RESEARCH ARTICLE

DOI: 10.5935/0946-5448.20240024

International Tinnitus Journal. 2024;28(1):163-167

Impact of Intermittent Exposure Oral Corticosteroids on Fracture Risk In Iraq: A Case Control Study

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ABSTRACT

Summary: Oral corticosteroid are commonly prescribed medications known for their proven clinical advantages in treating individuals with chronic inflammatory and autoimmune conditions, including arthritis, and dermatological disorders.

Objectives: Intermittent high daily doses of oral corticosteroids effect on the risk of fracture remains debated. As a result, our objective was to investigate the risk of fractures associated with intermittent doses of high dose corticosteroids taken orally. This study aimed to report about the relationship between such intermittent corticosteroid use and the risk of fractures.

Methods: Our study involved a case-control investigation utilizing data from the Iraq Baghdad medical city, spanning from 2010 to 2022. In this study, patients above 18 years, who experienced a fracture (totaling 1245 cases). Controls, matched on a one-to-one basis, were individuals without a history of fractures. We calculated total cumulative dose (CD) among individuals who had used these medications intermittently. Adjusted odd ratio (OR) for the fracture risk connected to intermittent corticosteroid use, as compared to individuals who had never used them, were estimated using conditional logistic regression.

Results: The study found that intermittent corticosteroids is independently related to an elevated risk of hip fractures, with an adj.OR of 1.87 (95% CI 1.43 to 2.44). Similarly, the risk of vertebral fractures associated with intermittent corticosteroid increased, with an adj.OR of 2.96 (95% CI 2.04 to 4.30). However, there was little to no significant association identified for forearm fractures.

Conclusion: The use of intermittent corticosteroids showed higher risk for hip fracture. Patients on intermittent corticosteroid use are adviced to refer to patient counseling..

Keywords: Intermittent oral corticosteroids, Osteoporosis, Fracture.

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Paper submitted on July 05, 2024; and Accepted on July 12, 2024

INTRODUCTION

Oral corticosteroid are frequently prescribed medications renowned for their well-established clinical advantages in treating chronic inflammatory and autoimmune conditions. These conditions encompass chronic respiratory diseases, inflammatory arthritis, dermatologic disorders, and more[1-3]. Globally, the estimated rate of adult oral corticosteroid use varies from 1.5%-3%[4]. Generally, the use of oral corticosteroid is restricted due to significant side effects that tend to emerge after prolonged exposure[5-7]. Among the side effects linked to oral corticosteroid use, musculoskeletal disorders, especially osteoporosis, present a significant and well-documented concern[8-13]. Notably, oral corticosteroid use is related a substantial higher risk of fractures. Specifically, individuals using these medications face an estimated 30-120 percent higher hip fractures risk, & a 2- to 3-times higher risk of vertebral fractures compared to those not using them[14-16]. In cases of inflammatory conditions, symptom management often necessitates short courses of high doses. While corticosteroid-associated loss of bone and risk of fracture are dose-dependent[15, 17], the association between cumulative exposures is still not firmly founded[15, 17]. This underscores the complex nature of corticosteroid -related bone health issues.

Osteoporosis is a significant and serious complication for individuals undergoing long-term oral corticosteroid drugs. It's well-established that this treatment leads to rapid bone density loss, with both the dose and length of oral corticosteroid treatment playing crucial roles in this process[18]. However, there's a notable lack of studies that directly address the risk of fractures, which is the clinically crucial outcome resulting from this bone loss[18]. Most of the available studies have been limited to patients with conditions and have often involved relatively small patient cohorts, resulting in limited statistical result.

In one study, it was observed that patients taking oral corticosteroids had a higher risk of hip fractures, although these differences didn't persist throughout the entire study period[18]. To mitigate the risk of fractures in individuals undergoing oral corticosteroid therapy, it is recommended considering osteoporosis treatment for patients receiving a dose equivalent to 5-7.5 mg of prednisone/day for duration of 3 to 6 months[19-21]. These guidelines aim to address the critical issue of the risks of fracture related to long-term use of corticosteroids.

Until now, there has been a shortage of data concerning the fractures risk related to various exposure to oral corticosteroids. The limited availability of data has posed difficulties in investigating the impacts of various cumulative and daily dosage scenarios using database research. Thus, this study employed data from Iraq with the primary aim of examining the association between intermittent oral corticosteroid use and the incidence of fractures. This investigation focused on hip fractures, which are regarded as one of the most serious fractures caused by osteoporosis. The proper identification of hip fractures is dependent on reliable hospital and physician diagnosis codes, which are known for their dependability in comparison to other frequent fractures associated with osteoporosis[22, 23]. This methodology enabled a thorough analysis of the correlation between sporadic oral corticosteroid usage and the likelihood of experiencing hip fractures.

MATERIALS & METHODS

We conducted our study by searching patient files from Baghdad medical city. Following a population-based case-control design. Here's how it was structured:

1. **Cases:** Included all patients aged older than 18 years who have hip, vertebral, or forearm fracture between Jan. 1, 2010, and Dec. 31, 2022. The primary focus was on hip fractures, but you also identified patients with forearm fractures and vertebral fractures.

2. **Controls:** For each case, a control was randomly selected, with matching based on year of birth and age. These controls were individuals who had not sustained any fractures during the study period.

This design allowed to compare the exposure to intermittent oral corticosteroid between cases (fracture patients) and controls (non-fracture individuals) while controlling for age and birth year, helping to study the relation between corticosteroid use and fractures risk.

Exposure

Patients were categorized according to the corticosteroid oral intake into two groups:

1. Patients with no prior corticosteroid use before the index date were categorised as control group for all analyses.

2. Intermittent oral intake.

Statistical analysis

Our study employed conditional logistic regression as the statistical method to detect the relationship between oral corticosteroid use and the risk of fractures. The findings in the form of odds ratios (ORs) along with their corresponding 95% confidence intervals (95% CIs). All of these statistical analyses were carried out using SPSS version 23 by IBM.

RESULTS

Hip Fracture

Our study identified a total of 2490 hip fracture cases, which were closely matched with controls in terms of age, with a mean age of 78.6 years. The distribution of sex was also balanced, with 68.5% women among the study population. 20.4% of the hip fracture had a history of oral corticosteroid use prior to the index fracture. Current use of oral corticosteroid was associated with an elevated risk of hip fractures, with an adjusted odds ratio (adj. OR) of 1.87 (95% CI 1.43 to 2.44) when compared to individuals who had never used oral corticosteroid.

Table 1: Results for hip fracture.

	No of cases n=2490	No. of controls n=2490	Adjusted OR	95% CI
Never GC use	1,982	2,069	1	Reference
intermittent GC use	160	89	1.87	1.43 to 2.44
By intermittent dose (oral prednisolone equivalents)				
<1gram	25	19	1.37	0.75 to 2.50
≥1grams	135	71	1.98	1.47 to 2.66
≥5grams	82	42	2.03	1.39to 2.97
≥ 10grams	46	24	2	1.21 to 3.29
1-4.9grams	54	29	1.94	1.23 to 3.06
5-9.9grams	35	18	1.94	1.23to 3.06

Table 2: Results for clinical symptomatic vertebral fracture.

	No. of cases n=1842	No. of controls n=1842	Adjusted OR	95% CI
Never GC use	1,490	1,610	1	Reference
intermittent GC use	107	39	2.96	2.04 to 4.30
By intermittent dose (oral prednisolone equivalents)				
<1gram	19	11	1.87	0.88 to 3.93
≥1grams	51	23	2.4	1.45 to 3.93
≥5grams	56	16	3.78	2.16 to 6.62
≥ 10grams	32	10	3.46	1.69 to 7.05
1-4.9grams	33	12	2.97	1.52 to 5.77
5-9.9grams	24	7	3.7	1.59 to 8.62

Table 3: Results for radius/ulna fracture.

	No. of cases n=3316	No. of controls n=3316	Adjusted OR	95% CI
Never GC use	2,835	2,872	1	Reference
intermittent GC use	83	74	1.14	0.82 to 1.56
By intermittent dose (oral prednisolone equivalents)				
<1gram	24	22	1.11	0.61 to 1.97
≥1grams	60	52	1.17	0.80 to 1.70
≥5grams	33	28	1.19	0.71 to 1.98
≥ 10grams	19	16	1.2	0.61to 2.34
1-4.9grams	26	23	1.15	0.65 to 2.01
5-9.9grams	14	13	1.09	0.51 to 2.32

Among intermittent users, a higher Cumulative Dose (CD) of oral corticosteroid was linked to an increased risk of hip fractures, CD of <1 g had an OR of 1.37 [95% CI 0.75 to 2.50], which increased to 1.98 (95% CI 1.47 to 2.66) for CD ≥1grams, and 2.03 (95% CI 1.39to 2.97) for doses higher or equal to 5. (**Table 1&2**). These findings demonstrate a clear association between oral corticosteroid use, particularly at higher cumulative doses, and an increased risk of hip fractures.

Vertebral and Forearm Fractures

Table 2 presents the Odds Ratios (ORs) for clinical symptomatic vertebral fractures based on corticosteroid exposure. Notably, a cumulative dose (CD) of ≥1 g had a substantial increase in risk, with an adjusted OR of 2.40 (95% CI 1.45 to 3.93). This indicates around a two and a half higher risk of clinical symptomatic vertebral fractures among patients with this level of corticosteroid exposure. Conversely, when analyzing patients who experienced forearm fractures, the analysis revealed low to negligible associations with oral corticosteroid exposure. Furthermore, there was no observable dose-response relationship in the risk of forearm fractures, as indicated in (**Table 3**).

DISCUSSION

This study made several important observations and showed that Intermittent use of corticosteroid independently had an increased risk of hip fractures, with an adjusted odds ratio ratio (adj. OR) of 1.87 (95% CI 1.43 to 2.44). The association was also significant for vertebral fractures, with a similarly elevated risk (adj.OR 2.96; (95% CI 2.04 to 4.30). However, there was little to no association identified for forearm fractures. We noted that corticosteroid drugs have a substantial effect on bone health, inhibiting both bone deposition and break. This effect is more pronounced with increased doses and increased durations of use. Corticosteroid can disrupt calcium absorption in the kidneys and intestines, reduce sex hormones, and contribute to muscle atrophy, all of

which collectively results in higher risk of fractures and bone loss. This suggests that extent of corticosteroid exposure plays a critical role in fracture risk. Importantly, our findings align with a previous cohort study, reinforcing our results. These findings underscore the importance of monitoring and managing bone health in individuals with intermittent corticosteroid use, particularly at higher doses and durations, to mitigate the increased risk of fractures[15].

Osteoporosis management with bisphosphonates often falls short of the optimal level, especially for patients who had oral corticosteroid, including those on shorter duration that don't meet the recommended guideline of 7.5 mg per day for at least three months. Consequently, they continue to face a heightened risk of hip fractures. Given that bone remodelling typically spans around three months[24], frequent intermittent durations will cause disruptions in bone metabolism and prevent the complete regeneration of the skeleton. Actually, studies indicated that the risk of fractures continue for up to a year after discontinuing oral corticosteroid treatment[15, 17]. Still, the relationship between intermittent daily use and fractures is still debated. Furthermore, the impact of cumulative doses of oral corticosteroid on risk of fracture remains unclear.

Indeed, there have been other studies in this area worth mentioning. For example, a case-control study examined both inhaled and oral corticosteroid users and identified 366 cases of hip fractures among oral corticosteroid users[25]. This study explored the daily dose and found an overall lower risk compared to what we observed in our study. Direct comparisons of the impact of short duration use on fracture risk cannot be made. Furthermore, another study conducted research showing an increase in hip fracture[26].

In the interpretation of our findings, it's crucial to recognize certain limitations. Given the nature of our case-control study, it inherently lacks the capacity[27]. It's important to emphasise that an ongoing debate persists regarding the specific thresholds of corticosteroid exposure associated with an elevated fracture risk[28]. This potential underestimation of the impact in our fracture results is a consideration. However, it's important to highlight our belief in a low likelihood of differential misclassification, as we utilised commonly accepted codes for osteoporotic fractures. Furthermore, there is the possibility of misclassification of exposure to corticosteroid, and the fact that we cannot ignore medication errors by the patient. It's worth noting that corticosteroid are sometimes prescribed as PRN, meaning that even if they were dispensed by the pharmacy they may not have been taken by the patient. This introduces an element of uncertainty regarding the true extent of corticosteroid exposure. Our current study possesses several noteworthy strengths. Additionally, it's noteworthy that all fracture data used in our study have been validated, minimising the potential impact of misclassification in our findings[29].

CONCLUSION

In conclusion, the intermittent utilisation of high-dose oral corticosteroid indeed elevates the risk of fractures, necessitating primary attention to patients with extensive usage. This is defined as individuals who have undergone intermittent doses of high corticosteroid doses, resulting in a cumulative exposure exceeding 1 g prednisone equivalent. The knowledge of a patient's drug history, particularly in identifying high daily doses of oral corticosteroid, can aid clinicians in identifying those at elevated fracture risk. Such patients should be the focal point of osteoporosis management strategies to mitigate their fracture risk.

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