Chapter 217

Therapeutic perspective of COVID-19 against corticosteroids

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ABSTRACT
Coronaviruses belong to a broad family called *Coronoviridae*, they are simple RNA viruses. In SARS-CoV-2 infection, a cytokine storm occurs in the body, responsible for tissue damage, and pulmonary and systemic inflammation. For this reason, corticosteroids appear as a viable option. This study conducted a systematic review of the pharmacotherapy of steroidal anti-inflammatory drugs used in hospitalized patients with COVID-19. The study was conducted in January 2023, using the SCIELO and PUBMED databases. The keywords were: corticosteroid, SARS-CoV-2, therapy, corticosteroids, hospitalized, and COVID-19 combined with the Boolean operators AND and OR. Articles published from 2020 to 2022 in the languages Portuguese and English were included. Of the 8 articles included in this review, 50% (n=4) are cohort studies, 37.5% (n=3) are clinical studies, and 12.5% (n=1) are observational studies. As for the year of publication, 25% (n=2) are from 2020, 62.5% (n=5) are from 2021 and 12.5% (n=1) are from 2022. Of the country where the survey was conducted, 37.5% (n=3) were conducted in Iran. China, South Africa, Spain, Colombia, and Lisbon had 12.5% (n=1) of studies each. The population samples visualized in the 8 studies ranged from 62 patients to 774 patients, with a mean age ranging from 53.5 to 64 years, 55.8% men, and 44.1% women. Among the comorbidities observed in each study, Diabetes Mellitus and hypertension were the most common, followed by cardiovascular events, Chronic Obstructive Pulmonary Disease, dyslipidemia, and obesity or HIV. Regarding the severity of COVID-19, 50% (n=4) of the studies were done with patients who had the severe form of the disease, 37.5% (n=3) moderate to severe, and 12.5% (n=1) of the studies reported that 63.6% of the sample (49/77) evolved to the severe form of the disease. Among the corticosteroids included in the studies, those that presented the best clinical outcomes were methylprednisolone in 50% (n=4) of the studies with doses ranging from 80mg/day to 500mg/day during the range of 3 to 14 days of treatment. Prednisolone was followed in 12.5% (n=1) of the studies at a dose of 25mg/day for 5 days of treatment and dexamethasone in 25% (n=2) of the studies. The therapeutic benefit of corticosteroids for the control of moderate and severe cases caused by the so-called "cytokine storm" that occurred in the body of human beings infected by SARS-CoV-2 is evident.

Keywords: COVID-19, Steroids, ICU, Cytokines, Inflammatory mediators.

1 INTRODUCTION

Self-medication consists of an individual medicating himself without the prior guidance of a health professional. They may be over-the-counter drugs (MIPs), leftovers from other treatments or inadequately sold, the latter being a very common practice in society (SOUZA *et al*., 2011). Currently, Brazil has a market of 22.1 billion dollars annually with the sale of medicines and according to the World Health Organization (WHO), 50% of this value is incorrectly sold drugs. In the ranking of world consumption of over-the-counter drugs, Brazil occupies fifth place and first in Latin America (DOMINGUES *et al*., 2015).

Some of the problems of self-medication are related to the irrational use of medications can be an example, polypharmacy, which implies the ingestion of several medications, since some of these may contain associations, causing hepatotoxicity, nephrotoxicity, or an imbalance in body homeostasis; irrational use of antibiotics, which can contribute to bacterial resistance (MINISTÉRIO DA SAÚDE, 2017). Given the above, self-medication, which has as its most common classes anti-inflammatories, the mechanism of action of steroidal anti-inflammatory drugs (AIES) is characterized by blocking inflammatory responses by increasing the expression of the gene responsible for the production of lipocortin, which acts by inhibiting the enzyme phospholipase A2, preventing the formation of arachidonic acid, which implies blocking the inflammatory cascade (WHALEN; FINKEL; PANAVELIL, 2016).

The COVID-19 pandemic began in December 2019 in Wuhan, China (BOGOCH *et al*., 2020). SARS-CoV-2 is the virus that causes the respiratory disease known as COVID-19 (ZHU *et al*., 2020). Coronaviruses belong to a broad family called *Coronoviridae*, they are simple RNA viruses containing nucleocapsid and spike proteins or spicules (CORMAN *et al*, 2018). From the intracellular habitat, the replicative cycle of SARS-CoV-2 starts from the interaction between the glycoprotein S of the virus with the cellular receptor ECA2 (Angiotensin-Converting Enzyme 2) belonging to the renin-angiotensin-aldosterone system located on the surface of the target cell present in the kidneys, intestines, blood vessels and lung (ALMEIDA *et al*., 2020; SOUTH *et al*. 2020). Soon after, viral penetration occurs, followed by denudation and ending replication. This process promotes cellular apoptosis and lesions in the vascular and alveolar epithelium contributing to the extravasation of cellular contents, proteins, and leukocytes, stimulating the innate immune system to trigger an immune response with the excessive secretion of pro-inflammatory cytokines (FU; CHENG; WU, 2020).

The cytokine storm is responsible for tissue damage, and pulmonary and systemic inflammation, which leads to the development of several complications, among them, the best known is a severe acute respiratory syndrome (SARS) (PROMPETCHARA; KETLOY; PALAGA, 2020). In addition, ACE2 is involved in controlling homeostasis of vascular function in tissues such as the heart, lungs, brain and kidneys (SANTOS *et al*., 2018). Therefore, its involvement in COVID-19 also contributes to circulatory and vascular complications (COSTA *et al*., 2020).

After the failure in the therapeutic efficacy of hydroxychloroquine, lopinavir/ritonavir, and tocilizumab has been demonstrated, corticosteroids appear as a viable option. It was evidenced that the

treatment with dexamethasone at a dose of 6 mg/day for 10 days in patients with pneumonia, which requires oxygen therapy or mechanical ventilation, showed a reduction in mortality in 28 days, so the recommendation is valid (TORTOSA *et al*., 2020; SALINAS, 2020). In addition, due to the pandemic, the practice of self-medication has become increasing, mainly using medications that had only OFF LABEL use.

In this context, the present study aims to conduct a systematic review of the pharmacotherapy of steroidal anti-inflammatory drugs used in hospitalized patients with COVID-19.

2 METHODOLOGY

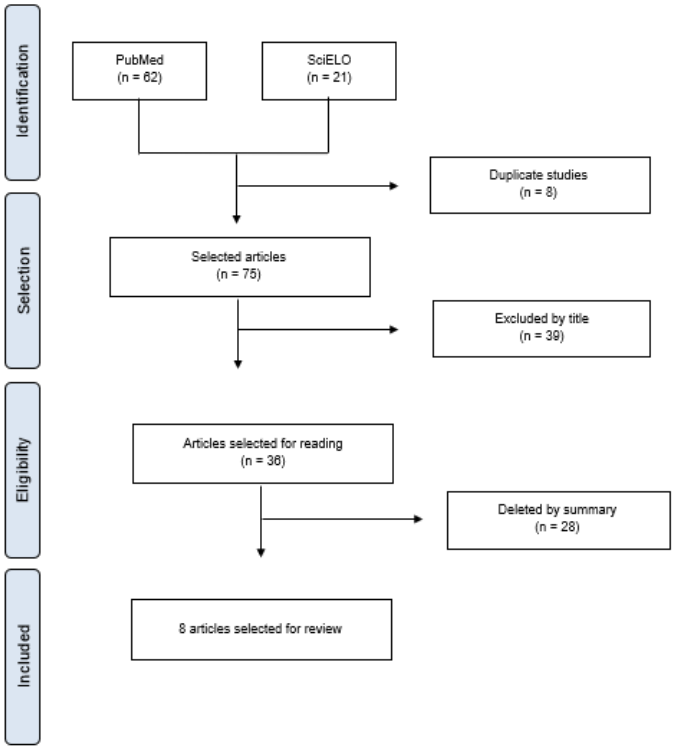
This is a descriptive, qualitative, and quantitative study of a systematic review of the pharmacotherapy of steroidal anti-inflammatory drugs used in hospitalized patients with COVID-19.

The study was conducted in January 2023, using the SCIELO and PUBMED databases. The keywords for the searches were: corticosteroid, SARS-CoV-2, therapy, corticosteroids, hospitalized and COVID-19 combined with the Boolean operators AND and OR.

The inclusion criteria were articles published from 2020 to 2022, in the languages Portuguese and English. Repeated articles, review studies, *preprints* and those that did not correlate with the objective of our study were disregarded.

After the selection of the articles that took place until February 15, 2023, at 20:16h and the complete reading of the works, the information was organized in a table containing the authors' names, title of the article, type of study, results and access link.

Figure 1 - flowchart of the process of search and selection of articles.



Source: authors, 2023.

3 FINDINGS

Of the 8 articles included in this review, 50% (n=4) are cohort studies (LIU *et al*., 2020; PINZÓN *et al*., 2021; PLESSIS *et al*., 2021; SANTOS et al., 2022), 37.5% (n=3) are clinical studies (EDALATIFARD *et al*., 2020; GHANEI *et al*., 2021; TOROGHI et al., 2021) and 12.5% (n=1) are observational studies (MUNÕZ *et al*., 2021).

As for the year of publication, 25% (n=2) are from 2020 (LIU *et al*., 2020; EDALATIFARD et al., 2020), 62.5% (n=5) are from 2021 (PINZÓN et al., 2021; MUNÕZ *et al*., 2021; PLESSIS *et al*., 2021; GHANEI *et al*., 2021; TOROGHI et al., 2021) and 12.5% (n=1) are from 2022 (SANTOS *et al*., 2022).

Regarding the country where the survey was conducted, 37.5% (n=3) were conducted in Iran (EDALATIFARD *et al*., 2020; GHANEI *et al*., 2021; TOROGHI *et al*., 2021). China (LIU et al., 2020), South Africa (PLESSIS et al., 2021), Spain (MUNÕZ et al., 2021), Colombia (PINZÓN et al., 2021) and Lisbon (SANTOS *et al*., 2022) had 12.5% (n=1) studies each.

The population samples visualized in the 8 studies ranged from 62 patients to 774 patients, with a mean age ranging from 53.5 to 64 years, 55.8% men and 44.1% women.

Among the comorbidities observed in each study, Diabetes Mellitus (DM) and hypertension were the most common, followed by cardiovascular events (LIU *et al*., 2020; GHANEI *et al*., 2021; TOROGHI *et al*., 2021; EDALATIFARD et al., 2020), Chronic Obstructive Pulmonary Disease (LIU *et al*., 2020; PINZÓN et al., 2021), dyslipidemia and obesity (MUNÕZ et al., 2021; SANTOS et al., 2022) or HIV (PLESSIS et al., 2021).

Regarding the severity of COVID-19, 50% (n=4) of the studies were done with patients who had the severe form of the disease (EDALATIFARD *et al*., 2020; LIU *et al*., 2020; PINZÓN et al., 2021, PLESSIS et al., 2021), 37.5% (n=3) moderate to severe (GHANEI *et al*., 2021; TOROGHI *et al*. 2021; MUNÕZ et al., 2021), and 12.5% (n=1) of the studies reported that 63.6% of the sample (49/77) evolved to the severe form of the disease (SANTOS *et al*., 2022). All studies were conducted with patients already hospitalized.

Among the corticosteroids included in the studies, those that presented the best clinical outcomes were methylprednisolone in 50% (n=4) of the studies with doses ranging from 80mg/day to 500mg/day during the range of 3 to 14 days of treatment. They were responsible for promoting the reduction of hospitalization and mortality rates (EDALATIFARD *et al*., 2020; PINZÓN et al., 2021), reduction of ICU admissions (PINZÓN *et al*., 2021; MUNÕZ et al., 2021) and the length of stay in the ICU avoiding episodes of sepsis (PLESSIS et al., 2021), followed by prednisolone in 12.5% (n=1) of studies with a dose of 25mg/day for 5 days of treatment that was associated with a significantly shorter length of hospital stay when compared to other therapies (GHANEI *et al* ., 2021). However, 12.5% of the studies (n=1) associate methylprednisolone corticosteroid therapy (MTP) followed by prednisolone with the worst clinical outcomes, which include the highest mortality rates. One possibility of justification is the administration of doses above 200mg in less than 3 days of hospitalization even with 6 days of duration of treatment (LIU *et*

al., 2020). Another corticosteroid tested was dexamethasone (DXM) in 25% (n=2) of the studies. One study sought to assess clinical improvement with different doses. The group that received 8mg of dexamethasone per day had better clinical outcomes (TOROGHI *et al*., 2021). However, in the other study that consisted of presenting the clinical impact of COVID-19 in a cohort of kidney transplant recipients, to adjust its immunosuppression after the diagnosis of COVID-19 it was necessary to increase the dose of corticosteroid therapy in 81.6% of those already hospitalized (40/49) and included dexamethasone in the therapy of 57.1% patients (28/49). As an outcome, mortality reached 20% (n=10) of hospitalized patients and Acute Kidney Injury reached 49% (n=24) (SANTOS *et al*., 2022).

Table 1. Relationship of corticosteroid therapy in hospitalized patients with COVID-19 from 2020 to 2022.

Author(s)	Title	Type of Study	Findings	Link
LIU *et al*., 2020	Corticosteroid treatment in severe COVID-19 patients with acute respiratory distress syndrome	Observational cohort	Patients who received corticosteroids (methylprednisolone and prednisolone) were more likely to develop the worst clinical outcomes. High doses of corticosteroids (greater than 200mg) and early onset were associated with higher mortality rates at 28 days even with a short duration of treatment.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7685724/
EDALATIFARD *et al*., 2020	Intravenous methylprednisolone pulse as a treatment for hospitalized severe COVID-19 patients: results from a randomized controlled clinical trial	Randomized clinical trial	Methylprednisolone at a dose of 250mg per day was responsible for the improvement of the clinical picture with a considerably higher survival rate and significantly lower mortality rate compared to the group receiving standard treatment.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7758541/
TOROGHI *et al*., 2021	Comparing efficacy and safety of different doses of dexamethasone in the treatment of COVID-19: a three-arm randomized clinical trial	Randomized clinical trial	The clinical outcomes of dexamethasone pharmacotherapy were significantly better in patients who received low doses (8mg daily) compared to those who received high	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8627167/

			doses (8mg three times daily). In addition, there was an increase in the number of adverse events, worsening of survival, and higher rates of deaths in patients with high doses of dexamethasone.	
GHANEI *et al.*, 2021	The efficacy of corticosteroids therapy in patients with moderate to severe SARS-CoV-2 infection: a multicenter, randomized, open-label trial.	Randomized clinical trial	The regimen with low-dose prednisolone (25 mg per day) for 5 days was associated with a shorter significant length of hospital stay when compared to groups with other pharmacotherapies.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8441037/
PLESSIS *et al.*, 2021	Corticosteroids in critical COVID-19: Are all corticosteroids equal?	Observational cohort	The methylprednisolone-treated group 40 mg 2 times a day for 10-14 days tend to have a shorter ICU stay and fewer episodes of sepsis when compared to the hydrocortisone and dexamethasone groups.	http://www.scielo.org.za/scielo.php?script=sci_arttext&pid=S0256-95742021000600015&lang=pt
MUNÕZ *et al.*, 2021	High-dose versus low-dose corticosteroid treatment strategy in patients hospitalized with COVID-19: effect on ICU admission rate	Observational study	Patients who received 125-250 mg of per day for 3 days of methylprednisolone entered the ICU less compared to the group who received dexamethasone 6mg per day.	https://scielo.isciii.es/scielo.php?script=sci_arttext&pid=S1699-714X2021000100003&lang=pt.
PINZÓN *et al.*, 2021	Dexamethasone vs methylprednisolone high dose for Covid-19 pneumonia	Ambispective cohort	Treatment with 250-500mg methylprednisolone for three consecutive days of prednisone 50mg for 14 days showed a considerable reduction in recovery time, less need for ICU transfer, decreased laboratory markers, and reduced mortality compared to the group that	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8148307/

			received 6mg of dexamethasone for seven to ten days.	
SANTOS *et al.*, 2022	SARS-CoV-2 infection in kidney transplant recipients: clinical impact and outcomes - a single center experience	Observational cohort	The management of immunosuppression in 95.9% of hospitalized patients (47/49) included, among other changes, the increase in corticosteroid dose in 81.6% of patients (n=40) and 57.1% of patients (n=28) dexamethasone was used. Mortality reached 20% among hospitalized patients (n = 10) and Acute Kidney Injury reached 49% (n = 24).	https://www.scielo.br/j/jbn/a/9FjMSCDg48YLXtpZLzhH5mB/?lang=en

Source: authors, 2023.

4 DISCUSSION

During COVID-19 disease it can be observed that the most affected system is the respiratory system and due to the lung damage caused by a cascade of inflammatory mediators in response to inflammation, it is justified to investigate new corticosteroid therapies (SAGASTI *et al.*, 2021). Given the good results in randomized trials, corticosteroids, also known as IEAs, have been widely used for the treatment of severe acute respiratory syndrome (ARDS) in COVID-19 (STERNE *et al.*, 2020). Anti-inflammatory and immunosuppressive effects are induced by the suppression of the synthesis of inflammatory mediators (SAGASTI *et al.*, 2021).

They have the characteristic of crossing the lipoprotein membrane of cells and binding to cytosolic receptors exerting their effect during interaction with DNA by binding to "glucocorticoid response elements" (GRE), which in turn induce transcription most often of various genes encoding some proteins, such as lip curtain, vasocurtain, endonuclease, ribonucleases, endopeptidases, somatostatin, migration inhibitor factor, receptors for hormones and cytokines - this mechanism is known as genomic action - or interact with proteins involved in transcription, in this mechanism, there is no binding with GREs because in the course there is an inhibition of the transcription of cytokines (IL-1, IL-2, IL-6, IL-11, TNF-a and chemokines), nitric oxide synthetase, cyclooxygenase, phospholipase A-2, elastase, collagenase, plasminogen activator and also inhibit the cyclooxygenase 2 coding gene (COX-2) - non-genomic, specific or nonspecific action. Another mechanism that may justify the rapid action of pulse corticosteroid therapy, and therefore its use, are the effects involved in respiration, protein synthesis, sodium (Na+), potassium (K+), adenosine triphosphatase enzyme (ATPase) and calcium enzyme ATPase (Ca2+-ATPase) in the cells

present in the thymus, a lymphatic organ of the immune system, thymocytes (BUTTGEREIT; BRAND; BRUTMESTER, 1999). They act on inflammation through the lipoxygenase pathway synthesizing proteins responsible for the inactivation of phospholipase A2, such as lip curtain-1, and this action leads to the inhibition of arachidonic acid and leukotrienes, prostaglandins, and platelet-activating factors that are present in the inflammatory process are not produced (DAMIANI *et al*., 2001).

During the SARS-CoV-2 replication cycle, adhesion begins due to the interaction of the virus glycoprotein S with the cell receptor, the angiotensin-converting enzyme 2 (ACE-2) located in the human cell. This glycoprotein S has conformations divided into regions, and two of them are the S2 subunit and the S1 subunit which has a receptor binding domain (RBD). The S1/S2 subunits are catalyzed by the enzyme furin which changes the conformation of the S2 subunit allowing the interaction of RBD with the ECA-2 receptor and concluding the viral penetration process. The denudation stage is characterized by the release of its genetic material (RNA) into the cytoplasm of the host cell initiating viral replication (LIU *et al*., 2020; SHANG *et al*., 2020; ALEXANDRE *et al*., 2020; WALLS *et al.*, 2020)

There is tropism between the virus and the alveolar epithelial cells that express ACE-2 and the incubation period can last from two to seven days up to two weeks. The infection triggers an inflammatory immune response mediated by excessive chemokines and pro-inflammatory cytokines due to tissue damage (HOFFMANN *et al.* , 2020; GIAMARELLOS-BOURBOU *et al.* , 2020) . Interleukin 6 (IL-6) is the main cause of the "cytokine storm" resulting in several clinical changes, such as increased vascular permeability, plasma leakage and coagulation disorders, resulting in SARS and/or multiple organ failure (YE; WANG; MAO, 2020). Symptoms can range from a cold to severe pneumonia, affecting people of all age groups, however, the average age most susceptible is from 47 to 63 years. Comorbidities (DM, SAH, heart disease, kidney disease, neoplasms, immunosuppression, among others) associated with age may confer a worse prognosis of the disease, and therefore corticosteroid therapy is an alternative already observed and used. Some manifested symptoms are fever, myalgia, cough, dyspnea, lack of appetite, and diarrhea among others (LOUREIRO *et al*., 2020)

The clinical efficacy of corticosteroid therapy depends on the dose, time of onset, route of administration, duration, and dose reduction. Steroid doses equivalent to prednisone less than 7.5 mg/day produce glucocorticoid receptor saturation of less than 40% with mild adverse effects. Intermediate doses equivalent to 7.5-30 mg/day of prednisone cause saturation in more than 50% of recipients. High doses equivalent to 30-100 mg/day of prednisone almost completely saturate glucocorticoid receptors and thus have the potential to produce serious adverse effects if used for an extended period. Very high doses (prednisone equivalent to > 100 mg/day) or pulse therapy (prednisone equivalent to ≥ 250 mg/day, for 1 to 5 days) saturate all recipients (SAGASTI *et al.*, 2021).

Therefore, most studies that compared groups with intravenous methylprednisolone corticosteroid therapy and other treatments had excellent clinical outcomes (EDALATIFARD *et al.* , 2020, PINZÓN et al., 2021, MUNÕZ et al., 2021, PLESSIS *et al*., 2021). According to the classification of doses of

SAGASTI et al., 2021 and the equivalence with prednisone, the doses of methylprednisolone used in the studies cited in common were very high (125-500mg) during an average time of 3 days except for PLESSIS *et al.* , 2021 that used high doses of methylprednisolone (80mg/day) for 10 to 14 days. The conversion data were obtained through a steroid converter calculator from Rapid Critical Care Consult (PITARCH, 2011). In contrast, the study by LIU *et al.* (2020) showed the worst clinical outcomes in a group in which 96.8% were treated with 40mg-80mg/day of methylprednisolone and, 7.8% had the steroid replaced by 50mg-100mg/day of prednisolone.

According to LIU *et al.* (2020), the study was conducted with 774 patients with a mean age of 64 years. They were divided into two groups, the first with 409 patients who received corticosteroids and the second with 365 who did not receive corticosteroids. As a clinical outcome, mortality reached a total of 38% of patients, those who received corticosteroid therapy had 44.3% fatalities in 28 days of hospitalization, being the highest mortality rate compared to the control. Other clinical outcomes included the highest probability of developing myocardial injury (15.6% versus 10.4%), acute liver injury (18.3% versus 9.9%), and shock (22.0% *versus* 12.6%) that may be related to the existing comorbidities of chronic heart disease, chronic liver disease, stroke, among others. Compared to the control group, patients with corticosteroid therapy had a higher need for ICU admission (47.7% versus 22.5%), longer hospital stay (median of 15 days versus 13 days) and longer ICU time (median 5 days *versus* 2 days). RNA clearance of SARS-CoV-2 is associated with corticosteroid use. The delay in RNA clearance by early-onset corticosteroid therapy did not significantly influence clearance. In addition, understanding the viral clearance profile is important to consider a retest plan at discharge and establish an end to social isolation for patients with COVID-19, due to the greater destruction of viral replication (CARMO *et al. 2020).*

The study by EDALATIFARD *et al.* (2020), presents that 62 eligible patients who had the severe form of the disease, with a mean age of 58.5 years, were randomized and divided into two groups: 34 patients in the standard treatment group with intravenous methylprednisolone of 250mg for 3 days and 28 patients in the standard treatment group. All patients had as main outcomes clinical improvement, hospital discharge and death. Some clinical parameters were analyzed at admission, on the 3rd day of treatment and at discharge, which had as main results the considerable increase in respiratory and heart rate levels in the first group and improvement of symptoms during treatment and discharge. Gastrointestinal symptoms, myalgia, chest pain and cough were associated, but after the 3rd day of treatment, there was a clinical improvement. They manifested greater benefits in clinical outcomes, among them can be mentioned the shorter time for clinical improvement (11.8 days versus 16.4 days); reduction of the time to discharge (11.6 days versus 17.6 days); significantly higher recovery (94.1% versus 57.1%); lower mortality rate (5.9% *versus* 42.9%); longer survival time; among patients who received noninvasive ventilation, reservoir mask or nasal cannula support, the incidence of mortality was significantly lower (7.7% versus 60%), (8.3% versus 57.1%), (0% *versus* 22%), respectively.

In the previous study, most patients had pulmonary involvement and all were receiving oxygen support. After 3 days of treatment, 55.8% of the patients (19/34) presented improvement in oxygen support and only 8.8% (3/34) presented worsening, while in the second group, 21.4% of the patients (6/28) presented improvement and 50% (14/28) had worsened. Between the beginning and end of treatment, it was observed that two patients in the first group presented infection and edema as adverse events. Finally, most patients in this same group required insulin due to diabetes and being overweight. Corticosteroids can increase susceptibility to infections mainly with increased doses, as well as contribute to the increase of glucose in the bloodstream, worsening pre-existing DM (Methylprednisolone Drug Leaflet). Chest pain and cough remained the same in both groups. After hospital discharge, two patients in the second group remained with gastrointestinal symptoms and myalgia. On the other hand, 18.8% of each group continued to present a cough 1 week after discharge (EDALATIFARD *et al.*, 2020).

The cohort of PLESSIS *et al*., (2021) was conducted with 242 ICU patients, with a mean age of 53 years and 58.2% men presenting hypertension (53.7%) and DM (50.8%) as the main comorbidities. The present study divided patients into three groups, group (I) hydrocortisone 100 -200 mg every 6 hours with 88 patients, (II) methylprednisolone 40 mg every 12 hours with 46 patients and (III) dexamethasone 8 mg once daily with 108 patients. In all groups, the drug enoxaparin 1mg/kg was used by most patients twice a day. The group that received the methylprednisolone therapeutic plan achieved a shorter ICU stay, fewer episodes of nosocomial sepsis, and a higher survival rate when compared to other groups. No other significant clinical outcomes were observed between the groups.

The study by MUNÕZ *et al.* (2021) of retrospective and observational character related the therapy with methylprednisolone 250 mg/day and dexamethasone 6mg/day evaluated the influence on the ICU admission rate. The study includes 127 patients, of which 82 (64.6%) were men. Patients were divided into two treatment groups, one with the use of dexamethasone with a mean age of 52 years and the other, with methylprednisolone with a mean age of 61 years. The existing comorbidities were: type II DM, SAH, obesity and dyslipidemia. In addition, 12.4% of the patients who used high-dose methylprednisolone were subsequently admitted to the ICU, compared to 30% of the patients in the group treated with low-dose dexamethasone. The author puts as predictors of hospitalization age over 50 years, gender, low dose of dexamethasone and serum levels of IL-6 higher than the normal rate. Given the results related to the rate of ICU admission with the use of dexamethasone, they proposed that this high-dose therapy for the treatment of COVID-19 infection could be a more effective strategy since corticosteroids can act on other pathways combining the effects, but the highlight within the study was the high dose of methylprednisolone. Other studies have specified the benefits of corticosteroid pulse therapies in influencing the mortality rate in severe forms of COVID-19 (EDALATIFARD *et al*., 2020; RUIZ-IRASTORZA *et al*., 2020).

The ambispective cohort of PINZÓN *et al.* (2021) reached a total of 216 patients, 58.8% men with an average age of 64 years, hospitalized with severe SARS-CoV-2 pneumonia. The main comorbidities affected by the patients were: HAS, DM, COPD, obesity and heart disease. Patients were divided into two

different corticosteroid groups, 111 patients using dexamethasone 6mg/day for 10 days and 105 patients using methylprednisolone 500mg/day for 3 days, followed by prednisone 50 mg orally for the entire treatment for 14 days. Colchicine was prescribed to 95.2% of patients in the methylprednisolone group and 79.3% in the dexamethasone group. During treatment, it was observed that the dexamethasone-treated group had a considerable worsening aggravating ARDS, compared to the second group. Other clinical outcomes observed were ICU admission and mortality rate that were less observed in the methylprednisolone-treated group (4.8% versus 14.4%) and (9.5% *versus* 17.1%), respectively, along with the shorter time for clinical improvement that lasted on average 3 days compared to the dexamethasone group that took an average of 6 days. According to the performance analysis of the study tracing a variable of the prescribed colchicine drug, it was seen that patients who received this drug added to the corticosteroid had better instant recovery. Thus, the treatment of severe pneumonia in COVID-19 achieved a better outcome with high doses of methylprednisolone associated with prednisone using biochemical markers and recovery times for comparison of the treatments addressed in the study.

The high mortality rate can be justified by the presence of severe pneumonia and its rapid evolution, usually these pathologies require high doses of corticosteroids. YANG *et al*., (2020) evaluated 175 patients with severe COVID-19 using methylprednisolone as a protective factor against progression from severe disease to critical disease, in short the group with the best clinical outcome were those who were under 65 years of age treated with methylprednisolone. In another study, SCARSI *et al*. (2020), on colchicine treatment, it is described that colchicine contributed to better survival rates compared to standard treatment in patients with COVID-19 pneumonia.

The study by TOROGHI *et al*., (2021), to study the efficacy of different doses of dexamethasone against COVID-19, involved 133 hospitalized patients diagnosed with moderate to severe COVID-19 who required supplemental oxygen, 60.1% were men with an average age of 58 years and main comorbidities DM and SAH followed by ischemic heart disease and hypothyroidism. The therapeutic plan used was corticosteroid therapy with dexamethasone in different doses. The first group received dexamethasone 8mg once daily for an average of 4 days, the second received dexamethasone 8mg twice daily for an average of 5 days, and the third 8mg three times a day for an average of 5 days. The regimen was initiated within the first 24 hours of hospitalization up to 10 days or discharge. Follow-up continued for up to 60 days after discharge through phone calls. The intuition of the present study was to consider the high-dose group as a reference and compare the other groups to this one. However, as a result of corticosteroid therapy, it was observed that the first group with a low dose of dexamethasone of 8mg per day was responsible for the best clinical outcomes, which were related to a significant reduction in serum CRP levels; shorter time to improve clinical response and to achieve peripheral oxygen saturation (SpO2) at values above 93%; less need for mechanical ventilation; reduction of the time of hospitalization and ICU stay; reduction of the mortality rate. The shorter duration of use of mechanical ventilation and the need for ICU admission were similar in the low and intermediate-dose groups. Adverse effects during hospitalization were more present

in the intermediate and high dose groups compared to the low-dose group, with leukocytosis and hyperglycemia being the most common findings. Bacterial infections were more present in the high-dose group. According to TAMEZ-PÉREZ *et al*., (2015), serum glucose increase is dose-dependent on corticosteroid therapy. With results close to the RECOVERY, controlled and open-label study with 6,425 patients hospitalized for COVID-19 with an average age of 66.1 years, the authors state that dexamethasone 6mg once daily for 10 days reduced mortality by one-third the mortality among patients using invasive mechanical ventilation compared to the group that received usual care, therefore, the mortality rate is represented by 29.3% versus 41.4% and the evolution of patients using oxygen without invasive mechanical ventilation represents 23.3% *versus* 26.2%. One of the adverse effects observed is also hyperglycemia (HORBY *et al*., 2021). Both studies showed that the lower the dose the better the clinical responses, but it is possible to verify that in one of them doses above the average stipulated by ANVISA were used, which is 0.75 to 15 mg per day (EMS, 2021), so a dose above 15mg can bring toxicity and aggravate the patient's condition.

The World Health Organization (WHO) considers corticosteroid therapy as part of the treatment of critically ill patients with COVID-19 and recommends the use of 6mg of oral or intravenous dexamethasone or 50mg of hydrocortisone through the intravenous route every 8 hours for 7 to 10 days, however, the recommendation is not considered for non-severe patients (WHO, 2021).

The randomized clinical trial of GHANEI *et al.* , (2021) aimed to observe the efficacy of corticosteroid therapy in 336 patients, with a mean age of 58.1 years and 51.5% men, with moderate to severe SARS-CoV-2. The study was conducted with hospitalized patients, aged 16 years, with positivity in polymerase chain reaction (PCR) and SpO2 lower than 94%. To conduct the study, three groups of therapeutic plan with initial duration of 5 days extended to 10 days were divided based on clinical responses and discharge in the first two groups. The first group was added prednisolone 25mg to another therapeutic plan. The other two groups received more oral and intravenous steroids in the course of treatment compared to the first, however, this one received more steroid pulse therapy. There was no significant difference in the outcomes of reduced mortality rate and ICU admissions between the groups, but the group with corticosteroid therapy was responsible for the shortest significant length of hospital stay. Finally, the therapeutic regimen of the other two groups did not differ in any of the established outcomes. In parallel to the study by BARTOLETTI *et al.*, (2021), it was reported that the dose >0.5mg/kg daily of prednisone had no significant improvement in the mortality rate in patients with COVID-19.

The prospective and observational single-center cohort of renal transplant recipients by SANTOS *et al*. (2022) demonstrated that of the 49 patients hospitalized for COVID-19, 53.2% of men with an average age of 61 years containing SAH, DM, dyslipidemia as the main comorbidities, 18.4% were admitted to the ICU. 95.9% of the patients had their immunosuppression adjusted after diagnosis, while corticosteroid therapy was intensified in 81.6% of the patients. 57.1% of the patients used dexamethasone and 34.7% treated with dexamethasone and redeliver 200mg on the first day followed by 100mg for 4 days. There is

no information on the dose of dexamethasone used. In 49% of the patients, there was acute kidney injury (AKI) and mortality was present in 20.4% of the patients. The mortality rate was more frequent in patients receiving kidney transplants and treated only with dexamethasone, with age being the impacting factor. According to the study authors, it was observed that non-survivors were older. Comorbidities seem to influence severity and clinical outcomes. Also people who had kidney transplantation had greater susceptibility to dehydration, nephrotoxicity and hemodynamic instability which may justify the development of AKI.

5 CONCLUSION

This systematic review shows important findings on the use of corticosteroids for the treatment of COVID-19. From the analysis of randomized clinical trials, it is noticeable the therapeutic benefit for the control of moderate and severe cases, caused by the so-called "cytokine storm" that occurred in the body of human beings infected by SARS-CoV-2.

In hospitalized patients, methylprednisolone, prednisolone and dexamethasone were responsible for promoting the reduction of hospitalization and mortality, reduction of ICU admissions and length of stay in the ICU avoiding episodes of sepsis. Although, when associated increased the mortality rate. However, we suggest further studies to elucidate the potential of corticosteroids in the treatment of COVID-19.

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