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High-Dose Corticosteroid Use and Risk of Hip Osteonecrosis: Meta-Analysis and Systematic Literature Review

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ABSTRACT

The effect of varying corticosteroid regimens on hip osteonecrosis incidence remains unclear. We performed a meta-analysis and systematic literature review to determine osteonecrosis occurrences in patients taking corticosteroids at varying mean and cumulative doses and treatment durations, and whether medical diagnoses affected osteonecrosis incidence. Fifty-seven studies (23,561 patients) were reviewed. Regression analysis determined significance between corticosteroid usage and osteonecrosis incidence. Osteonecrosis incidence was 6.7% with corticosteroid treatment of >2 g (prednisone-equivalent). Systemic lupus erythematosus patients had positive correlations between dose and osteonecrosis incidence. Each 10 mg/d increase was associated with a 3.6% increase in osteonecrosis rate, and >20 mg/d resulted in a higher osteonecrosis incidence. Clinicians must be wary of osteonecrosis in patients on high corticosteroid regimens, particularly in systematic lupus erythematosus.

Osteonecrosis can lead to destructive arthropathies affecting the hip, knee, shoulder, and other joints, and it occurs most commonly in the first four decades of life [1–3]. This disease represents 2% to 10% of total hip arthroplasties performed in the United States and Europe, but may be as high as 50% to 60% in Korea and Japan [1,4–6]. The etiology of atraumatic osteonecrosis remains multifactorial, and no consensus exists on common pathophysiologic mechanisms. Vascular impairment, abnormal cellular reparative processes, and genetic point mutations have been implicated [7–10]. Risk factors include direct causes such as trauma, radiation exposures, hematologic diseases (sickle cell), and dysbarism (Caisson disease), as well as numerous indirect associated factors, such as rheumatologic or metabolic diseases, corticosteroids, alcohol, and/or smoking [1–3,7].

Heimann and Freiberger [11] were among the earliest to report cases of osteonecrosis in patients treated with high corticosteroid doses. Multiple studies since then have implicated prolonged, high-dose corticosteroid use as an independent factor associated with osteonecrosis, and it has been reported that doses greater than 2 g within three-months present a risk for developing osteonecrosis [3,12]. However, there are marked heterogeneities in patient demographics and epidemiologic variabilities between studies. Furthermore, few reports have examined differences in osteonecrosis incidences as functions across different medical diagnoses.

A systematic literature review and a meta-analysis were conducted to investigate the association of high-dose corticosteroid therapy with osteonecrosis incidences. Primary research questions were: (1) what were the overall osteonecrosis incidences in patients taking high-dose corticosteroids; (2) does the underlying disease for which corticosteroids are used affect osteonecrosis incidences; (3) whether mean doses, cumulative doses, or treatment durations were associated with incidences; and (4) whether pulsed therapies affected incidences.

Methods

Publications in peer-reviewed literature were identified by searching medical databases: Medline (1966-to-present); EMBASE

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(1947-to-present); SCOPUS (1966-to-present); and Web-of-Science (1945-to-present). Boolean search queries included following search keys: (osteonecrosis[title] OR avascular necrosis[title] OR bone necrosis[title] OR aseptic necrosis[title]) AND (corticosteroid*[title] OR steroid*[title] OR prednisone[title] OR prednisolone[title] OR methylprednisolone [title] OR cortisone[title] OR hydrocortisone[title] OR dexamethasone[title] OR betamethasone[title]).

Data were independently extracted and recorded by two authors (RP and SB) into spreadsheets (Excel; Microsoft Corporation, Redmond, Washington). For inconsistencies in numerical values, a third author (KI) reviewed manuscripts and corrected potential errors. Each study was evaluated sequentially. Two authors reviewed manuscripts and if inconsistencies were identified, these were clarified before the next manuscript was reviewed. Inconsistencies recognized were typographical in nature (incorrect number accidentally inputted) and had minimal impacts on reporting quality.

Extracted data included study level-of-evidences, patient demographics, medical diagnoses, corticosteroid types, time-to-diagnoses, mean corticosteroid doses, maximal daily doses, cumulative doses, and treatment durations. Studies that reported differing corticosteroid agents and doses were normalized to relative potencies in prednisone-equivalent doses in milligrams [13]. For analyses of osteonecrosis incidences between high- and low-dose corticosteroids, a 10,000 mg prednisone-equivalents cut-off was utilized because several studies reported doses at or below this level, or substantially above this level (e.g. >15 g). Thus, this level represented cut-offs in published literature. A third investigator (KI) independently reviewed data accuracy and inter-reviewer consistencies to aid in standardization of pooled data.

The literature search yielded 372 articles between 1960 and 2011, of which twenty-one were review articles. Following assessment of abstracts, 319 *in vitro* studies on histological changes associated with corticosteroids or non-clinical data (e.g. review articles) were excluded, leaving fifty-three studies for review. Reference list examinations identified four additional reports, for a total of fifty-seven studies that were included in the systematic review. There were two level-I, seven level-II studies, and forty eight level-III studies (see Appendix 1) [10,12,14–68].

We evaluated the association of certain disease entities for which systemic corticosteroids were used with the development of osteonecrosis. Specifically, we assessed the association in patients with cardiac, liver, or renal transplants; myeloproliferative diseases (multiple myeloma, acute lymphoblastic leukemia); systemic lupus erythematosus (SLE); or severe acute respiratory syndrome (SARS). No studies assessed corticosteroid effects in other potentially at-risk populations, such as alcohol-users or smokers.

For the meta-analysis, our review resulted in the exclusion of 50 studies due to incomplete outcome reporting, such as inadequate information on mean daily corticosteroid intake, cumulative doses, and duration of treatment, which prevented estimation of odds ratios (i.e. odds that an outcome occurs, given a particular exposure, compared to odds of the outcome occurring in absence of the exposure). Seven studies remained for the meta-analysis [19,20,23,34,52,55,57,69], and these consisted of 1 high-level prospective cohort study, as well as 5 case–control studies (Level III) and 1 case series (Level IV), from which odds ratios could be deduced (Fig. 1). Studies not included in the meta-analysis were used for multivariate analyses to answer secondary questions. The seven studies included 1515 patients undergoing treatment with corticosteroids for SLE (n = 140), renal transplantation (n = 774), or bone marrow transplantation (n = 601; see Table 1 for further details). The mean age of patients in these studies was thirty-three years (range, 15 to 60 years). Studies were performed in the United States (n = 4), the United Kingdom (n = 1), Canada (n = 1), and Denmark (n = 1).

Validity assessment of RCTs was conducted independently by two authors (RP and SB) utilizing the Detsky scale cutoff score of 75% [70,71]. Extracted data were pooled from studies meeting inclusion criteria to calculate treatment effects (odds ratio and 95% confidence intervals) and weights utilizing statistical software (Comprehensive Meta-Analysis v2; Biostat, Englewood, New Jersey) to calculate effects of corticosteroid treatments and doses on incidences. Linear regressions and correlation statistics determined osteonecrosis incidences relative to corticosteroid doses (mean, cumulative, and duration; refer to Appendix for breakdown of included studies for each diagnosis category). Regression analysis was performed to find the quantitative relationship and its significance between the variables, corticosteroid daily dose, cumulative dose, and duration of treatment, and the incidence of osteonecrosis as a dependent variable. Due to the lack of complete dosage data in several studies, we were only able to assess this in SLE and renal transplant patients. The reported R- and R-square results were un-adjusted and reported only for simple linear regressions, rather than for multiple linear regressions to avoid distortion by strong associations between average doses, cumulative doses, and durations. A random effects model was used in the meta-analysis, with publication bias assessed using Orwin's fail-safe N and Duval and Tweedies trim and fill statistics. Furthermore, heterogeneity was assessed using Cochrane's Q and I^2 statistics. Statistical analyses were performed utilizing SSPS 17.0 statistical software (IBM, Armonk, New York). Significance was defined as P values ≤ 0.05 (Appendix 2 Statistics).

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There were no external sources of funding for this meta-analysis and systematic literature review.

Results

Incidence of Osteonecrosis

The systematic review demonstrated overall osteonecrosis incidence of 6.7% (range, 0.3% to 52%) in patients taking high-dose corticosteroids. Two level I studies proved a significant positive correlation between cumulative dose and the incidence of osteonecrosis, whereas, five level II studies failed to show it.

Disease and Incidence of Osteonecrosis

Osteonecrosis incidence for SARS was 21.8%, SLE 15.7%, renal transplant 14.7%, and BMT 6.6% (Fig. 2). Across all diagnoses, we observed positive associations between mean corticosteroid doses and osteonecrosis (Fig. 3). This was irrespective of underlying disease, as analysis of variance of osteonecrosis incidence between patients with different medical diagnoses (SLE, severe acute respiratory syndrome, bone marrow transplantation, renal transplantation) demonstrated no differences between diagnostic categories ($P = 0.16$). The regression analysis demonstrated a significant positive correlation in SLE patients ($r = 0.81$; $R^2 = 0.67$; $P < 0.05$), however, this was not significant in renal transplant recipients ($r = 0.32$; $R^2 = 0.09$; $P > 0.05$). It was also noted that renal transplant recipients and SLE patients were more likely to develop osteonecrosis if they were younger than 35 years compared to those who were older (22 versus 13%; $P = 0.04$, and 33 versus 7%; $P = 0.02$, respectively).

Mean Dose, Cumulative Dose, Duration of Treatment and Osteonecrosis Incidence

Meta-analysis of osteonecrosis in patients treated with greater than 20 mg per day demonstrated significantly higher odds than less than 20 mg per day corticosteroid users (OR 9.1; 95% confidence interval, 4.6 to 19.8) (Fig. 4A). For patients treated with high cumulative corticosteroid doses (greater than 10 g), the odds ratio for developing osteonecrosis was 2.4 (95% CI. 0.8 to 6.4), and lower dosing regimens were associated with a lower osteonecrosis incidence (OR 0.4; 95%, confidence interval 0.25 to 0.54) (Fig. 4B). Additionally, we observed that