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Effectiveness of chlorhexidine in the context of covid-19: integrative review

Eficácia da clorexidina no contexto da covid-19: revisão integrativa

Eficacia de la clorexidina en el contexto del covid-19: revisión integrativa

RESUMO

Objetivo: analisar a eficácia da clorexidina sobre a infecção do COVID-19. Métodos: Realizou-se uma revisão integrativa da literatura, a coleta de dados foi realizada entre a segunda e terceira semana de junho de 2021, tendo por limite temporal estudos publicados entre março de 2020 e junho de 2021, nas bases de dados PubMed, Lillacs e Clinical Trials. Resultados: A pesquisa identificou 70 artigos publicados no período de eleição, destes, 35 foram incluídos na revisão, sendo que 6 não tratavam da temática, e dos 27 restantes, 15 indicavam que a clorexidina tem um resultado positivo sobre o SARS-Cov-2, 6 indicaram que ela é ineficaz e 6 obtiveram resultados inconclusivos. Conclusão: Apesar da maioria dos estudos revisados indicarem pelo uso da clorexidina com eficácia sobre a COVID-19, o pequeno número de pesquisas sobre o tema e a falta de resultados robustos, indicam a necessidade de mais pesquisas sobre o efeito da substância no combate a infecção.

DESCRITORES: COVID-19; CLOREXIDINA; SARS-COV-2.

ABSTRACT

Objective: to analyze the effectiveness of chlorhexidine on COVID-19 infection. Methods: An integrative literature review was carried out, data collection was carried out between the second and third week of June 2021, having as a time limit studies published between March 2020 and June 2021, in the PubMed databases, Lillacs and Clinical Trials. Results: The search identified 70 articles published in the election period, of which 35 were included in the review, 6 of which did not address the topic, and of the remaining 27, 15 indicated that chlorhexidine has a positive result on SARS-Cov-2, 6 indicated that it is ineffective and 6 obtained inconclusive results. Conclusion: Although most of the reviewed studies indicate the use of chlorhexidine effectively against COVID-19, the small number of researches on the subject and the lack of robust results indicate the need for more research on the effect of the substance in combating infection.

DESCRIPTORS: COVID-19; Chlorhexidine; SARS-Cov-2.

RESUMEN

Objetivo: analizar la efectividad de la clorhexidina sobre la infección por COVID-19. Métodos: Se realizó una revisión integradora de la literatura, la recolección de datos se realizó entre la segunda y tercera semana de junio de 2021, teniendo como límite de tiempo los estudios publicados entre marzo de 2020 y junio de 2021, en las bases de datos PubMed, Lillacs y Clinical Trials. Resultados: La búsqueda identificó 70 artículos publicados en el período electoral, de los cuales 35 fueron incluidos en la revisión, 6 de los cuales no abordaron el tema, y de los 27 restantes, 15 indicaron que la clorhexidina tiene resultado positivo en SARS--Cov- 2, 6 indicaron que es ineficaz y 6 obtuvieron resultados no concluyentes. Conclusión: Aunque la mayoría de los estudios revisados indican el uso de clorhexidina de manera efectiva contra COVID-19, el pequeño número de investigaciones sobre el tema y la falta de resultados sólidos indican la necesidad de más investigación sobre el efecto de la sustancia en la lucha contra la infección.

DESCRIPTORES: COVID-19; Clorhexidina; SARS-Cov-2.

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INTRODUCTION

The year of 2020 was marked by the emergence of the New Coronavirus pandemic, decreed on March 11th, 2020 by the World Health Organization (WHO), and, on that date, it was already present in approximately 114 countries and reached more than 118.000 people with symptoms of SARS-Cov-2. (1)

SARS-CoV-2, an acronym for "severe acute respiratory syndrome caused by coronavirus 2" (2) is a virus of the coronavirus family and was identified in China at the end of 2019 and that is why it received the name COVID-19, belonging to a large family of viruses that affect the respiratory system.

SARS-CoV-2 has already been found in several tissues of the human body, but it is in the lung cells (pneumocytes) and intestine (enterocytes) that the greatest amount of virus is found. The possibility of virus transmission by aerosols became more robust after the identification that Angiotensin-converting enzyme 2 (ACE2), a cell surface receptor necessary for the virus to enter the human cell, is also present in oral mucosal cells and that the virus is found in saliva, despite having a higher viral load in the oropharynx. (3)

Viral infections are mainly transmitted by contact with contaminated environmental surfaces and by aerosolization. (4) Viral pathogens can survive on environmental surfaces for several days, in the case of COVID-19, it can survive for at least 3 days on various materials present in operating rooms, such as stainless steel and plastic. (5)

This makes the need and importance of environmental disinfection even more important. Chlorhexidine has been used for a long time in hospitals and outpatients with an anvil with hydrophilic and hydrophobic properties. Chlorhexidine is a substance with antimicrobial action, effective in controlling the proliferation of bacteria on the skin and mucous membranes, being a product widely used as an antiseptic in the prevention of infections. (6)

SARS-CoV-2 has already been found in several tissues of the human body, but it is in the lung cells (pneumocytes) and intestine (enterocytes) that the greatest amount of virus is found.

It was introduced on the market in 1954 as an antiseptic for skin wounds and was marketed in the forms of acetate, hydrochloride and digluconate. It soon stood out for its high bactericidal characteristics, low toxicity and high substantivity. (7) At high concentrations it is bactericidal and at low concentrations it has a bacteriostatic effect, remaining in the tissues for a period of 12 hours.

In addition, it does not cause microbiological resistance, is non-corrosive, has no odor and is not contaminating, (8) which made chlorhexidine the gold standard compared to other antimicrobial agents. (9)

There is a huge need to raise awareness among professionals about the virucidal activity of mouthwashes available on the market, as demonstrated by several in vitro studies, and to urge healthcare professionals to conduct more clinical trials and take a translational step towards clinical practice. (10)

In the context of the COVID-19 pandemic, several studies sought to understand the efficacy of chlorhexidine in SARS-CoV-2 infection, since little was known about this virus and which products could act on it. Some of the challenges faced by COVID-19 include the quality of information about the disease, adaptations related to biosafety, generation of protocols, fear and anxiety present in the daily lives of professionals in the current health context. (11)

Seeking to obtain evidence on the action that chlorhexidine may have on the New Coronavirus, an integrative review was carried out, which is a method that provides the synthesis of knowledge and the incorporation of the applicability of results of significant studies in practice, (12) with the aim of synthesizing the studies and analyzing the efficacy of chlorhexidine on COVID-19 infection and answering the following question: "Is chlorhexidine effective as an antimicrobial agent in COVID-19 infection?"

METHODS

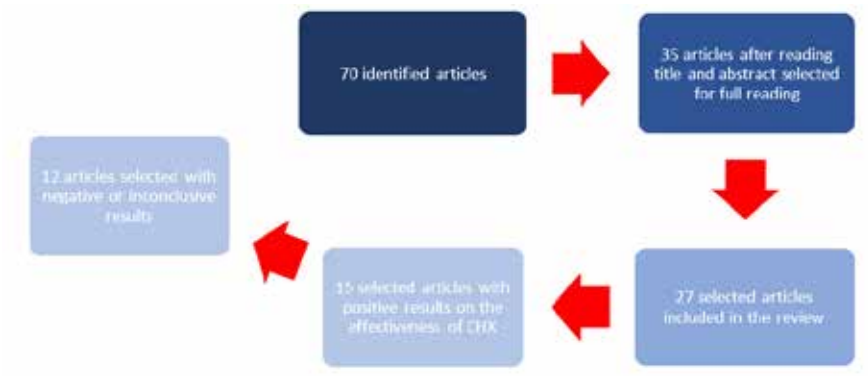
This is a study with data collection carried out from secondary sources, through a bibliographic survey to carry out an integrative review. The following steps were taken: 1°) identification of the problem (defining the purpose of the review); 2°) the search in the literature (with delimitation of keywords, databases and application of the criteria defined for the selection of articles); 3°) data collection, using the previously validated data collection instru-

TABLE1: CONSTRUCTION OF DESC AND MESH

(("clorexidina" [Termos MeSH] OR "clorexidina" [Todos os Campos] OR "cloresidina" [Todos os Campos]) AND ("covid 19" [Todos os Campos] OR "covid 19" [Termos MeSH] OR "vacinas covid 19 "[Todos os campos] OR" vacinas covid 19 "[Termos MeSH] OR" seroterapia covid 19 "[Todos os campos] OR" seroterapia covid 19 "[Conceito suplementar] OR" teste de ácido nucleico covid 19 "[Todos os campos] OR" covid Teste de ácido nucleico 19 "[Termos do MeSH] OR" teste sorológico covid 19 "[Todos os campos] OR" teste sorológico covid 19 "[Termos do MeSH] OR" teste 19 covid "[Todos os campos] OR" teste 19 covid "[Termos do MeSH] OR "sars cov 2" [Todos os campos] OR "sars cov 2" [Termos MeSH] OR "síndrome respiratória aguda grave coronavírus 2"[Todos os campos] OR "ncov" [Todos os campos] OR "2019 ncov" [Todos os campos] OR (("coronavírus" [Termos do MeSH] OR "coronavírus" [Todos os campos] OR "cov" [Todos os campos]) AND 2019 / 11/01: 3000/12/31 [Data - Publicação])))) E (2020: 2021 [pdat]).

Fonte: Nunes, PS; Nunes, V.2021

FIGURE 1- DATABASE ANALYSIS FLOWCHART.



Fonte: Nunes, PS; Nunes, CEB. 2021

ment; 4°) critical analysis of the included studies; 5th) the discussion of the results and 6th) the presentation of the integrative review.

The search for studies was performed on the platforms: Latin American and Caribbean Literature in Health Sciences (LILACS), PUBMED, which is a service of the US National Library of Medicine (NLM) and Clinical Trials, which is a national web registry from federally and privately supported research studies conducted in the United States and around the world, where we find studies in different status, from recruitment to completed. (13) This search was carried out between the second and third week of June 2021, following the following inclusion criteria: articles in English, Spanish and Portuguese, published between March 2020 and June 2021, whose theme was the use of chlorhexidine for reducing contamination by SARS-CoV-2 (COVID-19) infection.

To carry out the search, combinations were used between the following Descriptors in Health Sciences (DeCS) and Medical Subject Headings (MeSH), using the Boolean operators OR between similar terms and AND between the descriptors, as seen in table 1.

In this search, 70 articles were identified, 22 studies were registered in the Clinical Trials, 1 study in the LILACS database and 47 in the PUBMED database, all of which were transferred to the validated data collection instrument (14) and 2 independent and shielded researchers performed the initial reading of titles and abstracts, resulting in the inclusion of 35 studies that met the inclusion criteria and were read in full, as shown in the flowchart in figure 1.

RESULTS

After the independent reviewers read the titles and abstracts of the 70 articles obtained from the search in the databases, 13 (LILACS and PUBMED) were excluded for not dealing with the theme of the review. Of the 22 records in ClinicalTrials.gov, only 3 were completed, however, 1 was not part of the review topic and none presented the results. The remaining 35 were read in full and of these 27 were included in the review, 15 of which found positive results for the efficacy of chlorhexidine and 12 found ineffective or inconclusive results, as shown in table 2.

DISCUSSION

The COVID-19 pandemic installed in March 2020 brought many questions and doubts throughout the health area and the need for a lot of research and new studies to establish, through scientific evidence, which are the best and most effective treatments and substances that can help in this combat, often cruel and lonely.

Saliva contains a high viral load in COVID-19 with up to 1,2 × 108 infectious copies/ml when analyzing the saliva of patients at the time of admission to the hospital. (15)

SARS-CoV-2 has already been found in several tissues of the human body, but it is in the lung cells (pneumocytes) and intestine (enterocytes) that the greatest amount of virus is found. The possibility of virus transmission by aerosols became more robust after the identification that ACE2, a cell surface receptor necessary for the virus to enter the human cell, is also present in the cells of the oral mucosa and that the virus is found in saliva, despite having a higher viral load in the oropharynx. (16)

Table 2: Studies included in the review and their results.

STUDY AND YEAR OF PUBLICATION	AUTHOR	EFFECTIVENESS
Use of mouthwashes against COVID-19 in Dentistry. (2020)	Vergara-Buenaventura A,Castro-Ruiz C	Positive
Antiviral mouthwashes: possible benefit for COVID-19 with evidence-based approach. (2020)	Moosavi MS, Aminishakib P, Ansari M	Positive
Antimicrobial mouthwashes (gargling) and nasal sprays administered to patients with suspected or confirmed COVID-19 infection to improve patient outcomes and to protect healthcare workers treating them. (2020)	Burton MJ, Clarkson JE, Goulao B, Glenny AM, McBain AJ, Schilder AG, Webster KE, Worthington HV	Inconclusive
Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents. (2020)	Kampf G, Todt D, Pfaender S, Steinmann E	Inconclusive
Clinical Significance of a High SARS-CoV-2 Viral Load in the Saliva. (2020)	Yoon JG, Yoon J, Song JY, Yoon SY, Lim CS, Seong H, Noh JY, Cheong HJ, Kim WJ.	Positive
Antiviral Activity of Reagents in Mouth Rinses against SARS-CoV-2. (2020)	Carrouel F, Gonçalves LS, Conte MP, Campus G, Fisher J, Fraticelli L, Gadea- Deschamps E, Ottolenghi L, Bourgeois D	Positive
Efficacy of commercial mouth-rinses on SARS-CoV-2 viral load in saliva: randomized control trial in Singapore. Infection. (2021)	Seneviratne CJ, Balan P, Ko KKK, Udawatte NS, Lai D, Ng DHL, Venkatachalam I, Lim KS, Ling ML, Oon L, Goh BT, Sim XYJ	Positive
Disinfectants and antiseptics facing coronavirus: synthesis of evidence and recommendations. (2021)	León Molina J, Abad-Corpa E	Negative
Virucidal treatments for prevention of coronavirus infection. (2020)	Khokhar M, Roy D, Purohit P, Goyal M, Setia P	Positive
A critical appraisal of evidence in the use of preprocedural mouthwash to avoid SARS-CoV-2 transmission during oral interventions. (2020)	Sette-de-Souza PH, Soares Martins JC, Martins-de-Barros AV, Rodrigues Vieira B, Fernandes Costa MJ, da Costa Araújo FA	Inconclusive
COVID-19 and Oral Surgery: A narrative review of preoperative mouth Rinses. (2020)	Testori T, Wang HL, Basso M, Bordini G, Dian A, Vitelli C, Miletic I, Del Fabbro M	Positive
Interventions to reduce contaminated aerosols produced during dental procedures for preventing infectious diseases. (2020)	Kumbargere Nagraj S, Eachempati P, Paisi M, Nasser M, Sivaramakrishnan G, Verbeek JH	Inconclusive
Interventions to Reduce Aerosolized Microbes in Dental Practice: A Systematic Review with Network Meta-analysis of Randomized Controlled Trials. (2020)	Koletsi D, Belibasakis GN, Eliades T	Positive

Could antiseptic gargling prevent COVID-19? (2020)	Mohamed NA, Ahmad Zainol Hady A, Abdul Aziz AH, Isahak I	Inconclusive
Safety alert for hospital environments and health professional: chlorhexidine is ineffective for coronavirus. (2020)	Assis MS, Araújo RAAM, Lopes AMM	Negative
Potential Role of Oral Rinses Targeting the Viral Lipid Envelope in SARS-CoV-2 Infection. (2020)	O'Donnell VB, Thomas D, Stanton R, Maillard JY, Murphy RC, Jones SA, Humphreys I, Wakelam MJO, Fegan C, Wise MP, Bosch A, Sattar AS	Inconclusive
Differential effects of antiseptic mouth rinses on SARS-CoV-2 infectivity in Vitro. (2021)	Xu C, Wang A, Hoskin ER, Cugini C, Markowitz K, Chang TL, Fine DH	Positive
Physicochemical susceptibility of SARS-CoV-2 to disinfection and physical approach of prophylaxis. (2020)	Saadatpour F, Mohammadipanah F	Negative
Use of chlorhexidine to eradicate oropharyngeal SARS- CoV-2 in COVID-19 patients. (2021)	Huang YH, Huang JT	Positive
Dental workers in front-line of COVID-19: an in silico evaluation targeting their prevention. (2021)	Sette-DE-Souza PH, Costa MJF, Amaral-Machado L, Araújo FADC, Almeida Filho AT, Lima LRA	Positive
Methods to disinfect and decontaminate SARS-CoV-2: a systematic review of in vitro studies. (2021)	Kwok CS, Dashti M, Tafuro J, Nasiri M, Muntean EA, Wong N, Kemp T, Hills G, Mallen CD	Negative
Chlorhexidine: An effective anticovid mouth rinse. (2021)	Jain A, Grover V, Singh C, Sharma A, Das DK, Singh P, Thakur KG, Ringe RP	Positive
Effective in vitro inactivation of SARS-CoV-2 by commercially available mouthwashes. (2021)	Davies K, Buczkowski H, Welch SR, Green N, Mawer D, Woodford N, Roberts ADG, Nixon PJ, Seymour DW, Killip MJ	Negative
Evaluation of the effects of chlorhexidine and several flavonoids as antiviral purposes on SARS-CoV-2 main protease: molecular docking, molecular dynamics simulation studies. (2021)	Tatar G, Salmanli M, Dogru Y, Tuzuner T	Positive
Virucidal activity of oral care products against SARS-CoV-2 in vitro. (2021)	Komine A, Yamaguchi E, Okamoto N, Yamamoto K	Positive
Inactivation of SARS-CoV-2 through Treatment with the Mouth Rinsing Solutions ViruProX® and BacterX® Pro. Microorganisms. (2021)	Koch-Heier J, Hoffmann H, Schindler M, Lussi A, Planz O	Positive
Comparison of the in-vitro efficacy of different mouthwash solutions targeting SARS-CoV-2 based on the European Standard EN 14476. (2021)	Steinhauer K, Meister TL, Todt D, Krawczyk A, Paßvogel L, Becker B, Paulmann D, Bischoff B, Pfaender S, Brill FHH, Steinmann E	Negative

Source: Nunes, PS; Nunes, CEB. 2021

In a study in which the authors investigated the presence of SARS-COV-2 in periodontal tissue, performing minimally invasive video endoscopy post-mortem biopsy in seven fatal cases of COVID-19, using a regular video endoscope system associated with a smartphone to locate periodontal tissue and, analyzing the samples by RT-PCR, for identification of the RNA SARS-COV-2 and histopathological analysis, found positive periodontal tissue for SARS-COV-2 (RT-PCR) in five cases, demonstrating the presence of SARS-COV -2 in periodontal tissue in COVID-19 positive patients. (17)

In this way, both dental biofilm and SARS-CoV-2 can share a common enemy: mouthwashes. Widely used to help control diseases such as caries and gingivitis, it is possible to assume that these disinfectant solutions may temporarily reduce the virus count within the oral cavity. Therefore, washing patients' mouths before dental care sessions can also reduce the chance of contamination inside the offices. These assumptions lead to a major question: "Which oral antiseptic solution should be used?"

(18)

Chlorhexidine is already widely used in hospitals for antisepsis of skin and mucosal surfaces in the antisepsis of the hands and forearms of surgeons and asepsis and antisepsis of surgical patients or patients undergoing invasive and minimally invasive procedures, such as peripheral punctures, placement of catheters, bladder tubes, drains, central venous catheters and tracheostomies, all common procedures in intensive care unit (ICU) patients. (3)

Studies on the reduction of viral load with the use of substances such as chlorhexidine, although scarce and with a short follow-up period, are beginning to provide evidence of effectiveness. Of the 27 studies included in this integrative review, 15 found positive results and recommended the use of chlorhexidine for this purpose, 6 of which did not observe a positive correlation for the reduction in viral load and 6 had inconclusive results.

According to the Federal Council of Dentistry of Brazil (CFO - Conselho Federal de Odontologia do Brasil), it is best to continue using established substances to reduce biofilm and bacteria present in the mouth. The most studied and which showed the best results in this regard are 0,12% chlorhexidine gluconate and 0,05% cetylpyridinium chloride. (19)

Heating, ultraviolet light irradiation and chemicals can be used to inactivate SARS-CoV-2, but there is insufficient evidence to support one measure over others in clinical practice. (20)

It has been observed that other substances, such as Listerine Advanced Defense Sensitive and Total Care formulations and commercial mouthwashes containing 0,01-0,02% hypochlorous acid or 0,58% povidone iodine in vitro testing using TCF have been effective against SARS-COV-2, leaving these options as superior to mouthwashes with hydrogen peroxide or chlorhexidine gluconate, for reducing the viral load of SARS-CoV-2. (21)

There is also an economic importance with the use of chlorhexidine, which is cost-effective for patients with COVID-19 in relation to pneumonia. (22)

Another systematic review sought to show whether this substance would be effective in disinfecting surfaces, but it was also concluded that it is not efficient. (23)

CONCLUSION

Based on the included studies and their results, it can be seen that more research needs to be carried out and certain conditions must be present, such as time and other knowledge about the virus and its variants, are needed for more evidence to be found and can, conclusively, determine the best line of action in order to reduce the viral load, it can benefit the treatment and recovery of patients infected with SARS-Cov-2, however, there is already good evidence that chlorhexidine can be efficient in reducing the viral load in cases of COVID-19.

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