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Research Article

Effect of New Treatment Strategies of COVID-19 Intensive Care Unit Patients in the Second Wave and its Impact on Mortality

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Abstract

Aims: We analysed the differences in treatment strategies among COVID 19 patients requiring intensive care in the first and second COVID 19 waves and their impact on mortality in our hospital and compared them with the literature. **Subjects and Methods:** We included in our population all patients admitted to HELIOS Klinikum Krefeld, Germany, with a proven diagnosis of COVID-19 in the first wave (n = 84; from March 11, 2020-June 30, 2020) and the second wave (n= 344; from July 01, 2020-January 31, 2021). In addition, we searched PubMed and Medline for other publications reporting similar data of COVID-19 cases in the first and second waves and their treatment. Finally, we included 5 publications **Results**: The characteristics of our patients were similar in both waves, but slightly more men were treated in the ICU in the second wave. Despite obvious changes in treatment in the second wave, the mortality rate was higher at 34.7% in the second wave than at 28.6% in the first wave. The mortality rate was higher despite increased use of dexamethasone and remdesivir and a lower proportion of intubated patients. Comparison of the results with the literature shows a nearly linear relationship between increases in dexamethasone treatment and decreases in mortality (R^2 of 0.6509), suggesting that fewer people died with increasing use of dexamethasone. There is no relevant correlation for remdesivir (R^2 of 0.0712). There is also no correlation between the decrease in the number of mechanically ventilated patients and mortality (R^2 of 0.0253). Less mechanical ventilation does not correlate with lower mortality. **Conclusion:** Only the increased use of dexamethasone correlated with a decrease in mortality in the second wave; the increased use of remdesivir and the reduction in mechanical ventilation did not.

Keywords: COVID 19; Respiration; Intensive care unit; First wave; Second wave

Introduction

In early 2020, SARS-CoV-2 triggered a global pandemic called COVID-19 [1]. COVID-19 developed in several waves, caused by preventive strategies to stop one wave and by viral mutations that triggered another wave. At the beginning of COVID-19, physicians had no experience treating patients with severe disease. With each wave, patient presentation and treatment strategies changed because the health care system is a learning system. Ventilation and intubation were a central aspect of treatment in the first wave, but were managed more restrictively in the second wave [2]. According to data from the Federal Institute for Hospital Charges, the proportion of mechanically ventilated patients decreased from 19% of all hospital patients with COVID-19 in the first wave to less than 8% in the second wave, or from 64% to 54% when treated in the intensive care unit [3]. In other hospitals, a decrease from 82% to 39% was reported [4]. In addition to changes in ventilation strategies, pharmacologic treatment also changed. The role of anticoagulation increased [5], early administration of dexamethasone in patients with severe COVID-19 was recommended [6,7], and remdesivir was used more liberally in some countries [8]. Despite these changes in treatment strategies, mortality was higher in the second wave in most ICUs [3,9,10]. Few published reports systematically describe the treatment of COVID-19 patients in the ICU. Therefore, we analyzed the treatment of ICU patients in the first and second COVID-19 waves at Helios Klinikum Krefeld and compared it with the literature.

Methods

The HELIOS Hospital Krefeld is a 1,000-bed hospital providing all specialties of medicine. Krefeld is a large middle town in the west of Germany with 240,000 inhabitants. In December 2020, we initiated a retrospective register of all cases hospitalized with COVID-19 named **Be**o**b**achtungs**S**tudie **C**ovid **2** (BoSCo2). The register study was approved by the Ethics Committee of the North Rhine-Westhalian Physician Association (Ethic-vote from 20.04.2020, number 2020101).

In BoSCo2, we included data from 84 patients hospitalized for COVID-19 in the first wave (11.03.2020 - 30.06.2020) and 344 patients from the second wave (01.07.2020 - 31.01.2021). All data were carefully extracted from the medical forms and anonymized in an Excel database by three physicians. For data quality, parameters from every tenth patient were checked twice.

At admission, each patient received a physical examination. The temperature was measured, and blood was taken. Clinically indicated capillary blood gas analysis was performed. Medication was documented. Medical history at admission includes cardiac (arterial hypertension, coronary heart disease, heart insufficiency, arrhythmia), pulmonic (chronic obstructive disease, asthma), renal (chronic or acute insufficiency), autoimmune (rheumatoid arthritis, thyroiditis, polymyalgia rheumatica, psoriasis), metabolic (diabetes, metabolic syndrome, hypothyreosis) and malignant disease. With the beginning of the second wave, new treatment strategies evolved with the prescription of dexamethasone and remdesivir. For this analysis, we included data from 28 patients in the first wave and 98 patients from the second wave treated on ICU.

In addition, we looked in PubMed and Medline for other publications reporting similar data from COVID-19 cases in the first and second wave and their treatment. For search, we used the words “COVID-19”, “first and second wave”, “respiration”, “dexamethasone” and remdesivir. Finally we included 5 publications [2,11-13].

Statistics

Differences between the two waves were determined by using a two-sided t-test on continuous variables. Chi-square test was used on all categorical variables. In the plots correlation coefficient (R) was calculated to describe strength and direction of (linear) relationship between the vuantitative variables. Statistical analysis was performed using the python package Table 1 v.0.7.10 [5].

Results

Table 1 shows the characteristics of patients treated in the ICU in the first and second waves. Patients were similar in age, but slightly more men were treated in the ICU in the second wave. Despite obvious changes in treatment, the mortality rate was higher in the second wave: 34.7% in the second wave versus 28.6% in the first wave. The mortality rate was higher despite increased use of dexamethasone and remdesivir and a lower proportion of intubated patients.

	First Wave	Second Wave.	p value
Total	28	98	
Age, median (IQR)	62.4 (13.3)	63.5 (14.1)	0.704
Males, n (%)	15 (53.6)	69 (70.4)	0.150
Death, n (%)	8 (28.6)	34 (34.7)	0.705
Thromboembolic Event, n (%)	12 (42.9)	16 (16.3)	**0.007**
Remdesivir, n (%)	1 (3.6)	4 (4.1)	1.000
Time of treatment in days, mean ± SD	0.1 (0.6)	0.2 (0.8)	0.732
Dexamethason, n (%)	0.0 (0.0)	79 (80.6)	**<0.001**
Time of treatment in days, mean ± SD	0.0 (0.0)	7.0 (4.1)	**<0.001**
Mechanical respiration, n (%)	19 (67.9)	39 (39.8)	**0.016**

Table 1: Comparison of patient characteristics and treatment of patient on ICU in the first and second wave.

Table 2 lists the five populations that were finally included after the literature search for the analysis of the association between changes in the use of dexamethasone, remdesivir, and intubation and changes in mortality in the second waves. Unfortunately, not all figures were reported in the various publications.

	First Wave	Second Wave	Delta (%)
Death			
Krefeld, Germany	28.6 %	34.7 %	6.1 %
Hamburg, Germany	32 %	44 %	12 %
Rosenheim, Germany	48 %	62 %	14 %
Argenteuil, France	50 %	52 %	2 %
Athen, Greece	32 %	40 %	8 %
Dexamethasone			
Krefeld, Germany	0 %	80.6 %	80.6 %
Hamburg, Germany	0 %	29 %	29 %
Rosenheim, Germany	10.1 %	58.1 %	48 %
Argenteuil, France	12 %	100 %	88 %
Athens, Greece	10 %	100 %	90 %
Remdesivir			
Krefeld, Germany	3.6 %	4.1 %	0.5 %
Hamburg, Germany	6 %	15 %	9 %
Rosenheim, Germany	0 %	2.4 %	2.4 %
Argenteuil, France	n. r.	n. r.	-
Athens, Greece	6 %	42 %	36 %
Intubation			
Krefeld, Germany	67.9 %	39.8 %	28 %
Hamburg, Germany	32 %	20 %	12 %
Rosenheim, Germany	58.7 %	20.3 %	38.4 %

Argenteuil, France	88 %	64 %	24 %
Athens, Greece	82 5	66 %	16 %

Table 2: Comparison of mortality and treatment rates of these five populations used for the plots in Figure 1, Figure 2 and Figure 3, n. r. : not reported.

Figure 1 shows a reasonably good correlation (R2 = 0.6509) between increasing use of dexamethasone and decreasing mortality, suggesting that fewer people died with increasing use of dexamethasone. Figure 2 shows a similar plot for remdesivir, but the correlation is weak (R2 of 0.0712). Figure 3 shows almost no correlation between the decrease in the number of ventilated patients and mortality (R2 of 0.0253). Less mechanical ventilation does not correlate with lower mortality.

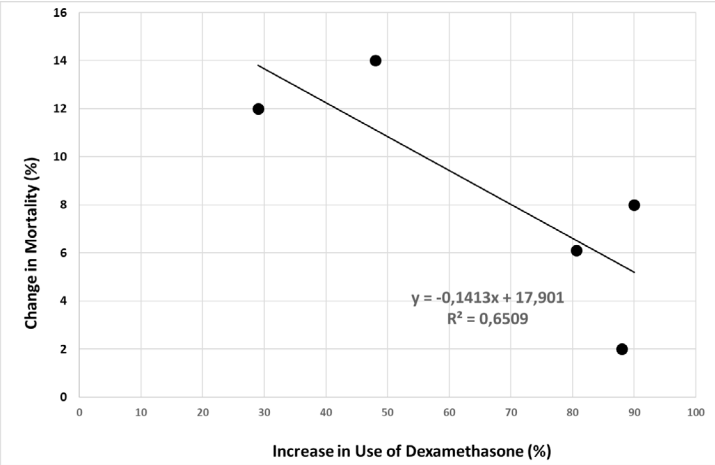

Figure 1: Correlation of the increase in the use of Dexamethasone and the changes in mortality between the first and the second wave.

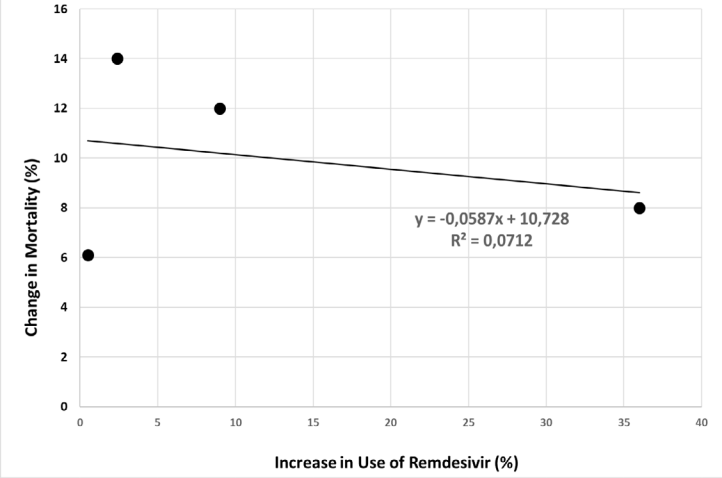

Figure 2: Correlation of the increase in the use of Remdesivir and the changes in mortality between the first and the second wave.

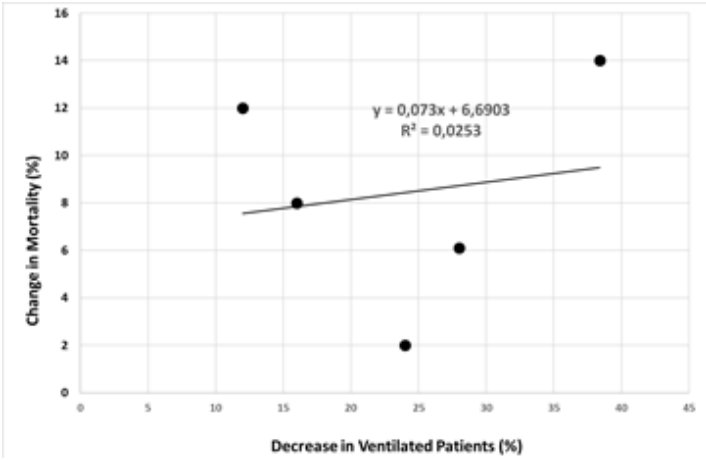

Figure 3: Correlation of the decrease in the use of intubation and the changes in mortality between the first and the second wave.

Discussion

Our analysis based on our own data and a systematic literature search showed that higher use of dexamthasone seems to be associated with a decrease in mortality in the second wave. On the other hand, higher use of remdesivir and decreasing rates of mechanical ventilation do not correlate with a decrease in mortality in the second wave. Mortality of COVID-19 ICU patients showed different trend in the second wave of COVID-19. There is still a discussion about explanations for the reduced incidence of mechanical ventilation on the ICUs. Changes in the use of high-flow oxygen treatment and non-invasive ventilation with more clearly defined algorithms may have influenced it [14] as well the establishment of pharmacological treatments, with the greatest treatment success most likely to be achieved by the early administration of Dexamethasone in patients with severe COVID-19. **A publication from Italy reported** that provinces with the most severe initial COVID-19 outbreaks, as assessed through mortality data, faced milder second waves [9]. Crichton et al. performed a systematic review of randomised controlled trials on dexamethasone based on nine studies [15]. Overall, mortality in the treatment groups was 714 (25.6%) out of 2793, and in the control groups was 1365 (27.4%) out of 4973. The pooled effect estimate showed OR 0.80 (95% CI 0.64–1.01, p=0.06), indicating a mortality benefit that narrowly failed to meet the pre-specified level of statistical significance. A Cochrane review including 11 RCTs with 8075 participants found moderate-certainty evidence only that systemic corticosteroids probably slightly reduce all-cause mortality in people hospitalised because of symptomatic COVID-19 [16]. RCTS for the effect of mechanical respiration are not available. One randomized, open-label clinical trial conducted in emergency units and ICUs in 3 hospitals in Colombia including 220 adults with respiratory distress and a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen of less than 200 due to COVID-19 concluded that use of high-flow oxygen through a nasal cannula significantly decreased need for mechanical ventilation support and time to clinical recovery compared with conventional low-flow oxygen therapy [17].

Our results are not based on RCTs but on clinical practice. As an advantage, we examined the effects of these three treatment strategies in the same populations in the second wave. In the five included populations, increasing use of dexamethasone correlates with a decrease in mortality in the second wave. The effect of dexamethasone is consistent with the Cochrane review (16). The increase in the use of remdesivir and the decrease in mechanical ventilation appear to have no benefit for COVID-19 patients treated in the ICU. Rates of remdesivir prescribing were low, with the exception of Athens, Greece. It is possible, that such low rates may not be effective in reducing overall mortality in a given population. It is surprising that the lower rates of mechanical ventilation do not correlate with a decrease in mortality. Indication for mechanical respiration is an individual decision in each case and it could have be handled in different ways in the different clinics. Thus, the effects on mortality could be heterogeneous.

Strengths and Limitations

A major strength of this study is the structured development of our own registry and the consecutive inclusion of all patients. We do not know the quality of the other included data.

There are factors that limit the interpretation of our results. First, our analysis is just descriptive. Second, only standard parameters that were documented routinely were analyzed. We did not differentiate the severity of comorbidities. Specific analysis of time of infection, source of infection or treatment prior to hospital admission were not done. Third, statistically speaking, despite a cohort sizes reaching a few hundred patients, the analysis is based on small, geographically localized populations.

Conclusion

The mortality of COVID 19 cases treated in the ICU was higher in the second wave than in the first, and this holds true despite new therapeutic strategies. According to our analysis, the use of dexamethasone seems to be effective in reducing mortality. This effect was not demonstrated for remdesivir and reduction of mechanical ventilation.

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