The Effect of Intra-articular Injection of Betamethasone Acetate/Betamethasone Sodium Phosphate at the Knee Joint on the Hypothalamic-Pituitary-Adrenal Axis: A Case-Controlled Study

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Background: Intra-articular corticosteroid injection (IACI) of betamethasone depot preparation is a popular procedure at the knee joint. Intra-articular corticosteroid injection in general could be associated with systemic effects including suppression of the hypothalamic-pituitary-adrenal axis. There are nearly no reports on the effect of IACI of betamethasone at the knee joint on the hypothalamic-pituitary-adrenal axis.

Method: Consecutive patients attending the rheumatology or orthopedic clinic with osteoarthritic knee pain who were not responding satisfactorily to medical and physical therapy were allocated to group 1 after consent and given IACI of 6 mg of betamethasone acetate/betamethasone sodium phosphate. After completion of this part, consecutive age- and sex-matched patients were allocated to group 2 and given intra-articular injection of 60 mg of sodium hyaluronate. Demographic, clinical, laboratory, and radiographic variables were documented. Just before the knee injection and 1, 2, 3, 4, and 8 weeks later, patients had 1-μg adrenocorticotropin hormone (ACTH) stimulation test. Secondary adrenal insufficiency (SAI) was defined as levels of less than 18 μg/dL and lack of a rise of more than 6 μg/dL in serum cortisol level, 30 minutes after the ACTH stimulation test.

Patients were blinded to the injected material, and all injections were ultrasound guided.

Results: Twenty patients were enrolled in each group and equally divided between the 2 sexes. The mean age of the patients was approximately 54 years in both groups. No significant difference in any variable was seen between the 2 groups. One patient only from group 1 (the betamethasone group) had SAI 3 weeks after the IACI compared to none in the control group ($P > 0.9999$). His serum cortisol level 30 minutes after the ACTH stimulation was 17 μg/dL, with a rise of 3 μg/dL from baseline.

Conclusion: Intra-articular corticosteroid injection of 6 mg of betamethasone acetate/betamethasone sodium phosphate at the knee joint was not significantly associated with SAI at the time points tested.

Key Words: intra-articular corticosteroid injection, betamethasone, osteoarthritis of the knee, hypothalamic-pituitary-adrenal axis, secondary adrenal insufficiency

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Intra-articular corticosteroid injection (IACI) at the knee joint is a popular procedure.[1] The main objective of the local injection is maximal local effect with minimal systemic spread. Yet, a considerable proportion of the steroid compound finds its way to the systemic circulation.[2] A wide spectrum of systemic effects including the effect on the hypothalamic-pituitary-adrenal (HPA) axis was reported in the literature.[3–8] Suppression of this axis with secondary adrenal insufficiency (SAI) is a real consideration whenever an individual is subjected to depot steroid compounds including IACI.

Traditionally, insulin tolerance test (ITT) has been used as the reference standard for the evaluation of the integrity of the HPA axis.[9] However, this test might have serious adverse effects and currently adrenocorticotropin hormone (ACTH) stimulation test, especially the low dose (1 μg), is a popular method to evaluate SAI.[10] This test is considered safer, quicker, and cheaper.[11]

There are very few studies in the literature assessing the HPA axis using ACTH stimulation test following IACIs.[6–8] All these studies were either not controlled, the IACIs not ultrasound guided, had a small number of patients, no fix dose of corticosteroids was used, or the IACIs were done at different joints.

The effect of IACI at the knee joint of betamethasone, on the HPA axis, was evaluated in 3 patients only.[7] The dose that was used was 7 mg. Secondary adrenal insufficiency was founded in all of them 2 days after the IACI, and serum cortisol levels were still low in one patient and intermediate in 2 others 2 weeks after the IACI.

In this case-controlled study, we wanted to evaluate the effect of intra-articular injection (IAI) of a fixed dose of 6 mg of betamethasone acetate/betamethasone sodium phosphate on the HPA axis, in patients with osteoarthritis of the knee, using IAI of sodium hyaluronate (SH) in the control group.

MATERIALS AND METHODS

Consecutive patients attending the rheumatology or orthopedic clinics at the Nazareth Hospital with knee pain who met the American College or Rheumatology criteria for the diagnosis of osteoarthritis (OA) of the knee[12] and failed nonsteroidal anti-inflammatory treatment (if not contraindicated) and physical therapy were asked to participate in our study. After consent, the patients initially were allocated to group 1. In this group, the patients had IACI of depot preparation of betamethasone acetate (3 mg) + betamethasone sodium phosphate (3 mg) (Celestone Chronodose; Schering-Plough, Heist-Op-Den-Berg, Belgium). The first component of this preparation is a slightly soluble ester, and the second component is a soluble ester. After completion of this part (enrollment of 20 patients), age- and sex-matched consecutive newly recruited patients had IAI of 60 mg of SH (Suplazyn; Bioniche, Galway, Ireland) (group 2).

The patients were blinded to the injected material. All the IAIs were ultrasound guided and followed maximal aspiration of knee fluid, if any.

Just before the IAIs (week 0) and at weeks 1, 2, 3, 4, and 8 after it, all the patients had ACTH stimulation test using 1 μg of tetracosactide acetate (Alliance Pharmaceuticals Ltd, Wiltshire, UK). All the ACTH stimulation tests were done at 9:00 AM after an overnight fast and no special physical activity in the morning.

Serum cortisol levels were obtained just prior (time 0) and 30 minutes after the ACTH stimulation test (time 30).

The inclusion criteria included patients older than 18 years, and patients able to sign a consent form. Exclusion criteria are the following: having IACI; systemic, intramuscular, local, nasal spray, eye drops, or inhalation of steroid compounds during the previous 3 months; IAI of SH in the past at the painful knee; evidence of acute illness (inflammatory or noninflammatory); uncontrolled hypertension; uncontrolled diabetes; anticoagulant treatment; tendency toward bleeding; allergy to corticosteroids or SH; skin infection at the site of the IAI; and pregnancy.

Data regarding demographic, clinical, and laboratory variables like age, sex, body mass index, duration of knee pain, level of knee pain (using visual analog scale of 0–100, where 0 stands for no pain and 100 stands for worse pain ever experienced), knee effusion, erythrocyte sedimentation rate, C-reactive protein, and radiographic changes (Kellgeren-Lawrence grading) were documented.

Blood samples were collected in polypropylene tubes with tripotassium ethylene diamine tetraacetic acid. Samples were then rapidly centrifuged at 3000 revolutions per minute for 10 minutes. An aliquot of each plasma sample was frozen at −30°C. All the frozen samples were analyzed by the end of the study using AxSYM cortisol assay (Abbott Diagnostic Division, Abbott Park, IL) using fluorescence polarization immunoassay technology according to the manufacturer's instructions. Normal morning serum cortisol levels for the hospital clinical laboratory were between 6 and 20 μg/dL. The technician assessing the samples was blinded to the type of IAI the patients had.

There are some disputes about the definition of SAI in the literature. Some reports consider serum cortisol level of 18 μg/dL obtained 30 minutes after the low-dose ACTH stimulation test as the cutoff level for the diagnosis of SAI.[10] However, some reports emphasize the lack of rise of serum cortisol level greater than 6 μg/dL at time 30 (above the level of time 0) after the low-dose ACTH stimulation test.[13] To maximize the specificity, both criteria were required to qualify for the definition of SAI in our study.

The continuous variable of the demographic, clinical, and laboratory parameters in the 2 groups were compared using the Mann-Whitney *U* test and the categorical variables using the χ^2/Fisher exact test. The χ^2/Fisher exact test was also used to compare the number of patients with SAI in the different groups.

The Wilcoxon rank singed test was used to compare between both basal and poststimulation serum cortisol levels at each time point after the IAIs to baseline basal and poststimulation serum cortisol levels, respectively.

The analysis of serum cortisol levels at each time point included all the patients who attended at that time point.

This study was approved by the local Helsinki committee of the Nazareth Hospital, and all the patients signed a consent form.

RESULTS

Twenty patients were enrolled in each group. Sixteen and 18 patients from group 1 and group 2, respectively, attended the whole sessions. There was no significant difference between the different baseline variables in the 2 groups (Table 1).

All the patients had normal adrenal response before the IACI or IAI of SH.

Only one patient from group 1 had SAI at week 3, whereas none in the control group had SAI at week 3 (P = >0.999; Table 2) (data from group 2 are not shown). The level of serum cortisol in this patient was 17 μg/dL 30 minutes after the ACTH stimulation, with a rise of 3 μg/dL from time 0 level.

There was no significant difference between basal serum cortisol levels at weeks 1, 2, 3, 4, and 8 compared to those at baseline (P = 0.07, P = 0.55, P = 0.861, P = 0.437, and P = 0.317, respectively). The P values for poststimulation serum cortisol levels were 0.032, 0.429, 0.428, 0.423, and 0.433 at weeks 1, 2, 3, 4, and 8, respectively, compared to baseline

TABLE 1. Patients' Characteristics in Groups 1 and 2

	Groups		
Parameter	**1 (n = 20)**	**2 (n = 20)**	***P***
Age, yrs*	53.25 ± 8.38 (43–75)	54.7 ± 11.04 (42–76)	0.643
Male:Female ratio	10:10	10:10	>0.999
VAS of knee pain*	77 ± 10 (58–98)	79 ± 9 (65–100)	0.861
Duration of knee pain, yrs*	1.98 ± 2.26 (0.25–9)	2.95 ± 3.76 (0.2–15)	0.330
Previous IACI at the knee	2	3	>0.999
Knee effusion	5	3	0.695
BMI*	29.94 ± 5.34 (19–40)	29.0 ± 4.0 (23–38)	0.5324
ESR*†	19.95 ± 8.17 (5–33)	17.30 ± 7.7 (7–31)	0.298
CRP*‡	2.93 ± 2.16 (0.5–7.7)	3.45 ± 2.28 (0.5–8)	0.464
Radiographic changes (Kellgeren-Lawrence grading)*	2.48 ± 0.93 (1–4)	2.38 ± 0.80 (1–4)	0.691

*Mean ± SD (range).

†Normal range: 5–25.

‡Normal range: 0.5–5 mg/dL.

BMI indicates body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; VAS

TABLE 2. Serum Cortisol Levels at Different Time Points in Group 1 Patients

	Time											
Patient	W 0 T 0	W 0 T 30	W 1 T 0	W 1 T 30	W 2 T 0	W 2 T 30	W 3 T 0	W 3 T 30	W 4 T 0	W 4 T 30	W 8 T 0	W 8 T 30
1	7	19	6	18	10	20	7	18	6	17	8	20
2*	13	18	7	15	8	20	**14**	**17**	12	19	10	21
3	9	16	12	21	19	20	15	20	16	23	14	19
4	1	24	6	20	8	22	8	26	7	22	7	18
5	20	27	21	24	14	24	22	26	19	24	18	25
6	13	21	10	18	8	23	9	21	7	18	10	22
7	6	18	6	19	7	20	6	17	NR	NR	9	17
8	8	18	6	16	10	24	10	20	6	16	8	18
9	8	16	6	16	9	20	7	15	12	22	10	20
10	14	20	4	17	5	17	6	19	8	18	10	21
11	7	26	5	20	12	27	14	23	12	27	10	25
12	14	27	9	21	10	25	13	21	10	26	11	24
13	7	19	7	15	8	18	5	16	9	18	6	17
14	8	21	10	24	8	22	5	22	7	21	8	20
15	14	24	13	27	19	28	15	26	14	24	14	22
16	9	17	7	15	5	17	5	16	NR	NR	NR	NR
17	12	24	NR	NR	16	20	14	21	12	19	16	22
18	7	20	5	18	8	21	13	27	10	20	11	19
19	11	25	10	21	13	23	10	19	14	26	12	25
20	6	19	5	17	6	20	7	19	11	21	NR	NR

*Patient with SAI (bold results).

W 0 indicates week 0; W 1, week 1; W 2, week 2; W 3, week 3; W 4, week 4; W 8, week 8; T 0, time 0; T 30, time 30; NR, not reported.

levels. The mean poststimulation serum cortisol level at baseline was 20.95 ± 3.6; whereas at week 1, it was 19.3 ± 3.5.

DISCUSSION

Our study shows that IACI of 6 mg of Celestone Chronodose at the knee joint is not associated with SAI in nearly all the patients one week and beyond after the injection. This means that patients who develop medical stressful event (like sepsis) or expected to do so (during planned surgical procedures) one week or later after IACI with 6 mg of Celestone-Chronodose do not need supplemental steroids. Supplemental steroids could be considered whenever SAI is suspected in such patients, and preferably after confirmation of this suspicion, using low-dose ACTH stimulation test.

Our findings support a previous study in which the effect of IACI of 6 mg of Celestone Chronodose at the knee joint on blood glucose levels was short lived, lasting less than 48 hours on average.[14]

It seems that the main effect of IACI of 6 mg of Celestone Chronodose in our study was at week 1, when there was a nonsignificant decrease of basal serum cortisol levels compared to those at baseline (P = 0.07) and a significant decrease in poststimulation levels compared to those at baseline (P = 0.032). However, in absolute numbers, the difference between the mean values of poststimulation levels was very slight (19.3 ± 3.5 μg/dl at week 1 vs 20.95 ± 3.6 at baseline).

The patient that was defined as having SAI in our study had basal serum cortisol level of 14 μg/dL at week 3 and poststimulation level of 17 μg/dL, very close to the cutoff point. In a previous study that correlated ACTH stimulation test with ITT, all the patients who had basal serum cortisol levels higher than 14.5 μg/dL had passed the ITT test.[15] Therefore, some endocrinologists would argue, understandably, that this patient had passed the test and did not have SAI.

We did not assess the adrenal response to ACTH stimulation in the first few days after the IAIs. Usually, patients after IACI are not planned for immediate optional procedures and asked to have some rest for at least a few days. Practically, we think it is very important to assess the adrenal gland beyond the first few days, as we did, when depot steroid preparations dissolve slowly at the joint cavity and might have a significant impact on the adrenal response even if serum cortisol levels were normal.

The results of our study cannot be extrapolated to IAIs using other depot steroid preparations, particularly the triamcinolone acetonide suspensions, which have different absorption phase and duration of action.

REFERENCES

1. Snippe JC, Gambardella RA. Use for injections in osteoarthritis in joints and sports activity. *Clin Sports Med*. 2005;24:83–91.
2. Gless KH, Klee HR, Vecsei P, et al. Plasma concentration and systemic effect of betamethazone following intraarticular injection. *Disch Med Wschr*. 1981;106:704–707.
3. Weitof T, Ronnblom L. Glucocorticoid resorption and influence on the hypothalamic-pituitary-adrenal axis after intra-articular treatment of the knee in resting and mobile patients. *Ann Rheum Dis*. 2006;65:955–757.
4. Lazarevic MB, Skosey JL, Djordjevic-Denic G, et al. Reduction of cortisol levels after single intra-articular and intramuscular steroid injection. *Am J med*. 1995;99:370–373.

5. 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.
6. Mader R, Lavi L, Luboshitzky R. Evaluation of the pituitary-adrenal axis function following single intraarticular injection of methylprednisolone. *Arthritis Rheum*. 2005;52:924–928.
7. Duclos M, Guinot M, Colsy M, et al. High risk of adrenal insufficiency after a single articular steroid injection in athletes. *Med Sci Sports Exerc*. 2007;39:1036–1043.
8. Weiss S, Kisch S, Fischel B. Systemic effects of intraarticular administration of triamcinolone hexacetonide. *Isr J Med Sci*. 1983;19:83–84.
9. Jacobs HS, Nabarro JDN. Tests of hypothalamic-pituitary-adrenal function in man. *QJM*. 1969;152:475–491.
10. Magnotti M, Shimshi M. Diagnosing adrenal insufficiency: which test is best—the 1-microg or the 250-microg cosyntropin stimulation test? *Endocr Pract*. 2008;14:233–238.
11. Dickstein G. The assessment of the hypothalamo-pituitary-adrenal axis in pituitary disease: are there short cuts? *J Endocrinol Invest*. 2003; 26(7 supp):25–30.
12. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and therapeutic criteria committee of the American rheumatism association. *Arthritis Rheum*. 1986;29:1039–1049.
13. Gandhi PG, Shah NS, Khandelwal AG, et al. Evaluation of low dose ACTH stimulation test in suspected secondary adrenocortical insufficiency. *J Postgrad Med*. 2002;48:280–282.
14. Habib G, Safia A. The effect of intra-articular injection of betamethasone acetate/betamethasone sodium phosphate on blood glucose levels in controlled diabetic patients with symptomatic osteoarthritis of the knee. *Clin Rheum*. 2009;28:85–87.
15. Stewart PM, Corrie J, Seckl JR, et al. A rational approach for assessing the hypothalamo-pituitary-adrenal axis. *Lancet*. 1988;1(8596):1208–1210.

