

Habib G, Jabbour A, et al. Intra-articular methylprednisolone acetate injection at the knee joint and the hypothalamic–pituitary–adrenal axis: a randomized controlled study. Clin Rheumatol 2014;33:99-103.

Design: Randomized clinical trial

Study question: Does an intra-articular injection of a corticosteroid (IACI) suppress the hypothalamic-pituitary-adrenal (HPA) axis?

Population/sample size/setting:

- 40 patients (27 men, 13 women, mean age 52) treated for knee osteoarthritis at a rheumatology department in Israel
- Eligibility criteria were age over 18 with knee osteoarthritis not responding to NSAIDs and physical therapy
- Exclusion criteria were previous IACI, administration of steroid compounds by any route in the past 3 months, previous knee injection with sodium hyaluronate (SH) at the painful knee, any evidence of acute illness, uncontrolled hypertension/diabetes; anticoagulant treatment or any bleeding diathesis, allergy to steroids or SH, skin infection at the proposed site of knee injection, or pregnancy

Main outcome measures:

- All patients had an intra-articular knee injection either with steroid (methylprednisolone acetate, MCA) or SH
- Randomization was to injection with 80 mg MCA (n=20) or with 60 mg SH (n=20)
 - o “Randomization” was by alteration of consecutive patients
- A “favorable clinical response” to the injection was defined as a decrease of 30 or more points on a 100 point pain VAS from baseline to followup
- All patients had their adrenal function evaluated by the response of serum cortisol to low-dose (1 mcg) of ACTH (tetracosactide acetate) 30 minutes after it was injected
 - o These tests were done at 9 AM on the date of the knee injection, and again at weeks 1, 2, 3, 4, and 8 after the knee injection
 - o A normal test was defined by the increase in cortisol after ACTH administration
 - If the 30 minute cortisol was 18 mcg/dL or greater, or if the 30 minuted cortisol was 7 mcg/dL greater than the pre-ACTH injection, the test was normal
 - In order to be considered evidence of adrenal insufficiency, both criteria had to be met: the 30 minute cortisol had to be less than 18 mcg/dL AND it had to have increased by less than 7 mcg/dL

- Thus, for example, if the pre-ACTH cortisol was 4 and the 30 minute cortisol was 11, the test was normal, since it had increased by 7, even though the 30 minute cortisol was less than 18
- Of the 20 patients who had Depo-Medrol, 5 had evidence of adrenal insufficiency between week 2 and week 4
 - None had adrenal insufficiency at baseline or at week 1, and none had adrenal insufficiency at week 8
 - None had symptoms of adrenal insufficiency (weakness or malaise)
- Of the 20 patients who had SH, none had adrenal insufficiency at any time after the injection
- At week 1, 17/20 patients in the MCA group had a “favorable clinical response” with at least a 30 point decrease in knee pain, but only 10/20 in the SH group had a “favorable clinical response” at week 1
 - However, at week 4 there was no difference in “favorable clinical response” between groups (14/20 MCA and 12/20 SH patients)
 - Similarly, at week 8, there was no difference between the groups in “favorable clinical response” (10/20 MCA and 12/20 SH patients)
- Several variables were tested for an association with adrenal insufficiency: age, sex, duration of knee pain, previous steroid injection, BMI, erythrocyte sedimentation rate, and C-reactive protein; none showed an association

Authors’ conclusions:

- An injection of 80 mg of MCA at the osteoarthritic knee was associated with laboratory evidence of adrenal insufficiency in 25% of patients, but no patient who had an injection of SH had lab evidence of loss of adrenal function
- Evidence of adrenal insufficiency was transient and variable; and usually remained for a few days when it was observed
- Requiring two criteria for adrenal insufficiency (failure of cortisol to increase by 7 mcg/dL AND failure of cortisol to reach 18 mcg/dL after ACTH stimulation) increased the specificity of the definition, and could decrease the sensitivity of the ACTH stimulation test
- In practical terms, patients having intra-articular steroid injections require no special observation, but their physicians should be made aware of the injections, and may require exogenous steroid treatment if they become acutely ill or stressed in the weeks after an injection

Comments:

- The definition of secondary adrenal insufficiency was fairly strict; many authors consider a 30-minute cortisol response to ACTH of less than 18 mcg/dL to be evidence of suppression of the HPA axis

- In Table 2, four patients had 30 minute cortisol of less than 18 mcg/dL at week 1 (patient # 6, 9, 14, and 19), but had increases of at least 7 mcg/dL
- Similarly, at week 2, four patients had 30 minute cortisol of less than 18 mcg/dL (# 9, 14, 17, and 20)
- There appears to be a misprint in Table 2; for patient #16, the cortisols for week 3 are 11 and 1 mcg/dL (author has been e-mailed); presumably the numbers should be 1 and 11 mcg/dL
- Having a randomized trial, even though small, is a great advantage over data which do not have an appropriate comparison group
 - Strictly speaking, the allocation of patients by alteration of consecutive participants is not randomized, but the validity of the comparison of MPA and SH does not suffer greatly

Assessment: Adequate for evidence that an intra-articular injection of 80 mg of methylprednisolone acetate into the knee has about a 25% probability of suppressing the adrenal gland response to exogenous ACTH for four or more weeks after injection, but recovery of the adrenal response is expected by week 8 after injection