Iraqi Journal of Pharmacy 20(Supp-01) (2023) 201-209

Online ISSN: 2664-2522

Print ISSN: 1680-2594

Iraqi Journal of Pharmacy

Journal homepage : https://iphr.mosuljournals.com

Research Paper:

Systemic Adverse Effects of Topical Clobetasol and Counterfeit Cosmetic Products on Iraqi Women

Teeba H. Sagban [1], Ausama Ayob Jaccob [2], Abdulla Ayob Yaqoub [3], Huda. A. Khadim [4]

[1] Ministry of Health, Maysan Health Department, Al-Kahla Hospital, Maysan, Iraq
[2] Department of Pharmacology and Toxicology, College of Pharmacy, Basrah University, Basrah, Iraq
[3] Department of Dermatology, Abu Al-Khaseeb Hospital, Basrah, Iraq
[4] Ministry of Health, Maysan Health Department, Al-Sader Hospital, Maysan, Iraq

Article Information

Article history:

Received on: 18 September 2023
Revised on: 12 October 2023
Accepted on: 17 October 2023
Published on: 30 December 2023

Keywords:

Adverse effects;
Clobetasol;
Counterfeit cosmetic products;
Glucocorticoids;
TCs.

Abstract

Background: Topical corticosteroids (TCs) are widely used for dermatologic diseases. Unfortunately, there exists many adverse effects (local and systemic). These adverse effects are comparable to those observed when glucocorticoids are administered systemically, but they are typically less severe. **Aim:** To assess the systemic adverse effects of topical clobetasol (TCL) and counterfeit cosmetic products (CCP) on Iraqi women. **Methods and patients**: This was a cross-sectional observational study; carried out from October 2022 to March 2023. Patients visited the outpatient clinic of the Department Dermatology and Venereology in Abu-al Khasib Hospital in Basra City, Iraq. Patients may be categorized into two distinct groups: the first group of subjects utilized TCL (n=31), while the second group consisted of patients with CCP (n=32), and the remaining participants were designated as the control group (n=35). A specialized dermatologist conducted a clinical examination to make a diagnosis. A questionnaire was collected, and blood samples were obtained for laboratory investigations. **Results**: TCs suppressed vitamin D (Vit-D), INTERLUKIN-6 (IL-6), testosterone, and estrogen and reduced cortisol concentrations significantly. TCs elevated red blood cells (RBC), neutrophils percent (NEU%), and hemoglobin (HB) levels significantly and prolong bleeding time. While not affecting WBCs, PLT, MPV, MCH, MCV, ACTH, or insulin levels. accompiend with decreased in HCT, MCHC, Eos%, and Lym% for all groups in comparison to control group. **Conclusion:** Topical corticosteroids are extensively used, mostly for the treatment of dermatological conditions. However, they can be misused for their cosmetic effects as fairness creams. TCs misuse is a big problem in Iraq, resulting in massive skin effects and systemic deterioration, such as hematological and hormonal effects. Nevertheless, the general population remains ignorant of the systemic adverse effects. Educational activities targeting the general public are suggested to address the systemic deterioration.

2023 Iraqi Journal of Pharmacy. Published by University of Mosul, Iraq,. This is an open access article licensed under CC BY: (https://creativecommons.org/licenses/by/4.0)

1. Introduction

Topical corticosteroids (TCs) have a well-established and extensive historical background, making them very prevalent as therapeutic treatments for dermatological conditions. TCs are often used in clinical practice owing to their demonstrated effectiveness in relieving pruritus, suppressing cellular proliferation, diminishing inflammatory responses, and stimulating melanogenesis in the cutaneous tissue (1). Unfortunately, there exists many side effects (local and systemic) , systemic absorption of TCs may result in laboratory indications of systemic adverse effects, and risk factors include high-strength, inappropriate and chronic use corticosteroids (Cs), application in thin-skinned locations or extended treatment duration, and occlusive. These adverse effects are comparable to those observed when glucocorticoids(GCs) are administered systemically, but they are typically less severe. Based on their clinical activity and capacity for suppressing the Hypothalamus pituitary adrenal- axis (HPA axis), TCs can be categorized as super potent, potent, medium, and mild. Systemic side effects may include neuropsychiatric problems, musculoskeletal-metabolic-endocrine, and life-threatening infections in addition to minor and reversible HPA axis suppression (2, 3).

***Corresponding author:** *Teeba Sagban, Ministry of Health, Maysan Health Department, Al-Sader Hospital, Maysan, Iraq.*
Email: hasanteeba66@gmail.com

How to cite:

Sagban, T., Jaccob, A., A., Yaqoub, A., A., Khadim, H., A. (2023). Systemic Adverse Effects of Topical Clobetasol and Counterfeit Cosmetic Products on Iraqi Women. Iraqi J. Pharm. 20(Supp-01), 201-209.

DOI: **https://doi.org/10.33899/iphr.2023.143457.1061**

In hospitals and clinical settings, topical clobetasol propionate (TCL) is most frequently used. TCL is a newly developed fluorinated topical corticosteroid, the most potent topical steroid (super potent) to date, and is roughly 1,800 times more potent than hydrocortisone (4).

TCL is an effective TCs that has shown potential for short-term and intermittent management of various inflammatory dermatoses that affect a large area of the skin. The adherence to limitations and safeguards is of utmost importance. TCL relive inflammation (swelling, pain and itching) caused by irritation or allergic reaction by reduces the production of inflammatory molecules. TCL use for treatment eczema, psoriasis, lichen planus and lupus erythematosus (5).

Additionally, it may inhibit the production of new skin cells, which may help certain skin conditions (such as psoriasis) by reducing patches or scales. Finally, it reduces the body's immunological reaction, which might assist with certain skin issues brought on by a sensitive immune system (such as eczema) (6, 7).

The drug is available in many different formulations, including ointment or cream , in concentrations ranging from 0.05% to 0.1%. It is also available as, a shampoo, lotion, and spray combined with an antifungal and an antibiotic. Most formulations of clobetasol aren't recommended to be used for more than two weeks at a time since they can cause serious side effects (8).

TCs have been shown to effectively brighten the skin tone. However, it is regrettable that a wide range of cosmetic products are being marketed under bogus names, sometimes without proper labeling including misleading information on the presence of natural or herbal ingredients, or with names that have been obscured or covered up. These products are found in the markets of Iraq, and a large proportion of them includes hydroquinone, corticosteroids (mostly clobetasol, betamethasone, and dexamethasone) and mercurial substances. Cosmetic formulations must be devoid of any corticosteroids. Nonetheless, several companies have been found to use such substances in the production of counterfeit cosmetic products (CCP). TCs are often used as a cosmetic cream by a large percentage of people. Many patients attribute the rapid and amazing effects of TCs as one of the primary factors influencing their decision to choose it for treating various skin-related concerns in their daily lives (7, 9).

A large number of individuals completely ignorant for the potential negative consequences of long-term TCs application. Because of the rebound phenomenon they experience when they attempt to stop using the medication, they continue to take TC even after they start to see the adverse effects it has on their skin. Since they are less costly than the conventional standard fairness and beauty creams on the market, several of the brands that are often used by patients are seen as low-income or poor (10, 11).

Accordingly, The main aim of this study was to assess the systemic adverse effects of TCL and counterfeit cosmetic products in Iraqi women.

2. Subjects and methods

2.1 Study design and ethical approval

This was a cross-sectional observational multicenter study carried out from October 2022 to March 2023. Patients visited the outpatient clinic of the Department Dermatology and Venereology in Abu-al Khasib Hospital in Basra City, Iraq were included in this study. Informed consent was obtained according to the Helsinki Declaration, and the study was authorized by the ethical committee at the Basra University College of Pharmacy (EC 10 in 2022).

2.2 Patients

A total of ninety-eight females between the ages of 16 and 60 years are enrolled. Sixty-three patients may be categorized into two distinct groups: the first group of subjects utilized TCL (n=31), while the second group consisted of patients with CCP (n=32), and the remaining thirty-five participants were designated as the control group.

Patients with continuous application of TCL or CCP to any part of the body for at least 30 days were recruited. We selected females with cutaneous adverse effects from TCs. This usage should have continued until the day of presentation to the center, or if discontinued, no more than two weeks before.

A questionnaire was distributed to the patient, which covers several aspects of information, such as participants' ages, levels of education, systemic adverse effects experienced, reasons for use or abuse, frequency and kind of drug utilized, and periods of usage of TCs.

A specialized dermatologist conducted the clinical examination to make the diagnosis. The researchers were given instructions to assess the appropriateness and Justification of using TCs in every given circumstance. The criteria used to identify inappropriate or unjustified use included instances of wrong indication (e.g., skin weighting), as well as cases of undiagnosed dermatitis, as determined by the investigator's opinion. The study excluded participants who had previously taken oral steroids for whatever reason, those with a medical background of chronic illnesses, patients with endocrine, pulmonary, or cardiovascular disorders, pregnant women, and lactating mothers.

2.3 Blood investigation

The blood samples were draw between 8 and 10 a.m., one ml of whole blood in an EDTA ,then centrifuged to plasma to check ACTH by (Roche cobas e 411); 2 ml in a sodium citrate tube, plasma take to check PT and INR by (STAGO STart MAX, France); 3 ml in a gel tube, take serum, and then stored in a cold setting to prevent any effects of the environment on the samples; they were then checked for other parameters. For all patients and control groups, hormonal and biochemical test was estimated by ELISA technology (cobas e 411), cortisol, international ratio (INR), prothrombin time (PT), interleukin-6 (IL6), vitamin D3 (Vit-D3), insulin, testosterone, and estradiol (E2).

2.4 Statistical analysis

This work was statistically evaluated using the Chi-square method for analysis and Fisher exact tests with the Koopman asymptotic score and the method of Katz to

evaluate the relative risk and correlations. One-way analysis of variance with Bartlett's post hoc analysis for multiple comparisons was utilized by GraphPad Prism for Windows (version 8.0).

3. Results

In total, 98 women were involved in this research. Among them, 31 women had a defined skin condition resulting from the use of TCL, whereas 32 women used CCP. The other 35 participants were chosen as the control group. The research included individuals with ages ranging from 16 to 60 years.

The majority of patients had a low level of education and were within the age range of 18 to 45 years, as seen in **Table 1**. Moreover, a significant proportion of patients used TCs for a duration exceeding 40 days, whereas only a few patients utilized TCs for a period less than 40 days. No statistically significant variation was seen between the TCL and CCP groups with regards to age, education level, or period of usage. Among the 63 patients included in the study, a significant number of TCL users (28 out of 31) reported applying the treatment more than once daily. In contrast, the majority of CCP users (27 out of 32) reported applying the treatment once daily.

Table 1. A Comparison of the demographic characteristics of females who used topical clobetasol (TCL) with cosmetic counterfeit products(CCP) users: represents the duration of use, graduation, and ages

Demographic information	TCL (n=31)			CCP(n=32)		
	Once		More	Once		More
Daily frequency use	3		28	27		5
	Yes		No	Yes		No
Graduation	2		29	1		31
	<40 days		>40 days	<40 days		>40 days
Duration of use	5		26	1		31
	<18	18-45	>45	<18	18-45	>45
Ages(years)	5	19	7	7	24	1

The differences between abuse groups are not statistically significant. The frequency of daily application showed a significant difference between study groups. Reveals that there has been no significant difference among the study groups in (age, education level, and duration of use)(P>0.05)

.

The TCL and CCP groups showed a highly significant decrease in cortisol levels compared to the control group (p<0.01), as shown in Table 2. On the other hand, there was no significant difference in serum ACTH and insulin levels between study groups (p-value >0.05) (**Table 2**).

As shown in **Table 2**, testosterone levels were evaluated in the current study.. The table summarizes the considerable and statistically significant decline in testosterone levels seen in patients who had TCL (0.1903± 0.039) and CCP (0.1920± 0.02) compared to the control group (0.3637± 0.037). To get comprehensive knowledge of the cause and adverse effects of TCs misuse, serum estrogen levels were assessed in the TCL (59.35± 13.11) and CCP (59.55± 6.56) groups as well as in the control group (143.1± 18.7). Significant differences were noticed across the groups (P <0.01), as seen in **Table 2**.

Table 2. Serum cortisol concentration, levels, testosterone level, and estrogen level of the subjects in the study (n=98)

Serum hormone concentration	Control (n=35) Mean± SEM	TCL (n=31) Mean± SEM	CCP(n=32) Mean± SEM	P-Value
Cortisol nmol\L	277.0± 24.21	196.2± 20.25 *	169.3± 22.03**	0.0023
ACTH pg\ml	3.876± 0.37	2.885± 0.544	3.259± 0.54	0.3225
Insulin µU\Ml	28.75± 3.78	45.90± 12.5	44.69± 8	0.2116
Testosterone ng\ml	0.3637± 0.037	0.1903± 0.039**	0.1920± 0.02**	0.0004
Estrogen pg/ml	143.1± 18.7	59.35± 13.11**	59.55± 6.56**	0.0010

*The results are given as Mean ±SEM, with * indicating a significant differences from the control (P<0.05). ** represent highly significant difference among groups P<0.01. * represent significant difference among groups P< 0.05. Plasma Adrenocorticotropic Hormone (ACTH) and serum insulin level no significant changes were observed among study groups*

In comparison to the control group, treatment with TCL or CCP resulted in substantial reductions in MCHC, Eos%, Mon%, and Lym%. WBCs, PLT, MPV, MCH, and MCV were similar in the study groups. The current study's findings show that the TCL group and CCP group had significantly higher RBCs, HB and NEU% than those in the control group as a showing in **Table 3**. The present finding showed a significant increase in RBCs and LYM% in females using the TCL and CCP groups P-values (≤ 0.05) and compared with the control group (Table 3). The results showed a highly significant increase in HB concentration and the TCL and CCP groups, comparisons with the control group had a p-value less than (0.01). The study shown no significant difference (p-value > 0.05) in WBCs, PLT, MPV, MCH, or MCV for all groups. This finding showed a significant decrease in HCT, MCHC, Eos%, and Lym% for patient groups, as documented in **Table 3**.

Table 3: Comparison of hematological parameters between topical clobetasol (TCL) or counterfeit cosmetic products (CCP) and control group

Haematological parameters	Control (n=35) Mean± SD	TCL (n=31) Mean± SD	CCP(n=32) Mean± SD	P-Value
RBCs 10^6\µl	4.890± 0.406	5.181± 0.7027	5.202± 0.5711*	0.0219
Hb gd\dl	11.76± 1.290	12.40± 1.72**	12.72± 1.17**	0.0097
WBCs 10^3\µl	7.269± 1.957	8.395± 3.114	8.008± 2.569	0.1423
PLT 10^3\µl	309.2± 61.37	274.8± 71.86	295.5± 59.64	0.0748
MPV (fl)	9.076± 1.154	8.681± 1.710	10.24± 5.837	0.1728
EOS%	4.656± 1.278	2.790± 1.312	3.424± 1.280	<0.0001
NEU%	39.24± 7.231	48.49± 11.90	46.44± 11.05	0.0013
MON%	4.544± 1.427	2.5± 1.15***	3.382± 1.57**	<0.0001
LYM%	29.08± 6.613	21.9± 7.88**	24.21± 9.029*	0.0004
HCT%	40.43± 4.053	42.8± 5.26**	42.36± 5.297*	0.0662
MCV(fl)	79.28± 7.754	82.55± 7.235	80.86± 6.444	0.1552
MCH (pg)	24.62± 2.773	25.34± 2.382	24.81± 3.015	0.5265
MCHC (g\dl)	31.00± 2.099	29.2± 1.88**	29.40± 2.697**	0.0011

*HB: hemoglobin, RBCs: red blood cell count, HCT: hematocrit, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, WBCs: white blood cell count, Neut%: neutrophil percentage, Lymp%: lymphocyte percentage, Mono%: monocyte percentage, Eos%: eosinophil percentage, Baso%: basophil percentage, MPV: mean platelet volume . The results are given as Mean±SD, with * indicating a signifcant diference from the control (P<0.05). * represent significant difference p, ** represent highly significant difference,*** represent very highly significant difference .*

In the current study, there was a significant reduction in the blood levels of IL6 in both the TCL and CCP groups as compared to the control group. A substantial decrease (P<0.0001) in blood IL6 levels has been seen in patients with TCL and CCP misuse when compared with the control group. This value relates to the systemic anti-inflammatory impact of topical corticosteroid (TCS) usage, as seen in **Figure 1.** The data's most striking finding is that the TCL and CCP groups have lower vitamin D blood concentrations. **Figure 2** illustrates a significant change from the control group.

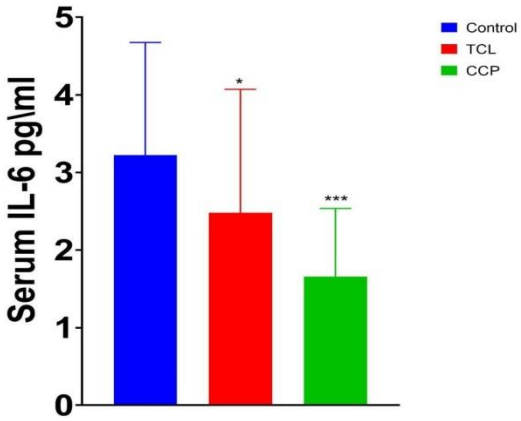

Figure 1. Serum Interleukin-6 level of the participants in the study groups. * considered a significantly decrease in the topical clobetasol (TCL) group . *** very highly significant decrease in counterfeit cosmetic products (CCP) group

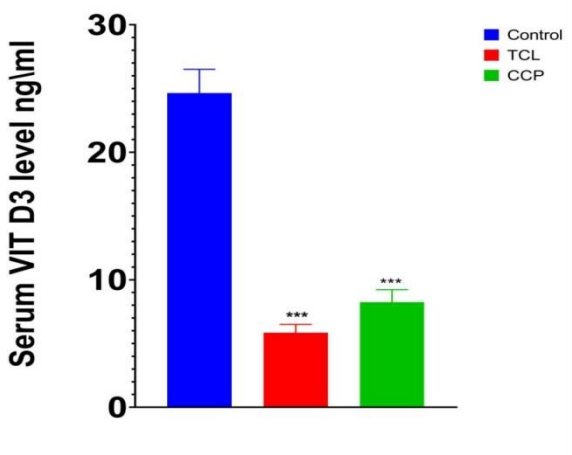

Figure 2. Serum vitamin D3 levels of the participants in the study (n=68). *** represents a very highly significant difference P<0.0001

4. Discussion

The phenomenon of using TCs for aesthetic purposes within the social context may be traced back to the increased recognition of some TCs as aesthetic creams. These creams are seen to be very effective, providing immediate benefits, and are also affordable, readily accessible, and socially endorsed. However, TCs are available for the asking in urban and rural areas. The disturbing part is that even the most potent TCs, like clobetasol propionate, especially in mixed creams, are available over the counter and are among the most popular brands in Iraq. Regrettably, a lack of knowledge of the potential side effects of TCs contributes to the occurrence of severe local and systemic adverse effects (12-14). An optimal topical medication should exhibit efficacy at the site of administration while minimizing the occurrence of adverse effects. The substance should not undergo systemic absorption or should undergo deactivation upon absorption into the circulatory system, thereby preventing any systemic effects. Nevertheless, the existing TCs now available are not considered optimal and have often been associated with systemic and local adverse effects. These consequences are mostly seen when the TCs are used inappropriately or for an extended period (15).

In the collection of patients included in this study, a majority of participants utilized TCs for prolonged periods that might potentially result in the development of laboratory markers indicating systemic adverse effects. To reduce the potential for adverse effects, it is generally advised that the utilization of topical corticosteroids should not exceed two weeks without further guidance from a medical professional(3). The prolonged use of topical steroids might lead to the development of tolerance and tachyphylaxis. It is not advisable to use ultra-high-potency steroids continuously for a duration beyond three weeks. If prolonged therapy is required, it is advisable to gradually reduce the dosage of the steroid to prevent the occurrence of rebound symptoms. Additionally, it is recommended to wait a minimum of one week after discontinuing the steroid before resuming treatment. The intermittent schedule has the potential to be repeatedly implemented over a prolonged period or until the situation is resolved. Adverse effects are infrequent when using low- to high-potency steroids for three months or less, with except in intertriginous regions, the face and neck, and areas subjected to occlusion(7). In our result, the majority of the patients used CCP once daily. This finding agrees with the results of studies by Jaccob et al. The current results are consistent with the results of Varshney I et al., which demonstrated that a large proportions of participants used TCL twice daily (16).

Our findings revealed a highly significant decrease in cortisol levels compared to the normal control group. On the other hand, no significant effect was observed regarding ACTH. Inhibition of the hypothalamus, pituitary, and adrenal axis. It is widely known that TCs have the tendency to be absorbed in large enough doses to inhibit HPA- axis activity. If a sufficient amount is applied, a wide surface area is covered, occlusion is employed, or parts of the treated skin are thin or scraped, almost any topical steroid may produce suppression. The more inherently potent a steroid, the more likely it is to suppress the HPA- axis(8). Exogenous TCs molecules have the potential to inhibit the production of CRH and ACTH, which would limit the stimulation of the adrenal glands and lower levels of naturally occurring cortisol(30). Allenby *and colleagues* studied the impact of TCL on the HPA-axis in thirty nine patients. They found that the application of more than 50 g per week of TCL results in adrenal suppression(6).In the same scenario, Rahila S. et al. conclude the same finding (17).

These results demonstrated that no significant variation in insulin level between groups. The prolonged use of glucocorticoids leads to an increase in hepatic gluconeogenesis, a reduction in peripheral glucose utilization, and an elevation in insulin levels and fasting insulin levels. The observed phenomenon is associated with a metabolic reaction of the pancreatic beta cells to elevated blood glucose levels, leading to a decrease in the body's responsiveness to insulin in peripheral tissues(18-20).

Additionally, the present data revealed that serum testosterone level was examined in patients and control groups. There was highly significant decrease in patient groups compared with control groups. These results match those of Alison S et al. (2019) measured testosterone blood levels after the administration of glucocorticoids, which were concluded to lower testosterone blood levels (21). High circulating glucocorticoid inhibits testosterone level reported by Whirledge et al, (2010)(22).

The most interesting aspect of our findings was the highly significant decrease in serum levels of estrogen in patient groups. The finding is consistent with the results of Danisova et al.(23). In contrast, Yahi D et al. showed that GCs treatment groups had no significant ($p > 0.05$) effect on estrogen concentrations (24). The inhibition of corticotrophin release mediated by GCs will result in adrenal atrophy and a decrease in the generation of adrenal androgens. GCs have been shown to have inhibitory effects on the synthesis and secretion of sex steroids, including luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, and growth hormone (GH). The suppression of pituitary gonadotropin production leads to a decrease in gonadal activation. In women, the release of luteinizing hormone (LH) in response to gonadotropin-releasing hormone (GnRH) is diminished. GCs were shown to induce a decrease in testosterone levels. Additionally, there is a reduction in follicle-stimulating hormone, which stimulates the synthesis of estrogen, ultimately resulting in a drop in estrogen levels (25, 26).

Regarding hematological markers, **Table 3** presents an increase in RBCs and HB concentration, Ami Ballin's also found similar results (27). Corticosteroids may increase the amount of hemoglobin and red blood cells (RBCs) in the peripheral circulation, possibly by stopping

erythrophagocytosis (28). However, these results were contradicted by the findings of Larsen MK, in 2020, who found that there is no statistically significant variation seen in the hematological parameters with the administration of glucocorticoids (29).

GCs generally improve erythropoiesis (induce stress erythropoiesis) directly by activating glucocorticoid receptor (GR). Erythropoiesis refers to the biological process by which fully developed red blood cells are generated from pluripotent hematopoietic progenitor cells. This intricate process leads to the generation of around two million erythrocytes per second (30). Also elevation of erythropoietin hormone (EPO) is a glycoprotein cytokine that is recognized for its pleiotropic effects on many cellular and tissue types, secreted by the kidney, stimulant production of bone marrow to RBCs and HB (31).

Data from **Table (3),** also showed that increase in the levels of circulating WBCs. Several mechanisms leads to an elevation in the number of polymorphonuclear leukocytes in the bloodstream, which occurs due to an accelerated entrance from the bone marrow and a reduced rate of elimination from the vascular compartment. Multiple mechanisms have been suggested to elucidate the underlying pathophysiology of the systemic corticosteroid-induced increases in white blood cell count. These mechanisms include an augmented release of neutrophils from the bone marrow, a delay in the process of apoptosis, a decrease in the migration of neutrophils into tissues, and a redistribution of neutrophils from the marginal to the circulating pool. On the other hand, the population of lymphocytes, eosinophils, monocytes, and basophils exhibits a decline after the administration of glucocorticoids (28, 32). GCs prolong neutrophil survival by inhibiting their apoptosis (33). GCs may increase apoptosis in the eosinophil, this effect may lead to a reduction of eosinophil when exposed to corticosteroids (34).

Additionally, they observed a significant decrease in platelet counts in Patients' groups who used TCs. Similarly, Royer et al. found that dexamethasone causes drug-induced thrombocytopenia (DITP) (35). However, Vogel et al. prednisolone and methylprednisolone have been reported to cause DITP (36, 37). In contrast, Praituan et al. concluded This use of steroids has been seen to result in a reduction in the synthesis of antibodies against platelets. Within two to four weeks of beginning steroid treatment, if it is successful, there will be an increase in the platelet count (38).

The most amazing finding, we can get from our research is that, when compared to the control group, blood levels of IL-6 in the patient groups have considerably decreased. This was in line with the findings of Gras MP et al., who reported that pro-inflammatory cytokines were down-regulated as TCS increased(39). Glucocorticoids prevent or decrease the whole inflammatory response to viral, physical, or immunologic stimuli by reducing both early and late inflammatory processes. The suppression of neutrophil and monocyte recruitment is a significant impact of glucocorticoids on the inflammatory process(28). The anti-inflammatory impact is also shown via the production of lipocortin, which acts as an inhibitor of phospholipase A2. This inhibition leads to a reduction in the generation of prostaglandins and leukotrienes. Topical corticosteroids exert their effects by directly modulating DNA activity, leading to an up-regulation of genes associated with anti-inflammatory responses. Additionally, they indirectly impede the activity of inflammatory transcription factors, such as NFkb, resulting in a down-regulation of genes associated with pro-inflammatory processes(40).

The results of our data was a very highly significant reduction of serum vitamin D levels in patient groups. Vitamin D insufficiency shown in control group, we considered both vitamin D insufficiency and Vit-D sufficiency as normal Vit-D states in this research (41). However , there are several factors that may affect the level of Vit-D including (Financial situation, weekly milk consumption, and time spe nt in the sun, using hijabs for social ,and cultural considerations) (42-44). The present finding also supports the study of Sanchez-Armendariz . study which concluded that the use of TCs is correlated with a reduction in blood vitamin D levels (45). TCs has been shown to elevate the excretion of calcium in the urine and reduce the absorption of calcium in the intestines, leading to a net reduction in calcium levels via its anti-vitamin D mechanism (45, 46).

5. Conclusion

Topical corticosteroids are extensively used pharmaceutical agents, mostly for the treatment of dermatological conditions. However, they can be misused for their cosmetic effects as fairness creams. The majority of women are aware that TCs may result in cutaneous adverse effects. Nevertheless, the general population remains ignorant of the systemic adverse effects. Educational activities targeting the general public are suggested to address the systemic deterioration, including its hematological and hormonal implications. Since general practitioners (GPs) and pharmacists often operate as the initial point of contact between the majority of patients and TCs, these activities must be focused on them.

6. Acknowledgment

Authors thank Basra University College of Pharmacy for continuous support. Thanks to staff of Abu AL-Khasib Hospital.

7. Funding

We were not funded by anyone.

8. Conflicts of Interest

No think declared.

9. Ethics Statements

This was a cross-sectional observational multicenter study carried out from October 2022 to March 2023.

Patients were admitted to outpatients dermatology clinics at Abu-al Khasib Hospital in Basra City, Iraq. Informed consent was obtained according to the Helsinki Declaration, and the study was authorized by the ethical committee at the Basra University College of Pharmacy (EC 10 in 2022).

10. References

1. Saraswat A. Ethical use of topical corticosteroids. *A Treatise on Topical Corticosteroids in Dermatology: Use, Misuse and Abuse.*2018; 73-79.

2. Horn E, Domm S, Katz H, Lebwohl M, Mrowietz U, Kragballe K. International Psoriasis Council. Topical corticosteroids in psoriasis: strategies for improving safety. *Journal of the European Academy of Dermatology and Venereology.* 2010; *24*(2), 119-124.

3. Devaraj N, Aneesa A, Abdul Hadi A, Shaira N . Topical corticosteroids in clinical practice. *Med J Malaysia.* 2019;*74*(2):187-9.

4. Humbert P, Guichard A. The topical corticosteroid classification called into question: towards a new approach. *Experimental Dermatology.* 2015;*24*(5):393-395.

5. Güven A, Gülümser Ö, Özgen T. Cushing's syndrome and adrenocortical insufficiency caused by topical steroids: misuse or abuse?. *Journal of Pediatric Endocrinology and Metabolism. 2007;20*(11):1173-1182.

6. Allenby C, Main R, Marsden R, Sparkes C. Effect on adrenal function of topically applied clobetasol propionate (Dermovate). *Br Med J.1975; 4*(5997): 619-621.

7. Ference J, Last A. Choosing topical corticosteroids. *American family physician. 2009; 79*(2): 135-140

8. Olsen E, Cornell R.. Topical clobetasol-17-propionate: review of its clinical efficacy and safety. *Journal of the American Academy of Dermatology. 1986;15*(2):246-255.

9. Mahe A, Ly F, Aymard G, Dangou J. Skin diseases associated with the cosmetic use of bleaching products in women from Dakar. Senegal. *British journal of dermatology.2003; 148*(3): 493-500.

10. Rathi SK, D'Souza P. Abuse of topical corticosteroid as cosmetic cream: a social background of steroid dermatitis. A Treatise on Topical Corticosteroids in Dermatology: Use, Misuse and Abuse. 2018;129-35.

11. Giaccone V, Polizzotto G, Macaluso A, Cammilleri G, Ferrantelli V. Determination of ten corticosteroids in illegal cosmetic products by a simple, rapid, and high-performance LC-MS/MS method. *International Journal of Analytical Chemistry.2017*.

12. Aljunaiyeh H, Naif A, Kadhim K. Non-prescription skin lightening preparations; their use & hazards in Iraq. *Int. J. Pharm. Res. Allied. Sci.2018; 7*(2): 209-17.

13. Alghamdi K. The use of topical bleaching agents among women: a cross- sectional study of knowledge, attitude and practices. *Journal of the European Academy of Dermatology and Venereology.2010; 24*(10): 1214-1219.

14. Jaccob A, Yaqoub A, Rahmani M. Impact of abuse of topical corticosteroids and counterfeit cosmetic products for the face: prospective demographic study in basrah city, Iraq. *Current Drug Safety.2020;15*(1): 25-31.

15. Dhar S, Seth J, Parikh D. Systemic side-effects of topical corticosteroids. *Indian journal of dermatology.2014;59*(5): 460.

16. Varshney I, Amin S, Adil M, Mohtashim M, Bansal R, Khan H. Topical Corticosteroid Abuse–Risk Factors and Consequences. *Indian Journal of Clinical Dermatology | Volume.2019; 2*(03).

17. Bhatti R, Flynn M. Adrenal insufficiency secondary to inappropriate oral administration of topical exogenous steroids presenting with hypercalcaemia. *Case Reports. 2012;* bcr0320125983.

18. Hwang J, Weiss R. Steroid- induced diabetes: a clinical and molecular approach to understanding and treatment. *Diabetes/metabolism research and reviews.2014; 30*(2): 96-102.

19. Poetker D, Reh D. A comprehensive review of the adverse effects of systemic corticosteroids. *Otolaryngologic Clinics of North America.2012; 43*(4): 753-768.

20. Alessi J, de Oliveira G, Schaan B, Telo G. Dexamethasone in the era of COVID-19: friend or foe? An essay on the effects of dexamethasone and the potential risks of its inadvertent use in patients with diabetes. *Diabetology & Metabolic Syndrome.2020; 12:*1-11.

21. Stout A, Friedly J, Standaert C. Systemic absorption and side effects of locally injected glucocorticoids. *PM&R.2019;11*(4): 409-419.

22. Whirledge S, Cidlowski J. Glucocorticoids, stress, and fertility. *Minerva endocrinologica.2010; 35*(2); 109.

23. Danisova A, Seböková E, Kolena J. Effect of corticosteroids on estradiol and testosterone secretion by

granulosa cells in culture. *Experimental and clinical endocrinology.1987; 89*(2): 165-173.

24. Yahi D, Ojo N, Mshelia G. Effects of dexamethasone on progesterone and estrogen profiles and uterine progesterone receptor localization during pregnancy in Sahel goat in Semi-Arid region. *Journal of animal science and technology.2017; 59*(1): 1-7.

25. De Nijs R. Glucocorticoid-induced osteoporosis: a review on pathophysiology and treatment options. *Minerva medica.2008; 99*(1): 23.

26. Canalis E, Giustina A, Bilezikian,J. Mechanisms of anabolic therapies for osteoporosis. *New England Journal of Medicine.2017; 357*(9):905-916.

27. Ballin A, Waisbourd- Zinman O, Saab H, Yacobovich J, Zoldan M, Barzilai- Birenbaum S, Tamary H. Steroid therapy may be effective in augmenting hemoglobin levels during hemolytic crises in children with hereditary spherocytosis. *Pediatric blood & cancer.2011;57*(2): 303-305.

28. McKay L, Cidlowski J. Physiologic and pharmacologic effects of corticosteroids. *Holland-Frei cancer medicine.2003; 6*.

29. Starch-Jensen, T, Deluiz D, Bruun N, Tinoco E. Maxillary sinus floor augmentation with autogenous bone graft alone compared with alternate grafting materials: a systematic review and meta-analysis focusing on histomorphometric outcome. *Journal of Oral & Maxillofacial Research.2020; 11*(3).

30. Macečková Z, Kubíčková A, De Sanctis J, Hajdúch M. Effect of glucocorticosteroids in Diamond-Blackfan anaemia: maybe not as elusive as it seems. *International Journal of Molecular Sciences.2022; 23*(3): 1886.

31. Zhang Q, Shan K, Raza A, Manda N, Nace T. A rare case report and literature review of anabolic-androgenic steroids (AAS)-induced acute myocardial infarction. *Cureus.2020; 12*(5).

32. Pasternak Y, Yarden-Bilavsky H, Kodman Y, Zoldan M, Tamary H, Ashkenazi S. Inhaled corticosteroids increase blood neutrophil count by decreasing the expression of neutrophil adhesion molecules Mac-1 and L-selectin. *The American journal of emergency medicine.2016; 34*(10): 1977-1981.

33. Barnes P. New molecular targets for the treatment of neutrophilic diseases. *Journal of Allergy and Clinical Immunology.2007; 119*(5): 1055-1062.

34. Nguyen L, Lim S, Oates T, Chung K. Increase in airway neutrophils after oral but not inhaled corticosteroid therapy in mild asthma. *Respiratory medicine.2005;99*(2): 200-207.

35. Royer B, Gruson B., Roszkiewicz F, Al Khedr A., Colson A., Marolleau J. Methylprednisolone-induced immune thrombocytopenia. *Blood, The Journal of the American Society of Hematology.2010; 115*(26): 5431-5432.

36. Vogel T, Verreault,R. Letter to Editor: Thrombocytopenia Following Steroid Therapy In An 83-year-old Woman. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences.2002. 57*(8): M519-M520.

37. Taguchi R, Tsuchihashi K., Okumura Y, Nakano M, Yoshihiro T, Ohmura H, Baba, E. Thrombocytopenia caused by dexamethasone in a patient with colorectal cancer. *Internal Medicine.2020;59*(20): 2571-2575.

38. Praituan W, Rojnuckarin P. Faster platelet recovery by high-dose dexamethasone compared with standard-dose prednisolone in adult immune thrombocytopenia: a prospective randomized trial. *Journal of Thrombosis and Haemostasis.2009; 7*(6):1036-1038.

39. Gras M, Verrecchia F, Uitto J, Mauviel A. Downregulation of human type VII collagen (COL7A1) promoter activity by dexamethasone: Identification of a glucocorticoid receptor binding region. *Experimental dermatology.2001; 10*(1): 28-34.

40. Whalen K. *Lippincott® illustrated reviews: pharmacology*. Wolters kluwer india Pvt Ltd.;2018.

41. Al Saleh Y., Beshyah S, Hussein W, Almadani A, Hassoun A, Al Mamari A, Al-Daghri N. Diagnosis and management of vitamin D deficiency in the Gulf Cooperative Council (GCC) countries: An expert consensus summary statement from the GCC vitamin D advisory board. *Archives of osteoporosis.2020; 15*, 1-8.

42. Hantoosh H, Mahdi M, Imran B, Yahya A. Prevalence of vitamin D deficiency in Iraqi female at reproductive age. *Med J Babylon.2019; 16*(2):119-122.

43. Hussein I, Mansour A, Nwayyir H ,Almomin A, Alibrahim N, Alidrisi H, Alhamza A. Real-Life Data on Total Vitamin D3 (25-Hydroxyvitamin D) Concentrations in Basrah, Iraq. *Biomedical & Pharmacology Journal.2021; 14*(4):2191-2198.

44. Al Janaby S, Al Timimy, G. Prevalence of Vitamin D Deficiency of Females in Karbala, Iraq, 2017. *Kerbala Jorunal of Medicine.2020; 13*(1).

45. Sánchez- Armendáriz K, García- Gil A, Romero C, Contreras- Ruiz J, Karam- Orante, M, Balcazar- Antonio D, Domínguez- Cherit J. Oral vitamin D3 5000 IU/day as an adjuvant in the treatment of atopic dermatitis: a randomized control trial. *International Journal of Dermatology.2018; 57*(12): 1516-1520.

46. Uva L, Miguel D., Pinheiro C, Antunes J, Cruz D, Ferreira J, Filipe P. Mechanisms of action of topical corticosteroids in psoriasis. *International journal of endocrinolog.2012:, 2012*.

التأثيرات الضارة الجهازية للكلوبيتاسول الموضعي ومستحضرات التجميل المزيفة على النساء العراقيات

الخلاصة

الخلفية: تستخدم الكورتيكوستيرويدات الموضعية على نطاق واسع لعلاج الأمراض الجلدية. لسوء الحظ، هناك العديد من الآثار السلبية (المحلية والجهازية). هذه الآثار الضارة قابلة للمقارنة مع تلك التي لوحظت عند إعطاء الجلايكورتيكويدات بشكل جهازي، ولكنها عادة ما تكون أقل حدة. **الهدف**: تقييم الآثار الضارة الجهازية للكلوبيتاسول الموضعي (TCL) ومستحضرات التجميل المزيفة (CCP) على النساء العراقيات. **الطرق والمرضى**: كانت هذه دراسة رصدية مقطعية؛ تم إجراؤها في الفترة من أكتوبر 2022 إلى مارس 2023. زار المرضى العيادة الخارجية لقسم الأمراض الجلدية والتناسلية في مستشفى أبو الخصيب في مدينة البصرة، العراق. يمكن تصنيف المرضى إلى مجموعتين متميزتين: المجموعة الأولى من الأشخاص الذين استخدموا TCL (ن = 31)، بينما تتألف المجموعة الثانية من المرضى الذين يعانون من CCP (ن = 32)، وتم تعيين المشاركين المتبقين كمجموعة مراقبة (ن = 32). 35). يقوم طبيب جلدية متخصص بإجراء فحص سريري للتشخيص. تم جمع استبيان وأخذ عينات الدم لإجراء الفحوصات المخبرية. **النتائج**: قامت TCs بقمع فيتامين د (Vit-D)، والإنترلوكين 6 (IL-6)، والتستوستيرون، والإستروجين وتقليل تركيزات الكورتيزول بشكل ملحوظ. قامت TCs برفع مستويات خلايا الدم الحمراء (RBC)، ونسبة العدلات (NEU٪)، ومستويات الهيموجلوبين (HB) بشكل ملحوظ وإطالة وقت النزيف. بينما لا يؤثر على مستويات خلايا الدم البيضاء، أو PLT، أو MPV، أو MCH، أو MCV، أو ACTH، أو الأنسولين، مع انخفاض في HCT، وMCHC، وEos%، وLym% لجميع المجموعات مقارنة بالمجموعة الضابطة. **الاستنتاج**: تستخدم الكورتيكوستيرويدات الموضعية على نطاق واسع، ومعظمها لعلاج الأمراض الجلدية. ومع ذلك، يمكن إساءة استخدامها لتأثيراتها التجميلية مثل كريمات تفتيح البشرة. إن سوء استخدام الـ TCs يمثل مشكلة كبيرة في العراق، مما يؤدي إلى آثار جلدية هائلة وتدهور جهازي، مثل التأثيرات الدموية والهرمونية. ومع ذلك، لا يزال عامة الناس يجهلون الآثار الضارة الجهازية. ويُقترح القيام بأنشطة تعليمية تستهدف الجمهور لمعالجة التدهور المنهجي.

الكلمات المفتاحية: الاعراض الجانبية، كلوبيتازول، المستحضرات المزيفة، الكورتيكوستيرويد الموضعي