Dexamethasone in Covid-19 hospitalized children: A single center experience

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ABSTRACT

Objectives: To evaluate role of dexamethasone in hospitalized children with COVID-19 and the benefit of early use of steroids on the outcome**.**

Methods This study was retrospective, and it was carried out by studying medical electronic data of all children who tested positive for COVID-19 PCR and received dexamethasone at Queen Rania Hospital for Children's Isolation Section from October 2020 to February 2022.

Results: A total of 24 patients infected with COVID-19 and received dexamethasone with a median age was 21 months (ranging from one month to 13 years) were identified, and 13 (54%) of the patients were male. Additionally, six patients (25%) had underlying diseases and co-morbidities. The in-hospital oxygen support included a simple face mask (16 patients, 67%), high-flow nasal cannula (5 patients, 21%), and nasal cannula (3 patients, 12%); additionally, none of these patients required mechanical ventilation.
The males significantly had longer hospital stays than females; furthermore, males who required oxygen supplementation, as well as those who received dexamethasone, significantly had longer hospital stays than females. All variables were statistically significant. ($P < 0.05$).

Conclusion
This study demonstrated that the males had longer hospital stays than females; furthermore, those who required oxygen supplementation, as well as those who received dexamethasone, spent more days hospitalized than females. The administration of dexamethasone to patients with severe COVID-19 pneumonia within 24 hours of oxygen supplementation can be helpful in reducing the rate of mechanical ventilation.

Keywords: dexamethasone, COVID-19, oxygen supplementation

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Introduction

The initial cases of the novel coronavirus (2019-nCoV) occurred in Wuhan, Hubei Province, China, in December 2019 and January 2020.[1] The virus was able to spread throughout the world, causing a global health emergency. The World Health Organization (WHO) later recognized SARS-CoV-2, namely known as coronavirus disease 2019 (COVID-19.[2]

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In Jordan, the first wave of the outbreak started in late September 2020.[3] The virus spread widely in Jordan causing several waves. The spread of COVID-19 in Jordan occurred in a cluster event, and then it distributed over multiple locations. A successive second pandemic wave has hit Jordan starting around January 27, 2021, and the COVID-19 morbidity and mortality were rising again. This pandemic wave has posed significant burden on healthcare institutions with high occupancy rates of isolation beds, ventilators, and ICU beds, especially in northern and central Jordan.[4]
Similar to adults, children are also affected by this pandemic. Generally COVID-19 is a mild disease in children compared to adults, and although a few children get a severe respiratory or systemic disease, most do not need intensive care.[5]
A viable therapy for COVID-19 has been sought since the beginning of the pandemic. In this regard, supportive treatment is recommended for all patients. Antiviral and immunomodulatory medications are given to hospitalized children who are in respiratory distress or have severe to critical illness. Several academic and health organizations have recommended subsequent practice guidelines regarding dexamethasone use in patients with severe COVID-19, and these recommendations have changed clinical practice for hospitalized patients on supplemental oxygen or mechanical ventilation.[6] The research also suggested that dexamethasone might increase mortality in hospitalized individuals who are not receiving oxygen.
In the current study, we aimed to note the clinical features of the hospitalized children who tested positive for COVID-19 PCR from October 2020 to February 2022 at Queen Rania hospital. Regarding children who received dexamethasone during hospital stay, we reviewed the factors influencing dexamethasone requirements in COVID-19 hospitalized children and the benefit of early use of steroids on the outcome.

Methods

This study was retrospective, and it was carried out by studying medical records of pediatric patients with proven severe acute respiratory syndrome coronavirus 2 infections (COVID-19) as determined by the polymerase chain reaction present at Queen Rania Hospital for Children's Isolation Section from October 2020 to February 2022.
This study had IRB committee approval Data were collected by the treating pediatric physicians (co-authors) from 24 inpatient medical electronic files.
This study included pediatric patients who required supplemental oxygen during their stay in the hospital. According to our hospital's policy, all critically ill patients with, $SpO_2 \leq 94\%$ in room air and those who require supplemental oxygen or mechanical ventilation must be given dexamethasone at a dose of 0.6 mg/kg/dose (maximum dose 6 mg) once daily for up to 10 days.
Dexamethasone was administered to 24 pediatric patients with COVID-19 in accordance with the protocol for COVID-19 pediatric patients. We defined the initiation time of dexamethasone treatment as the time interval from the occurrence of hypoxemia to the initiation of dexamethasone treatment. The primary outcomes were the need for invasive mechanical ventilation during treatment of dexamethasone and the need for ICU admission. The secondary outcomes were the total duration of oxygen supplementation and the length of stay in the hospital.
The confirmation of COVID-19 was based on a nasopharyngeal swab that was positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) according to a real-time reverse transcription polymerase chain reaction (rRT-PCR) assay.[7]

Data of age, gender, comorbidity index, oxygen supplementation, duration oxygen supplementation, length of hospital stay and outcomes were collected from children who received dexamethasone. Day 1 was defined as the first day of dexamethasone for children who received dexamethasone and the first day of supplemental oxygen.

To study if there is a statistical significant mean difference between gender on linear combination for duration of oxygen support, length of stay in hospital and duration of dexamethasone treatment, a multivariate analysis of variance analysis test was used (MANOVA).

The type of oxygen support on day 1 identified. Patients who were discharged alive from the hospital were considered free from oxygen support. A super infection was diagnosed if a new microbiological infection emerged within 48 hours of admission.

Results

24 patients were included in the analysis and their demographic and clinical outcomes are described in **Table I.**

The median age was 21 months (ranging from one month to 13 years), and 13 (54%) of the patients were male. Additionally, six patients (25%) had underlying diseases and co-morbidities, including acute lymphoblastic leukemia (two male patients), congenital heart disease (two female patients), pure red cell aplasia (one male patient), and brain tumor (one male patient).

All the patients had evidence of pneumonia as observed from chest X-ray or chest CT scan, and they required supplemental oxygen during the hospital stay due to $SpO_2 \leq 94\%$ in room air. The in-hospital oxygen support included simple face mask (16 patients, 67%), high-flow nasal cannula (5 patients, 21%), and nasal cannula (3 patients, 12%); additionally, none of these patients required mechanical ventilation.

The result in **Table II** yielded that there was a statistical significant mean differences between male and female for duration of oxygen support .$F(1,22)=7.515$, $p=0.012$, length of stay in hospital $F(1,22)=8.320$, $p=0.009$ and duration of dexamethasone treatment $F(1,22)=8.097$, $p=0.009$.

To investigate in favor whom the statistically significant mean difference related to, the main effect test result in **Table III** revealed that the male (M= 6.46, SD=3.95 days) significantly have higher length of oxygen support than female (M= 2.91, SD=1.81 days) $p=0.012$, Likewise the male (M= 7.38, SD=2.63 days) significantly have higher length of hospital stay than female (M= 4.73, SD=1.68 days) $p=0.009$, and male (M= 8.77, SD=4.44days) significantly have higher duration of dexamethasone treatment than female (M= 4.73, SD=1.68 days) $p=0.009$.

Antibiotic therapy was administered in 11 of 24 cases due to strong clinical suspicion of super bacterial infection, and the choice of antibiotics was third generation cephalosporin that was discontinued after negative bacterial cultures. None of 24 patients received antiviral therapy (Remdesivir). No mortality or super infection was reported in this study. Furthermore, in all 24 cases, patients were discharged alive and with no or only mild residual symptoms.

Table I: Demographic and clinical data of the patients who received dexamethasone.

baseline characteristics	All patients n =24
Age by months	21 (1-156)
Male	13 (54%)
Female	11 (46%)

Comorbidities	
ALL*	2 (8.33**%**)
CHD**	2 (8.33**%**)
PRCA***	1(4.16**%**)
Brain tumor	1(4.16**%**)
Type of oxygen support	
Simple face mask	16(6.66%)
HFNC ********	5(20.83%)
Nasal cannula	3(12.5%)
Dexamethasone	
Duration, days (all)	6.92 ± 3.97
-Males	8.77 ± 4.44
-Female	4.73± 1.68
Clinical outcomes	
Length of oxygen support, days (all)	4.83 ± 3.58
-Male	6.46 ± 3.95
-Female	2.91 ± 1.81
Length of hospital stay(all)	6.17 ± 2.58
-Male	7.38 ± 2.63
-Female	4.73 ± 1.68
Super infection	0 (0)
Hospital mortality	0 (0)

The data are presented as numbers (%), mean ± standard deviation, or median (interquartile range). *ALL: Acute lymphoblastic leukemia. **CHD: congenital heart disease. ***PRCA: Pure red cell aplasia. ** HFNC: high flow therapy nasal cannula.**

Table II: Test of between subject effects

Source	Dependent variables	Sum of square	Df	Mean square	F value	P-value
Gender	Oxygen support	75.193	1	75.193	7.515	0.012
	Hospital satay	42.075	1	42.075	8.320	0.009
	duration of dexamethasone treatment	97.344	1	97.344	8.097	0.009
Error	Length of oxygen support	220.140	22	10.006	---	---
	Length of hospital satay	111.259	22	5.057	---	---
	duration of dexamethasone treatment	264.490	22	12.022	---	---

Table III: pairwise of gender mean differences for study outcome

Dependent variables	Gender	Mean	SD	Mean differences	p-value	95%CI	
						Lower bound	Upper bound
Length of oxygen support	Male Female	6.46 2.91	3.95 1.81	3.56	0.012*	0.865	6.240
Length of hospital satay	Male Female	7.38 4.73	2.63 1.68	2.65	0.009*	0.747	4.568
Duration of dexamethasone treatment	Male Female	8.77 4.73	4.44 1.68	4.04	0.009*	1.096	6.988

Discussion

The majority of children infected with SARS-CoV-2 exhibit mild clinical symptoms and recover within 1–2 weeks of symptom onset. Children often develop milder diseases than adults; the majorities of infections are asymptomatic or present as upper respiratory tract infections or mild pneumonia. Nonetheless, severe and life-threatening cases in children have been documented.[8, 9]
There are currently no drugs that have been demonstrated to be helpful against SARS-CoV-2. Remdesivir has been questioned due to its low clinical impact, despite being licensed by the Food and Drug Administration (FDA) in the United States as an antiviral for SARS-CoV-2. The RECOVERY study found that a moderate dosage of dexamethasone (6 mg daily for 10 days) decreased mortality in hospitalized COVID-19 patients with respiratory failure who needed supplementary oxygen or mechanical ventilation.[10] Since then, clinical trials using corticosteroids to treat COVID-19 patients vary significantly in terms of the kind of corticosteroids used, the dose, the period of treatment, and whether patients are suited for the therapy.
The current focus has been directed towards the factors affecting the use of dexamethasone in the treatment of COVID-19 and its benefits. There is a shortage of data to clearly determine the risk factors for severe COVID-19 in children. In the current study, the mean and standard deviation of 13 males demonstrated longer hospital stays than that of 11 females. Additionally, male patients who required oxygen supplementation and those who received dexamethasone had a longer in-hospital stay than females. All variables were statistically significant. ($P< 0.05$).
In a European cohort study, significant risk factors for severe COVID-19 included the following: age less than one month, male gender, pre-existing medical problems, and the existence of lower respiratory tract infection signs or symptoms upon presentation.[11] In our study, a one-month-old newborn with severe COVID-19 required a 16-day hospital stay, oxygen supplementation for 12 days, and dexamethasone for 10 days.
Obesity, chronic lung disease, and preterm birth were the most common underlying conditions and diseases among children with COVID-19 admitted to North American PICUs, according to a

research. [12] Several studies found that being overweight or obese in adulthood was an independent risk factor for severe COVID-19.[13]

In this study, we had 6 patients with comorbidities: 3 hematological diseases, 2 congenital heart diseases, and 1 brain tumor. Among the 6 patients in our report, 2 were more critically ill and presented with underlying or coexisting conditions (case 1, acute lymphoblastic leukemia; case 2, congenital heart disease) and required a 16-day hospital stay, oxygen supplementation for 12 days, and dexamethasone for 10 days. However, none of them required mechanical ventilation.

Generally, the aim is to keep SpO2 between 92% to 96%, but an oxygen saturation ≥ 90% (in patients with visible continuous pulse oximetry in an appropriately monitored care environment) should be achieved. Non-invasive ventilation (NIV) and high flow nasal cannula oxygen (HFNC) were employed as respiratory support in this study according to the oxygenation protocol for severe COVID-19 patients, with care about aerosolization and an increased risk of disease transmission. It is essential to note that dexamethasone was administered in parallel with the use of oxygen support, and both began on the same day. Simple face masks were utilized by 16 patients (67%), HFNC was used by 5 patients (21%), and nasal cannula was used by three patients (12 %). Our study demonstrated a reduced the need for intubation. Furthermore, the requirement for more oxygen may have been a useful clue indicating that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection had produced some degree of lung damage and that these children would benefit from dexamethasone medication.

A recent network meta-analysis of 25 randomized controlled trials comparing standard oxygen treatment with NIV or HFNC showed a lower risk of intubation and mortality.[14] A retrospective analysis (n = 40) of COVID-19 patients who eventually required invasive mechanical ventilation found that time spent on NIV and HFNC before intubation was associated with higher mortality.[15] Because intubation and clinical monitoring thresholds were not pre-determined, it is difficult to draw clear conclusions from these observational investigations.

The results of our study did not show superinfection during the administration of dexamethasone. The largest meta-analysis on low-dose corticosteroid use in patients with sepsis did not demonstrate an increased risk of superinfection or gastro-duodenal bleeding, although an increased risk of hyperglycemia, hypernatremia, and muscle weakness was found.[16]

The half-life of dexamethasone is estimated at 4.1 to 5.4 hours.[17] Additionally, it has a good oral bioavailability estimated at around 70–80%. Dexamethasone is a corticosteroid that contains anti-inflammatory and immunomodulatory properties. It suppresses the immune response to endogenous autoimmune insults such as autoantibodies directed against self-antigens as well as external triggers such as SARS-CoV-2. Furthermore, it reduces pulmonary inflammation resulting in improved respiratory functions.[18]

We think that the good prognosis for pediatric patients is related to some factors, one of which that is COVID-19 is generally a milder disease in children than in adults. Additionally, it may react differently to pathogens in a child compared to an adult since the child's immune system in still developing. Angiotensin-converting enzyme II (ACE-2), which acts as the receptor for coronaviruses, may be structurally and functionally less mature in the airways of children.[19] The simultaneous presence of other viruses in the respiratory tract mucosa, which is very typical for young children, may limit the growth of SARS-CoV-2 by direct virus-to-virus interactions and competition. Another factor is the adequate time for administration of dexamethasone, which is effective during the host inflammatory response to viral infection. Ultimately, the good prognosis may be related to visible continuous pulse oximetry in an appropriately monitored care environment with trained staff to monitor for clinical deterioration.

We have some limitations in this retrospective study. The small population size and single-center nature of the study limits the generalizability of the findings. Additionally, data for some variables

is missing, and the electronic health records contain potential inaccuracies such as the possible lack of documentation of illnesses. Another limitation is the lack of any data on viral clearance, which is likely to be an important factor in determining the harm versus benefit of dexamethasone.

Conclusion

This study demonstrated that the males had longer hospital stays than females; furthermore, males who required oxygen supplementation, as well as those who received dexamethasone, had longer hospital stays than females. The administration of dexamethasone to patients with severe COVID-19 pneumonia within 24 hours of oxygen supplementation can be helpful in reducing the rate of mechanical ventilation. Further research is needed to establish the optimal treatment for children with severe or critical COVID-19. Risk factors for severe courses of COVID-19 in children still remain to be elucidated.

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