ORIGINAL ARTICLE

Adverse Events in Long-Term Corticosteroid Therapy in Elderly: A Case Series of 71 Patients

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ABSTRACT

Objective: **To assess the rate, risk factors of adverse events (AEs) during long-term corticosteroid therapy in elders.**

Patients and methods: **We enrolled a retrospective study of our patients over 65 year-old treated with a high corticosteroid regimen for greater than 4 weeks.**

Results: **Seventy one elders were assessed. The most common condition was giant cell arteritis. The most common AEs were metabolic disorders (45 cases, 63.4%). There were 14 patients (19.7%) with corticosteroid induced diabetes mellitus. Corticosteroid therapy induced arterial hypertension in 10 patients (14.1%). In addition, 25 patients (35.2%) developed at least one infection. Prevailing infectious sites were skin (15 cases, 21%), lung (11 cases, 15.5%), and urinary tract (7 cases, 9.9%). Moreover, 18 patients (25.4%) developed osteoporosis. Our analysis showed that the prevalence of osteoporosis and diabetes was significantly higher in women (p = 0,001). Similarly, corticosteroid induced diabetes showed a significant correlation with blood glucose and creatinine at admission (p = 0.01). Infections were strongly correlated to the duration of high corticosteroid regimen (p = 0.035). Our analysis revealed that subjects with lymphopenia were more likely to develop urinary infections (p = 0,039).**

Conclusion: **Long-term GC use is associated with an increased rate of serious AEs in elderly. Our study highlights different AEs in elders.**

KEY WORDS

corticosteroid, adverse event, side effect, elderly

INTRODUCTION

Corticosteroids are widely used in the treatment of several auto-immune diseases. Many adverse events (AEs) such as substantial osteoporosis, diabetes mellitus, serious infections, gastrointestinal bleeding and ulcer, cataracts, glaucoma and cardio-vascular diseases may be significantly increased in patients taking moderate to high dose corticosteroids[1,2)]. On the other side, multimorbidity is one of the common clinical characteristics in older patients and it is significantly associated with increased disability, higher mortality and impaired quality of life[3)]. Otherwise, it is difficult to avoid polypharmacy in this population with, thus, an increased risk of AEs[4)].

Several large reviews emphasize that long-term corticosteroid use is a significant independent risk factor of potentially serious AEs[2,5,6)]. However, the safety of this regimen has not been well studied in elders.

In order to better point out corticosteroid toxicity in elderly, we investigated the corticosteroid-associated AE in elderly in our department of Internal Medicine.

PATIENTS AND METHODS

Study design

This is a retrospective study of elders admitted in the department of Internal Medicine from 1 January 1996 to 31 December 2012.

We included in our study patients over 65 year-old who were treated with a high GC regimen (1 mg/kg/day), initiated or not with three Methylprednisolone pulses for greater than 4 weeks. GCs were evenly tapered by 5 mg prednisone per week. The cumulative steroid doses were calculated till the AE was recorded. Of note, Pulse steroid therapy contributes significantly to cumulative dose.

Epidemiological, clinical and laboratory data, characteristics of GCs therapy, other associated treatment input and AE were reviewed from the medical records of all patients. Any following event that could be considered as AE was noted during hospitalization and after discharge of patients: new onset arterial hypertension, out-of control of arterial hypertension, metabolic disorders, osteoporosis, avascular necrosis of bone, gastro-intestinal ulcer, infection, cardio-vascular events, cataracts, glaucoma, myopathy, cutaneous changes and psychiatric trouble.

Received on August 25, 2023 and accepted on September 12, 2023

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Table 1: Characteristics of Patients at Cohort initiation

	With AE (N = 54) (76%)	No AE (N = 16) (24%)	Total (N = 71)
Age (years)	73 ± 5 (65-92)	74 ± 5 (66-83)	
Sex			71
Male	31 (43.7%)	14 (87.5%)	
Female	40 (56.3%)	2 (12.5%)	
Disease (steroid therapy) duration	44 ± 45 (3-193)	18 ± 17 months (3-62)	31 ± 31 months (3-193)
Medical history			
Diabetes mellitus	10 (14.1%)	0	10
Arterial hypertension	38 (46.5%)	5 (31.3%)	43
Dyslipidemia	7 (9.9%)	1 (6.3%)	8
Ischemic heart disease	3 (4.2%)	0	3
Gastric ulcer	2 (2.8%)	0	2
Gout	3 (4.2%)	0	3
Chronic renal failure	2 (2.8%)	1 (6.3%)	3
Ophtalmologic disease		5	
Cataract			
Glaucoma	2 (2.8%)	1 (6.3%)	
	2 (2.8%)		
Hip fracture	1 (1.4%)	0	1
Medications			
Anti-vitamin K drugs	4 (5.6%)	1 (6.3%)	4
Anti-platlet drugs	3 (4.2%)	0	3

Table 2: Diagnoses associated with GC use

	N (%)
Horton disease	52 (73.2)
Periarteritis nodosa	3 (4.2)
Sjogren syndrome	3 (4.2)
Interstitial lung disease	4 (5.6)
Indeterminate connective tissue disease	2 (2.8)
Sarcoidosis	2 (2.8)
Dermatomyositis	1 (1.4)
Wegener vasculitis	1 (1.4)
Optic neuritis	1 (1.4)
Panuveitis	1 (1.4)
Relapsing polychondritis	1 (1.4)

Data Analysis:

Findings were analyzed using Statistical Package for Social Sciences (SPSS software version 18). Statistical analysis was performed using paired t-tests for continuous variables and X^2 tests and 95% confidence limits to determine the significance of any differences. A p value of ≤ 0.05 was considered statistically significant.

RESULTS

Patients and treatment

Seventy one patients were assessed according to the inclusion criteria, 40 (56.3%) of whom were female. Sixteen (22.5%) had experienced no side effects of corticosteroid therapy.

We report in table 1 the characteristics of patients at admission before the introduction of GCs. The mean age of patients was 74 ± 6 years (65-92 years).

The most common conditions for which patients were receiving corticosteroid therapy were Giant Cell Arteritis. (52 cases, 73.2% of patients) (table 2).

Fifteen patients (21.1%) received three pulses of Methylprednisolone linked with GC per os. The mean duration of induction regimen with GC was 6 ± 1 weeks (3-12 weeks). They were followed up for a mean duration of 44 ± 46 months (3-193 months).

All patients included in this study received also calcium, vitamin D, potassium and gastroprotective drug.

AEs of corticosteroid therapy

Table 3 describes AEs of the GC therapy. One hundred forty nine AEs attributable to corticosteroid treatment occurred overall in 55 patients (77.5%). Side effects occurred after a median of 30 ± 32 months from the initiation of treatment (few days-138 months). Forty three patients (60.5%) experienced 2 or more AEs. The most common AEs included metabolic disorders, infections, and arterial hypertension (Table 3).

The most common AEs were the **metabolic disorders** (45 cases, 63.4%). There were 14 patients (19.7%) with corticosteroid induced diabetes mellitus, occurring after a mean duration of 7 ± 27 months (0-84 months). Eight patients (11.3%) with type 2 diabetes had a loss of blood glucose control.

Furthermore, patients with increased level of cholesterol and mixed dyslipidemia accounted for 12 (16.9%) and 15 (21.1%) respectively.

Corticosteroid therapy induced **arterial hypertension** in 10 patients (14.1%) after23 ± 35 months (1-132 months) and a previously diagnosed disease was imbalanced in 9 other patients (12.7%) after a mean duration of 24 ± 35 months (1-132 months). Three patients (4.2%) suffered from **coronary ischemia** after 41 ± 59 months (3-108 months) and 2 others (2.8%) presented a **cerebral stroke** within a mean period of 138 months.

In addition, 25 patients (35.2%) developed at least one **infection** (Table 5). Prevailing infectious sites were skin (5 cases (7%) of mycosis and 10 cases (14.1%) of erysipelas), lung (11 cases, 15.5%), and urinary tract (7 cases, 9.9%). The infections occurred within 22 ± 31 months (1-144 months).

Eighteen patients (25.4%) developed **osteoporosis** after a mean duration of 39 ± 49 months (2-168 months). Only one patient presented **avascular bone necrosis** of the hip in the first year of treatment.

Moreover, GC led to **cataract** in 8 patients (11.3%) and glaucoma in 2 patients (2.8%) after a mean duration of 47 ± 45 months (3-126 months).

Five patients complained of **mood trouble** while taking up to 10 mg prednisone per day.

Factors influencing the occurrence of AEs

Our analysis showed that the prevalence of osteoporosis, and corticosteroid induced diabetes was significantly higher in women (p = 0,001 and 0.02 respectively). Similarly, cortico-steroid induced diabetes showed a significant correlation with blood glucose and creatinine at admission (p = 0.01 and 0.04 respectively).

Table 3: Distribution and Characteristics of AEs

	N (%)	Term (month)
AE type		
Diabetes mellitus	14 (19.7%)	7 ± 27 (0-84)
Out-of control of diabetes	8 (11.3%)	0 ± 1 (0-3)
Hypokaliemia	6 (8.45%)	9 ± 17 (0-47)
Hypercholesterolemia	12 (16.9%)	33 ± 30 (3-112)
Mixed dyslipidemia	15 (21.1%)	33 ± 29 (3-112)
Hypocalcemia	1 (1.4%)	1
Infection	25 (35.2%)	22 ± 31 (1-144)
Gastrointestinal bleeding ulcer	1 (1.4%)	12
Fracture	1 (1.4%)	26
Osteoporosis	18 (25.4%)	40 ± 49 (2-168)
Avascular necrosis	1 (1.4%)	12
Myopathy	1 (1.4%)	18
Ophtalmologic complications		48 ± 45 (3-126)
Cataract	8 (11.3%)	
Glaucoma	2 (2.8%)	
Arterial hypertension	10 (14.1%)	24 ± 35 (1-132)
Out-of control of arterial hypertension	9 (12.7%)	
Myocardial infarction	3 (4.2%)	41 ± 58 (3-108)
Cerebral stroke	1 (1.4%)	138
Skin fragility	11 (15.5%)	39 ± 31 (2-84)
Mood trouble	5 (7%)	

Table 4: Infections due to GC use (25 cases)

	N°	%	Term (month)
Only 1	16	64	
2	3	12	
3	3	12	
4	3	12	
Urinary infection	7	9.9	24 ± 53 (1-144)
Pulmonary infection	11	15.5	20 ± 24 (2-84)
Cutaneous infection	10	14.1	22 ± 16 (5-60)
Mycosis	5	7	21 ± 28 (2-72)

Infections were strongly correlated to the duration of high corticosteroid regimen (p = 0.035). Of interest, infections tended to be higher in patients with lymphopenia at onset of disease but did not reach statistical significance (p = 0,068). Thus, we studied different site infections. Our analysis revealed that subjects with lymphopenia were more likely to develop urinary infections (p = 0,039).

The mean cumulative Prednisone dose was higher in patients who developed osteoporosis (p = 0.001). Conversely, the cumulative dose of GCs was neither significantly associated with corticosteroid-induced diabetes (p = 0.372) nor infection (p = 0.436).

Our analysis showed else no significant relationship between Methylprednisolone pulse and the occurrence of any AE.

DISCUSSION

There has been a resurgence of interest in the use of GC in several auto-immune diseases[1,6], but long-term safety has not been well studied in elders[4,5].

Few studies were enrolled to assess AE in elders, with almost studies combining old patients with young adults[5,7,8]. These studies especially concern induced diabetes and osteoporosis and there was else significant variability in methods and results[9-12]. Because such data are lacking in elders, we compared our results with AE in adults.

Our study showed that more than 77% of elders treated with corticosteroids were affected by at least one AE. This high incidence of corticosteroid-induced AEs in elderly close with the results of several studies which counted more than two third of adults that developed frequent AEs[2,5,6].

Observed in more than a third of the adults[5,8], the occurrence of metabolic disorders during long-term corticosteroid treatment is obvious and was raised by several studies[5,9]. Forty five patients (63.4%) in our cohort developed afterwards metabolic disorders.

New onset steroid-induced diabetes may unexpectedly develop in 4.3-9% of old patients treated with GC during the first year[9,10,13]. Besides, corticosteroid therapy was associated with a 2-3-fold increased risk of diabetes in previously healthy patients[10,13]. In our study, we accounted 14 cases (19.7%) of steroid-induced diabetes. Few authors reported that the risk of steroid-induced diabetes increased significantly with the cumulative dose of GC, the age and the body mass index[1,10,14], unlike our study. Of note, patients had significant improvement of the blood glucose once the GCs were discontinued[1,15], like our study. Nevertheless, 6 patients in our series developed persistent diabetes. However, the anti-diabetic drugs were withdrawn in only one patient in our series though GCs were maintained at low dose. In our series, we found also that blood glucose at start of treatment was significantly correlated with corticosteroid induced diabetes. To our knowledge, these findings were not previously reported in literature.

Patients with diabetes mellitus may have worse control of hyperglycemia while taking either low or high-dose of steroids[1,5,7-9,13,16]. In our series, we described 8 cases (11.3%) of out control of diabetes mellitus.

Nonetheless, few studies focused on electrolyte disorders and their outcomes either in young adults or old patients receiving high dose of GC[8]. Six patients (8.45%) showed in our study hypokalemia and only one patient presented with hypocalcemia.

Other studies have reported an increased risk of arterial hypertension with GC therapy[1,16-18]. Newly developed hypertension occurred in nearly 10% of patients treated with high dose of GC[13,18,19]. Sato *et al* showed a high rate (37%) of steroid-induced arterial hypertension in patients over 65 years[18]. Panoulas VF *et al* showed also that even long-term low-dose GC treatment increased the risk of arterial hypertension with a rate of 84,7%[20] and it was significantly linked to a dose of GC greater than 7,5 mg/day[20,21]. In our series, 10 patients (14.1%) showed arterial hypertension during their follow-up.

Cardiovascular events are well-known adverse events of systemic GC therapy[1,2,8,13,16,22]. Wei *et al* compared 68,781 patients treated with systemic corticosteroids with 82,202 controls. The risk of cardiovascular events was 2.5 - 3 folds higher in the corticosteroid group[22-24] and it was significantly increased with GC dose[24] and with other induced GC risk factors[13,24]. In our study, we ascertained 5 cardio-vascular events: 3 cases of myocardial infarction after a mean of 41 months (3-108 months) and 2 cases of cerebral stroke after 138 months. (Table 3).

Otherwise, the heightened risk of ocular complications with GC is obvious[1,25,26]. GC therapy may lead to cataract, increased intraocular pressure, myopia, exophthalmos, papilledema, central serious chorioretinopathy, and subconjunctival hemorrhages even in elderly[1,2,25,26]. The most well-described ophthalmic AEs of prolonged corticosteroid use are cataract[17] and glaucoma with a frequency of 15% and 18-36% respectively[1]. In the analysis of Poetker DM *et al*, the increased risk of glaucoma was significantly correlated with diabetes mellitus and arterial hypertension[1]. Our study sustained the findings of literature and showed ocular AEs in 9 patients (12.7%): cataract in 9 cases and glaucoma in 2 cases.

High-dose steroid therapy can lead to an increased risk of serious infections requiring hospitalizations[1,2,6,16,17,27,28]. Stuck *et al*[27] reviewed 71 studies to assess the risk of infections related to GC. They found an overall rate of infections of 12.7% in patients receiving GCs. Conversely, infections after GC were found in more than 64% in our study. Then, the rate of occurrence of infectious AEs in old patients treated with GC seems to be higher than young adults, a result suggesting that the underlying state and comorbidities account for the steroid-induced infectious AEs. The most frequent reported infections in literature were the urinary and pulmonary infections[5], like our series.

The risk factors of infection in literature were cumulative corticosteroid dose, concomitant use of immunosuppressive therapy and presence of neurologic, hepatic and renal diseases[27]. In our series, we found that lymphopenia at start of treatment was significantly associated with infections. To our knowledge, these findings were not previously report-

ed in literature.

Several prior studies have documented an increased incidence of both osteoporosis and fractures in patients receiving long-term corticosteroids[11,29-31]. The rate of steroid-induced osteoporosis is estimated up to 50% of corticosteroid users[1,2,6-8,12,15,16,34]. Paglia *et al*[32] studied bone resorption and formation in 14 elderly men who were treated with Prednisone for less than 30 days at a mean cumulative dose of 338 mg of Prednisone and showed significant increases in markers of bone turnover[6,7,34]. Van Staa *et al*. achieved a meta-analysis and attested a stronger correlation between cumulative steroid dose and decline in bone mineral density[6,35], like our study. Fracture risks have also been correlated to dose, duration, age, gender, and body weight[2,6,11,12,15,17,28,29,35,36]. Our study showed a less pronounced rate of osteoporosis because the bone mineral density was not systematically measured in all patients.

Of interest, avascular necrosis of bone was documented in only one subject. This supports prior reports suggesting that avascular necrosis of bone is uncommon[1]. This complication has been correlated in literature with cumulative dose, longer duration of corticosteroids[1,8].

The myopathy was encountered in 41-64% patients receiving high-dose of corticosteroids[1,2,8]. The number of patients with myopathy in our series could have been underestimated because of the potential omission of this AE in the outpatient department.

Many patients receiving steroid therapy report a slight increase in their overall depression, insomnia and psychiatric disturbances[1,2,15,33]. Conn and Poynard reported that with a mean daily dose of 35 mg of Prednisone, psychiatric side effects occurred 2 times more often than in those receiving placebo[34]. In addition, Nielson *et al* reported that psychiatric features are significantly linked to female gender[33] like in our series.

Although most searchers agree that steroids are substantially less toxic to the upper GI tract than non steroid anti-inflammatory drugs[1,7,8,16,23,28], GC may increase the risk of adverse GI events such as gastritis, ulcer, and serious bleeding[1,17,34]. In our series, we described only one case of gastrointestinal bleeding due to GCs.

We enrolled a retrospective study. Thereby, it design may not allow accurate screening of all AEs. Furthermore, certain measures such as electrolytes disorders, the body mass index and bone mass density were either inconsistently recorded in patients' charts in the outpatient department. Thus, it does not let us to draw definitive conclusions and correlations. Special consideration and strategies to reduce polypharmacy are needed when treating elderly patients with corticosteroids because of frailty, complications and organ dysfunction[4].

In summary, long-term GC use is associated with an increased overall rate of serious AEs in elderly. Our study highlights different AEs in elders that were rarely discussed previously in the literature. These potential risks should be carefully weighed against perceived benefits when using chronic corticosteroids in the management of different diseases. Then, further prospective and comparative trials in elders might be enrolled to underpin the causality between GC and AEs in old population and to establish prophylactic strategies.

ETHICAL CONSIDERATIONS

Available patients' data were anonymously used in the study.

Informed patient's consent was signed.

The ethics committee of the regional hospital of Ben Arous approve the clinical research protocol.

CONFLICT OF INTEREST

Authors have no conflicts of interest.

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