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Major clinical approaches to endodontic treatment in the treatment scenario of patients with head and neck cancer: a systematic review

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Abstract

Introduction: In the context of endodontic treatments and cancer, head and neck squamous cell carcinoma is the 6th most common form of cancer in the world, with more than 400,000 deaths annually. The great challenge is endodontic treatment after radiotherapy processes. Furthermore, the promising applications of exosomes in targeted therapy and we propose future directions for the use of exosomes in clinical and endodontic treatment. **Objective:** The present study developed a systematic review to elucidate the main clinical approaches to endodontic treatment in the treatment scenario of patients with head and neck cancer. **Methods:** The PRISMA Platform systematic review rules were followed. The search was carried out from July to September 2024 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 124 articles were found, 35 articles were evaluated in full and 20 were included and developed in the present systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 25 studies with a high risk of bias and 22 studies that did not meet GRADE and AMSTAR-2. Most studies did not show homogeneity in their results, with X^2=89.2%<50%. It was concluded that biomechanical preparation using a reciprocating system and 2.5% NaOCl in irradiated teeth demonstrated efficacy in reducing endodontic contaminants. Moreover, $Ca(OH)_2$ as intracanal medication should be performed in irradiated patients with infected root canals. Also, radiotherapy causes changes in pulp behavior patterns in the short term; however, recovery and return to mean values occur after long periods. The probiotic SsK12 significantly reduced the incidence, onset, and duration of severe oral mucositis with a good safety profile. Artificial intelligence has valuable applications in the field of modern endodontics with promising results, especially in endodontic treatments in patients with head and neck cancer.

Keywords: Endodontic treatment. Head cancer. Neck cancer. Exosomes. Radiotherapies.

Introduction

In the context of endodontic treatments and cancer, head and neck squamous cell carcinoma is the 6th most common form of cancer worldwide, with over 400,000 deaths annually [1]. Although there has been a marked decrease in head and neck squamous cell carcinoma associated with tobacco use, the incidence and mortality rate of HPV-induced head and neck squamous cell carcinoma have increased significantly [2]. Current treatment modalities for head and neck squamous cell carcinoma include surgery, radiation, chemotherapy, EGFR inhibitors (Cetuximab), and immunotherapy (Pembrolizumab) [3,4].

In addition, salivary gland cancers account for approximately 6% of all head and neck cancers [5]. Mucoepidermoid carcinoma is the most common subtype of salivary gland cancer, followed by adenoid cystic carcinoma [6-8]. Therefore, oral diseases such as periodontitis, salivary gland diseases, and oral cancers pose challenging health conditions due to their detrimental effects on the patient's digestive functions,

pronunciation, and aesthetic demands.

Delayed diagnosis and untargeted treatment profoundly influence the prognosis and quality of life of patients. In this scenario, exosomes and microRNAs have attracted attention as valuable diagnostic and therapeutic tools due to their ability to transfer abundant biological functions and their intricate involvement in multiple cellular functions. The promising applications of exosomes in targeted therapy and we propose future directions for the use of exosomes in clinical and endodontic treatment, as it is necessary to perform biomechanical preparation using a reciprocating system followed by final irrigation protocols, then intracanal medicament, in reducing endotoxins and cultivable bacteria from infected teeth in irradiated head and neck cancer patients [9].

Given this, the present study developed a systematic review to elucidate the main clinical approaches to endodontic treatment in the treatment scenario of patients with head and neck cancer.

Methods

Study Design

The present study followed the international systematic review model, following the rules of PRISMA [20] (preferred reporting items for systematic reviews and meta-analysis). Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 09/10/2024. The methodological quality standards of AMSTAR-2 (Assessing the methodological quality of systematic reviews) were also followed. Available at: https://amstar.ca/. Accessed on: 09/10/2024.

Data Sources and Research Strategy

The literary search process was carried out from July to September 2024 and was developed based on Scopus, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from various eras to the present. The descriptors (DeCS /MeSH Terms) were used: *"Endodontic treatment. Head cancer. Neck cancer. Exosomes. Radiotherapies"*, and using the Boolean "and" between the *MeSH* terms and "or" between historical discoveries.

Study Quality and Risk of Bias

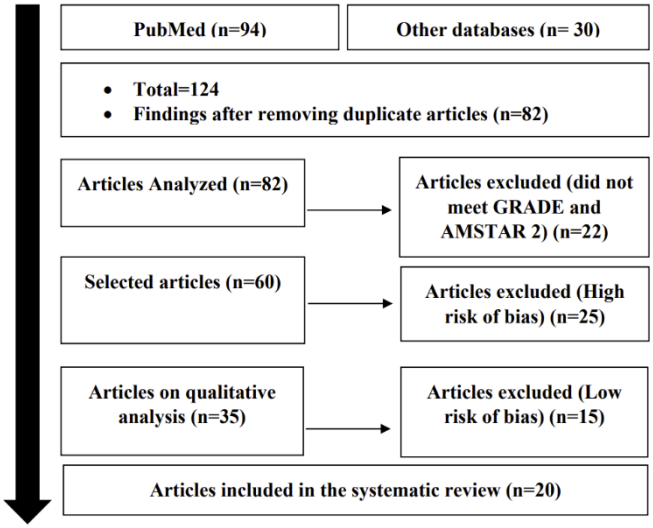
Quality was classified as high, moderate, low, or very low in terms of risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. The low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument by analyzing the Funnel Plot graph (Sample size versus Effect size), using the Cohen test (d).

Results and Discussion

Summary of Findings

A total of 124 articles were found that were subjected to eligibility analysis, with 20 final studies being selected to compose the results of this systematic review. The studies listed were of medium to high quality (Figure 1), considering the level of scientific evidence of studies such as meta-analysis, consensus, randomized clinical, prospective, and observational. The biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies showed homogeneity in their results, with X^2=89.2%<50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 25 studies with a high risk of bias and 22 studies that did not meet GRADE and AMSTAR-2.

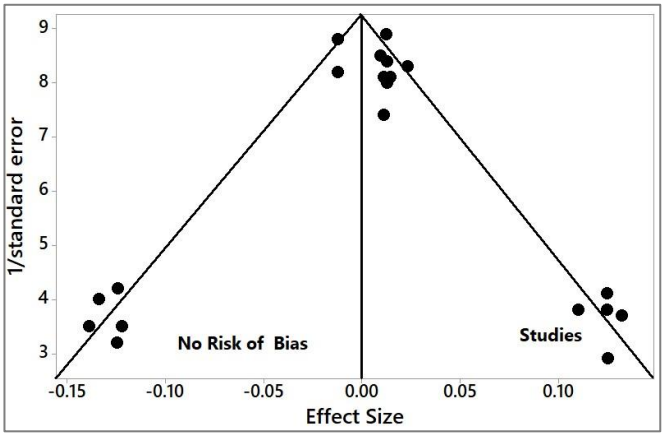
Figure 1. Articles eligibility process.



Source: Own authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using the Cohen Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both between studies with a small sample size (lower precision) that are shown at the bottom of the graph and in studies with a large sample size that are presented at the top.

Figure 2. The symmetric funnel plot suggests no risk of bias among the small sample size studies that are shown at the bottom of the graph. High confidence and high recommendation studies are shown above the graph (n=20 studies).



Source: Own authorship.

Major Findings

The authors of Rabello et al. (2023) [10] performed a randomized clinical study to analyze the efficacy of biomechanical preparation using a reciprocating system followed by final irrigation protocols, then intracanal medicament, in reducing endotoxins and cultivable bacteria from infected teeth in irradiated patients. A total of 22 infected single-root canals in patients undergoing head and neck radiotherapy were prepared by reciprocating motion and 2.5% NaOCl. Patients were randomly divided into two groups of 11 patients before the final irrigation protocol: apical positive pressure (APP) or passive ultrasonic activation (PUA). Both groups were treated in two sessions, using Ca(OH)2 as an intracanal medicament for 14 days. Sampling of the root canal content was performed after accessing the canal, after the biomechanical preparation plus irrigation protocol, and after intracanal medicament. The chromogenic limbus amebocyte lysate assay measured endotoxin levels (EU/mL) and bacterial load was determined by culture techniques (CFU/mL). Biomechanical preparation using a reciprocating system and 2.5% NaOCl in irradiated teeth, followed by the irrigation protocol (APP or PUA), demonstrated efficacy in reducing endodontic contaminants. Furthermore, $Ca(OH)_2$ as an intracanal medication should be performed in irradiated patients with infected root canals.

A major systematic review study conducted by the authors Ribeiro et al. (2023) [11] sought to answer the question: "Can radiotherapy cause changes in the condition of the dental pulp of patients treated with irradiation in the head and neck region?" Four of the evaluated studies applied the cold sensitivity test, two associated pulse oximetry, and cold sensitivity, and only one used only pulse oximetry. Evaluation by cold sensitivity test and pulse oximetry in the initial periods before radiotherapy showed a decrease in the sensory response and SpO_2 levels for a maximum period of 1 year. However, subsequent analyses indicated a normal response in both tests 5 to 6 years after the end of radiotherapy treatment. Therefore, radiotherapy causes changes in pulp behavior patterns in the short term; however, recovery and return to mean values occur after long periods.

Also, the authors Peng et al. (2024) [12] analyzed the incidence of oral mucositis associated with radiotherapy for malignant head and neck tumors through a prospective, randomized, double-blind, placebo-controlled study. These authors evaluated the efficacy and safety of Streptococcus salivarius K12 (SsK12) in reducing the incidence, duration, and severity of severe oral mucositis. A total of 160 patients with malignant head and neck tumors undergoing definitive or postoperative adjuvant radiotherapy were randomly assigned (1:1) to receive either the probiotic SsK12 (n = 80) or placebo (n = 80). Patients were instructed to suck SsK12 or placebo lozenges three times daily from the beginning to the end of radiotherapy. Baseline patient characteristics were similar in the SsK12 and placebo groups. The incidence of severe oral mucositis was significantly lower in the SsK12 group compared with the placebo group (36.6% v 54.2%). The duration and time to develop severe oral mucositis were also improved in the SsK12 group. Adverse events were similar between groups, and mild or moderate gastrointestinal reactions (flatulence or dyspepsia) associated with the lozenges were observed in two patients in the SsK12 group. In this scenario, infectious or traumatic etiologies, pulpal and/or apical diseases invariably result in an irreversible impairment of blood, neural, and nutrient supply to natural teeth [13]. Despite the well-established efficacy of root canal treatment, the search for biological pulp regeneration with full physiological functionality remains unrelenting, such as differentiation of mesenchymal stem cells (MSCs) into functional dental pulp cells, promotion of angiogenesis and facilitation of neural reconstruction [14].

Like pulp tissue stem cells, MSC-derived exosomes positively stimulated stem cell differentiation toward pulp and root canal regeneration via the P38/MAPK154 and miR-150-Tlr4 pathways [15,16]. Meanwhile, Schwann cells are recruited to enhance neurogenesis in the presence of exosomes, particularly under the condition of lipopolysaccharide (LPS) stimulation [17]. LPS also promotes angiogenesis through exosomes [18–20] that can simultaneously be increased by hypoxia with increased lysyl oxidase-like 2 (LOXL2) levels

[21,22]. In this regard, miR-27a-5p levels are elevated, which induces pulp and root cell differentiation [15,23]. Furthermore, evidence suggested that younger donors performed better in exosomal capacity for pulp regeneration [24], as exosomal miR-26a secreted by aggregating primary tooth stem cells strongly promotes the angiogenesis of HUVECs in pulp tissue through TGF-β/Smad2/3 signaling [25].

In addition, embryonic stem cell (ESC)-derived exosomes promote the maturation of DPCs through CD73 (a type of nucleotidase)-mediated activation of the AKT/ERK pathway [26]. Furthermore, exosomes from umbilical cord mesenchymal stem cells (UCMSCs) showed a great effect on inflammatory relief after pulp injury [27]. And platelet-derived exosomes also have the potential for pulp regeneration with thrombin activation [28].

Finally, the authors Ahmed et al. (2023) [29] collected studies on the application and performance of artificial intelligence (AI) models designed for application in the field of endodontics. The applications of AI were in the detection and diagnosis of periapical lesions, evaluation of root fractures, determination of working length, prediction of postoperative pain, study of root canal anatomy, decision-making in endodontics for retreatment, as well as endodontic treatment in patients with head and neck cancer. The accuracy of AI in performing these tasks can reach up to 90%. Therefore, artificial intelligence has valuable applications in the field of modern endodontics with promising results.

Conclusion

It was concluded that biomechanical preparation using a reciprocating system and 2.5% NaOCl in irradiated teeth demonstrated efficacy in reducing endodontic contaminants. Furthermore, $Ca(OH)_2$ as intracanal medication should be performed in irradiated patients with infected root canals. Moreover, radiotherapy causes changes in pulp behavior patterns in the short term; however, recovery and return to mean values occur after long periods. The probiotic SsK12 significantly reduced the incidence, onset, and duration of severe oral mucositis with a good safety profile. Artificial intelligence has valuable applications in the field of modern endodontics with promising results, especially in endodontic treatments in patients with head and neck cancer.

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Informed Consent

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No additional data are available.

Conflict of Interest

The authors declare no conflict of interest.

Similarity Check

It was applied by Ithenticate®.

Peer Review Process

It was performed.

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