Systemic Corticosteroids and Transition to Delirium in Critically Ill Patients*

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Objective: Corticosteroids are frequently used in critically ill patients. We investigated whether systemic corticosteroid use increases the probability of transitioning to delirium in a large population of mixed medical-surgical ICU patients.

Design: Prospective cohort study.

Setting: A 32-bed medical-surgical ICU at an academic medical center.

Patients: Critically ill adults (n = 1,112), admitted to the ICU for more than 24 hours without a condition that could hamper delirium assessment.

Interventions: None.

Measurements and Main Results: Systemic corticosteroid exposure was measured daily and converted to prednisone equivalents (milligrams). Daily mental status was classified as coma, delirium, or an awake without delirium state. Transitions between states were analyzed using a first-order Markov multinomial logistic regression model with 11 different covariables, with the transition from an awake without delirium state to delirium as a primary interest. Among the 1,112 patients, corticosteroids were administered on 35% (3,483/9,867) of the ICU days at a median dose of 50 mg (interquartile range, 25–75 mg) prednisone equivalent. Administration of a corticosteroid, and any increase in the dose of the corticosteroid given on exposure days, was not significantly associated with the transition to delirium (adjusted odds ratio, 1.08; 95% CI, 0.89–1.32 and adjusted odds ratio, 1.00; 95% CI, 0.99–1.01, per 10 mg increase in prednisone equivalent).

Conclusions: In a large population of mixed medical-surgical ICU patients, systemic corticosteroid use was not associated with an increased probability of transitioning to delirium. (Crit Care Med 2015; 43:e585–e588)

Key Words: corticosteroids; delirium; intensive care unit; risk factor

Systemic corticosteroids may have beneficial effects in certain critically ill populations (1, 2). However, corticosteroids have long been associated with delirium, albeit up to the year 2000 steroid-associated delirium was generally called steroid-associated psychosis (3–5). It is possible that corticosteroids will lead to limbic-hypothalamic-pituitary-adrenal axis dysfunction, dopaminergic system inhibition, or have a direct toxic effect on different brain regions, particularly the hippocampus, which may hamper selective attention and memory function and thus increase the odds of transitioning to delirium (6, 7)

A recent cohort study in ICU patients found that systemic corticosteroid administration was associated with an increased probability of transitioning to delirium (8). However, the patient cohort in this study was relatively small and limited to only patients with acute lung injury (ALI) (8). We evaluated the association between systemic corticosteroid use and the daily transition from an awake without delirium state to delirium in a larger population of mixed medical-surgical ICU patients.

METHODS
Data were gathered as part of a prospective cohort study of consecutively admitted adult patients who stayed in the 32-bed medical-surgical ICU of the University Medical Center Utrecht for at least 24 hours, between January 2011 and June 2013 (9). Patients were excluded when they had been transferred from an ICU of another hospital, or if they had any neurological...
disorder or another condition that could hamper delirium assessment. The Medical Research Ethics Committee of the University Medical Center Utrecht approved this study and waived the need for informed consent (protocols 12–421 and 10–056).

Patients’ mental status was assessed daily in a research setting using a validated multistep algorithm encompassing the full previous 24 hours. The algorithm was based on Confusion Assessment Method for the ICU assessments by the bedside nurse, a chart review for symptoms of delirium, whether anti-psychotic therapy was initiated and the results of an additional CAM-ICU assessment by a research nurse (10). Patients were classified each day as being in coma, delirium, or an awake without delirium state (10).

Systemic corticosteroid exposure was derived from medication administration records. After accounting for the lower bioavailability of oral administration, the daily dose of each corticosteroid administered was converted to the prednisone milligrams (mg) equivalent and a total daily prednisone equivalent dose was calculated. The conversion factors for bioavailability adjustment, as well as the conversion factor for calculating the prednisone equivalents, are outlined in Table E1 (Supplemental Digital Content 1, http://links.lww.com/CCM/B445).

On the basis of prior literature, we included the following potential confounders in the multivariable analyses (11). Covariates measured at ICU admission were age, corticosteroid use prior to ICU admission (yes/no), the Charlson Comorbidity Index, the type of ICU admission (i.e., medical, elective surgical, or acute surgical), and the Acute Physiology and Chronic Health Evaluation IV score. Covariates measured daily were the length of ICU stay until the defined transition occurred, the daily Sequential Organ Failure Assessment score without the neurological component, use of mechanical ventilation (yes/no), presence of inflammation (defined by Systemic Inflammatory Response Syndrome criteria; yes/no), use of opioids (yes/no), and use of benzodiazepines (yes/no).

Categorical variables were reported as frequencies. Continuous data, where appropriate, were presented as mean with SD or median with interquartile ranges (IQRs). First-order Markov multinomial logistic regression models were used to describe the relationship between corticosteroid exposure and the odds of transitioning from an awake without delirium state to delirium in terms of odds ratios (ORs). As previously described, these models included 12 possible transitions to account for competing events, with the transition from an awake without delirium state to an awake without delirium state defined as the reference (9). First, the association was established between any corticosteroid exposure and the transition to delirium. In addition, on those days that corticosteroids were administered, the association between the dose of corticosteroid administered and the transition to delirium was analyzed.

Considering that the potential deliriogenic mechanism of corticosteroids might be based on their direct toxic effect on the hippocampus, and that dexamethasone penetrates the blood-brain barrier poorly, we completed a secondary analysis that excluded dexamethasone exposure (7, 12). To explore whether the administration of a high corticosteroid dose on any ICU day affected the transition to delirium disproportionately, two other sensitivity analyses were completed. In the first analysis, the high-dose days (> 100 mg of prednisone equivalent) were excluded from the analysis. In the second, low-dose corticosteroid exposure (≤ 100 mg of prednisone equivalent) were excluded, and the analysis was performed with high-dose corticosteroid days versus days with no corticosteroid exposure. Furthermore, in an attempt to replicate the analysis of Schreiber et al (8), we completed a post hoc sensitivity analysis in patients who experienced one or more days with severe hypoxemia (i.e., PaO₂/Fio₂ ratio of ≤ 200 mm Hg).

All data analyses were performed with IBM SPSS Statistics 21.0 for Windows and R version 3.1.1 for Windows (R Foundation for Statistical Computing, Vienna, Austria). Null hypotheses were tested against two-sided alternatives, and statistical inference was done using a significance level of 0.05.

RESULTS

The study population consisted of 1,112 medical-surgical patients, accounting for 9,867 ICU observation days. Patient characteristics are described in Table 1. The flowchart of the applied exclusion criteria has recently been published (6).

Corticosteroids were administered on 35% (3,483/9,867) of the observation days to 513 patients (46%). The patients exposed to corticosteroids had more comorbidities, stayed longer in the ICU, were more severely ill, had more often received corticosteroids before ICU admission, and were more often delirious (Table 1). A comparison of the covariables that changed daily between the days a corticosteroid was administered and the days it was not are presented in Table E2 (Supplemental Digital Content 2, http://links.lww.com/CCM/B446). Patients were more severely ill on days that corticosteroids were administered (Table E2, Supplemental Digital Content 2, http://links.lww.com/CCM/B446). The administered corticosteroids included dexamethasone, fludrocortisone, hydrocortisone, methylprednisolone, and prednisone and were administered either IV or orally. The median daily prednisone equivalent dose was 50 mg (IQR, 25–75 mg). The transition from an awake without delirium state to delirium was observed 562 times (6%). On 205 of these transition days (37%), corticosteroids were administered, at a median dose of 38–mg (IQR, 20–66 mg) prednisone equivalent.

The administration of corticosteroids was not significantly associated with a higher probability of transitioning to delirium from an awake without delirium state (adjusted OR, 1.08; 95% CI, 0.89–1.32) (Table 2). In patients who received corticosteroids, the dose of corticosteroids was not associated with a transition to delirium (adjusted OR, 1.00; 95% CI, 0.99–1.01, per 10 mg prednisone equivalent increase). Exclusion of dexamethasone did not alter the odds of transitioning to delirium significantly (adjusted OR, 1.05; 95% CI, 0.86–1.28). High-dose corticosteroid therapy (> 100 mg of prednisone equivalent) was administered on 13% of corticosteroid days. The odds of transitioning to delirium were not significantly different on
days patients received low-dose corticosteroids (adjusted OR, 1.10; 95% CI, 0.89–1.34) and on those days patients received high-dose corticosteroids (adjusted OR, 0.87; 95% CI, 0.51–1.48) when compared with days patients exposed to no corticosteroid. Limiting the analysis to the 495 patients (45%) who experienced severe hypoxemia during their ICU stay did not alter the association significantly either (adjusted OR, 1.00; 95% CI, 0.79–1.25).

**DISCUSSION**

Using time-varying multivariable statistical analysis that incorporated both known risk factors for delirium and considered competing events, we found that the administration of corticosteroids in a large population of mixed critically ill adults is not a risk factor for the transition to delirium. Although it appears that neither the dose of corticosteroid administered nor the high doses of daily corticosteroid administered affect this transition, ICU clinicians should still down-titrate corticosteroid therapy to the lowest effective dose whenever clinically appropriate and focus on identifying and removing other modifiable delirium risk factors, where possible, which are more strongly associated with delirium.

A recent study suggested that administration of corticosteroids to patients with ALI increases the risk for a transition to delirium (8). It could be that the choice of this study population accounted for the discordance with our results. However, when we attempted to replicate these findings by investigating patients in our cohort who experienced at least 1 day of severe hypoxemia, we found that corticosteroid administration did not influence the odds of transitioning to delirium. However, the results of this secondary analysis must be interpreted with caution given that we used a nonspecific clinical marker to define ALI and had fewer patients with ALI than the Schreiber et al (8) cohort.

**TABLE 1. Characteristics of the Study Population**

| Characteristic                                      | All Patients (n = 1,112) | Patients Receiving No Corticosteroid (n = 599) | Patients Receiving Corticosteroid (n = 513) | p*     |
|-----------------------------------------------------|-------------------------|-----------------------------------------------|---------------------------------------------|--------|
| Age (yr), mean (sd)                                 | 60 (16)                 | 61 (16)                                       | 60 (17)                                     | 0.43   |
| Male, n (%)                                         | 672 (60)                | 379 (63)                                      | 293 (57)                                    | 0.04   |
| Charlson Comorbidity Index, median (IQR)            | 6 (0–10)                | 6 (0–10)                                      | 7 (3–11)                                    | < 0.001|
| Type of admission, n (%)                            |                         |                                               |                                             |        |
| Medical                                             | 519 (47)                | 258 (43)                                      | 261 (51)                                    | < 0.001|
| Elective surgical                                   | 307 (28)                | 195 (33)                                      | 112 (22)                                    |        |
| Acute surgical                                      | 286 (26)                | 146 (24)                                      | 140 (27)                                    |        |
| Acute Physiology and Chronic Health Evaluation IV, mean (sd) | 74 (28)                | 68 (26)                                       | 81 (29)                                     | < 0.001|
| Length of ICU stay (d), median (IQR)                | 5 (2–10)                | 4 (2–7)                                       | 7 (3–14)                                    | < 0.001|
| Home medication use of corticosteroid               | 181 (16)                | 20 (3)                                        | 161 (31)                                    | < 0.001|
| Delirium                                            | 535 (48)                | 251 (42)                                      | 284 (55)                                    | < 0.001|
| No. of delirium days during ICU stay, median (IQR)b | 3 (1–6)                 | 2 (1–5)                                       | 3 (2–7)                                     | 0.003  |

IQR = interquartile range.

*Comparison between patients with and without systemic corticosteroids administered during ICU stay were made using a t test for normally distributed continuous data, the Mann-Whitney U test for non-normally distributed continuous data, and the chi-square test for categorical data.

**TABLE 2. Odds Ratios for Daily Transitioning From an Awake Without Delirium State to Delirium**

|                | Odds Ratio (95% CI)* |
|----------------|---------------------|
|                | Crude               | Adjustedb             |
| Corticosteroid administration (vs no administration) | 1.12 (0.93–1.35) | 1.08 (0.89–1.32)  |
| Corticosteroid dose (per 10 mg prednisone equivalent increase) | 0.99 (0.98–1.00) | 1.00 (0.99–1.01)  |

*The transition from an awake without delirium to an awake without delirium state the next day was used as the reference transition.

*Adjusted for age, home use of corticosteroids, Charlson Comorbidity Index, type of ICU admission, Acute Physiology and Chronic Health Evaluation IV score, length of ICU stay until transition, Sequential Organ Failure Assessment score (without the neurological component), use of mechanical ventilation, presence of inflammation defined by Systemic Inflammatory Response Syndrome criteria, use of opioids, and use of benzodiazepines.
There are several other potential reasons for the discordance between our analysis and that of Schreiber et al (8). Although we used a validated algorithm that encompassed the full previous 24 hours to classify the daily mental status (10), Schreiber et al (8) used a single daily assessment. Given the fluctuating nature of delirium, a single daily bedside assessment could have missed some delirious patients, which may have resulted in an over-representation of more persistent delirium. With the patients most severely ill more likely to not only develop delirium but also, at the same time, receive corticosteroids, it is possible that the association observed by Schreiber et al (8) is only applicable to the sickest patients in the ICU. Differences in the method by which covariables were selected may also have led to the observed discordance between our results and those of Schreiber et al (8). Currently, no consensus exists on the preferred method for covariable selection (13). Although we used published literature to identify confounders that should be included in the multivariable analysis, Schreiber et al (8) relied on statistical testing. This approach may lead to the exclusion of important confounders (e.g., home corticosteroid use) resulting in residual confounding, or to the inclusion of redundant confounders that may result in model overfitting and the reporting of an apparent effect when one does not truly exist (13).

Our study also has limitations. Although a rigorous and validated multistep delirium assessment algorithm was used daily in all patients, it remains possible that delirium may have been misclassified on some ICU days. Although the first-order Markov assumption states that multiple records on a single individual are considered to be independent, in the case of day-to-day transitions, as was evaluated in our analysis, this does not necessarily hold true (9). Furthermore, the occurrence of confounding by indication cannot be ruled out. The number of occurrences included in some of the secondary analyses (e.g., days of high-dose corticosteroid therapy and patients with potential ALI) may have been too low to establish differences between the groups. Conclusions from our study on whether corticosteroid use effects either delirium severity or duration cannot be made. In addition, the results of our analysis may be different at centers where corticosteroid prescribing practices are different. Also, as with all observational studies, residual confounding might have occurred. To assess causality, a randomized controlled trial would be needed. Therefore, we agree with Schreiber et al (8) that future randomized controlled trials of corticosteroids in the ICU need to carefully evaluate the prevalence of delirium with their use (8).

CONCLUSION
In a large population of mixed medical-surgical ICU patients, corticosteroid use was not associated with an increased probability of transitioning to delirium.

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