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The effect of intra-articular injection of Diprospan at the knee joint on the hypothalamic-pituitary-adrenal axis

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Summary

QUESTIONS UNDER STUDY: In this work we wanted to evaluate the effect of intra-articular injection (IAI) at the knee joint of 1 ml of Diprospan on the hypothalamic-pituitary-adrenal (HPA) axis.

METHODS: Consecutive patients attending the rheumatology or orthopaedic clinic with osteoarthritic knee pain not responding satisfactorily to medical and physical therapy were asked to participate in our study. After consent, patients had ultrasound-guided IAI of 1 ml of Diprospan, containing 2 mg of betamethasone sodium phosphate and 5 mg of betamethasone dipropionate. Demographic, clinical, laboratory and radiographic variables were documented. Just prior to the knee injection and 1, 2, 4 and 6 weeks later, patients had a 1-µg adrenocorticotropic hormone (ACTH) stimulation test. Secondary adrenal insufficiency (SAI) was defined as a poststimulation (30 minutes after ACTH injection) serum cortisol level of less than 18 µg/dl (~500 nmol/l) and lack of a rise of >6 µg/dl (~166 nmol/l) over the basal level in poststimulation serum cortisol.

RESULTS: Twenty patients completed the study. There were 3 male and 17 female patients, with a mean age of 58.6 ± 9.5 years. Six (30%) patients had evidence of SAI and in five of them it was seen at one time-point, mostly at week 2 after the IAI. In one patient, SAI was prolonged and observed from week 1 to week 4.

CONCLUSIONS: IAI at the knee joint of 1 ml of Diprospan was associated with a transient high rate of SAI.

***Key words**: Diprospan; betamethasone; intra-articular; hypothalamic-pituitary-adrenal axis; cortisol; knee; osteoarthritis*

Background

Intra-articular injection (IAI) of steroids at the knee joint is a popular procedure [1]. It is a proven modality for pain relief in patients with osteoarthritis of the knee joint. Although it is given locally, a significant portion of the active compound might be absorbed into the circulation [2]. A wide spectrum of systemic effects including effects on the hypothalamic-pituitary-adrenal (HPA) axis, have been reported in the literature [3–8]. Suppression of this axis with secondary adrenal insufficiency (SAI) is a real consideration whenever an individual is exposed to depot steroid compounds including IAI of corticosteroids. This suppression is dependent on many factors, including the amount of the injected steroid, type of the injected depot preparation, type of joint, number of joints injected simultaneously and other factors. In a previous study we showed that an IAI of 1 ml of Celestone Chronodose (3 mg betamethasone sodium phosphate + 3 mg betamethasone acetate) at the knee joint was not significantly associated with SAI in patients with osteoarthritis [9]. Such a compound is composed equally of two components, a short-acting one, betamethasone sodium phosphate, and a long-acting one, betamethasone acetate. Another popular depot betamethasone preparation is Diprospan, which is also composed of a similar short-acting component, betamethasone sodium phosphateacetate and a different long-acting one, betamethasone dipropionate. However, 1 ml of Diprospan contains 2 mg of betamethasone sodium phosphateacetate and 5 mg of betamethasone dipropionate. Such a composition could have a different effect on the HPA axis following IAI of Diprospan at the knee joint.

Traditionally, an insulin tolerance test (ITT) has been used as the reference standard for the evaluation of the integrity of the HPA axis [10]. However, this test can have serious adverse effects and currently an adrenocorticotropic hor-

mone (ACTH) stimulation test, especially the low dose (1 µg), is the accepted method for evaluating SAI [11]. This test is considered safer, quicker and cheaper [12].

The aim of our study was to evaluate the effect of IAI at the knee joint of 1 ml of Diprospan on the HPA axis, using the 1 µg ACTH stimulation test.

Methods

Consecutive patients attending the rheumatology or orthopaedic clinics at the Nazareth Hospital with knee pain, who met the American College of Rheumatology criteria for the diagnosis of osteoarthritis of the knee [13], and failed to respond to nonsteroidal anti-inflammatory treatment (if not contraindicated) and physical therapy, were asked to participate in our study. After consent, patients had a 1-ml IAI of depot preparation of betamethasone sodium phosphate (2 mg) + betamethasone dipropionate (5 mg) (Diprospan) (Shering-Plough, Belgium). All the IAIs were ultrasound guided and following maximal aspiration of knee fluid, if any.

Just prior to the IAI (week 0) and at weeks 1, 2, 4 and 6 after it, all the patients had ACTH stimulation tests with 1 µg of tetracosactide acetate (Alliance Pharmaceuticals Ltd., UK). All the ACTH stimulation tests were at 09:00 in the morning, after an overnight fast and without any special physical activity in the morning.

Serum cortisol levels were obtained just prior to (basal), and 30 minutes after ACTH stimulation (poststimulation).

The inclusion criteria included age older than 18 years, and ability to sign a consent form. Exclusion criteria were: intra-articular, systemic, intramuscular or topical administration, nasal spray, eye drops or inhalation of steroid compounds during the previous 3 months; evidence of acute illness (inflammatory or noninflammatory); uncontrolled hypertension; uncontrolled diabetes; anticoagulant treatment, tendency towards bleeding; allergy to corticosteroids; skin infection at the site of the IAI; and pregnancy.

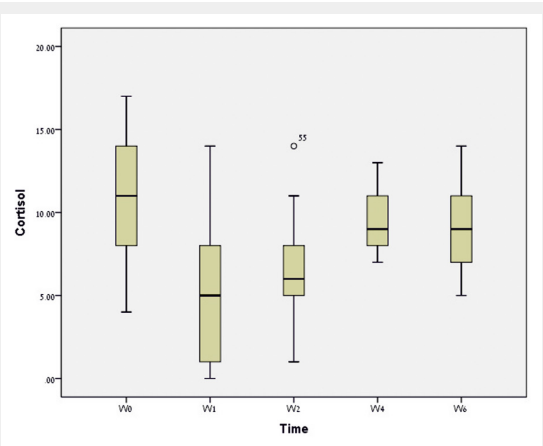

Figure 1

Basal serum cortisol levels at baseline and at different time points in all the patients.

Box plot showing distribution of serum cortisol levels at each time-point, where the lower and upper borders of the box and the line inside it represent quartile 1 (Q1), Q3 and the median values, and the upper and lower whiskers represent Q3+ 1.5 interquartile range (IQR) and Q1-1.5 IQR, respectively. The numbered circle represents the serial number of the patient had a cortisol level higher than the upper whisker.

W0 = baseline; W1 = week 1; W2 = week 2; W4 = week 4; W6 = week 6

Demographic, clinical and laboratory variables such as age, gender, body mass index (BMI), duration of knee pain, level of knee pain (on a visual analogue scale [VAS] of 0–100, where 0 stands for no pain and 100 stands for worse pain ever experienced), knee effusion, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and radiographic changes (Kellgeren-Lawrence grading) were documented.

Blood samples were collected in polypropylene tubes with tripotassium ethylene diamine tetra-acetic acid (K_3EDTA). Samples were then rapidly centrifuged at 3,000 revolutions per minute for 10 minutes. An aliquot of each plasma sample was frozen at –30 °C. All the frozen samples were analysed by the end of the study using ARCHITECT cortisol assay (Abbott Laboratories Diagnostic Division, Abbott Park, IL, USA) utilising fchemiluminescent microparticle immunoassay (CMIA) technology in accordance with the manufacturer's instructions. The test is designed to have a precision of ≤10% coefficient of variation for serum sample levels of ≥3 to ≤35 µg/dl, functional sensitivity of ≤1 µg/dl and a specificity of 97.3%–100% (determined by studying the cross reactivity of 36 compounds whose chemical structure or concurrent usage may potentially interfere with the cortisol assay).

Normal morning serum cortisol levels for the hospital clinical laboratory were 6–20 µg/dl.

The widely used criterion for the definition of SAI is a poststimulation serum cortisol level of ≤18 µg/dl (~500 nmol/l) [11, 14]. However, since there were not a few patients from previous studies of ours and also in this study with borderline poststimulation serum cortisol levels at baseline, we added another criterion to be used simultaneously with the previous main criterion in order to increase specificity and reduce the false positive rate. The second criterion is a lack of a rise of serum cortisol levels of >6 mµ/dl (166 nmol/l) over basal levels [15].

Wilcoxon's signed rank test was used to compare both basal and poststimulation serum cortisol levels at each time-point after the IAIs with baseline basal and baseline 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-one patients were enrolled in our study. One patient was excluded one week later owing to systemic steroid treatment for bronchitis. Demographic, clinical and laboratory parameters of the rest of the patients (20 patients) are shown in table 1.

Serum cortisol levels at baseline and at later time-points of all the patients are shown in table 2 and figures 1 and 2. All the patients had a normal adrenal response prior to the IAI. Six patients (30%) had evidence of SAI. In five of them it was observed on one occasion only, mostly at week 2 (four

patients) and even at week 6 (one patient). In one patient SAI was observed at week 1 through week 4.

Mean basal serum cortisol level was 10.95 (302 nmol/l) ±3.6 µg/dl, and mean prestimulation levels at weeks 1, 2, 4 and 6 were 5.1 (141 nmol/l) ±3.8 (p = 0.000), 6.65 (183 nmol/l) ±2.85 (p = 0.000), 9.25 (255 nmol/l) ±2.0 (p = 0.081) and 9.0 (248 nmol/l) ±2.5 µg/dl (p = 0.025), respectively. Mean poststimulation serum cortisol level at baseline was 20.4 (563 nmol/l) ±1.98 µg/dl, and at weeks 1, 2, 4 and 6 were 12.5 (345 nmol/l) ±5.1 (p = 0.000), 15.55 (429 nmol/l) ±3.82 (p = 0.000), 19.13 (528 nmol/l) ±1.59 (p = 0.015) and 19.4 (535 nmol/l) ±2.04 µg/dl (p = 0.009), respectively.

None of the patients reported special weakness or other special symptoms.

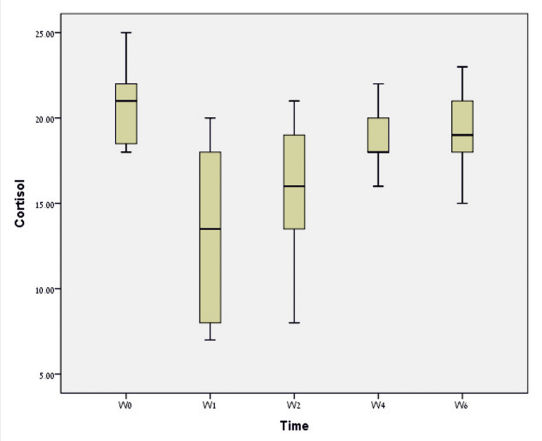

Figure 2

Poststimulation serum cortisol levels at baseline and at different time points in all the patients.

Box plot showing distribution of serum cortisol levels at each time point, where the lower and upper borders of the box and the line inside it represent quartile 1 (Q1), Q3 and the median values, and the upper and lower whiskers represent Q3+ 1.5 interquartile range (IQR) and Q1-1.5 IQR, respectively.

W0 = baseline; W1 = week 1; W2 = week 2; W4 = week 4; W6 = week 6

Discussion

Our study showed that IAI of 7 mg of betamethasone sodium phosphate / betamethasone dipropionate (Diprospan) at the knee joint was associated with SAI in 30% of the patients. SAI was transient and mostly seen at one time-point, mainly at week 2. In one patient only (5%), SAI was prolonged and seen over 3 weeks from week 1 to week 4. SAI could even occur late, at week 6 (5% of the patients) after the IAI.

Regardless of SAI, basal and poststimulation serum cortisol levels were significantly lower than baseline levels

Table 1: Demographic, clinical and laboratory variables of the patients (n = 20).

Variable	
Age (years)*	58.6 ± 9.5 (44–79)
Male: female	3:17
VAS of knee pain*	79 ± 12 (64–100)
Duration of knee pain (years)*	2.42 ± 2.10 (0.3–10)
Previous IACI at the knee (n)	4
Knee effusion (n)	2
BMI*	32.4 ± 6.1 (22.1–43.5)
ESR*#	22.5 ± 8.6 (7–39)
CRP (mg/dl)*†	4.2 ± 3.26 (0.5–12)
Radiographic changes (Kellgeren-Lawrence grading)*	2.26 ± 0.84 (1–4)

BMI = body mass index; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; IACI = intra-articular corticosteroid injection; VAS = visual analogue scale

* Mean ± standard deviation (range)

Normal range: 5–25

† Normal range: 0.5–5 mg/dl

Table 2: Serum cortisol levels at the various time-points in all individual patients.

Time Patient	W0 T0	W0 T30	W1 T0	W1 T30	W2 T0	W2 T30	W4 T0	W4 T30	W6 T0	W6 T30
1*	16	20	2	7	10	13	11	17	12	18
2*	12	18	8	18	7	15	9	16	9	15
3	8	18	4	13	NA	NA	NA	NA	9	19
4	10	21	7	19	9	19	10	19	8	20
5	8	19	4	13	7	16	7	18	10	18
6	10	25	7	17	5	17	8	19	8	21
7	11	22	7	15	8	19	10	20	7	23
8	15	21	1	9	5	14	8	18	NA	NA
9*	8	23	0	7	4	9	13	18	13	23
10	7	22	9	20	5	20	7	22	6	21
11	13	19	0	7	1	8	10	17	10	18
12	4	21	NA	NA	6	21	7	21	5	20
13	13	18	1	8	8	15	9	18	7	18
14	8	18	6	18	6	17	11	20	6	18
15	11	21	9	18	6	20	8	21	9	21
16*	12	22	NA	NA	5	11	NA	NA	10	21
17	6	19	1	9	4	15	7	17	7	19
18*	15	22	9	14	14	18	NA	NA	14	21
19	17	21	14	19	11	19	13	21	13	19
20*	15	18	1	8	5	10	11	18	14	18

NA = not available; T0 = basal levels; T30 = 30 minutes poststimulation, W0 = week 0; W1 = week 1; W2 = week 2; W3 = week 3; W4 = week 4; W6 = week 6

*Patients with secondary adrenal insufficiency

at all time-points (except week 4 for basal levels), supporting the tremendous and prolonged effect of the IAI of Diprospan injection at the knee joint on the HPA axis.

This important observation is in total contrast to the lack of SAI observed 1 week or beyond, after IAI of 1 ml (6 mg) of betamethasone sodium phosphate / betamethasone acetate (Celestone Chronodose), the other popular betamethasone depot preparation used at the knee joint (1 patient out of 20 (5%), p = 0.0457) [9]. Although the dose of betamethasone in Diprospan is larger by only 16.6% than that in Celestone Chronodose (7 vs 6 mg), we think that the significant difference in terms of SAI results mainly from the larger dose of betamethasone dipropionate (slow-acting compound) compared with that in Celestone (betamethasone acetate) (5 vs 3 mg). The slow-acting intra-articular corticosteroid compound had a more lasting absorption period from the joint cavity into the circulation, albeit in small doses, resulting in a significant and prolonged suppressive effect on the HPA axis leading to SAI. This observation is supported by a previous finding of a brisk and short lived increase of blood glucose levels after IAI of 6 mg of betamethasone of Celestone at the knee joint in patients with controlled diabetes [16]. The increase in blood glucose levels after IAI of 7 mg betamethasone in the Diprospan compound was much more gradual and lasted for a longer time (unpublished data). Also, when both betamethasone depot preparations were compared in another study, the compound containing betamethasone dipropionate had a more lasting clinical effect than the other [17].

It should be remembered that the comparison with Celestone Chronodose regarding SAI is a comparison between two different studies; however, both studies had similar population groups and utilised the same cortisol assay and laboratory.

In our opinion, if our results prove to be correct in repeated studies, physicians should be aware of the significantly suppressive effect of the IAI at the knee joint of Diprospan on the HPA axis, and other alternative depot steroids for IAI should be seriously considered. In any case, if Diproaspan has been used as an IAI, both the patient and the medical team should be aware of the potential of SAI in such patients during medical stressful events or prior to planned medical stressful events such as planned surgical procedures. In such circumstances, HPA should be evaluated prior to the procedure, using a low-dose ACTH stimulation test, and steroids supplemented accordingly, or even blindly in emergency cases or whenever such an evaluation could not be done.

If we had implemented only one criterion, the widely used criterion of a poststimulation serum cortisol level of <18 µg/dl, to our results, the number of patients with SAI would have been 15 (75% of all the patients). This figure is very high and, on top of that, the ACTH stimulation test, in contrast to the ITT, tends to give false negative (normal) results in patients with recent onset SAI [14].

As we mentioned in the Methods section, in our population there were not a few patients who had poststimulation serum cortisol levels of 18 µg/dl at baseline. It could be that the threshold of 18 µg/dl for the definition of SAI does not fully apply to our population, and it may be that it needs to be lower. Such an issue could be resolved in the future by correlating ITT (the gold standard test for SAI) with the low-dose ACTH stimulation test in our population.

One limitation of our study is the lack of a control group. However, in two previous case control studies evaluating the same effect and using either Celestone Chronodose or methylprednisolone acetate, at our laboratory, none of the patients in the control groups had SAI at any time-point during the study period [9, 18].

Conclusions: IAI of Diprospan at the knee joint had a relatively high rate of SAI. Both patients and physicians should be aware of this potential and its implication in stressful events. Other depot steroid compounds, such as Celestone Chronodose, might be considered as an option.

Disclosures: No financial support and no other potential conflict of interest relevant to this article was reported.

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Figures (large format)

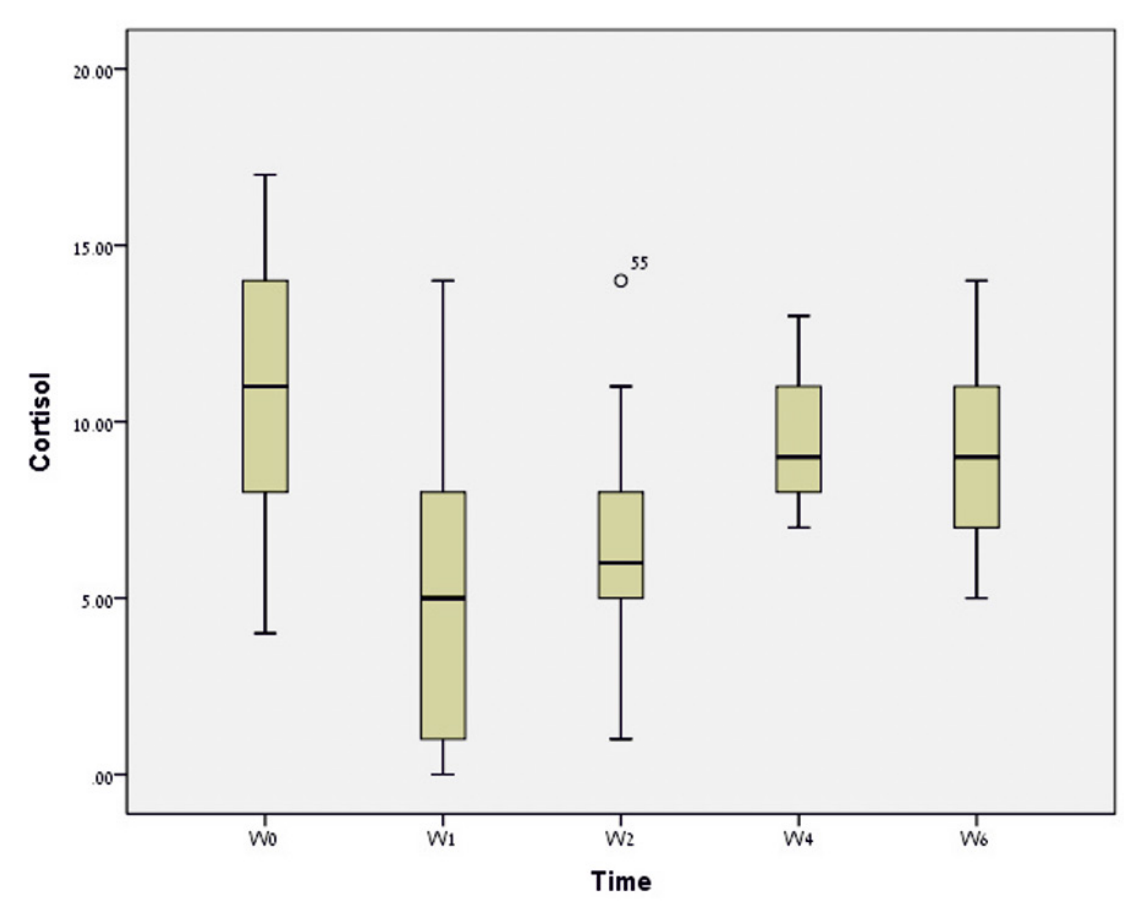

Figure 1

Basal serum cortisol levels at baseline and at different time points in all the patients.
Box plot showing distribution of serum cortisol levels at each time-point, where the lower and upper borders of the box and the line inside it represent quartile 1 (Q1), Q3 and the median values, and the upper and lower whiskers represent Q3+ 1.5 interquartile range (IQR) and Q1-1.5 IQR, respectively. The numbered circle represents the serial number of the patient had a cortisol level higher than the upper whisker.
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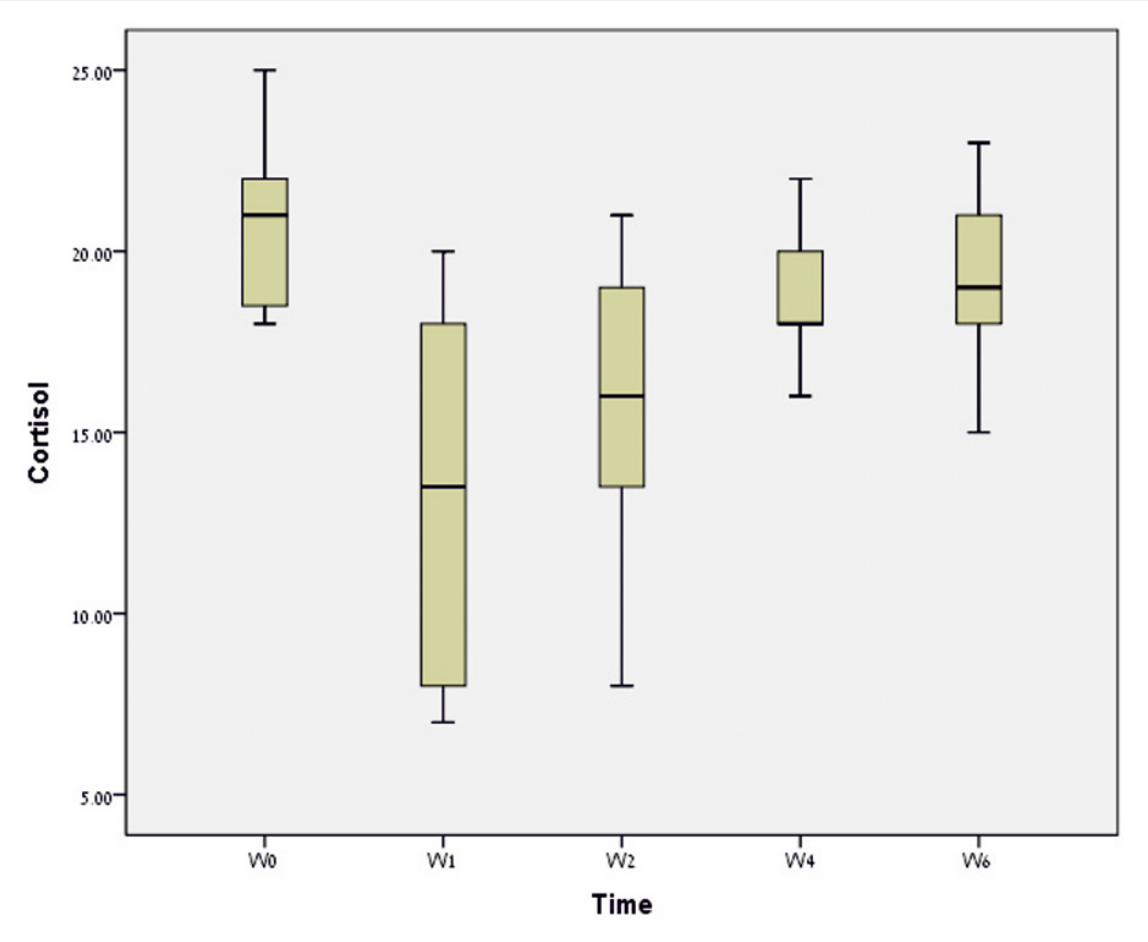

Figure 2

Poststimulation serum cortisol levels at baseline and at different time points in all the patients.
Box plot showing distribution of serum cortisol levels at each time point, where the lower and upper borders of the box and the line inside it represent quartile 1 (Q1), Q3 and the median values, and the upper and lower whiskers represent Q3+ 1.5 interquartile range (IQR) and Q1-1.5 IQR, respectively.
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