Blood Glucose Level After Administration of Glucocorticoids Via Physical Means

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ABSTRACT

The issue of effects of glucocorticoids has been increasing recently. Glucocorticoids may decrease glucose tolerance, produce hyperglycemia, and aggravate or precipitate diabetes mellitus especially in patients predisposed to diabetes mellitus. Their effects on bone rarefaction and development of osteoporosis limit their use. Different routes of administration may affect the dose of medication and their local and systemic effects. The recent and safety routes of delivery, iontophoresis and phonophoresis, are still under research for their directional effects. The aim of this study was to compare the effect of different methods of administration of glucocorticoids on blood glucose level. Fifteen rats were included in this current research. They were of same age and weight. They were equally and randomly grouped into three groups. The rats in the first group received intra-muscular injection of 0.5 cm3 4% Dexamethasone. In the second group, the rats received 0.5 cm3 4% dexamethasone iontophoresis. In the third group, rats received hydrocortisone cream phonophoresis. Treatment was daily for fifteen days. Blood glucose level was the dependent variable measured before and after treatment in the three groups. The results of this current study suggested that glucocorticoids administered via iontophoresis technique have adverse effects on bone minerals more than those administered via phonophoresis and intra-muscular techniques. Further studies are needed to fully evaluate the safety, efficacy and role of high-dose glucocorticoids.

Key Words: cortisone, bone, iontophoresis.

INTRODUCTION

Glucocorticoids (cortisol, cortisone, dexamethasone) are becoming popular medications for different inflammatory conditions since 1960. Although their potent effect on resolution of the pathological background of any inflammatory conditions, their toxic effects limit its usage and dosage. Corticosteroids may decrease glucose tolerance, produce hyperglycemia and aggravate or precipitate diabetes mellitus especially in patients predisposed to diabetes mellitus. If steroid therapy is required in patients with diabetes mellitus, changes in insulin or oral anti-diabetic agent dosage or diet may be necessary. Long-term therapy of corticosteroids may lead to atrophy of the protein matrix of the bone resulting in osteoporosis. Dexamethasone inhibits pituitary corticotrophin (ACTH) release and decreases output of endogenous corticosteroids[1]. Two categories of toxic effects are observed in the therapeutic use of glucocorticoids: those

resulting from withdrawal and those resulting from continued use of large doses. Acute adrenal insufficiency results from too rapid withdrawal of corticosteroids after prolonged therapy. Protocols for discontinuing corticosteroid therapy in patients who were subjected to suppressive therapy for long periods, have been described associates. There is a characteristic corticosteroid withdrawal syndrome, consisting of fever, myalgia, arthralgia and malaise, which may be extremely difficult to distinguish from reactivating of rheumatoid arthritis or rheumatic fever.

There are different methods of administration of glucocorticoids i.e. oral, topical, intra-muscular (IM), intra-venous (IV), subcutaneous, intra-articular, intra-bursal, intra-dermal, intra-synovial, intra-lesional or soft-tissue injection. It has been reported by AHFS[1] that topical corticosteroid therapy is preferable to systemic therapy (IM & IV). Because injections of slightly soluble glucocorticoids may produce atrophy at the site of injection, IM injections of their products should be made deeply into the gluteal muscle; repeated IM injections at the same site should be avoided, and these products should not be administered subcutaneously. The amount of drug, each patient receives, should be individualized according to the diagnosis, severity, prognosis and probable duration of disease and patient response as well as tolerance[1].

The recent and safety routes of delivery, iontophoresis and phonophoresis, are still under research for their directional effects. Iontophoresis is introduction of chemical substance at ionic level into the body for therapeutic purpose by means of direct current[9]. Phonophoresis is the movement of drugs through intact skin into soft tissue by ultrasound perturbation[3]. The technique involves placing the topical formulation on the skin over the area to be treated and measuring the area which treated by ultrasonic source. Drug penetration is much superficial by phonophoresis (2 mm.) than injection and iontophoresis (up to 3 cm.)[11].

The aim of this study was to compare the effect of three methods of administration of glucocorticoid (iontophoresis, phonophoresis, IM injection) on blood glucose level.

METHODS

Design:

It was 3x1 pre-test, post-test, research design. The independent variables were iontophoresis, phonophoresis, intera-muscular injection.. The dependent variable was blood glucose level. The pretest score was the base line to be compared with post-test score.

Sample:

Fifteen female albino rats of middle-age participated in this study. They were subjected to the same environment, temperature and diet. Every 3 rats lived in a special cabinet. They were classified randomly and equally into 3 groups (5 rats each). Group A: rats received intra-muscular injection of 0.5cm3 corticosteroid in the form of dexamethasone ampoule daily for 15 days. Group B: rats received 0.5cm3 4% dexamethasone via iontophoresis Group C: rats received hydrocortisone cream via phonophoresis.

MATERIAL AND EQUIPMENT

1. Drugs were used either in the form of 4% dexamethasone for intra-muscular injection and iontophoresis, and in the form of 1% hydrocortisone cream for phonophoresis.
2. Vett cream was used for removing rats hair.
3. Phoresor 600 MP with trans Q1 polymer-

gel electrode (IOMED Inc.).

4. Ultrasound apparatus (Enraff Co.), with 1-3 MH intensity was used for phonophoresis technique. Aqua-jell discs were used as a coupling medium for administration of hydrocortisone cream to increase the conductivity of the ultrasonic wave and prevent its reflection.
5. Test tube with sodium floride for taking of blood sample and the sodium floride to stop glycolysis processes.
6. Capillary tubes to take blood sample from tates.
7. Glass dissector with chloroform solution to anathesized the rates during blood sample taking were used.
8. Yashca photographic camera was used.

TREATMENT PROCEDURES

Group A received intra-muscular injection of corticosteroid in the form of $0.5cm^3$ dexamethasone daily. Injection was done in the postro-lateral thigh muscle for 15 days.

For group B & C, each rat was anesthetized and hair removal cream "vett" was applied at the postero-lateral part of rat's trunk for about 3 minutes, then the hair was shaved.

For the rats in group B, the shaved areas of the rate were cleaned with alcohol and left to be dried. Dexamethasone solution was injected into the active polymer gel electrode. Active electrode was tapped on the shaved area (abdomen), and the inactive electrode applied to the opposite side. Pheresor was adjusted for 3 mA. intensity for 5 minute duration for each rat daily for 15 days.

Corticosteroid in the form of 1% hydrocortisone cream was applied to one surface of the aqua-jell disc. The aqua-jell disc was placed on the shaved skin area where the cream in contact with the rat's skin. Ultrasound apparatus was set-up at 1 Mz, 1.5 watt/cm3 intensity for about 5 minutes duration. Ultrasound head was moved in the form of slow, rhythmic and circular motion.

EVALUATION PROCEDURES

All rats, before starting the treatment, were anesthetized and blood samples were taken from each rat in each group. Blood samples were taken by capillary tubes. Capillary tube was introduced through the medial eye corner to the vein. Samples were taken in 8 cm test tube with sodium floride. Samples were analyzed for detection of blood glucose level.

The same procedures, of taken blood sample, were done after finishing treatment. Blood samples were taken and analyzed for blood glucose level.

DATA ANALYSIS

2-tail t-test was conducted on blood glucose level to determine any significant difference between pre-test and post test scores of each group. Pre-test scores were used as a base line for comparison with post test scores. One way analysis of variance (ANOVA) was conducted on blood glucose level to determine significant differences between the effect of corticosteroid delivered by intra-muscular, iontophoresis and phonophoresis techniques. LSD test was conducted to determine significant difference between each two groups. A significant level of $P<0.05$ was chosen for all tests.

RESULTS

Rats were subdivided equally into 3 groups. Group "A" received glucocorticoid by intramuscular injection, group "B" received 4% dexamethasone iontophoresis and group

"C" received 1% hydrocortisone cream phonophoresis daily for 15 days. Blood samples were taken pre test and post test and blood glucose level was analysed.

It was found that in group "A" there is a significant difference equal to 0.001 with $P<0.05$ as shown in Table (1) with mean difference = 26.6, which is the lowest mean. This means that dexamethasone injection does increase blood glucose level at a level of 26.6.

Table (1): Pre-test, post-test, blood glucose level of group "A" (Dexamethasone via intramuscular injection).

	Pre-test	Post-test	Difference between pre-test and post-test (d)	(d-d)	$(d-d)^2$
1	93	131	38	11.4	129.96
2	97	121	24	-2.6	6.76
3	102	121	19	-7.6	57.76
4	105	131	26	-0.6	0.36
5	112	138	28	-0.6	0.36
Total			133	0	195.2

* Level of significance 0.05 * Mean difference d = 26.6 6.9857
*t -calculated = 8.51495 *t-tabulated at 9 (0.025, 4) = 2.776 so tc > tt

There is a significant difference between pretest and posttest scores of blood glucose level equal to 0.001.

In group B, there is a high significant difference between pretest and post test scores of blood glucose level as shown in Table (2) with mean difference = 72.6 which is the highest mean among all groups.

Table (2): Pre-test, post-test blood glucose level of group B (Dexamethasone via Iontophoresis technique)

	Pre-test	Post-test	Difference between pre-test and post-test (d)	(d-d)	$(d-d)^2$
1	111	225	114	41.4	1713.96
2	107	133	26	-46.6	2171.56
3	100	138	38	-34.6	1197.16
4	113	210	97	24.4	595.36
5	97	185	88	15.4	237.16
Total			363	0	5915.2

* Level of significance 0.05 * Mean difference d = 72.6 * SD = 38.45517
* t calculated = 4.2215 * t tabulated at t (0.025,4) = 2.776

There is a significant difference between pretest and post test scores of blood glucose level equal 0.013.

Also, table (3) shows a significant difference between pretest and posttest scores with mean difference equal 30.8.

Table (3): Pre-test, post-test blood glucose level of group C (hydrocortisone cream via phonophoresis technique).

	Pre-test	Post-test	Difference between pre-test and post-test (d)	(d-d)	$(d-d)^2$
1	103	135	32	1.2	1.44
2	110	137	27	-3.8	14.44
3	98	129	31	0.2	0.04
4	108	132	24	-6.8	46.24
5	96	136	40	9.2	84.64
Total			154	0	146.8

* Level of significance 0.05 * Mean difference d = 30.8 *SD ± 4.183
* t-calculated = 57.61823 * t-tabulated at t (0.025, 4) = 2.776
>> t caluclated > t tabulated

There is a high significant difference between pretest and post test scores of blood glucose level equal 0.000.

Analysis of variance (ANOVA) shows a high significant difference between 3 groups and LSD test shows a significant difference between group A & B and between group B & C as shown in table (4).

Graph (1) shows marked increase of blood glucose level in group B which received glucocorticoid via iontophoresis technique and moderate increase of blood glucose level in group "C" which received glucocorticoid via phonophoresis technique. In-group "A" which received glucocorticoid via intramuscular injection shows the least increase of blood glucose level.

Table 4: On way ANOVA table for group A, B, C.

Source	D.F.	Sum of square	Mean square	F ratio	F prob
Between groups	2	9817.3571	4908.67	11.7101*	.0019*
Within groups	12	4611.0000	419.1819		
Total	14	14428.3571			

* Level of significance 0.05

There is a significant difference between group A & C, group A & B.

The results of this current study showed that:

1. Iontophoresis technique had the greatest significant effect on increasing blood glucose level.
2. Phonophoresis technique had the second significant effect on increasing blood glucose level.
3. Injection had the least significant effect than iontophoresis and phonophoresis, on increasing blood glucose level.

DISCUSSION

It is reported in AHFS[1] that corticosteroids may decrease glucose tolerance, produce hyperglycemia, and aggravate or precepitate diabetes mellitus especially in patients predisposed to diabetes melitus. If steroid therapy is required in patients with diabetes mellitus, changes in insuline or oral antidiabetic agent dosage or diet may be necessary (AHFS)[1].

It is well documented that iontophoresis technique is safe and has a local application[6]. The researcher of IOMED Co.[11] repoted that,

iontophoresis is the convenient way to deliver corticosteroids medication to diabetic patients, since it has non-significant effect on systemic circulation. In diabetic patients suffering from rheumatic disease or those have a risk of osteoporosis, local application, as in iontophoresis and phonophoresis, of corticosteroid is preferable than injection to avoid increase blood glucose level.

The results of this current study suggested that iontophoresis and phonophoresis had a significant adverse effect on increasing blood glucose level by administration of corticosteroid than those delivered by injection. Since iontophoresis has more penetration inside the body than phonophoresis8, it has also more effect on increasing blood glucose level than those applied by phonophoresis. The only scientific reason for this adverse effect is that iontophoresis technique was applied near the abdomen of the rats. No past literature studied the effect and penetration of medication in the area of internal viscera. Concentration of corticosteroid in intestine may stop intestine from absorption of calcium from the regular diet for the period in which the experiment was done. Calcium deficiency may lead to osteoporosis (AHFS)[1]. This was obvious in the rats of group B. One of those rats got fractured ribs easily with a very little pressure. Others got debilitated and weight reduction at the end of the expriment.

Because of the fact that topical administration can cause systemic effects with adrenal suppression if significant absorption occurs[4]. It was found that blood glucose level was increased with topical administration of glucocorticoids via iontophoresis and phonophoresis.

Results showed that the highest increase in blood glucose level was in group "B" which received glucocorticoids via iontophoresis and moderate increase of blood glucose level in group "C" which received glucocorticoids via phonophoresis and the level of increasing of both was higher than that produced in group "A" which received glucocorticoids via intramuscular injection.

This results may be due to the other suggestions:

1. Exposure of large surface area with high vascularity to glucocorticoids treatment during application of phonophoresis and iontophoresis.
2. The effect of phoresor current and mechanical wave of ultrasound in increasing transdermal drug kinetics especially with vasodilator drugs.
3. The physiological effect of ultrasound wave and the electrical stimulation of the phoresor current can increase local heat and vasodilation and inturn increasing blood flow, and this effect can potentially increase drug delivery and washing out the medication in systemic circulation.
4. Another suggestion that could be taken in consideration is that the effect of ultrasound wave and phoresor current in increasing bio-availability of drugs due to these harmful effect on liver leading to its damage. This allows the drugs to pass through the liver to be not destroyed normally by hepatic metabolism, this will lead to increasing drugs bioavailability because a relatively greater portion of dose will reach systemic circulation and due to the rapid increase of glucocorticoid level in systemic circulation it can increase blood glucose level by decreasing glucose utilizaion by the cell through depression of oxidation of nicotinamide-a denine dinuclestides to form NAD+, Because NADH must be oxidized to allow glucolysis to occur.

5. Cellular actions inhibition by glucocorticoids is obvious in local administration, iontophoresis & phonophoresis, than in injection.. The drug remains in the plasma which is referred to as the drug's biological half-life loading to long continuation of gluconegenesis through liver and decreasing gluco-utilization by tissue cells. This results in elevation of blood glucose level[5].

However, the effects of electro-therapeutic devices in liver, kidney and increasing local drug delivery still unknown. No past literature described the effect of sonation and electrical stimulation on liver, kidney and systemic circulation.

SUMMARY

Glucocorticoids delivered via iontophoresis and phonophoresis have a greater adverse effect, than those delivered by intramuscular injection, on increasing blood glucose level. Iontophoresis and phonophoresis are not the convenient way to deliver corticosteroids in patients with diabeitis milltus. Such local techniques should be avoided to administr corticosteroid for a long therapy course.

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الملخص العربي

مستوى الجلوكوز في الدم بعد إدخال الجلوكوكورتيكويد بواسطة الوسائل الطبيعية

أجريت الدراسة على خمسة عشرة فأراً من نفس العمر والوزن ، قسموا إلى ثلاثة مجموعات متساوية . المجموعة الأولى أخذت العقار بالحقن الموضعي والمجموعة الثانية أخذت العقار بواسطة التأين والثالثة بالموجات فوق صوتية . ولقد ثبت أن إدخال الجلوكوكورتيكويد بواسطة التايين أو الموجات فوق صوتية له تأثير سيئ على زيادة مستوى الجلوكوز في الدم ومن الأفضل إدخاله عن طريق الحقن الموضعي لذلك فان التايين واستخدام الموجات فوق الصوتية في إدخال الجلوكوكورتيكويد ليستا الطريقة المناسبة خصوصاً مع مرضى السكر حتى نتجنب العلاج الطويل لضبط نسبة السكر مرة أخرى.