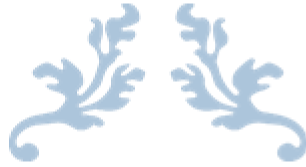

MAGNITUDE OF TOPICAL CORTICOSTEROID SIDE EFFECTS AMONG VITILIGO PATIENTS OF ALERT HOSPITAL, ADDIS ABABA, ETHIOPIA

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May, 2021

Addis Ababa, Ethiopia

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May, 2021

Addis Ababa, Ethiopia

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Abstract

Introduction: The global prevalence of vitiligo lies within the range of 0.1% – 2%. It is the most common disorder of pigmentation. It causes mild to severe psychological disturbance in more than a third of affected individuals. Additionally, public attitude towards vitiligo is negative in significant proportions of study subjects in countries like Ethiopia, adding to the psycho-social trauma. Topical corticosteroids are the mainstay of treatment in most government facilities of Ethiopia. Despite the relentless use of topical corticosteroids in general, and in Ethiopia in particular, studies giving exact account of the prevalence and types of side-effects are very few.

Objective: The major objective of this study is to determine the magnitude of topical corticosteroid side effects among vitiligo patients of ALERT Hospital, Addis Ababa, Ethiopia. This study will also try to look into the differences in the incidence of adverse effects based on age, sex and site of application. This study will further try to identify the intermittent application pattern of topical corticosteroids least associated with adverse effects.

Methodology: Institution-based, descriptive, cross-sectional study was conducted from May-August 2021. A total of 130 vitiligo patient who came to ALERT hospital for follow-up were included in the study. Face-to-face structured interview and observation was used for data collection. Data was entered using Epi-Info software version 7.1.4.0., and was cleaned, exported to and analyzed using SPSS version 21. Tables, Frequencies, proportion and Graphs along with measures of central tendency and dispersion were used to present the data as needed.

Results: In relation to the local side effects observed, 85 (65.4%) of the study subjects had no local side effect. Of the rest (45 patients), 27 (20.8%) had only 1 local side effect and 18 (13.8%) had 2 local side effects. The most frequent local side effect was telangiectasia (recorded in 30 patients), followed by Epidermal atrophy (seen in 21 patients). The highest proportion of local side effect per treatment site was observed over the flexural areas in which 5 (45.4%) of the 11 treatments in this region resulted in local side effects. This region was followed by breast and neck, 44.4% and 34.4% of sites affected respectively. There was no statistically significant difference based on sex or age in relation to the magnitude of local side-effects.

Conclusion: High incidence of local side effects was implicated in our study. The pattern of side effects is however similar to available studies with few exceptions. Neck is witnessed to be one of the side effect prone areas. Systemic side effects were negligible in our study.

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Acronyms

AASTU – Addis Ababa Science and Technology University

ALERT Center – All Africa Leprosy and Tuberculosis rehabilitation and training center

DLQI – Dermatology life quality index

FDA – Food and Drug Administration

ICD – Irritant contact Dermatitis

NB UVB – Narrow band ultraviolet B

NGO – Non-governmental organization

NSV –Non-segmental vitiligo

PUVA – Psoralen with ultraviolet A

QoL – Quality of life

SIRD – Steroid induced rosacea-like dermatitis

SV –Segmental vitiligo

TCI –Topical calcineurin inhibitors

TCS –Topical corticosteroids

WHO – World Health Organization

1. Introduction

1.1 Background

In general, disorders of pigmentation are among the top five most common dermatologic disorders in Africans and African-Americans. Vitiligo, on the other hand, is one of the tops in the list of disorders of pigmentations in people with skin of color [1,2,3]. It is even reported as the most common acquired pigmentary disorder in some literatures [2,4,5]. The global prevalence of vitiligo lies within the range of 0.1% – 2% [4,6,7,8,9]. The prevalence of vitiligo in children and adults appears to be comparable [10,11]. According to most representative literatures, we can conclude that there are no disparities with regards to race and sex in the prevalence of vitiligo. However, inclusive studies regarding the prevalence of disorders of pigmentation in nonwhite population is scarce [2,4,6]. Apart from its prevalence, Vitiligo can be a psychologically devastating disease which has a significant impact on quality of life (QoL) and self-esteem [12,13,14]. It causes mild to severe psychological disturbance in more than a third of affected individuals [2,15]. It may cause social isolation and significant depression,[16] create difficulties in sexual relationships, and affect perceived suitability for marriage [17,18]. Psychological effects are prominent when visible body areas, e.g., the hands and face, are affected [19]. Race, color and culture all influence how vitiligo affects QoL. Dermatology life quality index (DLQI) is higher in studies looking at more racially pigmented groups [20]. In the Ethiopian context, the prevalence of anxiety in vitiligo patients was found to be as high as 38.8% according to a study done at ALERT Hospital, Addis Ababa in 2016 [21]. Additionally, public attitude towards vitiligo is negative in significant proportions of study subjects in countries like Ethiopia, adding to the psycho-social trauma [22].

Vitiligo is an acquired disorder characterized by circumscribed depigmented macules and patches that result from the loss of functional melanocytes. Multiple theories have been proposed to explain melanocyte destruction in vitiligo. These include genetic susceptibility, autoimmunity, and oxidative stress [23,8]. Based upon the distribution pattern of depigmented lesions, vitiligo is classified into three broad categories, segmental Vitiligo (SV), non-segmental (NSV, most common) and undetermined vitiligo, and into several subtypes, such as generalized, acral or acrofacial, and universal, see table 1 below [8,23,24].

Finally, part of the treatment modalities currently employed in the management of vitiligo includes topical therapies such as topical corticosteroids (TCS)& topical calcineurin inhibitors (TCI); phototherapeutic modalities, such as Psoralen with ultraviolet A(PUVA), Narrowband ultraviolet B (NB UVB), and targeted phototherapy with 308nm excimer laser; systemic therapies like short course of systemic corticosteroids, and complementary and alternative therapies; depigmentation therapies as well as surgical interventions for selected cases. Several experimental modalities are also currently under development [8,23,25,26,27]. Mid- to super-high-potency topical corticosteroids are commonly used as a first-line therapy for the treatment of limited vitiligo. Their efficacy is attributed to modulation of the immune response. The efficacy of topical corticosteroids as monotherapy for the treatment of vitiligo is supported by few small

randomized trials [22]. Adverse effects related to a prolonged use of topical corticosteroids, including folliculitis, mild atrophy, telangiectasia, and hypertrichosis, have been reported in nearly all studies. Moreover, Systemic absorption resulting in adrenal suppression is also a concern when large areas of skin and areas with thin skin are treated for a prolonged time with potent steroids, especially in children. However, studies giving specific estimates of the prevalence of side effects in vitiligo patients are very few. Additionally, there are no universally accepted studies currently on optimal duration of TCS therapy and on interrupted applications that could improve the therapeutic index apart from expert opinion [25,28,29,30,31].

	Subtypes
Vitiligo ⁄ NSV	Acrofacial Mucosal (more than one mucosal site) Generalized Universal Mixed (associated with SV) Rare variants
Segmental Vitiligo	Uni-, bi-, or plurisegmental
Undetermined ⁄ unclassified Vitiligo	Focal Mucosal (one site in isolation)

Table i: Bordeaux VGICC classification and consensus nomenclature

1.2. Statement of the problem

Vitiligo is a common pigmentary disorder worldwide [1-8]. There are no nationwide prevalence studies, or meta-analytic studies concerning the prevalence of vitiligo in Ethiopia, but there are few studies in some regions. For example, according to a facility based cross-sectional study done at Ayder hospital, Mekelle, Ethiopia, the prevalence of Vitiligo among patients seen in dermatology clinic of this hospital was found to be 9.4% as of 2014 [31]. Another institution based cross-sectional study done in dermatology clinics of Mekelle city between the years 2017-2019 reported a vitiligo prevalence of 13.15% [27]. Regarding the treatment of this burdensome disease, available studies done in Ethiopia indicate that around 75% of these patients receive topical corticosteroid prescriptions. Unfortunately, alternative therapies such as phototherapy and surgical interventions are almost nonexistent [27]. Key informants from ALERT hospital also affirmed that topical corticosteroids are the mainstay of treatment in most government facilities. Despite the relentless use of topical corticosteroids in the treatment of vitiligo, there are no studies done to assess the prevalence of topical corticosteroid side-effects in vitiligo patients in Ethiopia. Answering this key question with this study will help us understand the degree of damage incurred by topical corticosteroids in vitiligo patients. Additionally, study will try to identify groups more susceptible to topical corticosteroid side

effects among vitiligo patients included in the study. This will help the clinicians develop an evidence-based protocol for topical corticosteroid administration, and to evaluate the necessity and timing of alternative treatment. Additionally, it will also help pressurize the concerned bodies to work on the availability of alternative treatment options whenever necessary. Furthermore, it will pave the road for subsequent studies focusing on addressing associated factors including steroid application patterns, and comparison of combination and alternative therapies in Ethiopian context.

2. Literature Review

Topical corticosteroids (TCS) have been applied since the 1950s for their anti-inflammatory and immunomodulating effects [9, 32]. They represent a significant milestone in dermatologic therapy [33]. However, despite encouragement to report observed adverse drug reactions associated with topical corticosteroids, the clinical practice of reporting is poor and incomplete. Likewise, adverse effects and safety of topical corticosteroids are neglected in the medical literature [32]. The available databases from (www.fda.gov/cder/drug/efault.htm) suggest that only life-threatening side effects were reported or published. Thus, the information available currently regarding the multitude of local and systemic side-effects after application of topical corticosteroids is limited.

Local therapy of vitiligo with topical corticosteroids was first introduced in 1970 by Kandel [34, 35, 36]. Currently, TCS are the most prevalent modes of treatment and are considered the first line treatment for mild or moderate vitiligo [5, 9, 33,]. Topical corticosteroids are the most effective monotherapy for the treatment of vitiligo [37].

Topical corticosteroids generally can be classified into four groups and seven classes based on their potency according to the WHO system of classification. Within this system of classification, Super-high potency (Class I), High potency (Classes II to III), Medium potency (Classes IV to V), and Low potency (Classes VI to VII) corticosteroids are recognized. According to one study, whether the steroid was of high potency or low potency slightly influenced the percentage of adverse reactions (<1.5%) [38]. Regarding the vehicles, gel vehicle caused more reactions (particularly pruritus and dryness) than the creams or ointments, respectively 9.4% vs 2.8% vs 1.5% [38]. With respect to the frequency of application of TCS, a study done by David A. et al. recommended that the frequency of application of ultrahigh-potency topical corticosteroids be reduced after the first two to three weeks to no more than four or five times a week [39].

In the treatment of vitiligo, there are variable recommendations regarding the potency of topical corticosteroid that should be used. According to drake et al., Mid- or lower potency

corticosteroids may be preferable to avoid the toxicity associated with long-term applications of high-potency corticosteroids [40, 41]. Some physicians recommend medium to higher potency preparations for the first month, tapering to the lower potency preparations [42]. Low-Medium potency topical corticosteroids should be considered in children younger than 9 years of age who are not candidates for topical PUVA. High potency steroids are efficacious for the treatment of vitiligo in children. However, the potential for systemic absorption should be kept in mind [40, 41,42, 43, 44, 45, 46]. Children are more prone to develop systemic reactions to topically applied medication because of their higher ratio of total body surface area to body weight (about 2.5- to 3-fold that of adults). However, the thicknesses of the stratum corneum and its structural components, such as keratins and lipids, have been found not to be statistically different from those in adults [32].

As potent topical corticosteroids appear to be at least as effective as very potent topical corticosteroids, the first category should be the safest choice. Systemic absorption and skin atrophy is a concern when large areas of skin are involved, regions with thin skin and children who are treated for a prolonged time with potent steroids. In such cases, topical corticosteroids with negligible systemic effects, such as mometasone furoate or methylprednisolone aceponate should be preferred [9,33,42]. Due to the potential side effects of increased intraocular pressure/ glaucoma and cataract, topical corticosteroids should also be used with caution in the periorbital region [32, 45, 47].

Currently, there are no studies available on optimal duration of TCS therapy and on intermittent applications that could improve the therapeutic index apart from expert opinion [9, 40, 41, 42, 48, 49, 50].

Although there is scarcity of institutional and community-based prevalence studies on the local and systemic adverse effects of topical corticosteroids, qualitative data is available as to the varieties of local and systemic adverse effects that a physician can encounter. According to Hengge et al., the most frequent adverse effects include atrophy, striae, rosacea, perioral dermatitis, acne, and purpura. Those that occur with lower frequency include hypertrichosis, pigmentation alterations, delayed wound healing, and exacerbation of skin infections. Of particular interest is the rate of contact sensitization against corticosteroids, which is considerably higher than generally believed (0.5% - 5%). Systemic reactions such as hyperglycemia, glaucoma, and adrenal insufficiency have also been reported to follow topical application [32, 51, 52, 53, 54, 55, 56]. To exemplify few studies on the prevalence, a total of 2,849 patients in which there were 5698 exposures were reviewed from 14 paired comparison studies by Akers et al. In this trial, fifty-five percent were female patients and 80% were white. Children under 10 years of age comprised about 8% of the population studied. The diseases treated are multiple inflammatory dermatoses of which psoriasis vulgaris (1,145 patients) was the most frequent diagnosis. A total of 249 (4.4%) subjective and objective local adverse reactions were reported. No severe (life-threatening) local or systemic reactions occurred. No systemic effects were observed or mentioned, but no laboratory examinations were performed.

Among the adverse reactions, irritation was recorded in 1.3%, itching in 0.99%, burning and stinging in 0.81%, dryness in 0.46%, Scaling in 0.3% and Vesicles in 0.16% of exposures. Secondary infections were also noted in 5 exposures, but these were atopic patients [38].

According to the FDA release of reported adverse events due to topical corticosteroids in pediatric patients, the most frequent reactions include local irritation, dyspigmentation, and striae or skin atrophy. Child specific adverse effects such as growth retardation are also mentioned. See table II [32].

Event	Frequency (n = 202) *
Local irritation	66
Skin depigmentation or discoloration	30
Striae or skin atrophy	30
Cushing syndrome	6
Growth retardation	5
Hyperglycemia (diabetes)	5
Scarring	5
Staphylococcal infection	5
Genital hypertrichosis	4
Hirsutism	4
Rosacea	4
Acne	3
Glaucoma	3
Hypersensitivity reaction	3
Adrenal insufficiency	2
Bruising	2
Fungal infection	2
Gynecomastia	2
Perioral dermatitis	2
Mental status or mood change	2
*** Adverse effects with frequency <2 were not reported**	

Table ii: Reported adverse events in pediatric patients, according to the FDA report

Regarding association of specific formulations of topical corticosteroids with adverse reactions, events that follow topical use of Budesonide include intraocular pressure changes (up to 30%); Itching, irritation, burning (up to 1%); contact dermatitis (100 of 7238 subjects). Similarly, reported severe reactions for topical hydrocortisone include pseudotumor cerebri, cataract and glaucoma. Additionally, for triamcinolone acetonide, Cushing syndrome has been reported [32].

Focusing specifically to the prevalence of topical corticosteroid side effects in vitiligo patients, 75 study participants with diverse racial contribution, including blacks, whites and Indian/Pakistani people, were treated with topical application of clobetasol propionate. clobetasol propionate 0.05% W/W in 50% isopropyl alcohol was used initially in a few cases for the treatment of vitiligo on the trunk and limbs. For vitiligo on the eyelids and elsewhere on the face, 0.05% clobetasol propionate (W/W in a paraffin base) was used. Treatment application was intermittent and of variable duration. The maximum duration of one course of treatment on the face was two months, whereas it was four months for other areas. A maximum of 50 ml of alcohol-based solution and/or 12.5 g of ointment was used in 4 weeks. Seven patients receiving clobetasol in isopropyl alcohol base had local soreness, erythema and/or xeroderma. No other cutaneous, ocular, or systemic side effects were noted in any of the cases [50].

In another study involving Vitiligo patients less than 12 years of age, participants were advised to apply 0.05% clobetasol propionate cream to the vitiliginous areas twice daily. Every 6 weeks, treatment was interrupted for 2 weeks. This treatment-free interval was prolonged to 4 weeks in 4 patients, in whom steroid-induced atrophy was observed. Among 22 patients which were evaluable at the end of 6 months of treatment, 4 children developed mild atrophy, 2 developed telangiectasia, 1child developed hypertrichosis and other two children developed acneiform eruption [49].

Moreover, one study underwent retrospective study of high-potency steroid use in children with vitiligo. One hundred and one children (0-18 years) with vitiligo treated with moderate to high potency topical corticosteroids were included in the study. Local steroid side-effects were noted in 25% (26 of 101) of patients and consisted of striae (8 of 101), atrophy (5 of 101), telangiectasia (5 of 101), and other skin findings (14 of 101), which included bacterial, fungal skin infections, nonspecific dermatitis, and acne. There was no statistically significant difference in the occurrence of the local side effects in the high versus moderate corticosteroids groups (P = .3). Two children with low cortisol levels were given the diagnosis of steroid-induced adrenal suppression. Children with head and/or neck involvement, affected areas were 8.36 times more likely to have an abnormal cortisol level compared with children affected over other body sites [46].

As reported by Schaffer et al. (2003), Superpotent corticosteroids have been used safely in children as young as 3–5 years of age in several studies. Patients should be monitored closely for early evidence of telangiectasias, cutaneous atrophy, or striae; the former often precedes atrophy. Other potential adverse skin reactions include hypertrichosis and acneiform eruptions, especially in older children and adolescents. However, specific figures about the incidence of

these adverse effects were not forwarded in this study. Treatment with superpotent corticosteroids should be reserved for limited areas of involvement to avoid suppression of the hypothalamic-pituitary-adrenal axis and other systemic side effects. Patients can be monitored at every 6-8 weeks during treatment and if no response is seen after 3-4 months or 2 "cycles," therapy should be altered [45].

Regarding individual side-effects, a comprehensive review of 60 articles was conducted in 2015 on the topic of corticosteroid-induced skin atrophy. Using Whole Skin Thickness as an Endpoint, Mometasone furoate shows relatively low atrophogenic activity while belonging to the class III of potent TCs. Other molecules such as fluticasone propionate and fluocinonide acetonide may be close to mometasone furoate in terms of benefit/risk ratio as they are poorly atrophogenic. Clobetasol propionate was found to be the most atrophogenic compound, the average skin atrophy reported being 15%; however, as clobetasol propionate (class IV) is also considered as the most powerful anti-inflammatory, its risk/benefit ratio can still be considered as good. Betamethasone valerate, a class III TCS that also has high atrophogenic power, has a weaker benefit/risk ratio. Prednicarbate, domoprednate, hydrocortisone butyrate, and triamcinolone acetonide show a worse benefit/risk ratio because of their higher atrophogenic power. The less powerful TCs, hydrocortisone and hydrocortisone valerate, are the less atrophogenic [57].

Epidermal atrophy, a new parameter to follow skin atrophy, was also used as an endpoint to measure incidence of atrophy. The interesting point regarding epidermal atrophy is that it looks proportionally greater than whole skin. Epidermal atrophy may be more likely to assess differences of atrophogenicity between two distinct TCS. According to epidermal atrophy, clobetasol propionate is the most atrophogenic TCS (-26 %). Betamethasone valerate (class III) presents a relatively high atrophogenic value (-18 %) on the epidermis. The low atrophogenic activity of hydrocortisone on the epidermis is also in agreement with what has been observed in hydrocortisone-induced skin atrophy [57].

Atrophy has now been recognized as the most common adverse effect of topical corticosteroid therapy [14]. The factors that influence the degree of skin atrophy include age, body site, potency of topical corticosteroid, and the presence of occlusion [14, 32, 44]. In a study done by Clayton R., one of the early studies of topical corticosteroid use, a double-blind trial of 0.05 % clobetasol propionate in the treatment of vitiligo, 25 patients were included. The patients were assessed monthly for 4 months by the same person and the areas treated were photographed under ultraviolet light at the beginning and end of the trial. At the end of the trial all patients showed evidence of dermal atrophy [58]. There was also a report of epidermal atrophy and telangiectasia in one case report in which flucinolone acetonide 0.01% was applied to the face, including eyelids in 1976 [47]. According to a more recent meta-analytic study, atrophy was found in 14% of patients using class 4 topical corticosteroids and, 2% of patients using class 3 topical corticosteroids [14].

Contact allergy to corticosteroids has been increasingly recognized worldwide as a problem of considerable clinical and therapeutic importance. The incidence of corticosteroid allergy

observed (from 0.5% to 5%) varies in every report from one center to another [32, 59, 60, 61,62, 63, 64]. The correct concentration and vehicle for patch testing with corticosteroids, however, has not yet been generally agreed upon. On this line, a retrospective study of patch testing to corticosteroid series over 6 years (Jan1, 2000 – Dec 31, 2005) was conducted on 1188 subjects and 127(10.69%) were found to have allergic reactions to at least one corticosteroid. 56 reacted to multiple corticosteroids. Patch test reactions to individual corticosteroids were 0.41% to 5.03%. Of the individual corticosteroids studied, Clobetasol-17-propionate 1% had a reaction rate of 1.44%, Mometasone furoate 0.1% had 1.1% reaction rate and Betamethasone 17, 21 dipropionate 1% had a reaction rate of 0.93% [65].

In relation to acneiform eruptions, a study involving application of clobetasol propionate (Dermovate) was done in 39 patients, and two of these study participants developed acneiform rash [66]. Similarly, 19 vitiligo patients were treated with 0.1 Betamethasone valerate in50% isopropyl alcohol in another study. Among these study participants, three of them developed localized acneiform eruption, and two other developed hypertrichoses.

The exact incidence of SIRD is not known, but it is believed to affect women more than men. The most common age at presentation is 40 to 50 years [67, 68]; however, it also has been described in infants, children, and elderly patients [69, 70, 71, 72, 73, 74, 75, 76]. Despite its morphologic resemblance to rosacea, SIRD currently is not considered a variant of rosacea [77, 78].

Another facial dermatosis which can result from long term use of potent topical corticosteroids over the face is Perioral dermatitis. It has been most frequently observed in young women, but it has also been seen in men and children.

The first case report of glaucoma following application of topical flucinolone acetonide to the face was by Cubey RB in 1975 [47]. In 2006, a review of topical corticosteroid side effects showed that topical use of budesonide caused Intraocular pressure changes (up to 30%); Itching, irritation, burning (up to 1%); contact dermatitis (100 of 7238 subjects). Similarly, topical hydrocortisone is reported to result in cataract and glaucoma [32].

In the light of systemic side-effects, Cushing's syndrome due to excessive topical corticosteroids, particularly clobetasol, is well described. 50 g clobetasol propionate 0.05% will suppress the hypothalamic-pituitary-adrenal axis [79, 80], and larger quantities of betamethasone will have a similar effect. However, since nonreversible clinical secondary adrenocortical-insufficiency disease has not been clearly documented with even class I topical corticosteroids, native adrenal supplementation in periods of stress appears unnecessary; rare exceptions cannot be excluded [81] Clinical Cushing's syndrome has been described with the use of 100 g of clobetasol per week without occlusion [79]. Cushing syndrome has also been reported for topical triamcinolone acetonide. At least 43 cases with iatrogenic Cushing syndrome from very potent topical steroid usage (Clobetasol) in children and adults have been published over the last 35 years particularly in developing countries [82].

In conclusion, topical corticosteroids are used widely for the treatment vitiligo throughout the world. The advantages of topical corticosteroids are ease of application, high compliance rate, and low cost [8]. In this respect, topical corticosteroids are commonly prescribed in developing countries like Ethiopia. It is also evident from available studies that months of treatment with topical corticosteroids of different potencies are required for best outcome in vitiligo patients. However, the available evidence on the prevalence of topical corticosteroid side effects is generally limited. It is also tempting to do comprehensive prevalence study on topical corticosteroid side-effects specifically among vitiligo patients from current standpoint.

3. Objectives of the study

3.1. General objective

- ✓ To describe the prevalence of topical corticosteroid side-effects, both local and systemic side effects, among vitiligo patients treated at ALERT hospital, Addis Ababa

3.2. Specific objectives

- ✓ To measure the difference in prevalence of topical corticosteroid side-effects between men and women
- ✓ To determine the difference in prevalence of topical corticosteroid side-effects between children and adults
- ✓ To identify vitiliginous site more commonly associated with increased prevalence of side-effects
- ✓ To Compare the prevalence of side-effects in different classes of topical corticosteroid potencies
- ✓ To identify the pattern of topical corticosteroid application (continuous vs various groups of intermittent use) least associated with onset of side effects.

4. Methodology

4.1. Study design

An institution based prospective, descriptive, cross-sectional study design was implemented within the allocated study period.

4.2. Study area

This study was undertaken within ALERT Center dermatology clinics. ALERT Center is located in Ethiopia, Addis Ababa city, Kolfe keranio sub-city, Zenebework area. It was established in 1932 by a philanthropist for the treatment of leprosy. During the regime of Emperor Haile Silassie I, it

served as a leprosy treatment center under the name Princess Zenebe Work memorial hospital. Due to the contemporary attention given to leprosy in Ethiopia, other African countries, and many non-governmental organizations (NGOs) started participating on the matter. With the aim to expand this leprosy treatment center, a memorandum was signed in 1965 to found ALERT Center (All Africa leprosy rehabilitation and training center). Currently, the name is extended to involve tuberculosis and is renamed "All Africa leprosy and Tuberculosis rehabilitation and training center". However, currently it is not limited to leprosy and tuberculosis treatment and training, and additionally services including the following are given: Trauma and emergency treatment, Ophthalmology treatment, Dermatology treatment, Plastic and reconstructive surgery, antenatal care, delivery and neonatal care, orthopedic treatment, pediatric treatment, Internal medicine and neurology and many more. It also serves as a dermatology training center among several others.

4.3. Study period

Study was conducted from May 22 – August22 of 2021

4.4. Source Population

Patients attending dermatology outpatient clinics of ALERT hospital, Addis Ababa, Ethiopia.

4.5. Study Population

All vitiligo patients attending dermatology outpatient clinic within the specified study period and meet the inclusion criteria set.

4.5.1 Inclusion and exclusion criteria

A. Inclusion criteria

- ✓ Vitiligo patients who come for follow-up at alert hospital, and are on topical corticosteroid treatment

B. Exclusion criteria

- ✓ Vitiligo patients who come for first visit during the study period.
- ✓ Vitiligo patients whose first visit was within the preceding 1 month.
- ✓ Vitiligo patients with comorbid cutaneous disorder at the site of treatable vitiligo lesion
- ✓ Patients on treatment for vitiligo with agents other than topical corticosteroids.
- ✓ Patients on combination treatment for vitiligo.

4.6. Sample Size

From the available similar studies, a proportion of 9.3% (0.093) was taken to calculate the minimum sample size. The sample size was determined using single population proportion statistical formula.

$$n = \frac{z^2 P (1-P)}{d^2}$$

Where:

n = sample size

Z = cut point on the right side of standard normal curve corresponding to 95% confidence interval = 1.96

P = Proportion among the study population

d = degree of accuracy required (maximum allowable error of the estimate); 0.05 was used in this study

Substituting the values into the formula, a sample size of 130 was found.

Adding 10% for non-response gives a final sample size of 143

4.7. Variables of the study

- ✓ Age
- ✓ Sex
- ✓ Place of residence
- ✓ Religion
- ✓ Level of education
- ✓ Duration of illness
- ✓ Site affected by Vitiligo
- ✓ Concomitant medical illness
- ✓ Potency of steroid used
- ✓ Site of application
- ✓ Duration of application

- ✓ Pattern of application
- ✓ Cutaneous side effects
- ✓ Ocular side effects
- ✓ Systemic side effects

4.8. Data collection procedure

Data was collected by Year II and Year III residents practicing at ALERT center. Both qualitative and quantitative data was collected using structured face to face interview and observation. The interview format was prepared by the principal investigator (see annex 2) and appropriate instruction was given to the data collectors before the commencement of the study.

4.9. Data analysis procedure

Template for data entry was prepared by the principal investigator on Epi-Info software version 7.1.4.0. The template was distributed to data clerks and data is entered. The entered data is collected and stored on a hard drive and backed up using flash disk. The entered data was merged, cleaned, and then exported to SPSS software version 21. Data was recoded, and analyzed using SPSS. Tables, Frequencies, proportion and Graphs along with measures of central tendency and dispersion were used to present the Result as needed. Binary logistic regression analysis was employed whenever appropriate

4.10. Data quality management

The questionnaire was tested on 5% of the sample size to check whether it is clearly understood. Adequate orientation was given to the data collectors concerning the questionnaire. Data collectors were supervised by the principal investigator to ensure data consistency. Each questionnaire was checked at the study area for its completeness by the data collectors. The principal investigator double-checked the consistency and completeness of each questionnaire at the end of each data collection day and incomplete forms were discarded.

4.11. Operational definitions

A vitiligo case: A vitiligo case in this study is defined as a patient presenting with acquired, circumscribed depigmented patches or macules and unequivocally diagnosed as vitiligo patent either clinically by a dermatologist/ dermatology resident and/or with the aid of histopathology.

Iatrogenic Cushing syndrome: Patients with itatrogenic Cushing's syndrome are defined in this study as patients who develop clinical features of cushing syndrome for the first time after the initiation of topical corticosteroid therapy. Manifestations include, but are not limited to, weight gain, moon face, buffalo hump, supraclavicular fat pads, central obesity; cutaneous features such as facial plethora, violaceous striae, ecchymoses, telangiectases, purpura, visible subcutaneous vasculature, increased facial lanugo hair, hirsutism or male pattern balding (in females), steroid acne and acanthosis nigricans; Gasterointestinal and musculoskeletal manifestations such as peptic ulcerations, proximal muscle weakness, osteoporosis and avascular necrosis of hip joint; psychological problems such as depression, cognitive dysfunction, or emotional lability; new onset or worsening of diabetes mellitus or hypertension; menstrual irregularity, amenorrhea or infertility in women.

Diabetes Mellitus: a case of diabetes mellitus is defined in this study as a patient who has recorded fasting blood glucose level of >/= 126 mg/dl

Pre-diabetic hyperglycemia (Impaired fasting glucose)**:** pre-diabetic hyperglycemia is defined in this study as a fasting blood glucose level between 100 mg/dl – 125 mg/dl

4.12. Ethical considerations

Ethical clearance was be obtained from Addis Ababa Science and Technology University (AASTU), college of health sciences, school of medicine, dermatovenerology department, ethical review committee.

5. Results

A total of 130 Vitiligo patients who attended ALERT hospital for follow-up visits, and met the inclusion criteria, managed to complete the interview, and were enrolled in the study. Subsequently, 45 (34.6%) of the patients were found to have local side effects during the study period. Eighteen of these subjects had 2 types of local side effects making the total of individual side effects recording 63. Details of the findings are discussed below.

5.1 Socio demographic characteristics

In light of age distribution of the subjects studied, the contribution of those ≤ 14 years of age is 20 (15.4%). Slightly more than half of our study participants were females (53.8%). Close to a quarter of our patients (29.2%) were from rural area, while the rest were from urban area. Most of the enrolled participants were Orthodox Christian religion followers (48.5%), followed by Muslim religion followers (24.6%), and Protestant religion followers (22.3%). With regard to highest educational achievement of study participants during the study period, 64.6% of the total have attended up to primary schools or less. Those with no formal education constitute 19.2% of the total. Around 68% of the study participants declared a monthly household income of 100$ or less. (See table III for details)

Variable	Frequency	Percent	Cumulative Percent
Age (in completed Years)			
≤14	20	15.4	15.4
15-24	20	15.4	30.8
25-34	38	29.2	60.0
35-44	20	15.4	75.4
45-54	12	9.2	84.6
≥55	20	15.4	100.0
Sex			
Female	70	53.8	53.8
Male	60	46.2	100.0
Residence			
Rural	38	29.2	29.2
Urban	92	70.8	100.0
Highest educational achievement			
No formal education	25	19.2	19.2
Primary school	59	45.4	64.6
Highschool diploma	30	23.1	87.7
College diploma or certificate	10	7.7	95.4
Bachelor's degree	6	4.6	100.0
Master’s degree or above	0	0	100.0
Religion			

Continued…	32	24.6	24.6
Orthodox Christian	63	48.5	73.1
Protestant	29	22.3	95.4
Others	6	4.6	100.0
Monthly household income			
<50$	38	29.2	29.2
51-100$	50	38.5	67.7
101-150$	21	16.2	83.9
>150$	21	16.2	100.0

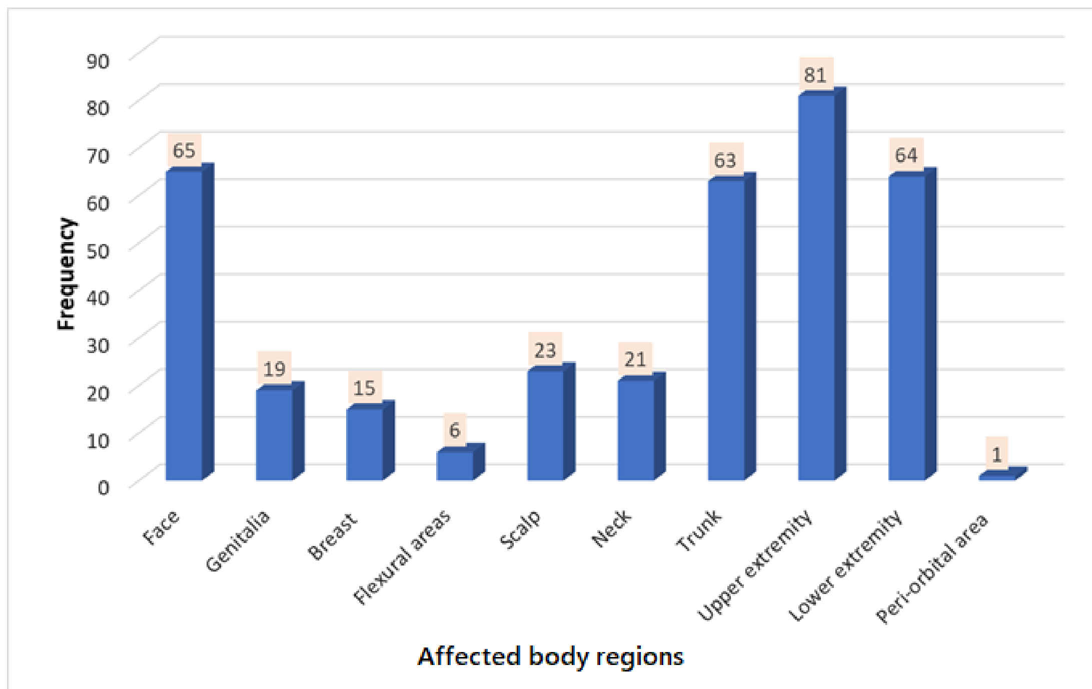
Table iii: Socio-demographic characteristics of vitiligo patients seen at ALERT hospital, Addis Ababa Ethiopia, Aug 2021.

5.2 Patient medical history

Of the 130 respondents, history of diabetes mellitus was reported by 7 of them and history of hypertension was reported by two respondents. Both of the hypertensive patients have concomitant diabetes mellitus. No other chronic medical illness was reported. Accordingly, the total number of patients with confirmed chronic medical illness is 7 (5.38%). Of the total subjects studied, only 6(4.6%) had family history of vitiligo.

The number of patients with only one body region affected by vitiligo account for 23.1% (30), those having only two affected body region account for 20.8% (27). Those having more than 3 affected body region account for 56.2% (73) of the total. Of the total of 358 affected body sites in 130 patients, Upper extremity is the most frequently affected region being involved in 81 patients. The face was affected in 65 patients, Neck in 21 patients, genitalia in 19 patients and breast in 15 patients. Flexural sites were also involved in 9 patients (See Figure1). Thirty percent of the participants had their current illness for 1 year preceding the study period, while 35.4% of them had their illness for more than three years; the rest lie in between (See Figure2 and table IV).

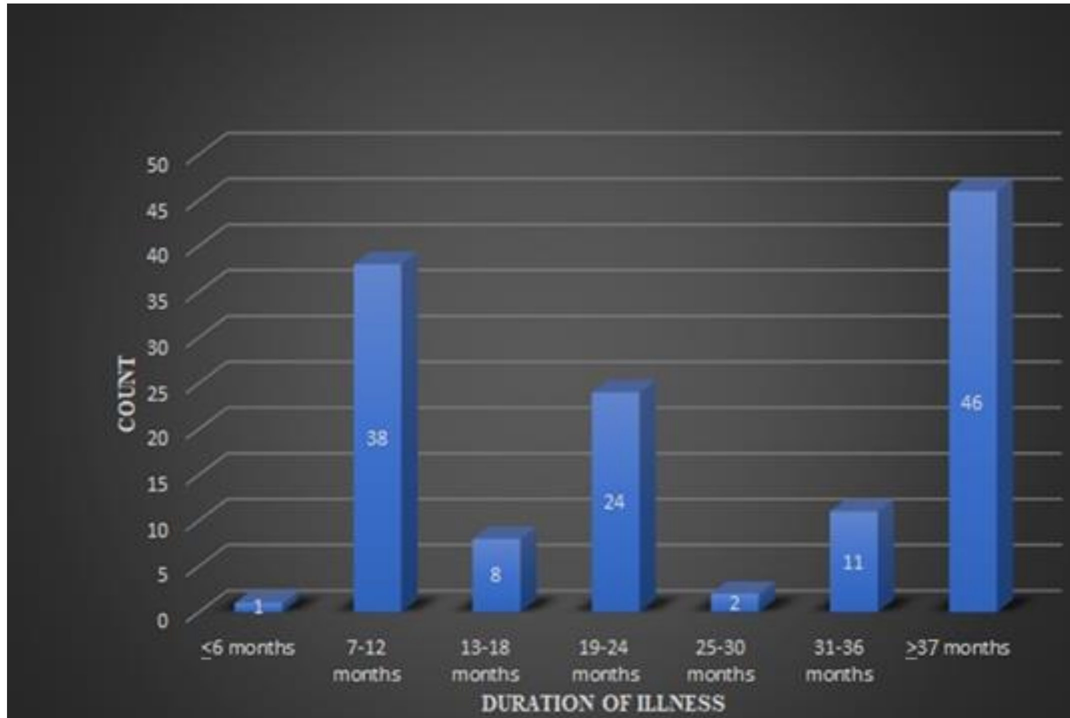
Figure 1: Sites affected by vitiligo among vitiligo patients seen at ALERT hospital, Addis Ababa Ethiopia, Aug 2021.



Duration of current illness	Count	Percent	Cumulative Percent
≤6 months	1	0.8	0.8
7-12 months	38	29.2	30
13-18 months	8	6.2	36.2
19-24 months	24	18.5	54.7
25-30 months	2	1.5	56.2
31-36 months	11	8.5	64.7
≥37 months	46	35.4	100
Total	130	100	

Table iv: Duration of current illness, among vitiligo patients seen at ALERT hospital, Addis Ababa Ethiopia, Aug 2021.

Figure 2: Duration of current illness, among vitiligo patients seen at ALERT hospital, Addis Ababa Ethiopia, Aug 2021.



5.3 Treatment

Sixty nine of the 130 patients were provided single agent topical treatment, while 61 were given two agents per treatment course. No more than two types of topical corticosteroids per patient were given for our study participants. Mometasone furoate 0.1%, Betamethasone dipropionate 0.05%, and clobetasol propionate 0.05% were used for treatment. The most frequently prescribed medication was Mometasone furoate which was given for 94 patients. Clobetasol propionate and Betamethasone dipropionate were given for 85 and 12 patients respectively. Among subjects treated with single agent topical corticosteroid, 11 of them were treated with Betamethasone Dipropionate, 25 with Clobetasol Propionate and 33 with Mometasone Furoate. Of participants who received two agents, 60 of them used a combination of Clobetasol Propionate and Mometasone Furoate. And only 1 person used a combination of Betamethasone dipropionate and Mometasone Furoate. No other combination treatment was evident in the study (see table V). In light of body regions treated, there were a total of 358 treated body regions in the 130 patients evaluated. Of these treatment sites, 152 of them were treated with Mometasone furoate. Betamethasone Dipropionate was used in 21 treatment sites. The rest (185 sites) were treated with Clobetasol Propionate ointment. Mometasone furoate was used in 100%, 86.7%, and of 52% of the treatments over face, breast and neck

respectively. Majority of the Mometasone furoate was used in cream vehicle, while most of the Betamethasone dipropionate and all of the Clobetasol protonate were prescribed in ointment vehicle (see Figure3). Most of the physicians dispensed 5 to 15 grams of each topical corticosteroid per month. The maximum amount of topical corticosteroid given was 40 grams per month for Clobetasol propionate ointment, and 30 gm per month for all the others. For details on pattern of topical corticosteroid application see Figure4 and table VI. Regarding treatment duration, 40 (30.8%) of the patients were treated for ≤ 6 months, and 44 (33.8%) were treated for 7 – 12 months. The preceding two categories sum up to 64.6% of the total. In line with this, 13.8 % of the participants were treated for more than three years.

		Treatment 2			
		Betamethasone Dipropionate	Clobetasol Propionate	Mometasone Furoate	No Second treatment
		Count	Count	Count	Count
Treatment 1	Betamethasone Dipropionate	0	0	0	11
	Clobetasol Propionate	0	0	27	25
	Mometasone Furoate	1	33	0	33

Table v: Treatment provided for vitiligo patients seen at ALERT hospital, Addis Ababa Ethiopia, Aug 2021.

Figure 3: Treatment and drug vehicle prescribed for vitiligo patients seen at ALERT hospital, Addis Ababa Ethiopia, Aug 2021.

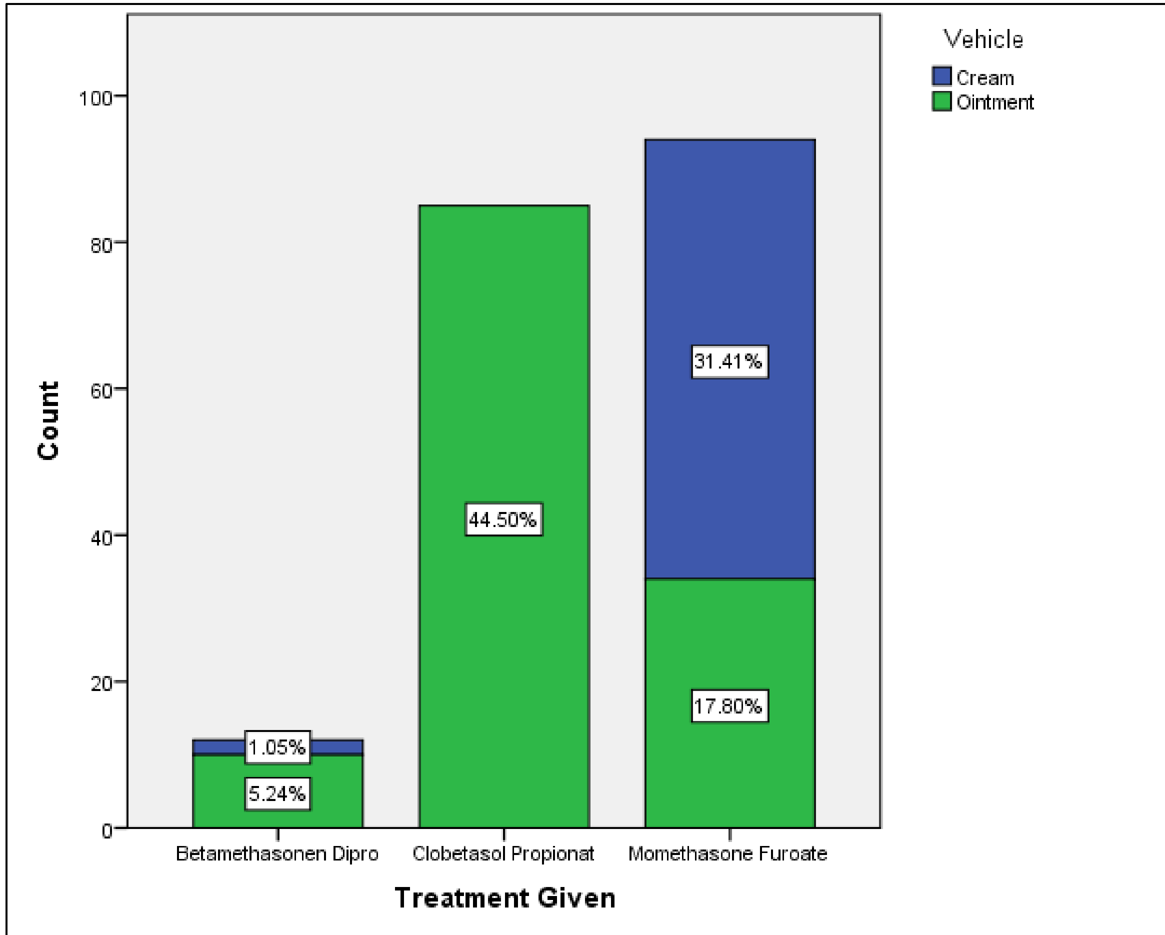
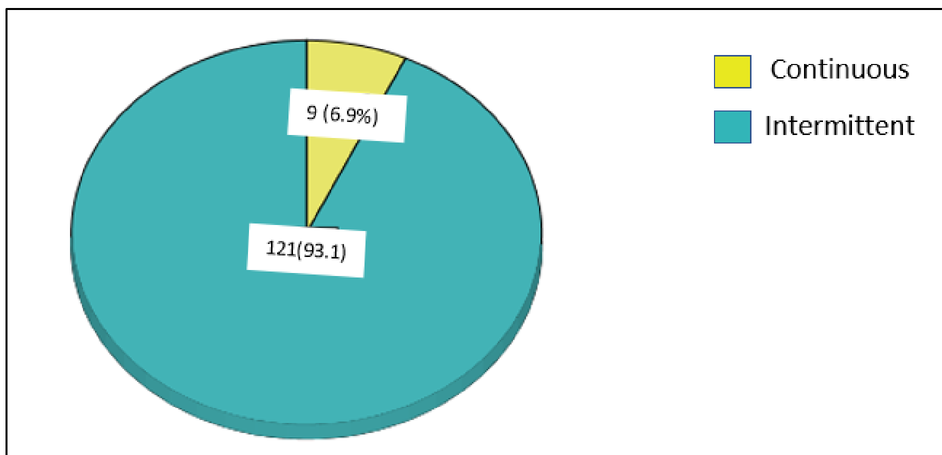


Figure 4: Topical corticosteroid application pattern of vitiligo patients seen at ALERT hospital, Addis Ababa Ethiopia, Aug 2021.



		Frequency	Percent (Intermittent pattern)	Cumulative Percent
	One week drug holiday per month	91	75.2	75.2
	Two weeks of continuous drug holiday per month	29	24.0	99.2
	Every other week treatment	1	0.8	100
	Total	121	100	

Table vi: Specifics of intermittent topical corticosteroid application pattern of vitiligo patients seen at ALERT hospital, Addis Ababa Ethiopia, Aug 2021

5.4 Side effects

In relation to the local side effects observed, 85 (65.4%) of the study subjects had no local side effect. Of the rest (45 patients, 34.6%), 27 (20.8%) of them had only 1 local side effect and 18 (13.8%) had 2 local side effects. These 45 patients had 63 individual local side effects. 58 of the local side effects were noticed in a single body region while 5 of the side effects were observed in 2 body regions. This makes the total body regions affected by local side effect 68. This implies that 19% of the treated sites had features of local side effects from a total of 358 treated sites. The most frequent local side effect was telangiectasia (recorded in 30 patients), followed by Epidermal atrophy (seen in 21 patients); *see Figure5 for detail*. No ocular side effect was observed in this study. Sixty percent of the local side effects were observed in females. On the other hand, 8 of the study subjects under the age of 14 had local side effects. This implies that 40% of study subjects in this age group had local side effects while 28.5% of the subjects 15 years or above had local side effects. However, based on binary logistic regression analysis there was no statistically significant difference based on sex or age in relation to local side-effects. The highest proportion of local side effect per treatment site was observed over the flexural areas in which 5 of the 11 (45.4%) of treatments in this region resulted in local side effects. This region was followed by breast and neck, 44.4% and 34.4% of sites affected respectively (see Figures6&7). On the face, on the other hand, 20 of the 85 treatments (23.5%) resulted in local side effects. In all body regions, binary logistic regression analysis revealed that, there was no statistically significant difference between continuous and intermittent pattern of topical corticosteroid application in relation to magnitude of local side-effects as it is also true for the various patterns of intermittent applications; however, a larger study comparing the various patterns is recommended as there is inadequate representation of some of the patterns. As a flaw of the study design, it was not feasible to compare the magnitude of local side-effects as a result of the treatment agents provided as majority of the treatment sites

were discordant between various treatment agents. See table VII for local side-effects caused by various agents used. Only 2 patients had blood sugar in the diabetic range, excluding those who were diabetic before commencement of current treatment. However, there was no baseline record of blood sugar in both cases. Otherwise, no systemic complication of topical corticosteroids was observed in the current study.

Figure 5: Frequency of local side effects among vitiligo patients seen at ALERT hospital, Addis Ababa Ethiopia, Aug 2021. (ICD- Irritant contact dermatitis)

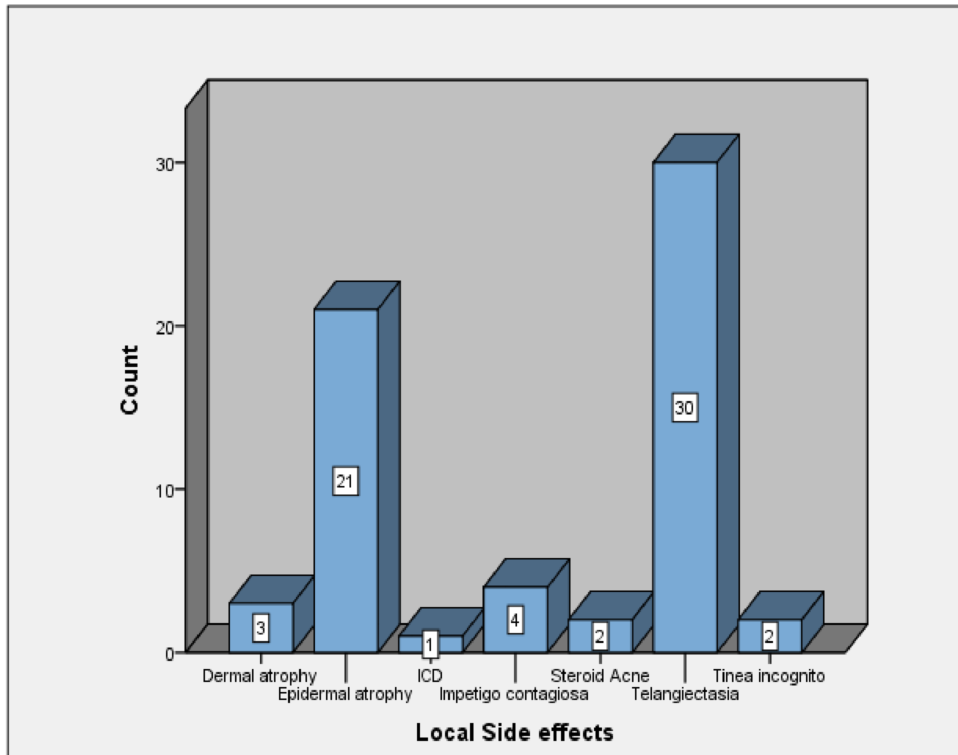


Figure 6: Frequency of local side effects in different treated body regions among vitiligo patients seen at ALERT hospital, Addis Ababa Ethiopia, Aug 2021.

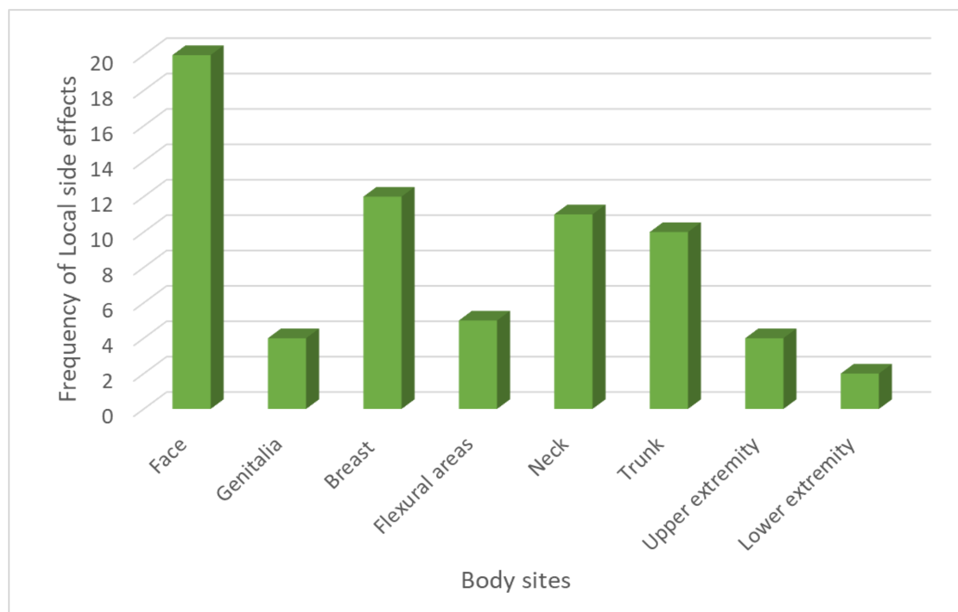
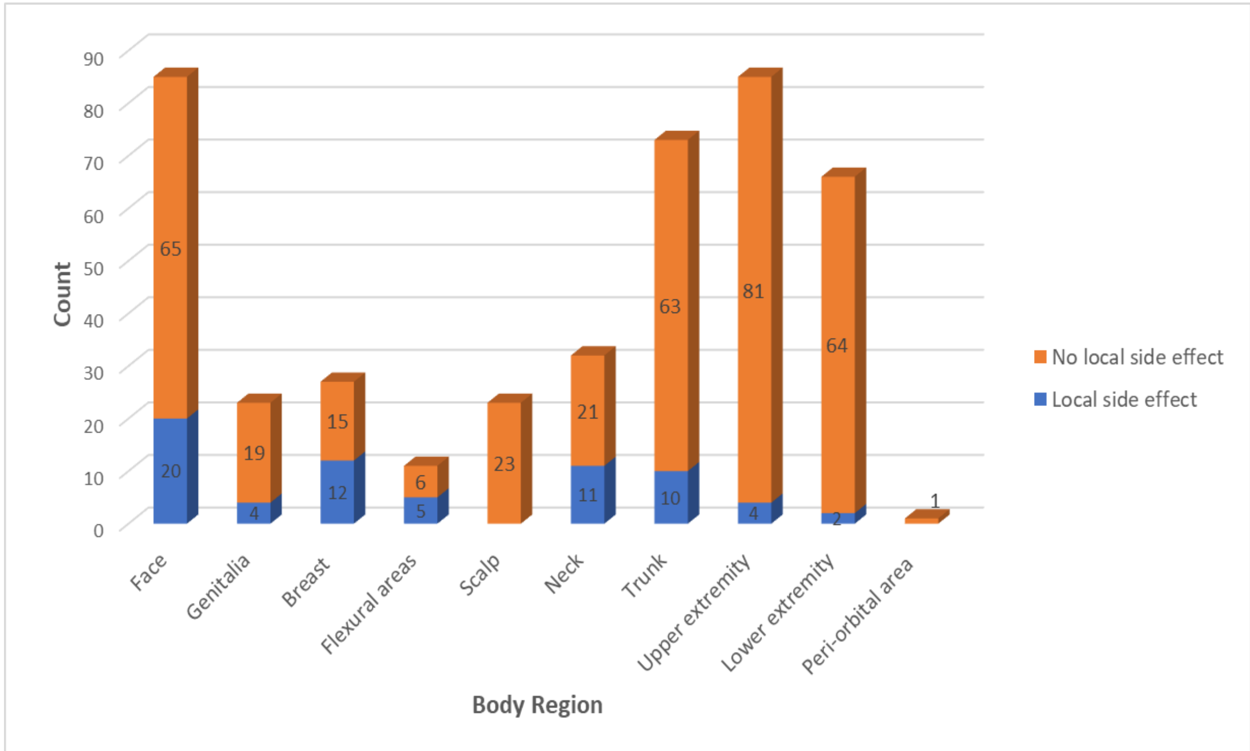


Figure 7: Comparison of treated sites with and without local side-effects among vitiligo patients seen at ALERT hospital, Addis Ababa Ethiopia, Aug 2021.



	Offending agent					Total
	Mometasone Furoate Cream	Mometasone Furoate Ointment	Betamethasone Dipropionate Cream	Betamethasone Dipropionate Ointment	Clobetasol Propionate Ointment	
	Count	Count	Count	Count	Count	**Count**
Dermal atrophy	3	0	0	0	0	**3**
Epidermal atrophy	12	0	0	2	7	**21**
ICD	1	0	0	0	0	**1**
Impetigo contagiosa	4	0	0	0	0	**4**
Steroid Acne	2	0	0	0	0	**2**
Telangiectasia	15	4	2	2	7	**30**
Tinea incognito	2	0	0	0	0	**2**
Total	**39**	**4**	**2**	**4**	**14**	**63**

Table vii: Frequency of local side-effects caused by various topical corticosteroids among vitiligo patients treated at ALERT hospital, Addis Ababa Ethiopia, Aug 2021.

6. Discussion

The representation of women and children in this study was in agreement with a similar large study on prevalence of topical corticosteroid adverse effects [38]. The maximum treatment duration in this study was higher in comparison to existing similar studies [45, 49,50]. Whereas close to 70% of the participants in our study were treated for more than 6 months, the maximum treatment duration at the time of evaluation for side effects in the abovementioned studies was no more than 6 months.

The overall incidence of local side effects, 45 (34.6%), was on the high end of magnitude of local side effects in comparison to similar available studies [38, 46, 49, 50]. As a reference, according to a study done on prevalence of topical corticosteroid side effects in vitiligo patients, a study of 75 vitiligo patients with diverse racial contribution, 7 (9.3%) of the study participants developed local side effects [50]. In the milieu of individual local side effects, cutaneous atrophy has now been recognized as the most common local side effect of topical corticosteroids [14, 32, 58]. Telangiectasia was also mentioned to commonly precede cutaneous atrophy in one study [45]. In harmony with these studies, Telangiectasia 30(23.1%) and cutaneous atrophy 24 (18.5%) ranked first and second among the list of local side effects in our study. As per the clinical diagnosis in our study, epidermal atrophy had a higher frequency 21 (16.2%) from the total of skin atrophies reported, and as it has been pointed out in one study, it appears a better parameter to assess cutaneous atrophy [57]. In an early report where there was frequent use of Isopropyl alcohol as a vehicle, there was high report of local irritation. In contrast, all the treatments in our study were either in cream or ointment base and only one participant of our study developed local irritation. While topical corticosteroid allergy was reported in 0.5-5% of study populations in various studies, there was no report of Allergic contact dermatitis in our study [32, 59, 60, 61,62, 63, 64,65]. The incidence of Acneiform eruptions was also grossly in line with similar other studies [32, 49, 66]. In our study 2 patients (1.5%) had steroid acne.

There are diverse recommendations on the choice of topical corticosteroid potency so as to minimize side effects [38, 40, 41, 42]. However, we were unable to determine association of local side effects with topical corticosteroid potency in this study since most of the exposure sites for different groups of corticosteroids used were discordant owing to the flaw of the study design.

With respect to systemic side-effects, none of the study subjects had confirmed steroid induced systemic side effects. This may be explained by the fact that the prescription trend in our study portrayed a relatively small amount of TCS was dispensed per month in contrast to studies reporting systemic side effects as a result of TCS application [79, 80, 82]. In our study, a maximum of 40 grams of clobetasol propionate 0.05% per month, even less for less potent ones, was used while studies reporting systemic side effects used at least 50 grams of clobetasol propionate 0.05% per week or comparable amount of another agent.

7. Conclusion

High incidence of local side effects was implicated in our study. The pattern of side effects is however similar to available studies with few exceptions. Neck is witnessed to be one of the side effect prone areas. Systemic side effects were negligible in our study.

8. Limitations and Recommendations

Owing to the study design, we encountered difficulty comparing association of factors with local adverse effects. These factors include Potencies of topical corticosteroids, and Patterns of topical corticosteroid application. Baseline record of blood sugar measurements were not available in patient records; and we were unable to ascertain causal link between TCS and hyperglycemia recorded during the study.

With the available results and limitations encountered, we recommend in-depth assessment of factors affecting the magnitude of TCS induced local side-effects aiming to help minimize the currently observed figure in our study. We also recommend cohort studies comparing magnitude of local side effects resulting from various TCS potencies and vehicles in vitiligo patients. It is also worth implying that duration required to achieve treatment target with TCS be analyzed in consortium with timing of incidence of local side effects in various body regions of vitiligo patients. From current standpoint, we also feel that there is a need for large scale studies comparing the response and adverse effects of other topical treatment modalities with TCS in various body sites. As a final remark, we would like to recommend development of local TCS treatment protocol for vitiligo patients and periodic assessment of the protocol so as to improve the patient care.

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