Clinical trial, prospective, double-blind, randomized between May 2004 to May 2007 | EG: 18 patients with OSCC treated surgically with a mean age of 54 years; CG: 18 patients with OSCC treated surgically with a mean age of 49 years; Both groups have at least 10 teeth, oral mucosa without pathology, no orthodontic therapy and not pregnant. | 7           | RT (50-80Gy cumulative/5 periods)              |

Abbreviations: OSCC (Oral Squamous Cell Carcinoma); RT (Radiotherapy); CRT (chemoradiotherapy); EG (experimental group); CG (control group); Gy (Absorbed dose in Gray).
| Oral complications (evaluation) | Managements                                                                 | Follow-up during therapy | Effectiveness (nº/total)                                                                 |
|--------------------------------|------------------------------------------------------------------------------|-------------------------|--------------------------------------------------------------------------------------|
| Oral mucositis of G² ≥ II = ulcerative or more severe (WHO) | EG: It was used MuGard (mucoadhesive hydrogel); CG: It was used mouthwash with saline solution sodium bicarbonate. | 4 weeks                  | Oral mucositis: EG-Excellent (89%=33/37 patients); CG-Excellent (87%=36/41 patients). |
| Dysphagia                       |                                                                             |                         | Oral pain: EG-Regular (35%=13/37 patients); CG-Regular (41%=17/41 patients).          |
| Little weight loss (BW)          |                                                                             |                         | Dysphagia: EG-Optimum (78%=29/37 patients); CG-Excellent (83%=34/41 patients).       |
| Oral pain                        |                                                                             |                         |                                                                                      |
| Oral pain of I² ≥ 6 = moderate to severe (Likert Pain Scale) | EG: It was used CAM2028 (Episil®, Camurus) plus benzylamine 28,2 mg/mL (nonsteroidal anti-inflammatory) - bioadhesive oromucosal gel; CG: only CAM2028 (Episil®). | 5 weeks                  | Oral pain: EG-Good (65%=13/20 patients); CG-Optimum (69%=12/18 patients).           |
| Fungal infections of Candida ssp. and periodontal bacteria | EG: It was used PerioAid Tratamiento® antiseptic mouthrinse (Dentaid, Cerdanyola del Vallés, Spain) combined with 0,12% chlorhexidine and 0,05% cetylpyridinium chloride; CG: It was used identical placebo to antiseptic mouthrinse without the active agents. | 4 weeks                  | Fungal infections: Oral mucosa EG-Excellent (95%=67/7151 ufc); CG-Excellent (89%=205/231 ufc). |
|                                                                 |                                                                             |                         | Tongue EG-Excellent (88%=597/682 ufc); CG-Poor (0%=0/17 ufc).                     |
|                                                                 |                                                                             |                         | Periodontal infections: P. gingivalis EG-Excellent (100%=178,679/178,679 ufc); CG-Poor (0%=0/161,700 ufc). |
|                                                                 |                                                                             |                         | E. corrodens EG-Excellent (100%=2,500/2,500 ufc); CG-Poor (0%=0/23,760 ufc).       |
| Oral mucositis of G² II = erythema with pain, edema or ulcer with or without dietary intake (WHO) | EG: It was used DLTLL-InGaALP (660 nm, 15 mw, 4 mm², 3,8 J/cm²); CG: It was used DLTLL-InGaALP (660 nm, 5 mw, 4 mm², 1,3 J/cm²). | 7 weeks                  | Oral mucositis: EG-Good (58%=16/35 patients); CG-Good (54%-14/35 patients).          |
| Dysphagia (IFC/BW)              |                                                                             |                         | Oral pain: EG-Excellent (94%=33/35 patients); CG-Excellent (89%-31/35 patients).     |
| Oral pain of I² ≥ 2 = mild to severe (VAS) | EG: It was used 0,03% of Triclosan mouthwash - Colgate Plax (M/S Colgate Palmolive India Ltd); CG: It was used 2g of sodium bicarbonate powder dissolved in warm water. | 5 weeks                  | Oral mucositis: EG-Excellent (89%=11/12 patients); CG-Poor (14%=0/12 patients).    |
|                                                                 |                                                                             |                         | Dysphagia: Normal diet EG-Regular (44%=20/45 dysas); CG=Poor (2%=1/45 dysas).       |
|                                                                 |                                                                             |                         | Weight gain ≥ 2Kg EG-Excellent (100%=45/45 dysas); CG-Poor (0%=0/45 dysas).          |
|                                                                 |                                                                             |                         | Oral pain: . EG-Excellent (84%=38/45 dysas); CG-Optimum (78%=35/45 dysas).           |
| Oral mucositis of G² I = erytematous or not with pain and without ulceration (WHO) | EG: It was used 0,03% of Triclosan mouthwash - Colgate Plax (M/S Colgate Palmolive India Ltd); CG: It was used 2g of sodium bicarbonate powder dissolved in warm water. | 5 weeks                  | Oral mucositis: EG-Excellent (89%=11/12 patients); CG-Poor (14%=0/12 patients).    |
| Dysphagia (IFC/BW)              |                                                                             |                         | Dysphagia: Normal diet EG-Regular (44%=20/45 dysas); CG=Poor (2%=1/45 dysas).       |
| Oral pain of I² ≥ 3 = mild to severe (VAS) | EG: It was used 0,03% of Triclosan mouthwash - Colgate Plax (M/S Colgate Palmolive India Ltd); CG: It was used 2g of sodium bicarbonate powder dissolved in warm water. | 5 weeks                  | Oral mucositis: EG-Excellent (89%=11/12 patients); CG-Poor (14%=0/12 patients).    |
|                                                                 |                                                                             |                         | Dysphagia: Normal diet EG-Regular (44%=20/45 dysas); CG=Poor (2%=1/45 dysas).       |
|                                                                 |                                                                             |                         | Weight gain ≥ 2Kg EG-Excellent (100%=45/45 dysas); CG-Poor (0%=0/45 dysas).          |
|                                                                 |                                                                             |                         | Oral pain: . EG-Excellent (84%=38/45 dysas); CG-Optimum (78%=35/45 dysas).           |
| Xerostomia (Flow and pH of Saliva) | EG: It was used PerioAid Tratamiento® antiseptic mouthrinse (Dentaid, Cerdanyola del Vallés, Spain) combined with 0,12% chlorhexidine and 0,05% cetylpyridinium chloride; CG: It was used identical placebo to antiseptic mouthrinse without the active agents. | 4 weeks                  | Oral mucositis: EG-Optimum (77%=14/18 patients); CG-Optimum (72%=13/18 patients).     |
| Xerostomia (Flow and pH of Saliva) | EG: It was used PerioAid Tratamiento® antiseptic mouthrinse (Dentaid, Cerdanyola del Vallés, Spain) combined with 0,12% chlorhexidine and 0,05% cetylpyridinium chloride; CG: It was used identical placebo to antiseptic mouthrinse without the active agents. | 4 weeks                  | Oral mucositis: EG-Optimum (77%=14/18 patients); CG-Optimum (72%=13/18 patients).     |

Abbreviations: WHO (World Health Organization); NIC (National Cancer Institute); RTOG (Radiation Therapy Oncology Group); VAS (Visual Analogue Scale); IFC (Ingestion of food consistency); BW (Body weight); G² (degree); I² (Intensity); DLTLL-InGaALP (Diode Laser Therapy of low-level of gallium aluminum–arsenate); CFU (colony forming unit).
Table 2. Classification of the studies included in the systematic review with high methodological quality followed by meta-analysis of studies with low risk of bias.

| Indicator of oral complications | Association to the result of the management of the experimental group | Primary author and year of high-quality studies (7-10 points) | Codification of results between studies equally associated | Codification of low risk of bias between four/more studies equally associated |
|--------------------------------|-------------------------------------------------------------------|-------------------------------------------------------------|---------------------------------------------------------|--------------------------------------------------------------------------|
| Oral mucositis                 | Positive                                                          | Allison et al., 2014                                       | +                                                       | +                                                                        |
|                                | Positive                                                          | Carvalho et al., 2011                                      | +                                                       | +                                                                        |
|                                | Positive                                                          | Satheeshkumar et al., 2010                                 | +                                                       | +                                                                        |
|                                | Positive                                                          | Lanzós et al., 2010                                        | +                                                       | +                                                                        |
| Oral pain                      | Positive                                                          | Allison et al., 2014                                       | +                                                       | +                                                                        |
|                                | Positive                                                          | Hadjieva et al., 2014                                      | +                                                       | +                                                                        |
|                                | Positive                                                          | Carvalho et al., 2011                                      | +                                                       | +                                                                        |
|                                | Positive                                                          | Satheeshkumar et al., 2010                                 | +                                                       | +                                                                        |
| Dysphagia                      | Positive                                                          | Satheeshkumar et al., 2010                                 | +                                                       | +                                                                        |
|                                | Positive                                                          | Lanzós et al., 2010                                        | 0                                                       | +                                                                        |
| Xerostomia                     | Positive                                                          | Lanzós et al., 2011                                        | 0                                                       | +                                                                        |
| Fungal infections              | Positive                                                          | Lanzós et al., 2011                                        | 0                                                       | +                                                                        |
| Periodontal infections         | Positive                                                          | Lanzós et al., 2011                                        | 0                                                       | +                                                                        |
|                                |                                                                   |                                                             |                                                         |                                                                          |
| Meta-analysis of studies with low risk of bias | OR | CI95% bottom-upper | Weight | Florest plot | RR | CI95% bottom-upper | Weight | Florest plot |
| Allison et al., (16) 2014      | 1,122 | 0,296-4,247 | 20% | + | 1,014 | 0,860-1,197 | 59% | + |
| Lanzós et al., (20) 2010       | 1,313 | 0,308-5,595 | 17% | + | 1,074 | 0,734-1,572 | 11% | + |
| Hadjieva et al., (17) 2014     | 0,936 | 0,255-3,441 | 21% | + | 0,977 | 0,620-1,540 | 18% | + |
| Carvalho et al., (19) 2011     | 1,295 | 0,477-3,512 | 35% | + | 1,138 | 0,690-1,876 | 7%  | + |
| Sathushkumar et al., (6) 2010  | 1,825 | 0,204-16,316 | 7%  | + | 1,095 | 0,787-1,523 | 15% | + |
|                                | 0,842-0,995 |                          | 100% | + | 1,049 | 0,360-3,050 | 100% | + |
| Combined                       | 0,916 | 0,995                  | 100% | + | 1,049 | 0,360-3,050 | 100% | + |

Abbreviations: RT (Radiotherapy); CRT (Chemoradiotherapy); X2 (Chi-square); df (Degrees of freedom); NNT (Number needed to treat); OR (Odds ratio); RR (Relative risk). Notes: Codification of the results between studies equally associated by three simple rule of 0-33% as “0” (association without), of 34-59% as “?” (indeterminate association) and of 60-100% as “+” (positive association) or “–” (negative association). codification of the low risk of bias between four/more studies equally associated with “0 0” (association without), “?” (indeterminate association) and “+ +” (positive association) or “– –” (negative association) according to the PEDro scale.

Discussion
- Summary of evidence and limitations
The most of the studies of high methodological quality and Low risk of bias according to PEDro Scale (9) and the associative direction classification (10) were devel-
Table 3. Distribution of protocols suggestive for management of oral complications of chemotherapy and/or radiotherapy for oral cancer.

| Primary author and year | Indicator of oral complications | Protocols Suggestive |
|-------------------------|--------------------------------|-----------------------|
| Allison et al. (13) 2014 | Oral mucositis | **Symptomatic management** – MuCland (mucoadhesive hydrogel); **Indication** – oral mucositis of G° ≥ II = ulcerative or more severe (WHO); **Patient** – adults with OSCC; **Age** – 58 years in mean; **Stage** – III and IV (preferably); **Oncological treatment performed** – surgical and CRT; **Procedure** – mouth rinse with 5mL of mouthwash solution for one minute, 4x/day, during CRT, Combined supportive therapy (analgesics, antifungal among other) and not avoiding eating or drinking for an hour after mouth rinse. |
| Lanzós et al. (17) 2010 | Oral mucositis | **Symptomatic management** – Ferio.Aid Tratamiento® antiseptic mouthrinse (Dentaid, Cerdanyola del Vallès, Spain) combined with 0,12% of chlorhexidine and 0,05% of cetylpyridinium chloride; **Contraindication** – pathologies of concomitant oral mucosa, tobacco, alcoholic beverages, orthodontic therapy and pregnant; **Indication** – oral mucositis of G° ≥ I = erythematous with mild pain that does not require analgesic or more severe (RTOG); **Patient** – adults with OSCC and at least 10 teeth; **Age** – 54 years in mean; **Stage** – not indicated; **Oncological treatment performed** – surgical and RT; **Procedure** – mouth rinse with 15 mL of mouthwash without alcohol, for 30 seconds, 2x/day (morning and evening) during 28 days after RT. |
| Hadjieva et al. (14) 2014 | Pain oral mucositis | **Symptomatic management** – CAM2028 (epsil®, Camurus) plus 28,2 mg/mL benzylamine (nonsteroidal anti-inflammatory) - bioadhesive oromucosal gel; **Contraindication** – use of concomitant medication; **Adverse effects** – nausea and vomiting (07 patients), infection of the upper respiratory tract and hemoptysis in a few patients; **Indication** – Oral pain of P° ≥ 6 = moderate to severe (Likert Pain Scale); **Patient** – adults with OSCC; **Age** – between 32-73 years; **Stage** – not indicated; **Oncological treatment performed** – surgical and RT; **Procedure** – mouth rinse with 2 mL of the mixture of topical solutions applied in the mouth via syringe during 15 seconds, after spitting and avoiding hot food or drink for 3 hours. |
| Carvalho et al. (16) 2011 | Oral mucositis | **Symptomatic management** – Diode Laser Therapy of low-level of gallium aluminum-arsenide - illumination consisted of a continuous 660 nm wavelength, power 15 mW, spot size 4 mm² and energy density delivered to the oral mucosa was 3.8 J/cm² (Twin laser – MMOptics, MMOptics Ltda., São Carlos, São Paulo, Brazil); **Indication** – Prophylactic pre-RT/CRT on the oral mucosa excluding the area of the tumor and cavitative in each oral mucositis of G° II = erythema with pain, edema or ulcer with normal dietary intake (NIC) / ulcer erythema or not with normal dietary intake (WHO), beyond area oral pain of P° ≥ 2 = mild to severe (VAS); **Patient** – adults with OSCC, adequate oral hygiene and topical fluoroterapia; **Age** – between 22 - 94 years; **Stage** – III and IV (preferably); **Oncological treatment performed** – surgical and RT/CRT; **Procedure** – applying the laser for 10 seconds daily on the oral mucosa excluding the area of the tumor, during 5 consecutive days for 7 weeks before sessions RT/CRT prophylactically and curative on each area of mucositis G° II and oral pain P° ≥ 2 developed. |
| Satheeshkumar et al. (6) 2010 | Oral mucositis | **Symptomatic management** – 0,03% of Triclosan mouthwash - Colgate Plax (M/S Colgate Palmolive India Ltd) (Colgate Plax); **Contraindication** – patients with oral deleterious habits and not currently treated or with surgery earlier, CT or RT palliative; **Indication** – oral mucositis of G° I = erythematous or not with pain and without ulceration (WHO) and oral pain of P° ≥ 3 = mild to severe (VAS); **Patient** – adults with OSCC; **Age** – 63,7 years in mean; **Stage** – not indicated; **Oncological treatment performed** – only RT; **Procedure** – mouth rinse content (not indicated ml) of mouthwash 3x/day, during the end of treatment after 45 days RT. |

Abbreviations: OSCC (Oral Squamous Cell Carcinoma); RT (Radiotherapy); CRT (chemoradiotherapy); G° (degree); P° (Intensity); WHO (World Health Organization); RTOG (Radiation Therapy Oncology Group); NIC (National Cancer Institute); VAS (Visual Analogue Scale).
from surgical oncologic treatment and RT with indicating mucositis G° I or II. The managements of EG and CG vary over their effectivenesses between good and excellent for all indicators of oral complications except for the CG to periodontal infection, being that the poor effectiveness was detonated only in the management of EG for oral mucositis, dysphagia, fungal infections and periodontal. However the suggested managements protocols of OCCROC through the systematic review are limited by small samples of the published studies and the not evidence of the target population of children, adolescents and young. But have low bias risk affirmed by PEDro Scale and associative direction classification, being suitable for dental practice faithfully in the methodology systematically evaluated.

In the meta-analysis with statistical significance for OR, the study of Hadjieva et al., (14) was the one who presented the management of EG with greater therapeutic efficacy and lower risk of development of OMP compared to treatments of other studies (6,13,16,17), being that only the study of Carvalho et al., (16) presented a higher statistical significance in the analysis of RR of management in the GC with therapeutic efficacy lower and higher risk of MDO compared to managements of other studies (6,13,14,17). This meta-analysis is limited to little combination of current studies on the thematic, but it is important for its high quality methodological and low risk of bias for dental clinical application, mainly of the study of Hadjieva et al., (14) with the protocol suggestive for management with CAM2028 (Episil®, Camurus) plus 28,2 mg/mL of benzydamine (nonsteroidal anti-inflammatory) - bioadhesive oromucosal gel for adults with pain coming from the oral mucositis of CT e/or RT of OSCC (Table 3).

- Implications for future research

The utilization of the protocols suggestive for managements of OCCROC is safe for non-allergic patients to treatment applied according to clinical parameters adopted as from the high methodological quality and low bias risk of the studies systematically reviewed. For future clinical research identified the need to develop study designs with more detailed and rigorous methods, mainly with the triple-blind blinding, representative samples, managements protocols of the OCCROC for children, adolescents and young. Of this form, increasing the number of studies with high methodological a quality and low risk of bias based on the recommendations of the clinical trial checklist for the production of new managements protocols of the OCCROC complete and safe for clinical care in oncology patients.

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Conflict of Interest
The authors have declared that no conflict of interest exist