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Use of oral antiseptics for SARS-CoV-2 infection☆

Utilización de antisépticos orales para la infección por SARS-CoV-2

Dear Editor,

The health crisis triggered by the SARS-CoV-2 (COVID-19) pandemic and its rapid onset have placed humanity in combat with a pathogen that cannot be won at this moment with any pharmacological treatment that boasts sufficient scientific evidence.[1] While awaiting the results of ongoing clinical trials with different therapeutic options and looking forward to a vaccine that allows population immunity to be achieved, intermediate, fast, safe and verifiable solutions are necessary with limited research effort. A recent study reports that patients affected by COVID-19 have a high viral load in the oropharynx, especially during the first week after the onset of symptoms, which would partly explain its high transmission rate, its contagiousness and its rapid geographical spread.[2]

It is also known that different antiseptics (povidone iodine) have virucidal action on skin and mucosa, and are well tolerated for short-term treatments.[3] In 2015, a study reported that the *in vitro* application of antiseptic products with povidone iodine achieved a decrease in the titres of the MVA (Modified Vaccinia Ankara) and MERS-CoV (Middle East Respiratory Syndrome) viruses, corresponding to a viral inactivation greater than 99% after 30 and 15 s of applying the mouthwash product (1% concentration) in MVA and MERS-CoV, respectively.[4] These investigations were later expanded and with similar results both in the case of bacteria (*Klebsiella pneumoniae* Y *Streptococcus pneumoniae*) and with other viruses (SARS-CoV, influenza A-H1N1 and rotavirus). These findings are summarised in another publication in August 2019, prior to the epidemic situation.[5]

It would be feasible to hypothesise that treatment with mouthwashes/gargling with antiseptics (povidone iodine or others) could contribute to reducing the viral load of COVID-19 in sick patients, as well as reducing contagiousness through respiratory droplets towards other persons and the environment.[4] This hypothesis could be tested quite simply and quickly by applying the scientific method with a study designed with paired data (*cross-over* or *within patient*), which would require a smaller number of patients. The viral load would be assessed before and after (at different times) the application of the oral antiseptic. Relevant questions to be resolved would be: an estimation of the minimum concentration necessary for the product to obtain positive results while minimising adverse effects; and determining the time during which the viral load in the oropharynx is low enough to have a protective effect for the patient, for others and for the environment. Likewise, it would be of interest to assess whether the decrease in the viral load in the oropharynx could have a clinically relevant effect in patients.

It should be noted that the studies cited above[4,5] were sponsored by a specific manufacturer of povidone iodine, therefore future studies should ensure the independence of the research groups to avoid conflicts of interest. The proposition of other possible prophylactic/therapeutic options would also be of importance, especially as an alternative to those subjects with COVID-19 infection in which povidone iodine presents some contraindication or precaution (pregnant women, children, goiter or hyperthyroidism), as stated in the product's technical data sheet: <https://cima.aemps.es/cima/dochtml/ft/36339/FT_36339.html>.

If positive results are obtained, this therapeutic option could be a practical and safe solution, pending more effective therapies or an adequate vaccine. It could be indicated for relatively short periods (1–2 weeks), coinciding with the greatest contagious wave. The application by the patient (in home isolation or during a hospital stay) would be simple to learn and to carry out. Additionally, antiseptics are easily accessible and are low cost, so this alternative could be feasible for countries with low economic resources.

This proposal has been sent to Spain's Ministry of Health on behalf of the Drug Use Working Group of the Spanish Society of Family and Community Medicine (semFYC). Family practitioners are on the front line caring for patients with COVID-19 and trying to manage the elevated level of uncertainty in general and especially regarding the use of current drugs, that are all 'off-label' and lack the 'backing' of scientific evidence.[1] Possible solutions such as the one proposed, if its effectiveness is confirmed, even though modest, would contribute to improving the management of SARS-CoV-2 infection in both primary care and hospitals. In the current situation of health crisis, any step forward is a great step forward.

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Cross-reactions between rheumatoid factor and IgM SARS-CoV-2☆

Reacciones cruzadas entre factor reumatoide e IgM SARS-CoV-2

To the Editor:

After the onset of the SARS-CoV-2 infection, special attention has been paid to the protection and transmission reduction in vulnerable populations. Of the methods described by Hernández-Pérez et al.[1] and the rapid immunoglobulin tests,[2] the most widely used methods are nucleic acid detection and tests based on the antigen-antibody reaction. We consider it important to focus attention on the possibility of IgM cross-reactivity between rheumatoid factors and IgM SARS-CoV-2 in patients with chronic inflammatory diseases and elevated rheumatoid factors, such as rheumatoid arthritis and Sjögren's syndrome.

The reverse transcription-polymerase chain reaction (RT-PCR) requires at least 4–6 h and it is very costly. It is the technique that is most used to diagnose active infection and it should be considered a technique of choice since: a) it detects the presence of the virus in nasopharynx samples in the acute phase; b) samples such as endotracheal aspirate, bronchial aspirate, and bronchoalveolar lavage can be used; c) it allows a large number of patients to be studied, due to the ease of automation of the procedures, and d) it is greater sensitivity (Se) and specificity (Sp) than the other methods available. It has fewer false positives (FP) and false negatives (FN). PCR-interpretation must be performed carefully and within the appropriate clinical context, especially when the result is negative.

Recent papers on COVID-19 have also focused on immunoassays (*enzyme-linked immunosorbent assay* [ELISA]) and on rapid antigen and antibody tests.[2] The ELISA test is an immunoenzymatic assay that determines the presence of IgM and IgG antibodies, or a combination of IgM + IgA. Within the second group there are those that detect antigens or those that detect antibodies (IgM / IgG).

Regarding antigen-detection, there are not many studies that demonstrate the Se and Sp of nasopharyngeal swabs in SARS-CoV-2. However, it appears that the viral load is higher in the nasal passages than in the oropharynx, and that in the first days of infection the viral load ranges from 104 to 108 RNA copies per mL. This would suggest that the SARS-CoV-2 Ag detection could have good Se if a good antibody is available. The advantages of this test are the adequate Se and the speed, since immunochromatography tests usually produce results in about 15–30 min. The main disadvantage is the difficulty in processing a large number of samples in a short period of time.

The detection of specific IgM and IgG antibodies allows the immune response to the virus to be qualitatively and quantitatively characterised. Once infected by SARS-CoV-2, IgM is detected from 3–5 days from the onset of symptoms and disappears around day 21 post-infection. IgG appears later, and is normally detected after 14 days, increasing during the convalescence period. IgG remain in the blood beyond the convalescence period, providing the hoped-for long-term immunity which is yet to be confirmed.[3,4]

Recently, the techniques *gold immunochromatography assay* (GICA) and ELISA were used to study the possible interaction in the detection test for SARS-CoV-2 IgM antibodies. A total of 86 serum samples from different patients were used: 5 influenza A virus (flu A) IgM-positive sera, 5 influenza B virus (flu B) IgM-positive sera, 5 *Mycoplasma pneumoniae* IgM-positive sera, 5 *Legionella pneumophila* IgM-positive sera, 6 sera of HIV infection patients, 36 for rheumatoid factor IgM (RF-IgM)-positive sera, 5 sera from hypertensive patients, 5 sera from diabetes mellitus patients, and 14 sera with SARS-CoV-2 infection.[5] The factors causing FP IgM antibodies were analysed. In addition, the urea dissociation test was used to dissociate the SARS-CoV-2 IgM-positive serum of using the best dissociation concentration. Positive SARS-CoV-2 IgM was detected in 22 middle-high level RF-IgM-positive sera and, as expected, in all 14 samples from COVID-19 patients. The other 50 sera were negative. When using GICA and ELISA to detect SARS-CoV-2 IgM, the level of RF-IgM in the serum is indirectly quantified and the urea dissociation test should be performed to avoid the risk of FP results. When the urea dissociation concentration was 6 mol/L, SARS-CoV-2 IgM was positive in one middle-high level RF-IgM-positive serum and in all 14 sera from COVID-19 patients. When the urea dissociation concentration was 4 mol/L and the avidity index (AI) lower than 0.371 was set to negative, the test results were positive for SARS-CoV-2 in 3 middle-high level RF-IgM-positive sera, as well as in the 14 COVID-19 sera. The authors concluded that, to detect SARS-CoV-2 IgM, the level of RF-IgM in the serum should be assessed and the urea dissociation test should be performed to avoid the risk of FP results.

However, the urea dissociation test cannot completely eliminate RF-IgM interference. Therefore, when SARS-CoV-2 IgM results are still positive after urea dissociation, PCR should be used for viral nucleic acid diagnosis. These data suggest that the methods described should be used to eliminate or reduce the impact of cross-reaction when using GICA and ELISA methods for the detection of SARS-CoV-2 IgM. This fact would mean an improvement in the screening of suspected cases and high-risk groups, as well as in the evaluation, prevention and control of SARS-CoV-2.

The rapid evolution of the pandemic has required an agile and accelerated response. Knowledge about SARS-CoV-2 is increasing, but there is still a need to study the discrepancies in the methods of diagnosing the disease. It is important to intensify studies of each of the tests and the causes of the possible FP results, and especially in RF-positive diseases such as rheumatoid arthritis and Sjögren's syndrome.

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