SYSTEMATIC REVIEW

In Patients Admitted to ICU with SARS-CoV-2 Infection, is Dexamethasone Superior to Standard Care in Improving Mortality? A Systematic Review of Evidence to Date

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Abstract

Introduction: Dexamethasone is a potent broad-spectrum corticosteroid that decreases the transcription of pro-inflammatory cytokines, whilst simultaneously increasing the transcription of anti-inflammatory cytokines. The cytokine storm that is central to the pathogenesis of acute respiratory distress syndrome (ARDS) and multi-organ failure is seen in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) related deaths. The objective of the study was to systematically review the use of dexamethasone for COVID-19 in adult ICU patients and to ascertain if there was a survival benefit compared to standard care (SC) alone.

Methods: A literature search of two databases, EMBASE and PubMed, was conducted using the terms "COVID-19", "Dexamethasone", and "ICU". The search was limited to studies published in the English language. The PRISMA guidelines were used to guide our search methodology.

Results: The database search identified 59 articles. Of these, two duplicates were discarded, and 57 studies were screened. 54 of these publications were deemed irrelevant based on the inclusion and exclusion criteria. Three were forwarded for full text review and met inclusion and exclusion criteria on full-text review. All three were deemed eligible. The selected studies consisted of two randomised controlled trials (RCTs) and one case series report. The results from the three papers were unanimous in their conclusion that dexamethasone was superior to SC in the treatment of patients admitted to ICU with SARS-CoV-2. There was also a shorter duration of hospitalisation seen in the patient group treated with dexamethasone.

Conclusion: Our systematic review found that dexamethasone was superior to SC in patients admitted to the ICU with SARS-CoV-2 infection. However, administration of dexamethasone to patients not on respiratory support resulted in a higher incidence of death, compared to SC.

Keywords: COVID-19, Dexamethasone, Intensive care unit

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly transmissible airborne virus that has led to the COVID-19 global pandemic due to its rapid spread via human-to-human transmission. The main pathophysiological findings of COVID-19 include diffuse alveolar damage, acute pneumonia with opacity clearly seen on a chest radiographic image and infiltration of inflammatory cells. The clinical course of this disease is highly heterogeneous, ranging from an asymptomatic presentation to varying degrees of hypoxia, acute respiratory distress syndrome (ARDS), and ultimately death in a considerable number with an infection fatality rate of 0.68% across populations[1]. The mortality rate is higher in those with comorbid conditions, namely diabetes, hypertension, heart failure, and obesity[2].

Most COVID-19 positive patients in the intensive care unit (ICU) require supplemental oxygen up to, and including, prolonged invasive mechanical ventilation[3]. This is due to persistent hypoxaemia and a reduced ventilation-perfusion ratio secondary to alveolar damage. Persistent hypoxaemia can induce a cascade of multi-organ failure if the precipitating inflammation is not managed[4]. Dexamethasone is a potent broad-spectrum corticosteroid that works by decreasing the gene transcription of pro-inflammatory cytokines while increasing the transcription of anti-inflammatory cytokines, therefore reducing the likelihood of the cytokine storm syndrome that can lead to ARDS and multi-organ failure seen in COVID-19 associated deaths[5]. The RECOVERY trial selected dexamethasone as the corticosteroid of choice that reduced mortality in SARS-CoV-2 patients with ventilatory support when administered for 10 days[6]. Therefore, this study will focus on dexamethasone, specifically in severe cases of COVID-19 seen in ICU patients.

The objective of this study is to perform a systematic review of the published literature to date to ascertain if dexamethasone provides a survival benefit as compared to standard care (SC) alone for patients with SARS-CoV-2 infection in the ICU setting. SC for SARS-CoV-2 treatment involves a combination of antivirals and immune modulators[1]. Antivirals commonly used include lopinavir-ritonavir, ribavirin, and hydroxychloroquine. Immune modulators included tocilizumab and convalescent plasma. Other clinical pharmacological interventions included a variety of antibiotics (meropenem, piperacillin/tazobactam, doxycycline, linezolid, and azithromycin) and anticoagulants, likely used as part of venous thromboembolism prophylaxis.

There have been multiple trials carried out over the last year examining the effect of dexamethasone on these patients. Our objective is to compile these findings and review whether the drug is effective and whether there have been any complications or specific patient groups where the drug has had adverse effects.

Methods

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) protocol[7] as shown in **Figure 1**.

Information Sources and Search Strategy

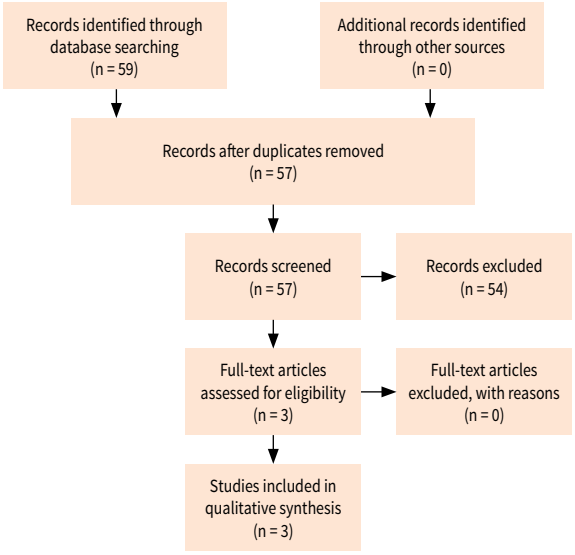
Publications from both EMBASE and PubMed databases were screened. The search parameters used included: "COVID-19", "Dexamethasone" and "ICU" with synonyms included. The chosen population were adult ICU patients with COVID-19 and the chosen intervention was exclusively dexamethasone.

Eligibility Criteria

Exclusion criteria included abstract only papers, non-English papers, and animal studies. The inclusion criteria were specific to ensure a representative sample. They were English language only, full text availability and human trials only. The type of papers included were randomised clinical trials (RCTs), systematic reviews, case studies, cohort analysis studies, meta-analyses, and multicentre and observational studies. The timeline for studies included was from December 2019, when COVID-19 just emerged, to the date the search took place.

The combined database search results were then reviewed. The remaining titles and abstracts were independently screened by a reviewer without consideration for the results. During this process, any article that did not meet our inclusion criteria was excluded. Deduplication was performed using "Covidence", a software management platform for systematic reviews[8].

Figure 1. **PRISMA Flow Diagram**



Results

The database searches yielded 57 results following deduplication. After review of titles and abstracts by a single reviewer, three studies remained to be included in the final study. These were then analysed, and data was extracted, compared, and compiled (**Table 1** & **Table 2**). These were: an RCT by Horby et al. in which the baseline was all hospitalised patients with confirmed SARS-CoV-2, including both ventilated and non-ventilated patients[9]; an RCT by Tomazini et al. in which all patients, 63% of whom were male, were receiving mechanical ventilation after a laboratory diagnosis of SARS-CoV-2 within 48 hours of meeting the criteria for moderate to severe ARDS according to the Berlin definition[10,11], and a case series report by Hassan et al. which included five patients that had acute lung injury (ALI) scores ranging from 1.25–3[12].

Of the three papers analysed, two were RCTs and one was a case series. As per the Oxford 2011 Levels of Evidence, the two clinical trials were designated as level 1b evidence, and the case series was designated as level 4 evidence. The first RCT was carried out in the United Kingdom[9] and the second was from Brazil[10], while the case series originated from Bahrain[12]. The average age in the RCTs was 65.8 years while it was 56.6 in the case series. Patients were predominantly male in the RCTs while all patients in the case series were female. The inclusion criteria for the RCTs varied but both included patients diagnosed with COVID-19 on invasive mechanical ventilation. Patient comorbidities were explicitly mentioned in one RCT[9] and in the case series[11], but not in the second RCT[10]. The dosage of dexamethasone used varied between the three papers (6mg–20mg) but were all administered once daily and intravenously. Similarly, SC varied greatly between the three papers and varied for each individual patient. In the paper by Horby et al. SC consisted of hydroxychloroquine, lopinavir-ritonavir, azithromycin, tocilizumab, and convalescent plasma[9]. In the paper by Tomazini et al. only one patient received lopinavir-ritonavir treatment, and the use of antibiotics and haemodynamic management varied between patients and were at the discretion of the ICU staff[10]. The SC in the paper by Hassan et al. also varied by patient: for

Table 1. **Summary of Papers Reviewed (RCTs)**

Title of Paper, Author, Year, Country of Origin	a) Sample Size (n) b) Mean Age c) % Male	Inclusion/ Eligibility	a) Oxygen/ Ventilation b) Median days since onset of symptoms/ hospitalization	Comorbidities	Dexamethasone (DM) Dose and Route of Administration	Comparator/Standard Care (SC)	Primary Outcome	Secondary Outcomes	Secondary Outcome Results
Dexamethasone (DM) in Hospitalized Patients with Covid-19 – Preliminary Report, Horby et al. 2020, United Kingdom[9]	a) n=6425 (DM=2104, SC=4321) b) 66.1 +/- 15.7 c) 64%	Hospitalised patients with suspected/ laboratory confirmed COVID-19 No age limit	a) 16% invasive mechanical ventilation/ extracorporeal membrane oxygenation, 60% oxygen only (with/ without non-invasive ventilation), 24% neither b) DM group: 8 days since onset of symptoms, 2 days since hospitalisation, SC group: 9 days since onset of symptoms, 2 days since hospitalization	Diabetes 24% Heart disease 27% Chronic lung disease 21%	Standard care + IV DM 6mg OD up to 10 days/ hospital discharge if sooner	Randomisation of patients to receive hydroxychloroquine, lopinavir-ritonavir, azithromycin, tocilizumab, convalescent plasma	All-cause mortality within 28 days of randomisation	Time until discharge from hospital Receipt of invasive mechanical ventilation Death (preceding 2 outcomes only apply if not receiving ventilation)	DM group shorter duration of hospitalization (median 12 days vs 13 days) and greater probability of discharge alive within 28 days (67.2% DM vs 63.5% SC) (RR 1.10) (95% CI 1.03-1.17) Patients who progressed to requirement of invasive mechanical ventilation/ subsequent death lower in DM group (25.6% vs 27.3%) (RR 0.92) (95% CI 0.84-1.01)
Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients with Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomised Clinical Trial, Tomazini et al. 2020, Brazil[10]	a) n=299 (DM=151, SC=148) b) 61+/- 14 c) 63%	Confirmed or suspected COVID-19 infection At least 18 years old Receiving mechanical ventilation within 48 hours of meeting criteria for moderate to severe ARDS (using Berlin Definition) with PaO2:FiO2 ratio of 200 or less	Mechanical ventilation was an inclusion criterion	Not explicitly stated	Standard care + IV DM 20mg OD for 5 days followed by IV DM 10mg for 5 days/ ICU discharge if sooner	1 patient received lopinavir-ritonavir treatment. Other therapeutic strategies such as tocilizumab and convalescent plasma were limited and not widely available 52 patients (35.1%) received at least 1 dose of corticosteroids, of whom 38 (73.1%) had other established clinical indications for corticosteroid use. The use of corticosteroids in 14 patients (9.4%) was considered a protocol deviation All clinical interventions, such as use of antibiotics, ventilatory strategy, laboratory testing, and hemodynamic management were left at the discretion of the ICU team for both groups	Ventilator-free days during the first 28 days, which was defined as being alive and free from mechanical ventilation	All-cause mortality at 28 days Clinical status of patients at day 15 using a 6-point ordinal scale (ranging from 1, not hospitalized to 6, death) ICU-free days during the first 28 days Mechanical ventilation duration at 28 days Sequential Organ Failure Assessment (SOFA) scores (range, 0-24, with higher scores indicating greater organ dysfunction) at 48 hours, 72 hours, and 7 days	There was no significant difference in the prespecified secondary outcomes of: all-cause mortality at 28 days (56.3% in the dexamethasone group vs 61.5% the standard care group; hazard ratio, 0.97; 95% CI, 0.72 to 1.31; P=.85); and ICU-free days during the first 28 days, (mean, 2.1; 95% CI, 1.0 to 4.5 days for the dexamethasone group vs mean, 2.0; 95% CI, 0.8 to 4.2 days for the standard care group; difference, 0.28; 95% CI, −0.49 to 1.02; P=.50) Mechanical ventilation duration at 28 days (12.5; 95% CI, 11.2 to 13.8 days for the dexamethasone group vs 13.9, 95% CI, 12.7 to 15.1 days for the standard care group; difference, −1.54; 95% CI, −3.24 to −0.12; P=.11) 6-point ordinal scale at 15 days (median, 5; IQR, 3-6 for the dexamethasone group vs median, 5; IQR, 5-6 for standard care group; odds ratio [OR], 0.66; 95% CI, 0.39 to 1.13; P=.07) At 7 days, patients in the dexamethasone group had a mean SOFA score of 6.1 (95% CI, 5.5-6.7) vs 7.5 (95% CI, 6.9-8.1) in the standard care group (difference, −1.16; 95% CI, −1.94 to −0.38; P=.004)

Abbreviations: RR = Respiratory Rate

Table 2. **Summary of Papers Reviewed (Case Report)**

Title of Paper, Author, Year, Country of Origin	Case	Age	Gender	Comorbidities	Date Diagnosed	ALI Score	Standard Care	Dexamethasone Commenced (Dose)	Labs
Dexamethasone in Severe COVID-19 Infection: A Case Series, Hassan et al. 2020, Bahrain[12]	1	38	F	Down syndrome	June 12	2.5	Lopinavir, Ritonavir, ribavirin, meropenem, LMWH, linezolid, doxycycline (June 12)	June 18 (IV 6mg OD)	C-reactive protein (CRP) declined from 227.6 to 17.5 mg/L; D-dimer (DD) from 21.55 to 4.94 µg/ml; lactate dehydrogenase (LDH) from 577 to 486 U/L; interleukin-6 (IL-6) from 15.2 to 11.39 pg/ml; and total white blood cell (WBC) count from 13.14 to 8.62 × 109/L
	2	44	F	Hypertension, Obesity	June 13	3	Lopinavir/ritonavir, ribavirin and interferon-β (June 13) Convalescent plasma (June 16)	June 18 (IV 6mg OD)	CRP declined from 69.4 to 14.4 mg/L; DD from 6.7 to 4.3 µg/ml; and IL-6 from 16.13 to 3.56 pg/ml.
	3	85	F	Hypertension, Hyperlipidaemia, Hypothyroidism	June 21	2.5	Lopinavir/ritonavir, interferon-β, linezolid, meropenem and enoxaparin (June 21) Convalescent plasma therapy x2, (June 26)	June 26 (IV 6mg OD)	CRP continued to increase from 31.2 to 276.8 mg/L; DD decreased from 14.3 to 3.16 µg/ml; LDH increased from 312 to 539 U/L; and WBC increased 12.1 to 14.3 × 109/L.
	4	45	F	None	June 19	3	Ribavirin, enoxaparin, piperacillin/tazobactam, doxycycline, convalescent plasma therapy x2	Not recorded (IV 6mg OD)	CRP declined from 152 to 32.9 mg/L; and LDH changed from 535 to 540 U/L
	5	71	F	Not explicitly stated	June 25	1.25	Lopinavir/ritonavir, interferon-β, ribavirin, piperacillin, doxycycline, and enoxaparin	Not recorded (IV 6mg OD)	CRP declined from 70.97 to 30.6mg/L

example, some patients received interferon therapy, and one patient received two courses of convalescent plasma therapy, which the other patients did not receive[12].

The three papers collectively showed that dexamethasone was superior to SC in the treatment of patients admitted to the ICU with SARS-CoV-2 infection. Horby et al. showed that the incidence of death was significantly lower in those on invasive mechanical ventilation (29.3% dexamethasone vs 41.4% SC, RR: 0.64, 95% CI: 0.51–0.81, Number Needed to Treat (NNT)=9), and was lower in patients on oxygen without invasive mechanical ventilation (23.3% dexamethasone vs 26.2% SC, RR: 0.82, 95% CI: 0.72–0.94, NNT=35)[9]. However, in this study, patients who were not on respiratory support, administration of dexamethasone resulted in a higher incidence of death than those that were given SC (17.8% dexamethasone vs 14% SC, RR: 1.19, 95% CI: 0.91–1.55, NNT=27). Overall mortality at 28 days among all patient groups was lower in those administered dexamethasone (22.9% vs 25.7% SC, RR: 0.83, 95% CI: 0.75–0.93, NNT=36) and there was a greater probability of being discharged alive within 28 days in the dexamethasone group (67.2% vs 63.5% SC, RR: 1.10, 95% CI: 1.03–1.17)[9].

Tomazini et al. showed that ventilator free days during the first 28 days was higher in those treated with dexamethasone (6.6 days [95% CI: 5.0–8.2 days] vs 4.0 days SC [95% CI: 2.9–5.4 days], difference 2.26, 95% C: 0.2–4.38)[10]. In this study, there was no significant difference in the prespecified secondary outcomes, including all-cause mortality at 28 days (56.3% dexamethasone vs 61.5% SC, RR: 0.97, 95% CI: 0.72–1.31).

The case series showed that dexamethasone had a possible protective effect in severe COVID-19 infections with significant improvement in laboratory markers including CRP, D-dimer, and IL-6[12]. In this study, there was also an observed general improvement in patient outcomes in the ICU.

Discussion

In this paper, three studies with a combined total of 6,729 patients from three different countries were reviewed. Upon analysis, all three studies supported the use of dexamethasone along with SC in patients requiring supplemental oxygen, rather than SC *alone*. The administration of dexamethasone reduced all-cause mortality at 28 days, increased ventilator free days, and improved laboratory markers of inflammation, namely CRP[9,10,12].

However, in spite of these promising results, it is important to note the difference in treatment outcomes in patients of particular groups. It is consistent across all three papers that dexamethasone is most effective in those invasively mechanically ventilated. This fact is particularly evident in Horby et al. where incidence of death in patients receiving invasive mechanical ventilation was 12.1% lower when dexamethasone was administered[9]. While substantial evidence can be drawn from these studies, showing that dexamethasone improves mortality in mechanically ventilated patients, little information is given about those requiring non-invasive ventilation or supplemental oxygen alone. For example, in the same study, limited information for patients who required oxygen but did not need mechanical ventilation was given. The results did suggest a reduction in the incidence of death within this cohort of patients (receiving oxygen without invasive mechanical ventilation) when treated with dexamethasone, however, the reduction is not as significant as in the invasive mechanically ventilated group[9]. It is difficult to determine possible reasons for this due to the limited information provided.

Information on the oxygen requirements or use of continuous positive airway pressure (CPAP) was not provided for the non-invasive ventilation group.

Another interesting finding was the detrimental effect of dexamethasone treatment on patients who did not require any respiratory support. Horby et al. clearly showed an increase in the incidence of death with the administration of dexamethasone to patients who were not receiving any respiratory support[9]. A possible explanation for this finding is that those who were mechanically ventilated were likely to have developed ARDS as a result of the immune system becoming hyper-responsive and causing a cytokine storm. In this study, the development and progression of ARDS could be a causative factor of death in this group[9]. However, the administration of dexamethasone, through the drug's anti-inflammatory effects, could possibly dampen down the immune system and subsequently reduce mortality. In contrast to this, those who were not mechanically ventilated would have been more likely to have a normal functioning immune system that was at least partially capable of clearing the virus. It was less likely for the immune system to be in a hyper-responsive state and therefore a lower likelihood of developing ARDS. An abnormal immune response would, as a result, not be as large of a threat to the patient's life in this group unlike those who were invasively mechanically ventilated. Therefore, administering dexamethasone would not be most suitable for this cohort of patients and could inadvertently increase mortality as the virus is permitted to replicate further.

Since the conclusion of our own research, various systematic reviews commenting on the efficacy of corticosteroid use for COVID-19 have been published. Most recently, Ma et al.'s review of 7 eligible RCTs found that corticosteroids were associated with decreased all-cause mortality (27.3 vs. 31.1%)[13]. However, in this study, dexamethasone was the corticosteroid of choice in only two of the seven trials, both of which were included in this review. Furthermore, it was stated that the survival benefit depended heavily on the RECOVERY trial, so much so that the aforementioned survival benefit was absent if the RECOVERY trial was excluded[13]. Another meta-analysis carried out by the World Health Organization (WHO) Rapid Evidence Appraisal for COVID-19 Therapies (REACT) working group also found that administration of systemic corticosteroids, compared with usual care or placebo, was associated with lower 28-day all-cause mortality[14]. However, in this study, much like Ma et al.'s review, of the 7 RCTs included in this meta-analysis, three involved dexamethasone with two of those being the RECOVERY Trial and the CoDEX Trial. Like Ma et al.'s systematic review, this meta-analysis relied heavily on the RECOVERY Trial, with 57% of the primary meta-analysis data of 28-day all-cause mortality contributed by the RECOVERY Trial[13].

Although this review indicates the quantifiable benefit of administering dexamethasone to COVID-19 patients, in particular those with invasive mechanical ventilation, some gaps in our knowledge remain. The optimum dose cannot be extracted from this analysis as various doses were used within the three studies, ranging from 6mg to 20mg IV once daily. As various doses were received, we must also recognise how this might have affected these patients differently. A paradoxical effect of a mixed anti-inflammatory and pro-inflammatory response has been associated with a high dose of corticosteroids and this might have contributed to different patient response[15]. We must also recognise that dexamethasone was not the sole treatment provided to the patients within these studies. The correct combination of other drugs and treatment that comprise SC will also have an impact on some of the previously mentioned primary outcomes. Our database search was also limited—the exclusion of Cochrane database, despite having more trials on steroid use with COVID-19, is a limitation to our study. Our screening process was limited by the exclusion of a dual author review. It should be noted that the long-term outcomes of patients were not measured. It would be appropriate to investigate this in further studies, comparing the outcomes of patients and extrapolating if the patient outcome varied by treatment type, when long term data becomes available.

It is undeniable that both the RECOVERY Trial and the CoDEX trial have had a significant role in proving the efficacy of corticosteroid—particularly dexamethasone—treatment of COVID-19 patients. Regulatory bodies such as NICE in the UK issued guidelines incorporating dexamethasone into treatment regimens for critically ill COVID-19 patients[16]. This guidance was based on the WHO's REACT working group meta-analysis. Therefore, both trials have come under scrutiny. Matthay and Thompson's critique of the "landmark" RECOVERY Trial noted that there was a lack of information provided on why 1707 patients were unsuitable for randomisation[17]. As a result, the "benefit–risk profile of corticosteroids across the full spectrum of patients with critical COVID-19 and a range of comorbidities remains uncertain"[17]. Johnson and Vinetz highlighted more evidence gaps in the RECOVERY Trial, making the point that adults requiring ventilation had a mean age of 59 years and in a post hoc subset analysis, dexamethasone did not benefit the two older age groups[18]. The efficacy of dexamethasone for older adults is therefore unclear. Less analysis has been done regarding the CoDEX trial in comparison to the RECOVERY Trial. Despite this, authors such as Salim Rezaie have mentioned the fact that the CoDEX trial was stopped early following the results of the RECOVERY trial and was underpowered as a result[19].

Conclusion

Following a systematic review of the evidence, it has been found that dexamethasone was superior to SC in patients admitted to the ICU with SARS-CoV-2 infection. Benefits included a significantly lower incidence of death in patients on invasive mechanical ventilation, higher ventilator-free days during the first 28 days and a lower overall mortality at 28 days among all patient groups. However, administration of dexamethasone to patients not on respiratory support resulted in a higher incidence of death compared to SC. ◄

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Declarations

The authors declare no conflicts of interest.

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