Are Corticosteroid Injections Associated with Secondary Adrenal Insufficiency in Adults With Musculoskeletal Pain? A Systematic Review and Meta-analysis of Prospective Studies

Running Title: Corticosteroid Injection and Secondary Adrenal Insufficiency

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Ethical approval was not sought for the present study. This systematic review was prospectively registered on PROSPERO (ID no: CRD42020193066) and reported according to the PRISMA statement.

This work was performed in York, Manchester, Keele, and Derby, UK.

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Abstract

Background Corticosteroid injection is a very common treatment for individuals experiencing musculoskeletal pain, and it is part of the management of numerous orthopaedic conditions. However, there is concern about offering corticosteroid injections for musculoskeletal pain because of the possibility of secondary adrenal insufficiency.

Questions/purposes In this systematic review and meta-analysis of prospective studies, we asked: (1) Are corticosteroid injections associated with secondary adrenal insufficiency as measured by 7-day morning serum cortisol? (2) Does this association differ depending on whether the shot was administered in the spine or the appendicular skeleton?

Methods We searched Allied and Complementary Medicine AMED, Embase, Emcare, MEDLINE, CINAHL, and Web of Science from inception to January 22, 2021. We retrieved 4303 unique records, of which 17 were eventually included. Study appraisal was via the Downs and Black tool, with an average quality rating of fair. A Grading of Recommendations, Assessment, Development, and Evaluations assessment was conducted with the overall certainty of evidence being low to moderate. Reflecting heterogeneity in the study estimates, a pooled random-effects estimate of cortisol levels 7 days after corticosteroid injection was calculated. Fifteen studies or subgroups (254 participants) provided appropriate estimates for statistical pooling. A total of 106 participants received a spine injection, and 148 participants received an appendicular skeleton injection, including the glenohumeral joint, subacromial bursa, trochanteric bursa, and knee.

Results Seven days after corticosteroid injection, the mean morning serum cortisol was 212 nmol/L (95% confidence interval 133 to 290), suggesting that secondary adrenal insufficiency was a possible outcome. There is a difference in the secondary adrenal insufficiency risk

depending on whether the injection was in the spine or the appendicular skeleton. For spinal injection, the mean cortisol was 98 nmol/L (95% CI 48 to 149), suggesting secondary adrenal insufficiency was likely. For appendicular skeleton injection the mean cortisol was 311 nmol/L (95% CI 213 to 409) suggesting hypothalamic-pituitary-adrenal (HPA) axis integrity was likely.

Conclusion Clinicians offering spinal injections should discuss the possibility of short-term secondary adrenal insufficiency with patients, and together, they can decide whether the treatment remains appropriate and whether mitigation strategies are needed. Clinicians offering appendicular skeleton injections should not limit care because of concerns about secondary adrenal insufficiency based on the best available evidence, and clinical guidelines could be reviewed accordingly. Further research is required to understand whether age and/or sex determine risk of secondary adrenal insufficiency and what clinical impact secondary adrenal insufficiency has on patients undergoing spinal injection.

Level of Evidence Level IV, therapeutic study.

Introduction

Musculoskeletal conditions, including osteoarthritis, tendon-related disorders, and low back pain, are extremely common. In 2017, they were estimated to affect 18.8 million people across the United Kingdom [58]. The World Health Organization estimates that approximately 1.71 billion people worldwide have a musculoskeletal condition [63]. Corticosteroid injection is a very common treatment for individuals experiencing musculoskeletal pain [3,14], and it forms part of the management of numerous conditions [2, 6, 10]. Synthetic corticosteroids mimic the action of cortisol, an endogenous steroid hormone secreted by the adrenal gland, and they influence inflammatory pathways by binding to hormone receptor sites within cell nuclei to inhibit inflammatory signalling and to activate transcription of anti-inflammatory proteins [7]. Natural levels of the hormone are controlled via a negative feedback loop by the hypothalamic-pituitary-adrenal (HPA) axis [28], and one of the potential side effects of administering synthetic glucocorticosteroid is suppression of this pathway, also known as HPA axis suppression [41]. In its most severe form, cortisol production can be completely suppressed, leading to secondary adrenal insufficiency [29]. There are numerous ways to diagnose secondary adrenal insufficiency, including the long and short adrenocorticotropin hormone (ACTH) stimulation tests, which directly assess the ability of the adrenal gland to secrete cortisol in response to HPA axis stimula3ion; the long ACTH test exhibits a high likelihood ratio for a positive test of 9.1 [44]. Unfortunately, the published use of these tests in relation to a corticosteroid injection is inconsistent, with only some authors presenting the results of ACTH stimulation testing [19 ,20, 22, 26, 27]; instead, many studies [1, 13, 15, 16, 21, 32 ,36, 56] measure morning serum cortisol using a simple blood test to assess peak level of circulating cortisol, from which to draw conclusions about HPA axis function. Although morning serum cortisol does not directly

measure HPA axis function, several authors have established thresholds that have a high positive and negative predictive value for secondary adrenal insufficiency [30, 35, 53].

Secondary adrenal insufficiency is associated with more infections compared with the general population, as well as more serious adverse events related to infection [47]. Although secondary adrenal insufficiency is a well-established risk associated with oral and inhaled corticosteroid use [38], whether or not the same risk exists with injected corticosteroids remains unclear. A previous study has identified a possible relationship between receiving a corticosteroid injection into a major joint and an increased susceptibility to influenza infection [55], for which secondary adrenal insufficiency would be a plausible mechanism. However, the retrospective design of the study and the multiple possible confounders in play make the validity of the conclusions uncertain. The possibility that corticosteroid injections may cause secondary adrenal insufficiency and subsequently increase susceptibility to infection has been a concern for clinicians and professional bodies throughout the COVID-19 pandemic and many clinical guidelines were developed in response [4, 5, 34], which have suggested limiting their use by, for example, reducing dosage, avoiding multisite injections, and providing alternative treatment. Given that reducing access to treatment is also likely to cause harm and that the WHO believe COVID-19 will continue to be a challenge in the medium term [61], clarity regarding the issue of secondary adrenal insufficiency after corticosteroid injection is urgently required. Current guidance has been based on expert opinion and engagement with a small number of primary studies. Therefore, a systematic review of the best available evidence would seem appropriate to clarify the risk in relation to secondary adrenal insufficiency. A key question around this issue is whether the risk of secondary adrenal insufficiency differs depending upon whether the injection is delivered into the spine or the appendicular skeleton. Previous authors [15, 36] have suggested

that corticosteroid injection into the spine may be associated with more systemic uptake into the central nervous system via cerebrospinal fluid (CSF) because corticosteroids are thought to diffuse easily through the blood-CSF barrier [33]. We therefore considered that analyzing data by injection site was appropriate to detect if any such effect existed.

In this systematic review and meta-analysis of prospective studies, we therefore asked: (1) Are corticosteroid injections associated with secondary adrenal insufficiency as indicated by 7-day morning serum cortisol? (2) Does this association differ depending on whether the shot was administered in the joints of the axial skeleton versus in the spine?

Materials and Methods

Search Strategy and Criteria

We searched the following databases from their inception until January 22, 2021: Allied and Complementary Medicine AMED (OVID), Embase (OVID), Emcare (OVID), MEDLINE (OVID), CINAHL, and Web of Science (Table 1). The search strategy was supplemented by manually searching the reference lists of included studies. Searches were not confined to English language sources and included grey literature such as non peer-reviewed conference proceedings; we did not search preprint servers.

All retrieved studies were imported into Mendeley and duplicates were removed electronically. Then, the studies were uploaded to Rayyan (https://www.rayyan.ai) [44] to enable independent screening of the titles and abstracts by two reviewers (GW, BS). Studies were eligible for the review if they met our inclusion criteria as per our protocol (PROSPERO ID no: CRD42020193066). We included studies as per our predefined criteria (Table 2) that evaluated morning serum cortisol in adults after corticosteroid injection for musculoskeletal pain, but we

excluded inflammatory joint pain (such as rheumatoid arthritis and axial spondyloarthropathies) because of the possible confounders at play in such populations. When duplicates were identified, these were marked as such during the review process. Subsequently, two reviewers (GW, MM) independently evaluated the full texts of potentially eligible studies to determine inclusion. Any disagreements were resolved through discussion (Fig. 1) [45]. Our search identified 5133 records for screening, which was reduced to 4303 once duplicate records were removed. Of these, 4231 were excluded during screening of the title and abstract. Full-text articles were obtained for the remaining 72 articles, and 52 of these were excluded. A further three studies were excluded because requests for additional data were not answered. (Supplemental Table 1; supplemental materials are available with the online version of *CORR*®). One of the remaining studies was a detailed report of conference proceedings [60] (the full text was retrieved via NHS library services) and contained sufficient detail for a quality appraisal to be conducted and outcome data extracted. Unfortunately, the paper did not report standard deviations alongside the 7-day morning serum cortisol values and thus the results were not included in our subsequent meta-analysis. We present the outcome data for this paper alongside the 16 other identified studies [1, 11, 13, 15, 16, 18, 19, 20, 21, 22, 26, 27, 32, 36, 56, 59] that were eligible for inclusion in the study characteristics table (Table 3).

Data Collection Process

The first author (GW) extracted the data and entered it into a bespoke form (not publicly available) in Microsoft Excel, as agreed by the review team. A second author (MM) verified this process. If the data provided in the published articles were deemed insufficient to facilitate statistical analysis, the articles' corresponding authors were contacted via email to request

additional information. If no response was received after 2 weeks, a reminder email was sent. If no response was received after 3 weeks, no further attempt was made to contact the authors.

Data Items

Data extracted included study type, characteristics of participants, sample size, corticosteroid preparation, site of corticosteroid injection, corticosteroid dosage, and morning serum cortisol outcomes before and after corticosteroid injection.

Morning serum cortisol levels are obtained by a blood test. The measure may be obtained by any of the following recognized methods: Porter-Silber chromogens [46], competitive protein binding assay, fluorometric assay, radioreceptor assay, radioimmunoassay, or structurally based assays [37]. In the included studies, results were expressed in mcg/dL or nmol/L, depending on the method used. For this review, results were standardized to nmol/L using an online calculator (www.unitslab.com/node/110). The normal range is 275 nmol/L to 555 nmol/L [42]. For this review, a morning serum cortisol of less than 100 nmol/L was considered to be highly suggestive of secondary adrenal insufficiency, with previous authors having identified a positive predictive value of 93.2% for values below this cutoff [53]. Additionally, a morning serum cortisol greater than 234.2 was considered highly suggestive of HPA axis integrity, with previous authors having identified a negative predictive value of 95.8% for adrenal insufficiency for values above this cut off [30,35]. Because timepoints for morning serum cortisol blood draws were not uniform across studies, we clustered our reporting around the most consistently reported timepoint. For example, we reported cortisol levels for Day 6 or Day 8 in the absence of a value for Day 7.

Previous authors have described the absorption profile of different injected corticosteroids [8]; at 7 days post-injection, between 60% and 90% of the corticosteroid has been absorbed, depending on the type of corticosteroid and dosage. We therefore focused the presentation of our results at

this critical timepoint when substantial absorption of the corticosteroid would have occurred. To enable a comparison, we converted the corticosteroid preparation and dosage to an equivalent dosage of depomedrone using validated conversion tables [31]. Our review identified 17 prospective studies that measured morning serum cortisol levels after a corticosteroid injection for musculoskeletal pain (Table 3). Dosages of corticosteroid used ranged from the equivalent of 40 to 160 mg of depomedrone.

Quality Appraisal of Individual Studies

We used the Downs and Black quality appraisal checklist, which consists of 27 items and is valid and reliable for assessing the quality of randomized and nonrandomized studies [12]. One author (GW) completed the quality appraisal and another author (MM) verified it. In this review, we used a modification commonly adopted by other authors [24, 39, 49] to determine the score assigned to the 27 items. A single point was awarded for studies that had sufficient power to detect a clinically important effect. A total score of 28 was obtained for each study, and the following grading system was used, as originally suggested by Hooper et al. [24]: excellent (24-28 points), good (19-3 points), fair (14-18 points), or poor (< 14 points).

Of the 17 identified studies, one was rated as excellent, one as good, 10 as fair, and five as poor (Table 4). Therefore, the overall quality of evidence was considered fair.

Synthesis of Results

Owing to the absence of the necessary data in a large number of studies, we could not calculate a pooled estimate of the mean change in cortisol from baseline to 7 days, which had been specified in our study's original protocol. We therefore used a random-effects model [54] to provide a pooled estimate of mean 7-day cortisol levels for studies that provided the required data, using a

DerSimonian-Laird estimator [9] in the Meta-Essentials program [54]. A random-effects model was chosen in view of the level of heterogeneity of the study estimates; this allows the pooled estimate to better reflect the underlying variation in study contexts than a fixed-effect model and provides more conservative standard errors for the calculation of confidence intervals [48]. When there were distinct subgroups of participants in a study, we included separate estimates for these subgroups, rather than a single estimate for the study concerned, in the calculation of the pooled estimate. As well as calculating this estimate for all of the included studies, we derived separate estimates for spinal and peripheral injections. The associated 95% confidence interval for the pooled estimates was calculated, as well as the 95% prediction interval. The prediction interval is the boundary within which 95% of the estimates of other similar studies would be expected to lie, and when there is any heterogeneity in study estimates, this interval will be wider than the corresponding 95% CI [25]. These interval estimates assume that point estimates from individual studies have an approximately normal distribution.

Heterogeneity or inconsistency of the study estimates was quantified by the I^2 statistic, which estimates the percentage of variability in individual study estimates attributable to heterogeneity rather than to random sampling error. Higgins et al. [23] suggested that values of I^2 up to 25% are low, those from 26% to 74% are moderate, and those above 75% are high. We also calculated the SD of study effects, represented by the T statistic. Heterogeneity of the pooled baseline and 7-day estimates was high: the I^2 statistic was 96.83% and 99.59% for baseline and 7 days, respectively. The T statistic was 51.80 and 91.88, respectively.

Additionally, in individual studies, we determined whether the estimates of morning cortisol levels lay within the normal range or in the ranges that suggest either possible or definite secondary adrenal insufficiency.

We were unable to provide an assessment of the role of age and sex of participants in the risk of secondary adrenal insufficiency after corticosteroid injection because we did not have access to individual participant data from our included primary studies.

Certainty of Evidence

We undertook a Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) [17] assessment to evaluate certainty in the available evidence (Table 5). There was evidence of low certainty that corticosteroid injections for musculoskeletal pain were associated with possible secondary adrenal insufficiency across all sites at 7 days. There was evidence of low-to-moderate certainty that corticosteroid injection into the spine was associated with secondary adrenal insufficiency at 7 days. There was evidence of low-to-moderate certainty that corticosteroid injection into the appendicular skeleton was not associated with secondary adrenal insufficiency at 7 days.

Primary and Secondary Study Outcomes

Our primary outcome was to determine whether corticosteroid injection was associated with a reduction in morning serum cortisol at 7 days and if this was indicative of secondary adrenal insufficiency. We derived a pooled estimate of morning serum cortisol at 7 days and associated 95% CI.

Our secondary outcome was to determine whether there was a difference in the reduction in morning serum cortisol at 7 days when injecting the spine compared with the appendicular skeleton, and whether secondary adrenal insufficiency was associated with either site of injection. We derived a pooled estimate of morning serum cortisol for both subgroups of patients and associated 95% CIs.

Results

Secondary Adrenal Cortical Insufficiency 7 Days After Injection

The pooled estimate of the mean 7-day morning serum cortisol was calculated as 212 nmol/L (95% CI 133 to 290), suggesting possible secondary adrenal insufficiency (Fig. 2). The associated 95% prediction interval was 0 to 424. The corresponding baseline estimate was calculated as 379 nmol/L (95% CI 336 to 422, with a 95% prediction interval of 260 to 498). These calculations represented 254 participants in 15 studies, or subgroups within studies, and exclude the studies by Dickson et al. [11], Friedly et al. [15], Jacobs et al. [27], and Weyland et al. [60], for which 7-day morning serum cortisol levels and/or the associated SDs were missing.

We conducted a sensitivity analysis for outlier effects. This comprised recalculating the pooled mean estimates after excluding studies or subgroups whose 95% CIs lay wholly outside the 95% CI for the pooled estimate. For 7-day morning cortisol levels the resulting estimate was very similar at 215 nmol/L (95% CI 142 to 289); the corresponding baseline estimate was also similar at 346 nmol/L (95% CI 324 to 368). Three studies included in the pooled analysis were rated as being of poor quality [13, 18, 32]. When these were excluded, the estimate of mean 7-day cortisol rose slightly to 229 nmol/L (95% CI 137 to 322). Similarly, when we excluded the two studies [13, 22] in which the highest dosage of steroid (equivalent to 160 mg depomedrone) had been used, the estimated mean 7-day cortisol rose very slightly to 217 nmol/L (95% CI 127 to 307). We also ran a sensitivity analysis in which we omitted the very small study (n = 2) by Dubois et al. [13]; this had a negligible effect on the pooled estimates.

Comparing Injections in the Spinal Versus the Appendicular Skeleton

The pooled mean estimate for the eight studies or subgroups involving peripheral corticosteroid injections (148 participants) was 311 nmol/L (95% CI 213 to 409) and for the seven studies or subgroups involving spinal injection (106 participants) was 98 nmol/L (95% CI 48 to 149). The corresponding mean baseline estimates were 400 nmol/L (95% CI 320 to 480) and 345 nmol/L (95% CI 312 to 377). The decrease in cortisol levels was markedly greater for spinal injections than for peripheral injections and was highly suggestive of secondary adrenal insufficiency for the spinal injection group, and conversely, it was highly suggestive of HPA axis integrity in the peripheral injection group.

Discussion

Corticosteroid injection is a widely used treatment for musculoskeletal pain, but the risk of secondary adrenal insufficiency associated with this treatment has to this point been unclear. Quantifying the secondary adrenal insufficiency risk is important because those experiencing it may have an increased susceptibility to infections [47]. Understanding whether a corticosteroid injection is likely to cause secondary adrenal insufficiency will allow clinicians to engage in shared decision-making with patients about the potential risk and benefits of treatment. Given that several clinical bodies [4, 5, 34] have suggested limits to corticosteroid injection treatment during the COVID-19 pandemic based on limited evidence review, an urgent systematic appraisal of the evidence was needed to either validate or initiate a review of these guidelines.

Limitations

Our review is limited by a lack of between-group comparative studies available, meaning that we could not evaluate associated between-group effects. However, we were able to identify a large

number of pretest/posttest studies, and we were able to derive baseline and 7-day estimates. All studies demonstrated a reduction in morning serum cortisol at 7 days, indicating an association between lower morning serum cortisol level at 7 days and corticosteroid injection, albeit it with less certainty than if between-group comparisons against a control condition had been available.

A further limitation of the review is the usage in many of the primary studies of morning serum cortisol as an outcome measure for HPA axis integrity. As we have discussed, morning serum cortisol is not a direct indicator of HPA axis integrity, but previous authors have identified cutoff values where morning serum cortisol has a high positive predictive value [53] and a high negative predictive value [30, 35] for secondary adrenal insufficiency. These values have been validated against ACTH stimulation testing, which itself has been shown to exhibit a good likelihood ratio for diagnosing secondary adrenal insufficiency [43]. In this review, we interpreted our results using these previously validated thresholds for morning serum cortisol to decide if secondary adrenal insufficiency is likely or unlikely, and although the presented morning serum cortisol figures do not themselves directly assess HPA axis integrity, we believe that our conclusions are robust.

Our review is also limited because of how the results of the primary studies were reported; we were unable to evaluate whether sex or age was a risk factor for secondary adrenal insufficiency because we did not have access to individual patient data. A previous study of 143 healthy adults [50] demonstrated that both factors determine the secretory profile of cortisol for individuals. It may therefore be the case that secondary adrenal insufficiency risk after corticosteroid injection could increase depending on patient age and sex. However, further empirical data are required to confirm this.

A further limitation of our review was that we were unable to include the results of the identified study from the grey literature [60] within our meta-analysis. Including studies from the grey literature can be important because it can potentially mitigate against the issue of positive outcome bias. Unfortunately the presented outcome data for this study was insufficient to allow meta-analysis, we have presented the available study data within our study characteristics table (Table 3).

Although our findings signal that secondary adrenal insufficiency is likely at 7 days after spinal injection, it is unclear what the implications of this are clinically. It has been established that serum cortisol secretion is upregulated in response to viral infection, and that frequent modulation of this occurs over the course of infection, suggesting that cortisol is involved in tailoring the immune system response to the infection [41, 51, 57]. A previous study has shown an increased risk of infection and associated adverse outcomes in those experiencing secondary adrenal insufficiency [47]. However, it is not clear whether the transient secondary adrenal insufficiency associated with spinal corticosteroid injection confers clinical risk and further empirical data are required to confirm this.

Secondary Adrenal Insufficiency 7 Days After Injection

Across all pooled studies we found that the point estimate of morning serum cortisol was in the range where secondary adrenal insufficiency was possible but was above our defined threshold for likely secondary adrenal insufficiency and below our defined threshold for likely HPA axis integrity. However, our estimates for pooled spinal and appendicular skeleton injection led to rather different conclusions regarding secondary adrenal insufficiency at 7 days after treatment, and therefore are more informative for clinical practice than the pooled estimate. Clinicians should therefore alert their patients that secondary adrenal insufficiency is a possibility 7 days

after corticosteroid injection, but clinicians should tailor their approach depending upon the injection site as detailed later.

Comparing Injections in the Spinal versus the Appendicular Skeleton

Our results suggest that spinal injection is likely to be associated with secondary adrenal insufficiency 7 days after administration. Clinicians should therefore use this information to consider whether such injection confers additional risk for their patients. For example, when considering the increased infection risk associated with secondary adrenal insufficiency, clinicians may wish to account for various other factors before deciding with the patient how best to proceed. For COVID-19, this assessment may account for the patient's age and comorbidities through the use of a risk-stratification tool such as that developed by the British Medical Association [52], the patient's vaccination status, and whether there are any variants of concern currently in circulation. In the case of influenza, both age and multimorbidity are predictors of mortality and morbidity [62]. If patients are considered to be at risk, shared decision making should take place to consider whether alternative treatment options are available, or whether the treatment could take place with appropriate risk-mitigation strategies in place. Risk mitigation could take the form of those suggested in the National Institute for Clinical Excellence guidance on arranging planned care [40] and the use of personal risk mitigation strategies such as self-isolation after the procedure, mask wearing, and/or social distancing.

Conversely, our data suggest that those undergoing injection in the appendicular skeleton are unlikely to experience secondary adrenal insufficiency as a result of their treatment. Clinicians may therefore continue to offer corticosteroid injection into the appendicular skeleton as clinically indicated and are unlikely to need to limit its use based on the current best available

evidence. The only exception to this might be if the patient is on concurrent steroid therapy by another route (for example inhaled steroids for asthma) as concurrent steroid therapies are likely to increase risk.

Conclusion

In our meta-analysis, we found low- to moderate-certainty evidence that spinal corticosteroid injections are likely to be associated with secondary adrenal insufficiency 7 days after administration, but that corticosteroid injections of the appendicular skeleton are likely to be associated with HPA axis integrity 7 days after administration. Our sensitivity analyses do not materially alter our conclusions. Clinicians should use this information to inform shared decision-making with patients considering corticosteroid injection for musculoskeletal pain. For patients considering appendicular skeleton injection, reassurance should be given that on the basis of current best available evidence, secondary adrenal insufficiency is an unlikely outcome of the injection and clinicians should not limit access to treatment because of concerns regarding secondary adrenal insufficiency. Clinicians offering spinal injection should discuss the possibility of short-term secondary adrenal insufficiency as an outcome of the injection as well as the ongoing uncertainty regarding the real-world implications of this to patients which possibly include increased susceptibility to infection. Whether this is a particular concern to the clinician or patient may depend upon multiple factors, including the patient's age, comorbidities, vaccination status, and in terms of COVID-19, the current prevalence of variants of concern. These things should be considered when deciding whether or not to proceed with spinal injection and whether mitigation strategies are required to facilitate treatment. Current policy guidance should be reviewed considering these findings and should reflect the different risk profiles of spinal and appendicular skeleton injection for secondary adrenal insufficiency. Although this

review signals that secondary adrenal insufficiency is likely 7 days after spinal injection, whether or how this might manifest clinically is not understood. Further research is needed to understand the frequency and clinical course of secondary adrenal insufficiency after corticosteroid injection of the spine. Further research is also required to understand if age and/or sex are risk factors for developing secondary adrenal insufficiency after corticosteroid injection.

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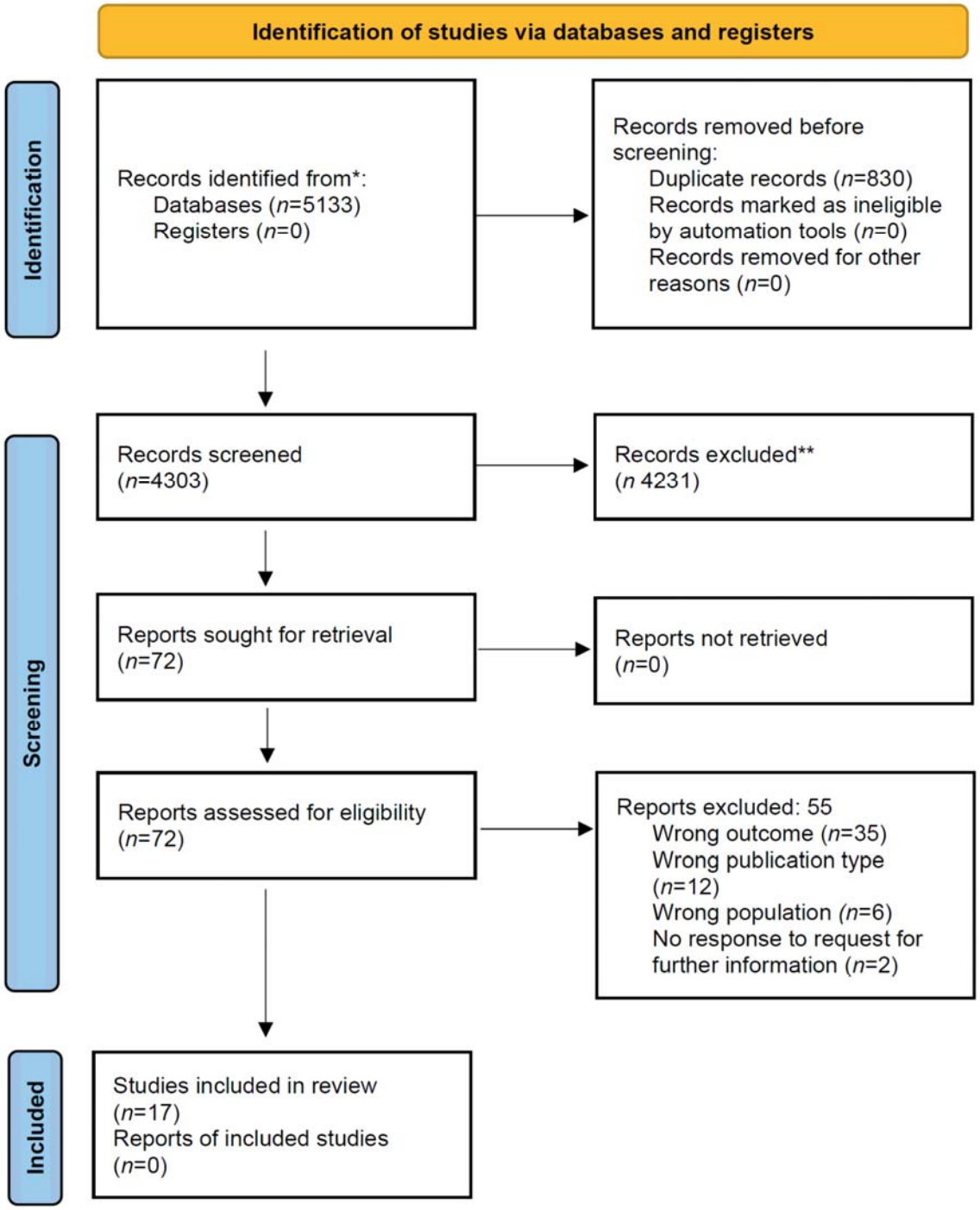

Fig. 1 PRISMA flowchart showing the studies that were included in our review.

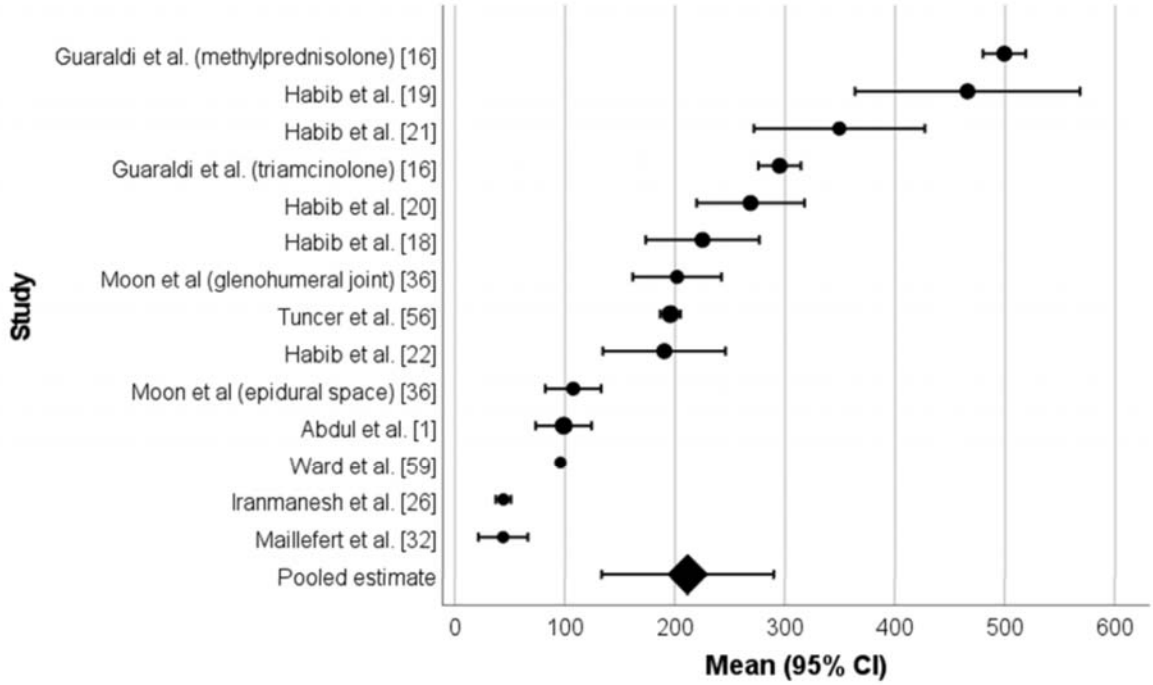

Fig. 2 Forest plot shows morning 7-day serum cortisol (nmol/L) for the included studies or subgroups and for the pooled estimate. The very small study by Dubois et al. [13] (n = 2) was omitted owing to the effect of its very wide CI (-1204.50 nmol/L to 1425.63 nmol/L) on the scale of the graph, but its data are included in the displayed pooled estimate.

Table 1. Full search strategy results

AMED

#1	EXP Pain or EXP Musculoskeletal Disease or EXP Musculoskeletal Pain	50,038
#2	EXP Corticosteroids OR EXP glucocorticoids OR Corticosteroid .mp OR glucocorticosteroid.mp OR glucocorticoids.mp OR Triamcinolone .mp OR Depomedrone.mp OR Betamethasone.mp OR Dexamethasone.mp OR Methylprednisolone.mp OR Hydrocortisone.mp	867
#3	EXP injection/ or injection.mp. or inject OR intraarticular drug administration or intraarticular or peritendinous or infiltration OR local infiltration OR infiltrating	3135
#4	Adrenal gland/ OR adrenal cortex hormones.mp OR Hypothalamic pituitary adrenal axis.mp. OR hypothalamus hypophysis adrenal system/ OR adrenal insufficiency.mp. OR adrenal insufficiency/ OR cortisol.mp OR corticosterone.mp. OR Corticosterone/ OR adrenal cortex function tests.mp. OR adrenocortical function test/ OR immunosuppression.mp. or immunosuppressive treatment/ OR immune suppression.mp	847
#5	#1 AND #2 AND #3 AND #4 limited to humans	60

Embase results

#1	EXP Pain or EXP Musculoskeletal Disease or EXP Musculoskeletal Pain.	3,043,995
#2	EXP Corticosteroids OR EXP glucocorticoids OR Corticosteroid .mp OR glucocorticosteroid.mp OR glucocorticoids.mp OR Triamcinolone .mp OR Depomedrone.mp OR Betamethasone.mp OR Dexamethasone.mp OR Methylprednisolone.mp OR Hydrocortisone.mp	949,982
#3	EXP injection/or injection.mp. or inject OR intraarticular drug administration or intraarticular or peritendinous or infiltration OR local infiltration OR infiltrating	982,189
#4	Adrenal gland/OR adrenal cortex hormones.mp OR Hypothalamic pituitary adrenal axis.mp. OR hypothalamus hypophysis adrenal system/ OR adrenal insufficiency.mp. OR adrenal insufficiency/OR cortisol.mp OR corticosterone.mp. OR Corticosterone/OR adrenal cortex function tests.mp. OR adrenocortical function test/OR immunosuppression.mp. or immunosuppressive treatment/OR immune suppression.mp	365,624
#5	#1 AND #2 AND #3 AND #4 limited to humans	1601

Emcare results

#1	EXP Pain or EXP Musculoskeletal Disease or EXP Musculoskeletal Pain.	883,785
#2	EXP Corticosteroids OR EXP glucocorticoids OR Corticosteroid .mp OR glucocorticosteroid.mp OR glucocorticoids.mp OR Triamcinolone .mp OR Depomedrone.mp OR Betamethasone.mp OR Dexamethasone.mp OR Methylprednisolone.mp OR Hydrocortisone.mp	156,436
#3	EXP injection/ or injection.mp. or inject OR intraarticular drug administration or intraarticular or peritendinous or infiltration OR local infiltration OR infiltrating	138,924
#4	Adrenal gland/ OR adrenal cortex hormones.mp OR Hypothalamic pituitary adrenal axis.mp. OR hypothalamus hypophysis adrenal system/ OR adrenal insufficiency.mp. OR adrenal insufficiency/ OR cortisol.mp OR corticosterone.mp. OR Corticosterone/ OR adrenal cortex function tests.mp. OR adrenocortical function test/ OR immunosuppression.mp. or immunosuppressive treatment/ OR immune suppression.mp	43,555
#5	#1 AND #2 AND #3 AND #4 limited to humans	345

MEDLINE results

#1	EXP Pain or EXP Musculoskeletal Disease or EXP Musculoskeletal Pain.	1,404,915
#2	EXP Corticosteroids OR EXP glucocorticoids OR Corticosteroid .mp OR glucocorticosteroid.mp OR glucocorticoids.mp OR Triamcinolone .mp OR Depomedrone.mp OR Betamethasone.mp OR Dexamethasone.mp OR Methylprednisolone.mp OR Hydrocortisone.mp	452,772
#3	EXP injection/ or injection.mp. or inject OR intraarticular drug administration or intraarticular or peritendinous or infiltration OR local infiltration OR infiltrating	827,115
#4	Adrenal gland/ OR adrenal cortex hormones.mp OR Hypothalamic pituitary adrenal axis.mp. OR hypothalamus hypophysis adrenal system/ OR adrenal insufficiency.mp. OR adrenal insufficiency/ OR cortisol.mp OR corticosterone.mp. OR Corticosterone/ OR adrenal cortex function tests.mp. OR adrenocortical function test/ OR immunosuppression.mp. or immunosuppressive treatment/ OR immune suppression.mp	284,387
#5	#1 AND #2 AND #3 AND #4 limited to humans	1798

Databases accessed via OVID (open Athens-NHS) January 2021

CINAHL

#1	EXP Pain or EXP Musculoskeletal Disease or EXP Musculoskeletal Pain.	339,512
#2	EXP Corticosteroids OR EXP glucocorticoids OR Corticosteroid .mp OR glucocorticosteroid.mp OR glucocorticoids.mp OR Triamcinolone .mp OR Depomedrone.mp OR Betamethasone.mp OR Dexamethasone.mp OR Methylprednisolone.mp OR Hydrocortisone.mp	37,614
#3	EXP injection/ or injection.mp. or inject OR intraarticular drug administration or intraarticular or peritendinous or infiltration OR local infiltration OR infiltrating	82,374
#4	Adrenal gland/ OR adrenal cortex hormones.mp OR Hypothalamic pituitary adrenal axis.mp. OR hypothalamus hypophysis adrenal system/ OR adrenal insufficiency.mp. OR adrenal insufficiency/ OR cortisol.mp OR corticosterone.mp. OR Corticosterone/ OR adrenal cortex function tests.mp. OR adrenocortical function test/ OR immunosuppression.mp. or immunosuppressive treatment/ OR immune suppression.mp	14,751
#5	#1 AND #2 AND #3 AND #4 limited to humans	1329

Web of Science

#1	EXP Pain or EXP Musculoskeletal Disease or EXP Musculoskeletal Pain.	712,304
#2	EXP Corticosteroids OR EXP glucocorticoids OR Corticosteroid .mp OR glucocorticosteroid.mp OR glucocorticoids.mp OR Triamcinolone .mp OR Depomedrone.mp OR Betamethasone.mp OR Dexamethasone.mp OR Methylprednisolone.mp OR Hydrocortisone.mp	5585
#3	EXP injection/ or injection.mp. or inject OR intraarticular drug administration or intraarticular or peritendinous or infiltration OR local infiltration OR infiltrating	511,799
#4	Adrenal gland/ OR adrenal cortex hormones.mp OR Hypothalamic pituitary adrenal axis.mp. OR hypothalamus hypophysis adrenal system/ OR adrenal insufficiency.mp. OR adrenal insufficiency/ OR cortisol.mp OR corticosterone.mp. OR Corticosterone/ OR adrenal cortex function tests.mp. OR adrenocortical function test/ OR immunosuppression.mp. or immunosuppressive treatment/ OR immune suppression.mp	85,132
#5	#1 AND #2 AND #3 AND #4 limited to humans	0

Table 2: Eligibility criteria for studies included in the review

Population
Inclusion: Adult humans receiving a corticosteroid injection for a musculoskeletal condition, for example a corticosteroid injection to the shoulder for someone complaining of shoulder pain. Exclusion: Intramuscular corticosteroid injection for systemic benefit, e.g., for the treatment of rheumatoid arthritis, spondyloarthropathies, fibromyalgia, gout, lupus, Sjögren's syndrome, psoriatic arthritis, scleroderma, or reactive arthritis.
Intervention
A single corticosteroid injection provided for a musculoskeletal condition. Any dosage and any steroid preparation were accepted. Co-administration of local anaesthetic was also accepted.
Comparator/Control
Placebo, local anaesthetic only, or other non-steroid based comparators, or no comparator.
Outcome
Morning serum cortisol.
Study design
All prospective study designs.

Authors	Year	Study design	Sample size	Age (mean unless stated otherwise)	Sex (M:F %)	Drug	Dosage standardized to equivalent dose methylprednisolone (mg)	Site(s) of injection	Standardized mean serum cortisol (nmol/l ± SD)		Secondary adrenal insufficiency (cortisol < 100 nmol/L	
									Baseline	Day 7 ± 24 hours	Day 7 ± 24 hours	Day 14 ±24 hours
Corticosteroid injection equivalent to 40 mg depomedrone												
Guaraldi et al. [16]	2019	Single blinded prospective comparative study	20	51	30:70	Methylprednisolone	40 mg	Subacromial bursa	484 (41)	499 (41.)	No	No
			20	46	60:40	Triamcinolone acetonide	40 mg		474 (41)	295 (41)	No	No
Habib et al. [21]	2017	Prospective comparative study study	12	59.7	17:83	Betamethasone	40 mg	Knee	381 (154)	349 (122)	No	No
Habib et al. [18]	2013	Prospective comparative study	20	53.25	50:50	Betamethasone	40 mg	Knee	268 (115)	225 (110)	No	No
Weyland et al. [60]	1992	Prospective comparative study	11	nr	nr	Triamcinolone acetonide	40 mg	Lumbar epidural space	321 (nr)	147(nr)	No	No (day 21)
			9	nr	nr	Triamcinolone acetonide	40 mg	Cervical epidural space				
Moon et al. [36]	2014	Prospective comparative study	15	63.2	47:53	Triamcinolone acetonide	40 mg	Gleno-humeral joint	360 (55)	202 (73)	No	No (day 21)
			14	61.9	57:4743	Triamcinolone Acetonide	40 mg	Lumbar epidural space	338 (48)	108 (44)	No	No (day 21)
Dickson et al. [11]	2018	Prospective observational study	5	42 (median)	40:60	Triamcinolone acetonide	40 mg	Lumbar epidural space	unknown	unknown	unknown	unknown
Corticosteroid injection equivalent to 60-80 mg depomedrone												
Tuncer et al. [56]	2004	Prospective observational study	33	32-56 (range)	36.4:63.6	Betamethasone	66.7 mg	Lumbar epidural space	343(42)	196 (26)	No	No
Habib et al. [19]	2017	Prospective observational study	21	55.2	9.5:90.5	Methylprednisolone	80 mg	Greater trochanteric region	566 (250)	466 (224)	No	No
Habib et al. [20]	2014	Prospective comparative study	20	53.3	60:40	Methylprednisolone	80 mg	Knee	310 (91)	268 (104)	No	No.
Abdul et al. [1]	2017	Prospective observational study	30	49.5	47:53	Methylprednisolone	80 mg	Lumbar epidural space	321 (117)	99 (68)	Yes	No

Iranmanesh et al. [26]	2017	Prospective observational study	8	25–63 (range)	100:0	Triamcinolone acetonide	80 mg	Lumbar epidural space	331 (44)	44 (8)	Yes	NR
Maillefert et al. [32]	1995	Prospective observational study	9	47	55:45	Dexamethasone	80 mg	Lumbar epidural space	499 (124)	44(29)	Yes	No
Ward et al. [59]	2002	Prospective observational study	10	43.4	40:60	Triamcinolone acetonide	80 mg	Lumbar epidural space	352(1.5)	96 (3)	Yes	NR
Jacobs et al. [27]	1983	Prospective observational study	6	nr	nr	Methylprednisolone	80 mg	Lumbar extradural injection	385 (30)	nr	nr	No (day 21)
	Corticosteroid injection equivalent to 160 mg depomedrone											
Habib et al. [22]	2014	Prospective comparative study	20	60.29	75:25	Methylprednisolone	160 mg	Bilateral knees (80 mg/knee)	383 (122)	190 (119)	No	No
Dubois et al. [13]	2003	Prospective observational study	2	42 and 36	50:50	Depomedrone	160 mg	Lumbar epidural space	394.00 (105)	111 (146)	No	No (day 21)
	Corticosteroid injection dosage not defined											
Friedly et al. [15]	2018	Prospective multi-center randomized controlled trial	183	68	45:55	Triamcinolone acetonide or Betamethasone or Dexamethasone or Methylprednisolone	40-120 mg	Lumbar epidural space	333 (196)	nr	nr	Possible at day 21

Table 3. Study characteristics

nr = not reported

Table 4. Results of quality assessment using the Downs and Black appraisal tool

Study	Score (of a possible 28)	Quality rating
Abdul et al. [1]	17	Fair
Dubois et al.[13]	13	Poor
Friedly et al. [15]	26	Excellent
Dickson et al. [11]	17	Fair
Guaraldi et al. [16]	22	Good
Habib et al. [18]	12	Poor
Habib et al. [19]	16	Fair
Habib et al. [20]	17	Fair
Habib et al. [21]	18	Fair
Habib et al. [22]	18	Fair
Iranmanesh et al. [26]	14	Fair
Jacobs et al. [27]	9	Poor
Maillefert et al. [32]	13	Poor
Moon et al. [36]	17	Fair
Tuncer et al. [56]	14	Fair
Ward et al. [59]	15	Fair
Weyland et al. [60]	8	Poor

Table 5. Results of certainty assessment using the GRADE framework

	Certainty assessment							
	Number of studies/ subgroups (participants)	**Study designs**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Certainty**
In adults a corticosteroid injection for musculoskeletal pain results in a morning serum cortisol level of 100-234 nmol/L, suggesting possible secondary adrenal insufficiency	15 (254)	Prospective	Low	low	Low	low	—	Low
In adults a corticosteroid injection into the peripheral musculoskeletal system results in a morning serum cortisol level above 234 nmol/L suggesting HPA axis integrity	8 (148)	Prospective	Low	Moderate	Moderate	Moderate	—	Low/moderate
In adults a corticosteroid injection into the spine results in a morning serum cortisol level below 100nmol/L, suggesting secondary adrenal insufficiency	7 (106)	Prospective	Low	Moderate	Moderate	Moderate	—	Low/moderate

Supplemental Table 1 Full text articles retrieved and excluded from the review with reason for exclusion

	Record	Reason for rejection
1	Barman A, Mukherjee S, Sahoo J, et al. Single Intra-Articular Platelet-Rich Plasma Versus Corticosteroid Injections in the Treatment of Adhesive Capsulitis of the Shoulder: A Cohort Study. *Am J Phys Med Rehabil*. 2019;98:549-557.	Wrong outcome
2	Baych L, Caldwell C, Schauf K, Clemenson N. Do epidural corticosteroid injections improve symptoms in the short or long term versus conventional or sham therapies in adult patients with chronic back pain with or without radicular pain?. *J Okla State Med Assoc*. 2011;104:9-10.	Wrong publication type
3	Bellamy JL, Goff BJ, Sayeed SA. Economic Impact of Ketorolac vs Corticosteroid Intra-Articular Knee Injections for Osteoarthritis: A Randomized, Double-Blind, Prospective Study. *J Arthroplasty*. 2016;31:293-297.	Wrong outcome
4	Bias P, Lorenz,R. Sustained-release dexamethasone palmitate: Pharmacokinetics and efficacy in patients with activated inflammatory osteoarthritis of the knee. *Clin Drug Investig.* 2001;21:429-436.	Wrong outcome
5	Boonard M, Sumanont S, Arirachakaran A, et al. Short-term outcomes of subacromial injection of combined corticosteroid with low-volume compared to high-volume local anesthetic for rotator cuff impingement syndrome: a randomized controlled non-inferiority trial. *Eur J Orthop Surg Traumatol.* 2018;28:1079-1087.	Wrong outcome
6	Brys DA. Corticosteroid compared with hyaluronic acid injections for the treatment of osteoarthritis of the knee. *J Bone Joint Surg Am.*2013; 86 :874-875	Wrong publication type
7	Carette S, Marcoux S, Truchon R, et al. A controlled trial of corticosteroid injections into facet joints for chronic low back pain. *N Engl J Med.* 1991;325:1002-1007.	Wrong outcome
8	Casutt M, Huebner T, Henzen C, Konrad C, Gerber H, Schuepfer GK. Suppression of the hypothalamic-pituitary-adrenal axis after epidural glucocorticoid injection: identification of inherent at-risk patients. *J Pain Manag.*2010;3:255-261.	Wrong publication type
9	Chon JY, Moon HS. Salivary cortisol concentration changes after epidural steroid injection. *Pain Physician*. 2012;15:461-466.	Wrong outcome
10	Chutatape A, Menon M, Fook-Chong SMC, George, J. Metabolic and endocrinal effects of epidural glucocorticoid injections. *Singapore Med J.* 2019;60:140-144.	Wrong outcome and request for further data unanswered
11	Cohen SP, Narvaez JC, Lebovits AH, Stojanovic MP. Corticosteroid injections for trochanteric bursitis: is fluoroscopy necessary? A pilot study. *Br J Anaesth*. 2005;94:100-106.	Wrong outcome

12	Coll, S. Matabosch, J, lorante-Onaindia, M. et al. Elimination profile of triamcinolone hexacetonide and its metabolites in human urine and plasma after a single intra-articular administration. *Drug Test Anal*. 2019;11:1589-1600.	Wrong outcome and request for further data unanswered
13	Dernek B, Aydin T, Koseoglu PK, et al. Comparison of the efficacy of lidocaine and betamethasone dipropionate in carpal tunnel syndrome injection. *J Back Musculoskelet Rehabil.*2017;30:435-440.	Wrong outcome
14	Dickson, R, Lamar,T. Serum triamcinolone levels following intra-articular lumbar facet joint injections. *Pain Medicine*.2018;19:881-882	Wrong publication type
15	Fan PT, Yu DT, Clements PJ, Fowlston S, Eisman J, Bluestone R. Effect of corticosteroids on the human immune response: comparison of one and three daily 1 gm intravenous pulses of methylprednisolone. *J Lab Clin Med.* 1978;91:625-634.	Wrong population and wrong outcome
16	Friedley, J, Akuthota, V, Jarvik, J, et al. Cortisol suppression following epidural corticosteroid injections in older adults with spinal stenosis. *Arch Phys Med Rehabil.*2014;95:e40.	Wrong publication type
17	Friedley, J, Comstock, B, Standaert S, et al. Patient and procedural risk factors for cortisol suppression following epidural steroid injections for spinal stenosis. *PM R.*2016;8:S159-160.	Wrong publication type
18	Friedley J, Comstock B, Turner J, et al. Long-Term Effects of Repeated Injections of Local Anesthetic With or Without Corticosteroid for Lumbar Spinal Stenosis: A Randomized Trial. *Arch Phys Med Rehabil.* 2017;98:1499-1507.	Wrong outcome
19	Friedman DM, Moore ME. The efficacy of intraarticular steroids in osteoarthritis: a double-blind study. *J Rheumatol.*1980;7:850-856.	Wrong outcome
20	Gerszten PC, Smuck M, Rathmell JP, et al. Plasma disc decompression compared with fluoroscopy-guided transforaminal epidural steroid injections for symptomatic contained lumbar disc herniation: a prospective, randomized, controlled trial. *J Neurosurg Spin.* 2010;12:357-371.	Wrong outcome
21	Gless KH, Klee HR, Vecsei P, Weber M, Haack D, Lichtwald K. Plasma concentration and systemic effect of betamethasone after intra-articular injection (author's transl)]. *Deutsche Medizinische Wochenschrift.*1981;106:704-707.	Wrong outcome
22	Gosens T, Peerbooms JC, van Laar W, den Oudsten BL. Ongoing positive effect of platelet-rich plasma versus corticosteroid injection in lateral epicondylitis: a double-blind randomized controlled trial with 2-year follow-up. *Am J Sports Med.* 2011;39:1200-1208.	Wrong outcome

23	Habib, G, Jabbour A, Salman J. The effect of epidural methylprednisolone acetate injection on the hypothalamic-pituitary-adrenal axis. *J Clin Anesth.* 2013;25:629-633.	Wrong outcome and request for further data not answered
24	Habib G, Zahran R, Najjar R. The effect of intra-articular injection of Diprospan at the knee joint on the hypothalamic-pituitary-adrenal axis. *Swiss Med Wkly*. 2015;145:w14134.	Wrong outcome
25	Housman L, Arden N, Schnitzer TJ, et al. Intra-articular hylastan versus steroid for knee osteoarthritis. *Knee Surg Sports Traumatol Arthrosc*. 2014;22:1684-1692.	Wrong outcome
26	Hsieh L-F, Lizano-Diez X, Gines-Cespedosa A, et al. Platelet-rich plasma compared with other common injection therapies, in the treatment of chronic lateral epicondylitis. *J Sport Rehabil.* 2016;25:77-82.	Wrong outcome
27	Huppertz HI, Pfuller H. Transient suppression of endogenous cortisol production after intraarticular steroid therapy for chronic arthritis in children. *J Rheumatol.* 1997;24:1833-1837.	Wrong publication type
28	Imran, M, Barathan, J, Wick, B. Effects of intraarticular (IA) corticosteroid injections on bone markers and endogenous cortisol in patients with knee osteoarthritis (OA): A randomized, double-blind, placebo controlled trial. *Arthritis Rheumatol.*2014;66:S975-976.	Wrong publication type
29	Jain K, Murphy, PN, Clough TM. Platelet rich plasma versus corticosteroid injection for plantar fasciitis: A comparative study. *Foot*. 2015;25:235-237.	Wrong outcome
30	Kennedy DJ, Huynh L, Wong J, et al. Corticosteroid injections into lumbar facet joints: a prospective, randomized, double-blind placebo-controlled trial. *Am J Phys Med Rehabil.* 2018;97:741-746.	Wrong outcome
31	Labrosse JM, Cardinal E, Leduc BE, et al. Effectiveness of ultrasound-guided corticosteroid injection for the treatment of gluteus medius tendinopathy *Am J Roentgenol.* 2010;194:202–6.	Wrong outcome
32	Leopold, S, Redd, B., Warme,W. Corticosteroid compared with hyaluronic acid injections for the treatment of osteoarthritis of the knee: A prospective, randomized trial. *J Bone Joint Surg Am.* 2003;85:1197-1203.	Wrong outcome
33	Malliferet. J-F, Aho S, Piroth-Chatard, C. Cortisol levels after single local steroid injection. *Am J Med.*1996;100:586-587.	Wrong publication type
34	Macro M, Reznic Y, Leymarie P, Loyau G. The effect of intrathecal dexamethasone injection on plasma cortisol level. *Br J Rheumatol.* 1991;30:238.	Wrong outcome and wrong publication type
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