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Abstract

Use of high-dose glucocorticoids for coronavirus disease 2019 (COVID-19; caused by SARS-CoV-2) is controversial because of safety concerns. We examined long-term consequences in severe acute respiratory syndrome (SARS; caused by SARS-CoV-1) survivors. Results showed that high-dose glucocorticoids greatly increased long-term risk of avascular necrosis, but not other major diseases.

Introduction

High-dose glucocorticoids have been widely used in critically-ill patients to suppress inflammation response.[1] While short-term outcomes of such treatment have been reported[2], long-term clinical outcomes are unknown.

Hong Kong had an outbreak of severe acute respiratory syndrome (SARS; caused by SARS-CoV-1) in 2003, resulting in 1,755 cases and 299 deaths[3] Short course of very-high-dose (VHD) glucocorticoids was used for the treatment of SARS, especially to prevent cytokine storm. In the recent pandemic of coronavirus disease 2019 (COVID-19; caused by SARS-CoV-2), glucocorticoids has been suggested but there is controversy because of safety concerns. To understand the long-term consequences of VHD glucocorticoids, we studied the clinical outcomes of SARS survivors after 17 years.

Materials and Methods

Study cohort

We identified SARS survivors using an electronic medical record database, Clinical Data Analysis and Reporting System (CDARS) of the Hong Kong Hospital Authority, the details of which have been described elsewhere.[4] Patients who i) were screened positive for SARS during the outbreak from 22 Feb to 2 Jun, 2003[3]; ii) received glucocorticoid therapy during hospitalization; and iii) recovered and discharged, were included. In the analysis of each outcome-of-interest, we excluded patients with history of that outcome. Clinical data including demographics, diagnosis and prescription records were retrieved. Patients who did not receive glucocorticoid therapy were not included in the analysis due to the concern on treatment allocation bias. These patients were generally frail or in poor comorbid, leading to potential bias to the long-term outcomes.

Exposure and outcome

Exposure was defined by the daily dose of glucocorticoid (or its equivalent prednisone dose) prescribed for each patient. Glucocorticoid doses were classified according to the recommendation by EULAR.[5] Patients receiving VHD or pulse regimen (>100 mg prednisone equivalent a day) were compared with patients receiving low-to-high-dose regimen (LTHD; ≤100 mg prednisone equivalent a day).

Outcomes of interest were common diseases and diseases associated with long-term use of glucocorticoid (Table 1). These diseases were defined using ICD-9 codes (Supplementary Table 1).

Statistical analysis

Patients were followed from the date of discharge until the occurrence of an outcome-of-interest, death or study end (31 Dec 2019), whichever was earlier. Cox-proportional hazard regression was used to examine the association between use of glucocorticoid and clinical outcomes. Hazard ratio (HR) and 95% confidence interval (CI), adjusted for age, sex, and Charlson comorbidity index were estimated.

Sensitivity analysis was conducted using propensity score (PS) matching. Details of the PS matching were provided in Supplementary Methods. Additional analysis was performed for outcome showing significant association with exposure. Common risk factors for the outcome at baseline (i.e. on/before patient discharge) were further adjusted in the Cox model. The follow-up was censored at the occurrence of risk factors, in addition to death and study end.

Statistical analysis was performed using R (version 3.5.2). A p-value<0.05 was considered statistically significant.

Results

Characteristics of study cohort

We identified 1,326 SARS survivors in CDARS. Of these, 184 survivors who did not received glucocorticoid were excluded, resulting in 1,142 SARS survivors (VHD: 850; LTHD: 292) in the analysis. Overall, the mean±sd age of the cohort was 38±15.2 and 40% was male. There is no significant difference in age and gender between the groups but the mean Charlson comorbidity index in VHD was significantly lower than that in LTHD (Supplementary Table 2). The median (interquartile rage) daily dose equivalent to prednisone were 625 (625-937.5) mg and 45 (31-60) mg in VHD and LTHD, respectively. The treatment duration and median total dose of glucocorticoids the patients received were provided in Supplementary Table 2. The PS-matched cohort included 847 patients in VHD and 289 patients in LTHD. The variables in the matched cohort were balanced (Supplementary Table 2).

Association of VHD glucocorticoids and long-term outcomes

Over a median follow-up of 16.7 years, we observed a much higher incidence of avascular necrosis (AVN) in VHD than LTHD (4.83 vs 0.67 per 1000 person-year). A significant 7.5-fold increased risk of AVN (HR 7.50; 95% CI 2.34-24.04; $p<0.001$) in the VHD, compared with the LTHD, was estimated. There was no significant association in other clinical outcomes. Similar findings were observed in the PS-matching cohort. (Table 1)

Additional analysis for AVN was conducted by adjusting for common risk factors including trauma (bone fractures or joint dislocation), systemic lupus erythematosus, rheumatoid arthritis, cancer, HIV/AIDs, sickle cell anemia, hyperlipidemia, pancreatitis, chemotherapy, radiotherapy and use of bisphosphonates (ICD-9 codes for the diagnosis and procedures are provided in Supplementary Table 1). A consistent result was obtained (HR 7.06; 95% CI 2.20-22.69; $p = 0.001$).

Discussion

In this retrospective study of SARS survivors with 17 years of follow-up, a short-course use of VHD glucocorticoids was not associated with major diseases except AVN.

Comparison with other studies

The association between high-dose glucocorticoids and AVN in SARS patients has been reported.[6,7] However, these studies had a short follow-up time ranging from 6 months to 3 years. Study by Hui et al. reported that among 41 patients developed AVN, 11 (27%) of them were diagnosed with AVN after 3-years of follow-up. In our study, 48% (30 out of 62) patients developed AVN 3 years after their recovery from SARS, suggesting that the risk persisted for a long time. Thus, long-term monitoring for AVN is necessary even the use of high-dose glucocorticoids is short.

Osteoporotic fracture is a well-known adverse effect of chronic use of glucocorticoids. A study using national claim data showed that short course of low dose glucocorticoids (median dose 20mg/day) was associated with increased risk of fractures by 83%, compared with non-users, within first 30 days of drug initiation.[8] Our study did not show such association. The discrepancy could be due to the heterogeneity of study design. In addition, bone remodeling is a slow process and thus, occurrence of fracture in a short period of time should be unlikely. More studies are warranted to examine the risk of fractures in short-term use of glucocorticoids.

Similarly, it is well-reported that chronic use of glucocorticoids is associated with diabetes mellitus (DM) but the effect of short course use is unknown. In this study, the incidence of DM in VHD was higher than that in LTHD (4.54 vs 3.77 per 1000 person-years) but the association was not significant. A prospective study in patients with perioperative use of high-dose glucocorticoids showed that hyperglycemia was observed but the condition was resolved 6 weeks after the therapy[9], suggesting that the effect of short-term glucocorticoids on diabetes could be transient and reversible.

Clinical implication

Amid the COVID-19 pandemic, glucocorticoids are once again being considered for selected patients.[10,11] Given that cytokine storm is the most life-threatening condition in SARS-CoV-2, VHD glucocorticoids may be used in the treatment. Our study showed that short-course of VHD glucocorticoids was not associated with major diseases. However, given the high risk of AVN, long-term surveillance and clinical care in patients is recommended.

A multi-center study in US showed that early short-course of glucocorticoids had a significant reduction of death, mechanical ventilator use, and length of stay in hospital.[10] A recent report from the RECOVERY trial showed that dexamethasone improved survival in patients requiring oxygen or mechanical ventilation, compared to usual care alone.[12] The trial used 6mg dexamethasone once daily for 10 days. The daily dose was equivalent to 40mg prednisone which is classified as LTHD in this study. Our study provides useful safety data on the potential long-term comorbidity if glucocorticoids therapy is needed.

Strengths and limitations

Strengths of this report include a long-term follow-up in a large SARS cohort. In addition, Hong Kong Hospital Authority implemented a follow-up programme for SARS survivors. Thus, under-diagnosis of comorbidity should be minimal. Conversely, there were limitations. First, this study may have limited power in detecting small effect size. Thus, studies with larger sample sizes are warranted to verify our findings. Second, data on excess alcohol use, a common risk factor for AVN, was not available. Nevertheless, the per capita alcohol consumption in Hong Kong according to government statistics in 2010 was 2.6 litre/year (https://www.change4health.gov.hk/), compared to 9.2 litre/year in US and 11.6 litre/year in UK (WHO statistics https://www.who.int/substance_abuse/activities/gsrah/en/). Therefore, alcohol as a risk factor for AVN is relatively less important in Hong Kong. There is no study in Hong Kong reporting significant difference of alcohol consumption between VHD and LTHD glucocorticoids users. Thus, confounding by alcohol use should be minimal. Third, further exposure of glucocorticoid during the follow-up might bias the results of short-course use of glucocorticoids. To address this concern, we conducted a post-hoc analysis by excluding patients with further exposure of glucocorticoids (n=337) and the results remained consistent (HR 8.33; 95% CI 2.01-34.58; p = 0.004).

In conclusion, our study shows clearly that short-term use of VHD glucocorticoid greatly increases the risk of AVN, but fortunately not the risk of other major diseases like cardiovascular disease or cancer. COVID-19 affects patients of all ages. Doctors must therefore weigh up the potential benefits against the long-term risks whenever high-dose glucocorticoids are contemplated.

Acknowledgement:

The study protocol was approved by the institutional review boards of the University of Hong Kong and Hong Kong Hospital Authority (HKHA); Reference: UW20-172

Source of funding

There is no funding source for the study.

Conflict of interest

No author has conflict of interest in the study.

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Table 1 Association of very high dose glucocorticoid and clinical outcomes, compared with low to high dose, in patients with SARS.

	Low to high dose (reference)				Very high dose or pulse therapy							
Outcome	N	person years	event	incidence, per 1000 person-years	N	person years	event	incidence, per 1000 person-years	HR[a] (95% CI)	P	HR[b] (95% CI)	P
Avascular necrosis	292	4458	3	0.67	850	12833	62	4.83	7.50 (2.34-24.0)	<0.001	6.98 (2.17-22.4)	0.001
Cancer	285	4433	8	1.8	834	13218	43	3.25	1.81 (0.85-3.89)	0.126	1.88 (0.82-4.30)	0.14
Coronary heart disease	287	4393	13	2.96	831	13302	20	1.5	0.76 (0.37-1.57)	0.456	0.79 (0.37-1.70)	0.55
Heart failure	289	4451	6	1.35	842	13549	9	0.66	0.55 (0.18-1.63)	0.28	0.75 (0.24-2.33)	0.62
Stroke	285	4395	7	1.59	835	13396	11	0.82	0.57 (0.21-1.52)	0.26	0.79 (0.29-2.12)	0.63
Thyroid disorder	290	4435	3	0.68	843	13425	11	0.82	1.29 (0.35-4.80)	0.702	1.33 (0.35-5.06)	0.67
Diabetes mellitus	279	4247	16	3.77	755	11907	54	4.54	1.30 (0.74-2.30)	0.359	1.40 (0.74-2.64)	0.30
Osteoporosis fractures	287	4364	10	2.29	843	13371	24	1.79	0.78 (0.37-1.64)	0.509	1.12 (0.50-2.52)	0.79
Chronic kidney disease	287	4445	5	1.12	846	13560	11	0.81	0.79 (0.26-2.39)	0.68	0.59 (0.18-1.97)	0.39
Chronic liver diseases	285	4345	6	1.38	844	13329	19	1.43	1.09 (0.43-2.75)	0.863	1.27 (0.45-3.57)	0.65
Cataract	289	4434	9	2.03	847	13418	29	2.16	1.53 (0.69-3.39)	0.297	1.05 (0.44-2.54)	0.91

a model adjusted for age, sex, and Charlson comorbidity index

b Sensitivity analysis using propensity score matching