Hip fracture risk with corticosteroids in patients with COPD: a systematic review and meta-analysis

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Research Article

Keywords: Hip fractures, chronic obstructive pulmonary disease, corticosteroids, COPD

Posted Date: March 17th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-238943/v1>

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is a complex respiratory disease. The risk of osteoporosis and fragility fractures can increase in COPD patients treated with glucocorticoids.

Objectives: The purpose of this systematic review and meta-analysis was to investigate the relationship between the risk of hip fractures and patients with COPD treated with corticosteroids

Methods: We searched both randomized controlled trials (RCTs) and observational studies (case-control, prospective cohort or retrospective cohort) of hip fractures in patients with COPD. A meta-analysis was performed to calculate the odds ratio (OR) with 95% confidence intervals (CI) employing a random effect (RE) model or fixed effect (FE) model. Review Manager 5.3 was used for statistical analysis.

Results: The risk of hip fractures significantly increased in patients with COPD compared to patients without COPD. (OR: 1.38; 95% CI: 1.15-1.66; $p=0.09$; $I^2=43\%$). Patient treated with oral corticosteroids (OCS) has a significantly higher risk of hip fractures (OR: 1.45; 95% CI: 1.36-1.55).

Conclusion: The result of this meta-analysis showed that there is a significantly increased risk of hip fracture among patients with COPD.

Introduction

Chronic obstructive pulmonary disease (COPD) is a complex respiratory disease characterized by the progressive limitation of the airflow and the abnormality of the inflammatory response of the airways ¹. The disease remains serious health problems around the world ². COPD patients treated with glucocorticoids have an increased risk of osteoporosis and fragility fractures ³. Glucocorticosteroids (GCs), is prescribed in patients with COPD for their anti-inflammatory effect ⁴. Oral corticosteroids (OCS) have a different role in treatment for COPD, for stable COPD, the guideline did not recommend treatment with long-term use of OCS, for its multiple side effects with no proof of benefits ⁵. Short course of systematic GCs was only used for patients with acute exacerbations accompanied with bronchodilators and antibiotics according to the guidelines, the treatment can improve oxygenation, lung function (FEV1), recovery time and hospitalization duration can also be shortened ^{5,6}. Inhaled corticosteroids (ICS) are proved to be effective for preventing exacerbations ⁷ and the guidelines recommended ICS for treatment of COPD when patients experienced exacerbations ⁵. The potential adverse effects like diabetes, cataract, osteoporosis, and fractures counterbalanced the treatment benefits ⁸, the therapeutic benefit achieved at 400 to 1000 µg per day ⁹. Although it has been proven that oral glucocorticoid can lead to osteoporosis and fractures ^{10,11}, the negative effects of ICS on bone health, on the other hand, were inconsistent ^{12,13}.

Osteoporosis in COPD patients can be caused by multiple reasons including age, smoking, immobility, vitamin D deficiency, systemic inflammation and the treatment of OCS ¹⁴. Hip fracture is a common site of fracture due to osteoporosis, is the most fatal site of fragility fractures ^{15,16}. It can happen without any

incentive, but it can also be induced by falling, which is commonly seen in COPD patients¹⁷. A hip fracture can be of great pain, and required hospitalization¹⁸. The objective of this meta-analysis is to ascertain the risk of hip fractures in patients with COPD treated with corticosteroids.

Methods

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement¹⁹. The protocol for this systematic review was registered on INPLASY (ID 202040098) and is available in full on the inplasy.com (<https://doi.org/10.37766/inplasy2020.4.0098>). Ethical approval was considered unnecessary since it was a systematic review of existing works of literature and patient data did not involve.

Eligibility criteria

Our inclusion criteria were:

1. Randomized controlled trials, and observational studies were included.
2. Patients diagnosed COPD according to the guideline.
3. Both oral and inhaled corticosteroids as intervention.
4. Outcome data on hip fractures.

Studies did not report hip fractures on both experiment group and control group were excluded.

Search strategy

PubMed, Embase and Cochrane Library databases were searched to identify randomized controlled trials (RCTs) and observational studies (case-control, prospective cohort or retrospective cohort) reporting on the hip fractures among patients with COPD. The following search terms were used for the initial literature search: *COPD, chronic obstructive pulmonary disease; cortisone or steroid or glucocorticoid; fracture*. Two authors searched for pertinent studies independently through April 2, 2020. The collection of the studies was then performed by 2 of the authors independently, and different views were decided through discussion. In addition, the reference lists of the articles were also reviewed manually to detect other potentially appropriate publications.

Study selection

Titles and abstracts were first screened to identify relevant studies and full texts of these studies were read. Studies included in this meta-analysis based on the following criteria:

- Type of publication: published articles in a peer-reviewed journal.
- Study design: randomized controlled trials (RCTs) and observational studies (case-control, prospective cohort or retrospective cohort).

- Study population: excluded the studies involving the same population.
- Only studies reporting hip fractures among patients with COPD were included.

All discrepancies between the two reviews were solved by WS.

Data extraction

For each eligible study, data were extracted individually by 2 authors including characteristics (age, sex, and other baseline characteristics), the drugs for treatment, and the number of hip fractures of patients. For studies that involved control groups, risk estimates [odds ratio (ORs) relative risks (RRs) or hazard ratios (HRs)] of hip fractures in patients with COPD were extracted.

Quality Assessment

The quality of RCTs was assessed by 2 authors using the tools introduced from the Cochrane Handbook²⁰. 8 domains were assessed according to the Cochrane Handbook:

- random sequence generation;
- allocation concealment;
- blinding of participants;
- blinding of personnel;
- blinding of outcome assessment;
- incomplete outcome data;
- selective reporting;

other biases (baseline imbalance, the similarity in using cointerventions between groups, and inadequate statistical analysis).

Newcastle Ottawa Scale was used to assess the quality of observational studies. With an overall quality score ranging from 0 to 9, the selection was assigned for 4 scores, comparability for 2 scores and outcomes for 3 scores. 0-3 scores were considered as low quality, 4-6 was deemed as moderate quality and over 6 scores were determined as high quality²¹. The dispute was solved by a third author.

Data synthesis and analysis

The main outcome in this meta-analysis was the number of hip fractures among patients with COPD using glucocorticoids. Pooled data were calculated as an OR with 95% CIs. Forest plots were created showing a summary of results with 95% CIs. I^2 analyses were used to assess heterogeneity between studies, $I^2 > 50\%$ indicated a significant heterogeneity²¹. The fixed effect (FE) model was first used, and if the $I^2 > 50\%$ which indicates the substantial level of heterogeneity, the random effect (RE) model was chosen. Publication bias was shown visually using funnel plots. Review Manager 5.3 (Cochrane IMS, Copenhagen, Denmark) was used to analyze the data and generate a forest plot. Sensitivity analyses were

made by excluding studies serially and assess its effect on the overall results. Publication bias was evaluated visually using funnel plots.

Subgroup analysis

To detect potential causes of heterogeneity, we conducted subgroup analyses based on the different corticosteroids used in treating COPD.

Results

Study selection

The flowchart (Figure 1) showed the process of our selection. We identified 982 studies from searching the databases. 91 full-text articles were assessed after excluding the duplicates and screening the titles and abstracts of the articles, reviews and case reports were also excluded. 8 studies were included in the final qualitative synthesis.

Study characteristics

The characteristic of all 8 included studies was shown in Table 1. Two studies were randomized controlled trials ^{22, 23}, six studies were observation studies ^{21, 24-28}. A total of 1419464 patients were involved in this meta-analysis, ranging from 452 to 1271072. There were six studies involving over 50% of male participants. And the mean age of participants in every study was over 60 years old. The intervention for COPD was various in experiment groups, two studies were OCS ^{21, 24}, four studies were ICS ^{22, 23, 25, 27} and two studies were both ICS and OCS ^{26, 28}. The duration of follow-up ranges from 6 months to 6 years.

The association between COPD and hip fractures

The results of the fixed-effect meta-analysis showed that the risk of hip fractures in patients with COPD significantly increased compared to the patients without COPD (OR: 1.38; 95% CI: 1.15-1.66; p=0.09; I²=43%; Figure 2). The pooled results consist of that of Walsh et al., Tsai et al., Lee et al., Dam et al. and Akyea et al. ^{21, 24, 25, 27, 28}.

The association between the dose of corticosteroids and hip fractures

Three studies reported the relationship between the risk of hip fracture and the dose of systematic corticosteroids ^{26, 29, 30}. The pooled meta-analysis cannot be performed due to the difference in their grouping by the dose of corticosteroids. A similar dose-dependent increase in the risk of hip fractures was observed in both three studies. Vestergaard et al. ²⁹ found the maximum risk of hip fracture at the dose at ≥ 7.50 mg/d (OR: 1.79 95% CI:1.68–1.91). Balasubramanian et al. ³⁰ reported the highest risk of hip

fracture in patients with systemic glucocorticoid exposure at 0-5 mg/d. Oshagbemi et al.²⁶ found the cumulative dose of 5.0–9.9 g/d were at a higher risk (OR: 2.88 95% CI: 1.27–6.57) than ≥ 10 g/d.

Subgroup Analysis

We performed a subgroup analysis according to the treatment for COPD. A total of 8 studies were all included in the analysis and grouped into ICS, OCS, ICS, and OCS. The result of the subgroup analysis was shown in Figure 3. There were 3 studies reported the results of ICS treatment, 2 reported the results of OCS and 3 reported the results of ICS and OCS. The result indicated that patient treated with OCS has a significantly higher risk of hip fractures (OR: 1.45; 95% CI: 1.36-1.55), and the total results showed similar finding of a pooled OR of 1.44 (95% CI: 1.35-1.53; $I^2 = 59\%$; $P = 0.02$).

Quality assessment

The risk of bias assessment for each RCT was shown in Figure 4 and observational studies were presented in Table 2. There was a study have unclear allocation concealment and both studies were unclear regarding the reporting bias. All observational studies included were of high quality (Newcastle-Ottawa Scale >6). In general, both RCTs and observation studies we included have a good quality with low risk.

Publication bias

There was mild to moderate asymmetry by inspection visually of the funnel plot (Supplemental figure 1). This may due to the small amount (<10 studies) of the studies included in our meta-analysis. And further analysis of publication bias did not conduct.

Sensitivity analysis

The pooled OR rates ranged from 1.36 to 1.47 after consecutively removed every study. A notably higher OR (OR: 1.47) of hip fractures was observed after removing the study by Dam et al.²⁸. And I^2 also decreased to 0% after removing their study, indicating the origin of heterogeneity.

Discussion

The result of this meta-analysis showed that there is a significantly increased risk of hip fracture among patients with COPD. Previous meta-analyses by Loke et al. and Chang et al. have shown the association between COPD and fractures³¹ or vertebral fractures³² respectively. Loke et al. only analyzed the risk of fracture when treated with ICS, whereas Chang et al. focused only on vertebral fractures and the treatment were limited to OCS. This meta-analysis focused on hip fractures among patients with COPD, and the treatments included both ICS and OCS.

Eight studies were included in this meta-analysis with a total of 1419464 patients. The overall results suggested that COPD patients have a high risk of hip fracture compare to patients without COPD.

However, the result is difficult to determine whether it was due to the adverse effects of glucocorticoids or the severity of COPD. The result from the subgroup analysis indicated that different treatments for COPD have various impacts on the possibility of hip fractures. OCS has a significantly higher risk of hip fractures, which is consistent with previous studies^{32 10}. The subgroup of ICS and the subgroup of ICS and OCS did not show a statistic different on the possibility of hip fractures. RCTs and observational studies involved in our meta-analysis have a high quality in general. The tunnel plot showed mild to moderate asymmetry, which may result from we included less than 10 studies in our meta-analysis. According to Cochrane Handbook²⁰, a small amount of studies minors the power of tests to detect real asymmetry. Therefore, publication bias can occur in this study notwithstanding we endeavored to reduce this bias throughout the search and screening process. A sensitivity assessment identified one study²⁸ that resulted in heterogeneity.

The association with fractures and COPD has been inconsistent. A nested case-control study conducted by Rodriguez et al.³³ concluded that ICS can lead to a small but significant rise in fracture risk, especially when ICS at higher doses. Tsai et al.²⁵ concluded that both medium and high doses of ICS can result in elevated risk of hip fractures. A significant association between ICS and vertebral fractures were observed in a cross-sectional study conducted by McEvoy et al.³⁴. Gonnelli et al.³⁵ found there were significantly increased risk of vertebral fractures in COPD patients and the severity of the disease is also significantly associated with the risk of fractures. But different results were also revealed. Lee et al. and Ferguson et al.^{22,36} found no statistically significant association between ICS with fracture risk. Johannes et al.³⁷ also concluded no increased nonvertebral fracture risk for patients treated with ICS. Studies of COPD patients treated with OCS was not numerous since the treatment was not recommended by the guideline. But the conclusion from these studies was identical. The authors^{21,24} all concluded that COPD patients treated with OCS were at a significant risk of fractures. It was commonly known that OCS can increase the risk of fragility fractures^{10,11}, but osteoporosis can be observed in GC naïve patients with COPD³⁴.

There were several limits to this meta-analysis. First, only two RCTs were included in our analysis. This is due to most of RCTs considered fractures as an adverse effect and did not present data of hip fractures independently. Thus, the risk of bias regarding randomization was high in other observational studies. Second, most of the studies included were lack of data of dosage, therefor a dose-response meta-regression cannot be performed. There was a therapeutic benefit of treatment using corticosteroids⁹, a dose-response meta-regression can provide evidence for physicians to determine the dose for the treatment of COPD. Third, our meta-analysis failed to establish whether the result was because of the use of corticosteroids or COPD severity. It was due to insufficient studies reported about the relationship between the severity of the disease and the rate of hip fractures. And we included six observational studies, which few studies were able to exclude the influence of corticosteroids since it was a common treatment for COPD. Fourth, the diagnosis of COPD was not elaborated in all studies. The difference in diagnosing COPD may result in inaccuracy to our results.

In conclusion, corticosteroids, play an important role in patients with COPD for its anti-inflammatory effect. Our pooled results showed that patients with COPD treated with corticosteroids were at a higher risk of hip fractures. The increasing risk of hip fractures may due to the adverse effect of corticosteroids and the development of COPD. Physicians should be aware of these fatal side effects when treating patients.

Declarations

Funding

This meta-analysis did not received any funding.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Tables And Figures

Tables 1-2 and Figures 1-4 are not available in this version.

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