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REVIEW PROTOCOL

Use of convalescent plasma in the treatment of COVID-19: a systematic review protocol

Uso de plasma convalescente no tratamento da COVID-19: protocolo de revisão sistemática

Uso de plasma convaleciente en el tratamiento de COVID-19: protocolo de revisión sistemática

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ABSTRACT

Objective: to analyze the therapeutic effectiveness of convalescent plasma used in patients with confirmed COVID-19 diagnosis. **Method:** systematic review for health technology assessment to answer the PICO question: Is convalescent plasma effective in reducing the viral load of patients diagnosed with SARS-CoV-2 (COVID-19) when compared to not using plasma? A systematic search was performed in Pubmed/Medline, BVS, Embase, CINAHL, LILACS, Cochrane and Google Scholar databases. The initial screening of titles and abstracts will be independently assessed by two reviewers. To assess the risk of bias in systematic reviews, AMSTAR-2 will be used, and to assess the quality of evidence, GRADE will be used.
Descriptors: Plasma; COVID-19; SARS-CoV-2.

RESUMO

Objetivo: analisar a efetividade terapêutica do plasma convalescente utilizado em pacientes com confirmação de diagnóstico de COVID-19. **Método:** revisão sistemática para avaliação tecnológica em saúde para responder à pergunta PICO: O plasma convalescente é efetivo na redução da carga viral de pacientes com diagnóstico SARS-CoV-2 (COVID-19) quando comparado ao não uso do plasma? Foi realizada uma busca sistemática nas bases de dados Pubmed/Medline, BVS, Embase, CINAHL, LILACS, Cochrane e *Google Scholar*. A triagem inicial dos títulos e resumos será avaliada de forma independente por dois revisores. Para avaliação do risco de viés de revisões sistemáticas será utilizado o AMSTAR-2; já para avaliação da qualidade da evidência será aplicado o GRADE.
Descritores: Plasma; COVID-19; SARS-CoV-2.

RESUMEN

Objetivo: analizar la efectividad terapéutica del plasma convaleciente utilizado en pacientes con confirmación de diagnóstico de COVID-19. **Método:** revisión sistemática para evaluación tecnológica en salud para responder a la pregunta PICO: ¿Es el plasma convaleciente efetivo en la reducción de la carga viral de pacientes con diagnóstico SARS-CoV-2 (COVID-19) cuando se la compara a la no utilización del plasma? Se realizó una búsqueda sistemática en las bases de datos Pubmed/Medline, BVS, Embase, CINAHL, LILACS, Cochrane y *Google Scholar*. La selección inicial de los títulos y resúmenes serán evaluados de forma independiente por dos revisores. Para evaluación del riesgo de sesgo de revisiones sistemáticas se utilizará el AMSTAR-2, mas para evaluación de la calidad de la evidencia será aplicado el GRADE.
Descriptores: Plasma; COVID-19; SARS-CoV-2.

INTRODUCTION

The SARS-CoV-2 outbreak originated in Wuhan, China, in December 2019. This virus is the cause of coronavirus disease 2019 (COVID-19), a serious illness characterized by pneumonia with increased infiltration of inflammatory cells and higher levels of pro-inflammatory cytokines[1].

This viral infection can trigger clinical cases of mild to moderate respiratory symptoms, however, about 11.7% of those infected end up developing the severe form of the disease, often leading to death[2].

The scientific community has already found that convalescent plasma for COVID-19 can be a safe treatment for patients, based on studies carried out in the United States of America (USA), China and Europe. Thus, it is plausible that it contains antibodies capable of neutralizing the action of SARS-COV-2. Such antibodies are extracted from the blood of patients recovered from COVID-19 who have not had symptoms in the last 14 or 28 days and serological result of COVID-19, by the plasmapheresis procedure[3,4].

Through this emerging therapy in the fight against the disease, studies indicate that the use of this technique reduces the replication of the virus in the patient and his immune system is able to respond better to the aggression of the virus[5].

The Food and Drug Administration has issued an opinion on the use of experimental convalescent plasma in the US, which implicates patients with antibodies for treatment hospitalized with COVID-19 early in the course of the disease or with compromised immunity[6].

In the past, convalescent plasma was also used to fight infection during the SARS epidemic in 2003 and the Middle East Respiratory Syndrome in 2012, and no significant side effects were identified[7].

Considering the knowledge gap on this topic and the limited number of studies published so far on the use of convalescent plasma as an experimental procedure, it is important to verify the potential of this treatment in patients infected with SARS-CoV-2.

According to the Ministry of Health, Health Technology Assessment (HTA) consists of investigating the clinical, economic and social consequences of the development, dissemination and use of technologies in the context of the health system and services. Through the information generated, the manager can make the best decision to contribute to health care (efficacy, effectiveness, safety and cost) to encourage the adoption of effective technologies[8].

The relevance of the study in assessing the use of convalescent plasma in the treatment of these patients in order to reduce viral replication and, consequently, the cure of infected patients, also becomes fundamental to support the adoption of strategies and actions that promote the development and improvement of the service provided.

Therefore, health professionals and managers should be concerned with identifying the health needs of the population and assessing existing technologies as a path to equitable and universal care in the SUS, contributing to its sustainability promotion.

Thus, recommendations on the use of convalescent plasma in COVID-19 require systematic summaries of the available evidence. Therefore, the objective of this review is to analyze the therapeutic effectiveness of convalescent plasma used in patients with confirmed diagnosis of COVID-19.

METHOD

A systematic review for HTA will be carried out based on the recommendations of the PRISMA checklist[9]. Therefore, the methodology proposed in the Cochrane Collaboration Manual was adopted[10] in order to answer the research question: "Is convalescent plasma effective in reducing the viral load of patients diagnosed with SARS-CoV-2 when compared to not using plasma?". The protocol was registered in the PROSPERO database CRD42021249359.

Source of information

Electronic searches were performed in the following databases: Medline/Pubmed, BVS, Embase, CINAHL, LILACS and John Wiley & Son Cochrane Library databases, Google Scholar and the TRIP DATABASE meta-search.

Eligibility criteria

In the present review, two researchers independently applied the following eligibility criteria: languages in Portuguese, English and Spanish; articles published between 2020 and 2021; randomized clinical trial and systematic reviews that include viral load reduction and measurement time (in the first days of symptom until negative conversion of viral RNA to SARS-CoV-2 in all clinical samples); both sexes; ages between 18 and 65 years; patients admitted to a hospital unit; and available in full text.

Estudos realizados com animais, bem como teses, dissertações e editoriais foram excluídos da presente revisão. No caso de discordância entre os pesquisadores, um terceiro avaliador resolveu as divergências.

Search strategy

To identify the descriptors and free terms that composed the strategies developed, the Medical Subject Headings (MeSH) controlled vocabularies were consulted, Health Sciences Descriptors (DeCS) and Embase Subject Headings (Emtree) combined using Boolean operators (OR/AND). The representations of the search strategies are described in Figure 1.

Data extraction

After identifying the included studies, data will be extracted by the same researchers, using the Handbook Cochrane Collaboration[10] form, prepared in Microsoft Excel. The extracted data will include information on: study design; trial participants and characteristics; diagnostic criteria; number of participants selected for eligibility; allocation randomization and concealment method; use of

DATABASES	STRATEGY
PUBMED	((“COVID-19”[mh] OR “COVID-19” OR “COVID 19” OR “COVID-19 *Virus Disease”* OR “COVID 19 *Virus Disease*” OR “COVID-19 *Virus Infection*” OR “COVID 19 *Virus Infection*” OR “COVID-19 *Virus Infections*” OR “2019-nCoV *Infection*” OR “2019 nCoV *Infection*” OR “2019-nCoV *Infections*” OR “*Coronavirus Disease-19*” OR “*Coronavirus Disease 19*” OR “2019 *Novel Coronavirus Disease*” OR “2019 *Novel Coronavirus Infection*” OR “2019-nCoV *Disease*” OR “2019 nCoV *Disease*” OR “2019-nCoV *Diseases*” OR “*Coronavirus Disease* 2019” OR “SARS *Coronavirus 2 Infection*” OR “SARS-CoV-2 *Infection*” OR “SARS CoV 2 *Infection”* OR “SARS-CoV-2 *Infections*” OR “COVID-19 *Pandemic*” OR “COVID 19 *Pandemic*” OR “COVID-19 *Pandemics*” OR “SARS-CoV-2”[mh] OR “SARS-CoV-2” OR “*Coronavirus Disease* 2019 *Virus*” OR “2019 *Novel Coronavirus*” OR “2019 *Novel Coronaviruses*” OR “*Wuhan Seafood Market Pneumonia Virus*” OR “SARS-CoV-2 Virus” OR “SARS CoV 2 Virus” OR “SARS-CoV-2 *Viruses”* OR “2019-nCoV” OR “COVID-19 Virus” OR “COVID 19 Virus” OR “COVID-19 *Viruses”* OR “*Wuhan Coronavirus*” OR “*Coronavirus*, *Wuhan”* OR “SARS *Coronavirus 2*” OR “*Severe Acute Respiratory Syndrome Coronavirus* 2”) AND (“*COVID-19 serotherapy*” OR “*convalescent plasma therapy*”))
REGIONAL BVS/ LILACS	(“*coronavirus infections”* OR *“2019 novel coronavirus”* OR *“2019-novel coronavirus”* OR “2019-nCoV” OR *“2019-new coronavirus”* OR “COVID-19” OR *“coronavirus infection”* OR *“coronavirus infections”* OR “MERS” OR *“middle east respiratory syndrome”* OR *“novel coronavirus pneumonia”* OR *“wuhan coronavirus”* OR *“infecciones por coronavirus”* OR “infeccoes por coronavirus” OR “betacoronavirus” OR “2019 *new coronavirus*” OR “betacoronaviruses” OR “HCoV-HKU1” OR “*human coronavirus* HKU1*”* OR *“pipistrellus bat coronavirus* HKU5*”* OR *“rousettus bat coronavirus* HKU9*”* OR “SARS-CoV-2” OR *“severe acute respiratory syndrome coronavirus 2”* OR *“tylonycteris bat coronavirus HKU4”* OR *“wuhan coronavirus”* OR *“wuhan seafood market pneumonia virus”*) AND (“*convalescent plasma*” OR *“convalescent plasma therapy”* OR “plasma convalescente” OR “terapia de plasma convalescente” OR “plasma de convalecencia” OR “terapia de plasma convaleciente”)
EMBASE	(‘*coronavirus disease* 2019’/exp OR ‘2019 *novel coronavirus disease’* OR ‘2019 *novel coronavirus epidemic*’ OR ‘2019 *novel coronavirus infection’* OR ‘2019-ncov *disease’* OR ‘2019-ncov *infection’* OR ‘covid’ OR ‘covid 19’ OR ‘covid 19 *induced pneumonia’* OR ‘covid 2019’ OR ‘covid-10’ OR ‘covid-19’ OR ‘covid-19 *induced pneumonia’* OR ‘covid-19 pneumonia’ OR ‘covid19’ OR ‘sars *coronavirus 2 infection’* OR ‘sars coronavirus 2 pneumonia’ OR ‘sars-cov-2 *disease’* OR ‘sars-cov-2 *infection’* OR ‘sars-cov-2 pneumonia’ OR ‘sars-cov2 *disease’* OR ‘sars-cov2 *infection’* OR ‘sarscov2 *disease’* OR ‘sarscov2 *infection’* OR ‘*wuhan coronavirus disease’* OR ‘*wuhan coronavirus infection’* OR ‘*coronavirus disease 2’* OR ‘*coronavirus disease 2010’* OR ‘*coronavirus disease 2019’* OR ‘*coronavirus disease* 2019 *pneumonia’* OR ‘*coronavirus disease-19’* OR ‘*coronavirus infection 2019’* OR ‘ncov 2019 *disease’* OR ‘ncov 2019 *infection’* OR ‘*new coronavirus* pneumonia’ OR ‘*novel coronavirus* 2019 *disease’* OR ‘*novel coronavirus* 2019 *infection’* OR ‘*novel coronavirus disease* 2019’ OR ‘*novel coronavirus infected pneumonia’* OR ‘*novel coronavirus infection* 2019’ OR ‘*novel coronavirus pneumonia’* OR ‘*paucisymptomatic coronavirus disease* 2019’ OR ‘*severe acute respiratory syndrome 2’* OR ‘*severe acute respiratory syndrome 2 pneumonia’* OR ‘*severe acute respiratory syndrome* cov-2 *infection’* OR ‘*severe acute respiratory syndrome coronavirus 2 infection’ OR ‘severe acute respiratory syndrome coronavirus* 2019 *infection’* OR ‘*severe acute respiratory syndrome coronavirus 2’*/exp OR ‘2019 ncov’ OR ‘2019 *new coronavirus’* OR ‘2019 *novel coronavirus’* OR ‘2019 *severe acute respiratory syndrome coronavirus 2’* OR ‘2019-ncov’ *OR ‘covid 19 virus’* OR ‘hcov-19’ OR ‘*human coronavirus* 2019’ OR ‘sars *coronavirus 2’* OR ‘sars-cov-2’ OR ‘sars-*related coronavirus 2’* OR ‘sars2 *(virus)’ OR ‘sever acute respiratory syndrome coronavirus 2’ OR ‘severe* acute respiratory coronavirus 2’ OR ‘*severe acute respiratory syndorme coronavirus 2’* OR ‘*severe acute respiratory syndrome coronavirus 2’* OR ‘*severe acute respiratory syndrome coronoavirus 2’* OR ‘*severe acute respiratory syndrome coronvirus 2’* OR ‘*severe acute respiratory syndrome related coronavirus 2’* OR ‘*severe acute respiratory syndrome virus 2’* OR ‘*severe acute respiratoy syndrome coronavirus 2’* OR ‘*wuhan coronavirus’* OR ‘*wuhan seafood market pneumonia virus’* OR ‘ncov-2019’ OR ‘*novel* 2019 *coronavirus’* OR ‘*novel coronavirus* 2019’ OR ‘*novel coronavirus-19’* OR ‘*severe acute respiratory syndrome 2* virus’ OR ‘*severe acute respiratory syndrome cov-2 virus’* OR ‘*severe acute respiratory syndrome corona virus 2’* OR ‘*severe acute respiratory syndrome coronavirus* 2019’) AND (‘*covid-19 serotherapy’* OR ‘*covid-19 convalescent plasma treatment’* OR ‘*convalescent plasma treatment for covid-19’* OR ‘*convalescent plasma therapy’*/exp OR ‘*convalescent plasma* (cp) *therapy’* OR ‘*convalescence plasma therapy’* OR ‘*convalescent plasma* (cp) *immunotherapy’* OR ‘*convalescent plasma immunotherapy’* OR ‘*convalescent plasma therapy’*) AND [embase]/lim

DATABASES	STRATEGY
COCHRANE	ID Search #1 MeSH descriptor: [COVID-19] explode all trees #2 "COVID-19" OR "COVID 19" OR "COVID-19 *Virus Disease*" OR "COVID 19 *Virus Disease"* OR "COVID-19 *Virus Infection"* OR "COVID 19 *Virus Infection"* OR "COVID-19 *Virus Infections"* OR "2019-nCoV *Infection"* OR "2019 nCoV *Infection"* OR "2019-nCoV *Infections"* OR "*Coronavirus Disease*-19" OR "*Coronavirus Disease* 19" OR "2019 *Novel Coronavirus Disease"* OR "2019 *Novel Coronavirus Infection"* OR "2019-nCoV *Disease"* OR "2019 nCoV *Disease"* OR "2019-nCoV *Diseases"* OR "*Coronavirus Disease* 2019" OR "SARS *Coronavirus* 2 *Infection*" OR "SARS-CoV-2 *Infection*" OR "SARS CoV 2 *Infection*" OR "SARS-CoV-2 *Infections*" OR "COVID-19 *Pandemic*" OR "COVID 19 *Pandemic*" OR "COVID-19 *Pandemics*" #3 #1 OR #2 #4 MeSH descriptor: [SARS-CoV-2] explode all trees #5 "SARS-CoV-2" OR "*Coronavirus Disease* 2019 Virus" OR "2019 *Novel Coronavirus"* OR "2019 *Novel Coronaviruses*" OR "*Wuhan Seafood Market Pneumonia* Virus" OR "SARS-CoV-2 Virus" OR "SARS CoV 2 Virus" OR "SARS-CoV-2 *Viruses*" OR "2019-nCoV" OR "COVID-19 Virus" OR "COVID 19 Virus" OR "COVID-19 *Viruses*" OR "*Wuhan Coronavirus*" OR "SARS *Coronavirus* 2" OR "*Severe Acute Respiratory Syndrome Coronavirus* 2" #6 #4 OR #5 #7 #3 OR #6
CINAHL	(("COVID-19" OR "COVID 19" OR "COVID-19 *Virus Disease*" OR "COVID 19 *Virus Disease"* OR "COVID-19 *Virus Infection*" OR "COVID 19 *Virus Infection"* OR "COVID-19 *Virus Infections*" OR "2019-nCoV *Infection*" OR "2019 nCoV *Infection*" OR "2019-nCoV *Infections*" OR "*Coronavirus Disease*-19" OR "*Coronavirus Disease* 19" OR "2019 *Novel Coronavirus Disease*" OR "2019 *Novel Coronavirus Infection*" OR "2019-nCoV *Disease*" OR "2019 nCoV *Disease*" OR "2019-nCoV *Diseases*" OR "*Coronavirus Disease* 2019" OR "SARS *Coronavirus 2 Infection*" OR "SARS-CoV-2 *Infection*" OR "SARS CoV 2 *Infection"* OR "SARS-CoV-2 *Infections*" OR "COVID-19 *Pandemic*" OR "COVID 19 *Pandemic*" OR "COVID-19 *Pandemics*" OR "SARS-CoV-2" OR "*Coronavirus Disease* 2019 Virus" OR "2019 *Novel Coronavirus*" OR "2019 *Novel Coronaviruses*" OR "*Wuhan Seafood Market Pneumonia Virus*" OR "SARS-CoV-2 Virus" OR "SARS CoV 2 Virus" OR "SARS-CoV-2 Viruses" OR "2019-nCoV" OR "COVID-19 Virus" OR "COVID 19 Virus" OR "COVID-19 *Viruses*" OR "*Wuhan Coronavirus"* OR "SARS *Coronavirus* 2" OR "*Severe Acute Respiratory Syndrome Coronavirus* 2") AND ("COVID-19 *serotherapy*" OR "*convalescent plasma"* OR "*convalescent plasma therapy*"))

Figure 1 – Database search strategy. Rio de Janeiro, RJ, Brazil, 2021
Source: Prepared by the authors, 2021.

intent-to-treat analysis; detailed interventions; duration of studies; and outcome measures (reduction in viral load presented as continuous data: final anti-SARS-CoV-2 IgG protein titers and dichotomous: reduced versus not reduced).

References found in the selected search strategies will be exported to the reference manager, Mendeley®, to remove duplicates. Disagreements regarding data extraction will be resolved by a third reviewer. When there is insufficient data, there will be attempts in contacting the corresponding authors for possible clarifications.

Treatment effect measures.

Relative risk (RR) and 95% confidence interval (CI) will be used to analyze dichotomous data. For continuous data, the mean difference method will be used, with their respective 95% CIs (dispersion data and standard deviation will also be extracted).

Heterogeneity assessment

Statistical heterogeneity between studies will be investigated using Cochran's Q test with a significance level of p value lower than 0.01 and quantified by the I^2 test. Although inconsistency is estimated using Cochran's Q test, the I^2 test is a statistic that provides complementary information because it is not influenced by statistical power. The I^2 statistic ranges from 0 to 100% and is interpreted as low (25%), moderate (26-74%) and high (75%) heterogeneity.

Data synthesis

The Review Manager software (v.5.3) will be used for data analysis and synthesis of quantitative data. The mean differences and/or the RR with their respective 95% CIs will be calculated using the random effect model for data synthesis, exceptionally the fixed effect will be used if there is a single study with an order of magnitude 50% greater than the other included studies.

Subgroup analysis

In the presence of heterogeneity (moderate to high) subgroup and/or sensitivity analyzes will be performed. Some factors that may be considered in the subgroup analysis are: type

of intervention, concentration of inflammatory cytokines and increase in C-reactive protein. For the sensitivity analysis, if necessary, an analysis will be performed considering the studies that demonstrate low risk of bias in order to increase the confidence of the result.

Risk of bias assessment

Two authors will independently assess the risk of bias of systematic reviews through the tool Assessing the Methodological Quality of Systemathic Reviews (AMSTAR-2)[11], while for RCTs the Cochrane criteria will be used, which include: random sequence generation, allocation concealment, participant and outcome assessor masking, incomplete outcome data, selective outcome reporting, and other bias[11]. The risk of bias will be classified as "low", "high" or "some concern". Incomplete outcome data will be judged as low risk of bias when the numbers and causes of dropouts are balanced across arms and appear to be unrelated to the outcome itself. Selective bias will be assessed by comparing outcomes reported in study protocols with published outcome results. Any discrepancy between the authors will be resolved by a third reviewer.

Evidence quality assessment

Since the weighting of other aspects can increase or decrease the quality of evidence about the effect of an intervention on an outcome, the present review will assess the outcome of viral load reduction through The Grading of Recommendations, Assessment, Development and Evaluation System (GRADE)[12].

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CONFLICT OF INTEREST

The authors have declared that there is no conflict of interest.

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Data collection: Santos MR
Data analysis and interpretation: Santos MR
Writing and/or critical review of the intellectual content: Santos MR
Final approval of the version to be published: Santos MR, Silva CRL
Responsibility for the text in ensuring the accuracy and completeness of any part of the paper: Santos MR, Silva CRL