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An assessment of biophysical profile in Indian patients with topical steroid abuse : A case-control study

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ABSTRACT

Background: Despite being one of the most useful therapeutic agents for a dermatologist, the topical corticosteroids continue to be used inappropriately as "fairness or cosmetic" creams. Also, there is a major lack of adequate knowledge about the possible adverse effects and the phenomenon of steroid addiction among a great portion of the Indian population. The adverse effects are mainly attributed to the impact on the biophysical profile of the skin due to their prolonged use. TEWL, skin hydration and skin pH are most affected parameters.
Objective:To study the biophysical profile of the patients of topical corticosteroid abuse, and compare the same with age and sex matched controls and study their clinical implications.
Methods: A case control study was carried out at our tertiary center for a period of 6 months.160 cases of topical corticosteroid abuse and 160 age and sex matched controls were evaluated for TEWL, skin hydration and skin pH by using tewameter, corneometer and pH meter respectively. The findings were compared and p value was determined. **Results**:107 patients in the case group, showed abnormal TEWL, whereas in the control group, 11 patients showed abnormal TEWL values. Abnormal hydration of the stratum corneum was seen in 100 patients in the case group, whereas in the control group, 21 patients showed abnormal hydration of the skin. Abnormal pH was seen in 140 patients in the case group, whereas in the control group, 47 patients showed abnormal pH value. The p value was significant in all our findings (<0.05).
Conclusions: Long term application of topical corticosteroids has significant effects on the biophysical parameters of skin such as TEWL, hydration and pH.
Key Words: Topical corticosteroids, misuse, biophysical profile, TEWL, Skin pH

INTRODUCTION:-

Despite being one of the most useful therapeutic agents in the field of dermatology, the topical corticosteroids continue to be used inappropriately as "fairness or cosmetic" creams. It is this so called usefulness that has been proved to be paradoxical.The dramatic symptomatic relief from the topical corticosteroids in various types of dermatoses, have led to their inappropriate use in treatment for a wide range of dermatological disorders and as "fairness or cosmetic" creams by non-registered practitioners or pharmacists[1-3].The easy over the counter accessibility of TCs at pharmacies across the country, without any valid prescription is further adding to this problem of abuse. Also, there is a widespread lack of adequate knowledge about the possible adverse effects and the phenomenon of steroid addiction among the Indian population.

Paradoxically, the same mechanisms which mediate these anti-inflammatory properties and underlie their effectiveness are also responsible for their undesired adverse effects[4].

Apart from their anti-inflammatory effect, TC also have potent atrophogenic, melanopenic, anti-pruritic, and immunosuppressive effects over the skin. All these can lead to significant local adverse effects if TCs are used indiscriminately[5].

The adverse effects of topical steroids can be local, systemic and psychological.The most common side effects are localized to sites of application.[6]These include atrophy, striae, telangiectasias, purpura, hypo-pigmentation, acneiform eruptions, rosacea, perioral and periorbital dermatitis, and hypertrichosis[5, 7-21].

Other side effects include delayed wound healing , exacerbation of skin infections, photosenstivity[22]and Tinea incognito .

Topical steroid dependent facies (TSDF), a condition associated with topical corticosteroid abuse[23] , is characterized by severe rebound erythema, burning and scaling of the face on attempted stoppage of the TC after its prolonged use[24]. Any attempt to stop the offending drug leads to a rebound or fare up of the symptoms which becomes both physically and psychologically distressing to the patient. Thus, in order to avoid these symptoms, , the individual continues to use the drug. This results in progressive utilization of more and more potent TCs to avoid the rebound adverse effects associated with withdrawal, a condition known as steroid addiction[25].

The prolonged use of topical corticosteroids effects the entire depth of skin and leads to histopathological changes like epidermal thinning , marked thinning of dermis and loss of dermal ground substance.

An interesting aspect of prolonged use of topical corticosteroid is that it also has an impact on the biophysical profile of the skin.

Biophysical profile is the study of physiological functions of skin, where the parameters studied are- pH, skin hydration, transepidermal water loss, sebum content and elasticity.

Transepidermal water loss (TEWL) and skin hydration have been widely used as indices in evaluating skin barrier function[26–32], and are measured by tewameter and corneometer respectively.

Skin pH stands for the amount of acidification of skin, and is measured by pH meter. Skin elasticity is the ability of the skin to be stretched and return to its original state, and is measured with the help of a cutometer.

In this study , we attempt to assess the biophysical profile of the patients of topical corticosteroid abuse, and compare the same with age and sex matched controls and furthermore study their clinical implications. The parameters that we studied are- Transepidermal water loss (TEWL), skin hydration and skin pH. To our best knowledge, there are very limited studies on the biophysical profile of the patients of topical corticosteroid abuse.

MATERIALS AND METHODS :-

This was a hospital based, case control study conducted at the Department of dermatology at a tertiary care center in Northern India. Ethical clearance was taken from institutional ethical committee and informed consent was taken from each participating subject. Study duration was 6 months (January 2019- June 2019) where consenting 160 patients, of age group- 18-60 yearsshowing signs of topical corticosteroid abuse were studied for their biophysical profile (Case group). 160 age and sex matched controls with no history and signs of use of topical corticosteroid , who came to the department with other dermatoses or were patient's attendants, were included in the control group.

Biophysical parameters including - Skin hydration, Skin pH and TEWL were measured.

For measurement of skin hydration using Corneometer825 , the reference value of 45 was taken as the normal/sufficient level of hydration of skin where all values below 45 were considered abnormal and the skin was rendered as insufficiently hydrated/dry[33].

pH is the power of hydrogen of skin and is maintained between 4.5-5.5, which is responsible for maintaining homeostasis. pH meter 905 E was used to measure pH of skin where the cutoff value of 5.5 was taken as the upper limit, all values above this were considered to be abnormal[34].

TEWL was measured using Tewameter TM300 where 10-25 grams/hour/m^2 was taken as normal range, and values above 25 were rendered abnormal, which signified increased TEWL[35].

All the instruments used in the study were supplied by Courage and Khazaka , Germany.

Above mentioned parameters were measured in all subjects from 4 sites (both cheeks, forehead, chin) and mean was taken for all parameters. These findings were compared with readings from that of the control group.

Biophysical profile parameters were measured according to international guidelines given by the 5th international conference on occupational and environmental exposure of skin to chemicals (OEESC) for their in vivo measurement[36].

Procedure- The instrument was switched on 15-30 mins prior to taking the readings. According to the guidelines , the participants of the study were acclimatized with the measuring environment for a period of 15-30 mins at an ambient temperature of 20-22 °C and relative humidity of 50% to avoid errors caused by environmental temperature or sweating. Areas under study were also exposed to ambient air for atleast 10 minutes prior to measurement[37] after which the readings were taken.

Data thus collected was entered in MS excel to prepare the master chart. Statistical analysis was done using Medcalc 16.4 software.

RESULTS:-

Our study included 27 males and 133 females subjects between the ageof 18-60 years.Most of the patients (46.8%) belonged to the age group of 21-30years, followed by 22.2%, belonging to the age group 31-40 years.

There was a wide variation in the duration of use of topical corticosteroids, ranging from 1 week to 5 years. It was observed that the severity of adverse effects of the patients was directly proportional to the duration of application of

TCs. Most of the patients in our study used TCs for 1-3 months (33%), followed by 22% who used the topical corticosteroids for 3-6months, 9% who used them for 6-12months and 19% who used them for >1year.

The different clinical presentations of corticosteroid abuse were recorded in a tabular form (Table 1). Most of the patients presented with more than one side effect. A few representative clinical photographs are shown in figures 1-5.

In our study, the most common adverse effect was acneiform eruptions (55%). Erythema and photosensitivity were also quite significant findings in our study, and found in 53.7% and 45.6% of the patients, respectively. Pigmentary changes were observed in about 25% of the patients. About 11% patients misused TCs for self-treating tinea, resulting in Tinea incognito. Telangiectasias, hypertrichosis and skin atrophy was found in 12.5%, 20% and 9.37% respectively.

About 10% of the patients presented with steroid addiction or Topical Steroid Dependent Face (TSDF), where they showed signs of physical and psychological dependency on the TC molecule they were using.

The biophysical profile of thesepatients was measured using tewameter, pH meter and corneometer to evaluate the TEWL, pH and stratum corneum hydration respectively.

The results were summarized and presented as proportions (%). Chi-square and fisher exact tests were used to compare abnormal findings in males and females respectively . 'p' value ≤0.05 was taken as significant. Medcalc 16.4 version software was used for all statistical calculations. Table 2 and figure 6 shows the abnormal values of TEWL, hydration and pH in our case and control group.

TEWL was measured using tewameter and values above 25 were rendered abnormal. In the case group, 20 males and 87 females showed abnormal TEWL, whereas in the control group, 3 males and 8 females showed abnormal TEWL values. The p value in both the males and females was <0.001, which was statistically significant.

Skin hydration was measured using Corneometer and all values below 45 were considered abnormal. In the case group, 14 males and 86 females showed abnormal hydration of the stratum corneum, whereas in the control group, 4 males and 17 females showed abnormal hydration of the skin. The p value was in males was 0.008 and in females was <0.001 , which was statistically significant.

Skin pH was measured by pH meter and all values above 5.5 were considered as abnormal.In the case group, 19 males and 121 females showed pH of more than 5.5. In the control group, 8 males and 39 females showed abnormal value. The pH value in males and females were statistically significant (i.e. 0.006 and <0.001 respectively) .

Therefore, long term application of topical corticosteroids has significant effects on the biophysical parameters of skin such as TEWL, hydration and pH. However, there was no significant correlation between the duration of corticosteroid abuse and biophysical parameter values.

Tables:

Table 1 : Adverse Effects

Adverse effects	No. of Patients (N=160)	Percentage
Acneiform eruptions	88	55
Hypertrichosis	32	20
Erythema	86	53.7
Rosacea	16	10
Photosensitivity	73	45.6
Telangiectasia	20	12.5
T. incognito	18	11.25

Pruritus	69	43.12
Hypopigmentation	5	3.12
Dyspigmentation	35	21.87
Steroid addiction	16	10
Burning irritation	64	40
Skin Atrophy	15	9.37
Atrophic striae	4	2.5
Others (milia, perioral dermatitis, xerosis)	58	36.25

Table 2 : Abnormal TEWL, hydration and pH values

Parameters	Cases	Control	p value
Abnormal TEWL (increased) Males	20	3	<0.001 *
Females	87	8	<0.001#
Abnormal hydration(decreased) Males	14	4	0.008*
Females	86	17	<0.001#
Abnormal pH (increased)Males	19	8	0.006*
Females	121	39	<0.001#

***fisher Exact test ; # chi square test**

Figure legends

Figure 1: Topical corticosteroid induced acneiform eruptions

Figure 2: Topical corticosteroid induced papulo-pustular rosacea

Figure 3: Topical corticosteroid induced erythema and photosensitivity

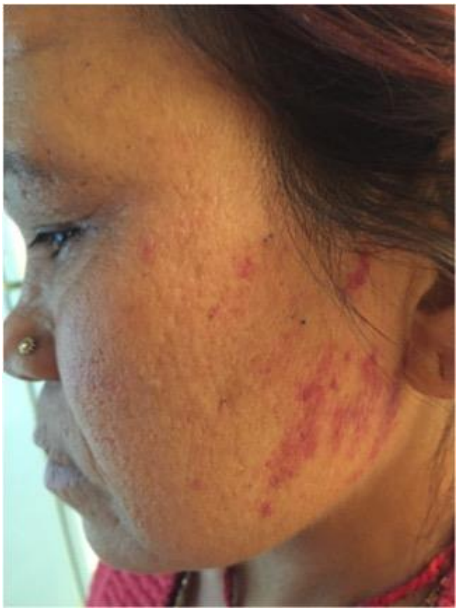

Figure 4: Topical corticosteroid induced skin atrophy

Figure 5: Topical corticosteroid induced hirsutism, scaling, erythema-TSDF

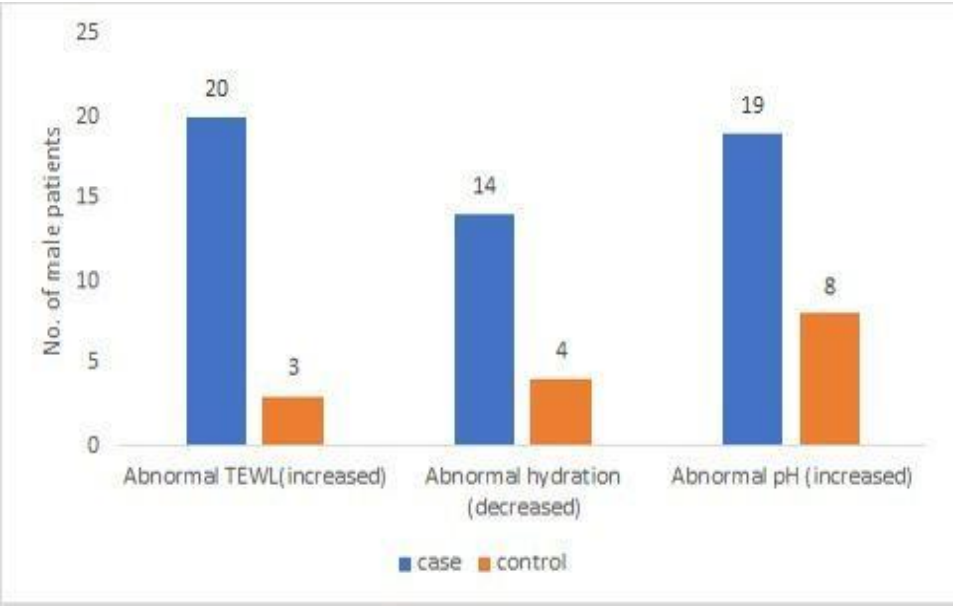

Figure 6 : Graph showing abnormal TEWL, skin hydration and pH values

DISCUSSION:-

The problem of topical corticosteroid abuse is a growing matter of concern in our country since many years now. Easy availability of many topical corticosteroid combinations as OTC drugs, lack of awareness about the consequences of its overuse and its so called reputation as " fairness or brightening creams" have all contributed to this menance.

The results of our study clearly show that misuse of topical corticosteroids is quite common in our country.

In our study, the highest number of patients (75;46.8%) belonged to the age group of 21-30 years and were females (133,83%).This was in accordance with a study by Anup K Mishra et al[38] , in which 38.82% of the patients belonged to 21-30 years age group. This is probably because female patients in this age group are overcautious about their appearance and skin problems.

Almost all our patients presented with more than one side effect. The most common adverse effect was acneiform eruptions (55.21%). High prevalence of acne in our study may be partly also due to the hot climate of Rajasthan and the more use of these agents in the acne prone age group. Studies on facial TC misuse from China by H Lu et al.[39], and by Saraswat et al[1], also showed that the acneiform eruptions were the most common adverse effect arising from misuse of TCS.

About 10 % of the patients presented with steroid addiction or Topical Steroid Dependent Face (TSDF), where they showed signs of physical and psychological dependency on the TC molecule they were using. This finding was quite less in our study, as compared to the finding in a study by Sharma R et al. [40] , where a significant number of patients (44.5%) presented with features of TSDF.

Skin barriers can be classified into - Physical, Chemical, Microbiological, and Immunological barriers[41].

The stratum corneum (SC),actsas a permeability barrier. The SC is a two-compartment system, consisting of corneocytes that providemechanical resistance embedded in a lipid-enriched extracellularmatrix, which is responsible for the permeability barrier.Corneocytes are formed by the terminal differentiation of keratinocytes, a process that includes thecross-linking of proteins like loricrin and involucrin by transglutaminaseto form the cornified envelope, as well as the loss of internal organelles. Corneodesmosomes link adjacent corneocytes, contributing to the skin's resistance to injury. The extracellular matrix lipids are organizedinto lamellar membranes enriched in free fatty acids,cholesterol, and ceramidesthat are derived from the secretion of lamellar body contents[42,43].Any disruption in physical cohesion among skin layers is reflected by TEWL.

Chemical barrier is formed by natural moisturising factors (NMFs) and lipid matrix of the SC mainly comprising of lipids from three distinct classes: cholesterol, free fatty acids and ceramides, densely packed and stacked in a 3D structure. Lipid bilayer provides a physical layer of protection and helps in maintaining the integrity of barrier[44].

Normal skin pH of 4.5-5.5 is slightly acidic in nature and acts as a chemical barrier. This pH is maintained by generation of free fatty acids, breakdown of filaggrin and lamellar body secretion[45] .

Microbiological barrier is formed by the antimicrobial peptides that are sequestered from the lamellar bodies of stratum granulosum. HBD1(human beta defensins) , secreted in all layers of epidermis and has potent antimicrobial activity against bacteria and fungus. Other AMPs that help maintain homeostasis are- Cathelicidin LL37, RNAse7 ,CXCL14 , S100A7, Psoriasin, Calprotectin. AMPs are under the influence of acidic pH of skin, shift of pH to alkaline side leads to decreased activity of AMPs which makes skin more prone to infections[46].

The immunological barrier of skin is formed by the antigen presenting cells, innate lymphoid cells, adaptive memory cells, skin associated lymphoid tissue (SALT), chemokines ,cytokines and AMPs in action. All of these work in harmony and generate a T-cell response[47].

Thus , we can say that TEWL and subcorneal hydration are good indicators of the physical barrier and skin pH , an indicator of chemical and microbiological barrier of skin.

Topical GC treatment impairs integrity and cohesion in SC as a result of reduced corneodesmosome density. They also delay barrier recovery due to inhibition of epidermal lipid synthesis.GC's also decrease AMP production, thus affecting the antimicrobial barrier. Also, GCs decrease chemokines, cytokines and T and B cell responses in the skin , thus affecting the immunological barrier.

Thus, GCs affect all the four barriers of the skin and derange the corresponding biophysical parameters. Prolonged GC therapy is also well known toproduce epidermal thinning, which, in turn, has been attributed tobothinhibition of keratinocyte proliferation and an accelerationin keratinocyte maturation[48-51].

These defects are responsible for the adverse effects such as xerosis, acneiform eruptions, increased infections, inflammation and skin atrophy.

TSDF is characterized by severe rebound erythema, burning, scaling ,dryness and sometimes extensive pustulation over the face on attempted stoppage of the TC after its prolonged use[11], thus prompting the patient to use them continuously leading to addiction. These flares correlate well with severity of barrier abnormality, particularly subcorneal hydration and TEWL. Withdrawl of corticosteroid leads to a burst in epidermal DNA synthesis with resulting epidermal hyperplasia and initiation of inflammatory cytokine cascade leading to inflammatory responses of epidermis and dermis[52].

Treatment of patients with topical steroid abuse and TSDF is always difficult and a matter of discussion. Looking into the deranged biophysical parameters in these patients, we suggest that moisturizers and barrier repair creams should be regularly used in treatment of these patients. Moisturizerscontaining occlusives- petrolatum and paraffin, humectants and emollients , hydrate the skin and act as barrier agents.

CONCLUSION:-

Topical steroids abuse is quite significant in our country. Understanding the physiological, chemical, and biophysical characteristics of the skin by evaluating parameters like skin hydration, transepidermal water loss and skin pH help us to understand the pathophysiology of various steroid induced dermatoses and have a better approach intheir management.Our study, however has a limitation. Some biophysical parameters like skin elasticity and erythema index could not be evaluated due to lack of facilities.

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