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Low-dose aspirin should be initiated for sickle cell patients

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ABSTRACT

Background: We tried to understand whether or not there is an association between platelet (PLT) count of peripheric blood and severity of sickle cell diseases (SCDs).

Methods: SCDs patients with red blood cell (RBC) transfusions of less than 50 units in their lives were put into the first and 50 units or higher were put into the second groups.

Results: The study included 224 patients (70.8%) in the first and 92 patients (29.1%) in the second groups ($p < 0.001$). Mean ages were similar in both groups (28.9 and 30.0 years, respectively, $p > 0.05$). Male ratio was significantly higher in the second group (45.5% versus 64.1%, $p < 0.001$). Although smoking was also higher in the second group (12.0% versus 17.3%, $p > 0.05$), the difference was nonsignificant probably due to the small sample size of the second group. Mean units of transfused RBCs were 12.9 and 99.0 in the groups ($p < 0.000$). Although white blood cell and PLT counts of peripheric blood were higher in the second group, the difference was only significant for the PLT counts ($p = 0.005$), probably due to the same reason above. Number of painful crises per year, digital clubbing, chronic obstructive pulmonary disease, leg ulcers, stroke, chronic renal disease, and coronary heart disease were higher in the second group, significantly ($p < 0.05$ for all).

Conclusion: SCDs are chronic inflammatory processes on endothelium mainly at the capillary level, and there was a highly significant association between PLT count and severity of the SCDs. So low-dose aspirin will probably be beneficial for patients with SCDs.

Key words: Sickle cell diseases, low-dose aspirin, chronic endothelial damage, atherosclerosis

Introduction

Atherosclerosis may be the major cause of aging by inducing tissue hypoxia all over the body. For example, cardiac cirrhosis develops due to the prolonged hepatic hypoxia in patients with pulmonary and/or cardiac diseases. Probably whole afferent vasculature including capillaries are involved in the process. Some of the currently known accelerator factors of the obliterative process are physical inactivity, overweight, and smoking for the development of irreversible consequences including obesity, hypertension, diabetes mellitus (DM), peripheral artery disease (PAD), chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), coronary heart disease (CHD), cirrhosis, mesenteric ischemia, osteoporosis, and stroke, all of which terminate with early aging and death. They were researched under the title of metabolic syndrome in the literature, extensively (1-3). Similarly, sickle cell diseases (SCDs) are chronic inflammatory processes on endothelium mainly at the capillary level. Hemoglobin S (HbS) causes loss of elastic and biconcave disc shaped structures of red blood cells (RBCs). Probably, loss of elasticity instead of shapes of RBCs is the major problem, since sickling is very rare in the peripheral blood samples of the SCDs patients with associated thalassemia minors, and human survival is not so affected in hereditary elliptocytosis or spherocytosis. Loss of elasticity is probably present in whole lifespan, but it is exaggerated with increased metabolic rate of the body. The hardened cells induced prolonged endothelial inflammation, edema, remodeling, and fibrosis mainly at the capillary level terminate with disseminated tissue infarcts all over the body (4,5). On the other hand, obvious vascular occlusions may not develop in greater vasculature due to the transport instead of distribution function of them. We tried to understand whether or not there is an association between platelet (PLT) count of peripheral blood and severity of SCDs in the present study.

Material and Methods

The study was performed in Medical Faculty of the Mustafa Kemal University between March 2007 and January 2014. All patients with the SCDs were enrolled into the study. SCDs are diagnosed by the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Their medical histories including numbers of painful crises per year, mean units of transfused RBC in their lives, smoking habit, regular alcohol consumption, leg ulcers, and stroke were learnt. Cases with a history of one pack-year were accepted as smokers, and one drink-year were accepted as drinkers. A check up procedure including serum iron, iron binding capacity, ferritin, creatinine, liver function tests, markers of hepatitis viruses A, B, and C and human immunodeficiency virus, a posterior-anterior chest x-ray film, an electrocardiogram, a Doppler echocardiogram, an abdominal ultrasonography, a computed tomography of brain, and a magnetic resonance imaging (MRI) of hips was performed. Other bones for avascular necrosis were scanned according to the patients' complaints. So avascular necrosis of bones was diagnosed by means of MRI (6). Cases with acute painful crises or any other inflammatory event were treated at first, and then the laboratory tests and clinical measurements were performed on the silent phase.

Stroke is diagnosed by the computed tomography of brain. The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in 1 second/forced vital capacity of less than 70% (7). CRD is diagnosed with a permanent creatinine level of 1.3 mg/dL or higher in males and 1.2 mg/dL or higher in females during the silent period. Cirrhosis is diagnosed with liver function tests, ultrasonographic findings, and histologic procedure in case of indication. Digital clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter which is greater than 1.0 and with the presence of Schamroth's sign (8,9). Associated thalassemia minors are detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC. A stress electrocardiography is performed just for cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is taken just for the stress electrocardiography positive cases. So CHD was diagnosed either angiographically or with the Doppler echocardiographic findings as the movement disorders in the cardiac walls. Eventually, cases with RBC transfusions of less than 50 units in their lives were put into the first and 50 units or higher were put into the second groups, and the groups were compared in between. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 316 patients with the SCDs (155 females and 161 males). There were 224 patients (70.8%) in the first and 92 patients (29.1%) in the second groups ($p < 0.001$). The mean ages of the groups were similar (28.9 and 30.0 years, respectively, $p > 0.05$). Interestingly, the male ratio was significantly higher in the second group (45.5% versus 64.1%, $p < 0.001$). Although the prevalence of smoking was also higher in the second group (12.0% versus 17.3%), the difference was nonsignificant probably due to the small sample size of the second group ($p > 0.05$). There was a nonsignificant difference according to the prevalence of associated thalassemia minors ($p > 0.05$). The mean units of transfused RBCs were 12.9 and 99.0 in the first and second groups, respectively ($p < 0.000$) (Table 1). Although both the WBC and PLT counts of the peripheral blood were higher in the second group, the difference was only significant for the PLT counts ($p = 0.005$), probably due to the small sample size of the second group again. Mean hematocrit values were similar in the first and second groups (23.8% versus 23.7%, respectively, $p > 0.05$) (Table 2). Although the prevalences of avascular necrosis of bones, cirrhosis, and exitus were similar in both groups ($p > 0.05$ for all), the mean number of painful crises per year, digital clubbing, COPD, leg ulcers, stroke, CRD, and CHD were significantly higher in the second group ($p < 0.05$ for all) (Table 3). Mean ages of the mortal cases were 29.5 ± 9.8 (19-50) and 34.6 ± 6.7 (26-44) years in the first and second groups, respectively ($p > 0.05$). Mean ages of the mortal cases were 29.7 ± 9.6 (19-50) and 33.3 ± 8.5 (21-44) years in males and females, respectively ($p > 0.05$). On the other hand, there was no patient with regular alcohol consumption among the study cases. Although antiHCV was positive in two of the cirrhotics, HCV RNA was detected as negative by polymerase chain reaction in both.

Table 1: Sick cell patients with the units of red blood cell transfusions

Variables	Patients with RBC* transfusions of less than 50 units	p-value	Patients with RBC transfusions of 50 units or higher
Prevalence	<u>70.8% (224)</u>	<u><0.001</u>	<u>29.1% (92)</u>
Mean age (year)	28.9 ± 9.9 (5-59)	Ns†	30.0 ± 9.2 (9-56)
Male ratio	<u>45.5% (102)</u>	<u><0.001</u>	<u>64.1% (59)</u>
Smoking	12.0% (27)	Ns	17.3% (16)
Thalassemia minors	62.0% (139)	Ns	58.6% (54)
Mean RBC units	<u>12.9 ± 11.2 (0-48)</u>	<u><0.000</u>	<u>99.0 ± 56.5 (50-362)</u>

*Red blood cell †Nonsignificant (p>0.05)

Table 2: Sick cell patients with peripheric blood values

Variables	Patients with RBC* transfusions of less than 50 units	p-value	Patients with RBC transfusions of 50 units or higher
Mean WBC† count (μL)	14.931 ± 6.791 (2.460-39.200)	Ns‡	15.346 ± 5.640 (1.580-36.900)
Mean PLT§ count (μL)	<u>435.670 ± 236.693 (48.000-1.827.000)</u>	<u>0.005</u>	<u>498.310 ± 224.570 (53.000-1.370.000)</u>
Mean hematocrit value (%)	23.8 ± 4.8 (11-42)	Ns	23.7 ± 4.9 (13-39)

*Red blood cell †White blood cell ‡Nonsignificant (p>0.05) §Platelet

Table 3: Sick cell patients with associated disorders

Variables	Patients with RBC* transfusions of less than 50 units	p-value	Patients with RBC transfusions of 50 units or higher
Painful crises per year	<u>3.8 ± 6.3 (0-52)</u>	<u>0.000</u>	<u>8.4 ± 10.9 (0-52)</u>
Digital clubbing	<u>7.1% (16)</u>	<u><0.01</u>	<u>15.2% (14)</u>
COPD‡	<u>6.6% (15)</u>	<u><0.001</u>	<u>20.6% (19)</u>
Leg ulcers	<u>11.6% (26)</u>	<u><0.01</u>	<u>21.7% (20)</u>
Stroke	<u>5.8% (13)</u>	<u><0.05</u>	<u>11.9% (11)</u>
CRD§	<u>4.9% (11)</u>	<u><0.001</u>	<u>14.1% (13)</u>
Avascular necrosis of bones	20.5% (46)	Ns	17.3% (16)
Cirrhosis	4.4% (10)	Ns	4.3% (4)
CHD¶	<u>4.0% (9)</u>	<u><0.05</u>	<u>8.6% (8)</u>
Exitus	4.4% (10)	Ns	5.4% (5)

*Red blood cell †Nonsignificant (p>0.05) ‡Chronic obstructive pulmonary disease §Chronic renal disease ¶Coronary heart disease

Discussion

Chronic endothelial damage and atherosclerosis is the most common type of vasculitis, and the leading cause of morbidity and mortality in elderlies. Probably whole afferent vasculature including capillaries are involved in the body. Much higher BP of the afferent vasculature may be the major underlying cause, and efferent vessels are probably protected due to the much lower BP in them. Secondary to the prolonged endothelial damage and fibrosis, vascular walls become thickened, their lumens are narrowed, and they lose their elastic natures which can reduce the blood flow and increase BP further. Although early withdrawal of the causative factors including smoking, physical inactivity, excess weight, increased serum glucose and lipids, and elevated arterial BP may prevent terminal consequences, after development of COPD, cirrhosis, CRD, CHD, PAD, or stroke, the endothelial changes may not be reversed completely due to the fibrotic natures of them (10).

SCDs are life-threatening genetic disorders affecting nearly 100,000 individuals in the United States (11). As a difference from other causes of atherosclerosis, the SCDs probably keep vascular endothelium mainly at the capillary level (12), since the capillary system is the main distributor of the hardened RBCs to tissues. The hardened cells induced chronic endothelial damage, inflammation, edema, and fibrosis build up an advanced atherosclerosis in much younger ages. As a result, the lifespans of patients with the SCDs were 48 years in females and 42 years in males in the literature (13), whereas they were 33.3 and 29.7 years in the present study, respectively. The great differences may be secondary to delayed initiation of hydroxyurea therapy and inadequate RBC transfusions in emergencies in our country. On the other hand, longer lifespan of females with the SCDs and longer overall survival of females in the world can not be explained by the atherosclerotic effects of smoking alone, instead it may be explained by physical power requiring role of male sex in life (14,15), since physical power induced increased metabolic rate may terminate with an exaggerated sickling and atherosclerosis in human body.

Painful crises are nearly pathognomonic for the SCDs, and precipitated by infections, operations, depressions, and disseminated tissue damage. Although painful crises may not be life threatening directly (16), increased metabolic rate may terminate with multiorgan failures on the chronic inflammatory background of the SCDs (17). The severe pain may be secondary to the disseminated inflammation of the capillary endothelium, and the increased WBC and PLT counts and decreased hematocrit values may show presence of a chronic inflammatory process during whole their lives in such patients in the present study. Similar to us, increased WBC counts even in the absence of a painful crisis was an independent predictor of the disease severity (18), and it was associated with an increased risk of stroke by causing disseminated endothelial damage in brain (19). Due to the severity of pain, narcotic analgesics are usually required (20), but according to our experiences, simple and repeated RBC transfusions are highly effective during the severe crises both to relieve pain and to prevent sudden death that may develop secondary to the multiorgan failures on the chronic inflammatory background of the SCDs. Simplicity of preparation of RBC suspensions in a short period of time pro-

vides advantages to clinicians to use them even in small public hospitals without the requirement of specialized health workers and equipments as in RBC exchange. Additionally, preparation of one or two units of RBC suspension in each time provides time to clinicians to prepare more units by preventing sudden death of the patients. By this way, we can prevent some of deaths developed during transport of severe cases to tertiary health centers.

Hydroxyurea is an effective drug in chronic myeloproliferative disorders and SCDs (12). It interferes with cell division by blocking the formation of deoxyribonucleotides which are building blocks of DNA. Although the action way of hydroxyurea is thought to be the increase of gamma globin synthesis for fetal hemoglobin (HbF) (21,22), its main action may be suppression of hyperproliferative WBC and PLTs in the SCDs. As in autoimmune disorders, although presence of a continuous damage of hardened RBCs on endothelium, the severity of endothelial destruction is probably exaggerated by the patients' own WBCs and PLTs in the SCDs. Due to the same action way, hydroxyurea is also used in moderate and severe psoriasis to suppress hyperproliferative skin cells. Similarly, lower neutrophil counts were associated with lower crisis rates, and if a tissue infarction occurs, lower neutrophil counts may limit severity of pain and extent of tissue damage (23). On the other hand, final HbF levels in hydroxyurea users did not differ from their pretreatment levels, significantly (23). Similarly, the Multicenter Study of Hydroxyurea studied 299 severely involved adults with sickle cell anemia (HbSS), and compared the results of patients treated with hydroxyurea or placebo (24). The study especially searched effects of the drug on painful crises, acute chest syndrome, and requirement of RBC transfusions. The results were so overwhelming in the favour of hydroxyurea that the study was terminated after 22 months, and hydroxyurea was initiated to all patients. The patients treated with hydroxyurea had a 44% decrease of hospitalizations, and there was an independent association of lower neutrophil counts with the lower crisis rates (24). But this study was performed in severe HbSS cases alone, and the mean number of painful crises was decreased from 4.5 to 2.5 per year (24). Whereas in one of our studies, we studied 337 patients with all subtypes and severities of the SCDs, and the mean number of painful crises was decreased from 10.3 to 1.7 per year ($p < 0.000$) with an additional decreased severity of them (7.8 versus 2.2, degree of severity according to patient's self-explanation between 0 and 10, $p < 0.000$) (25). Additionally, adult SCDs patients using hydroxyurea appear to have a reduced mortality rate after a 9-year follow-up period (26). Although the underlying disease severity remains critical to determine prognosis, hydroxyurea may decrease severity of disease (26) and prolong survival (12). Furthermore, infants with lower hemoglobin levels were more likely to have higher incidences of acute chest syndrome, painful crises, and lower neuropsychological scores, and hydroxyurea reduced the incidences of them (27). Hydroxyurea in early years of life may also protect splenic function, improve growth, and prevent multiorgan dysfunctions. Transfusion programmes can also reduce the complications, but they carry some major risks including infections, development of allo-antibodies, and iron overload. Beside that, using an oral drug is a much more easier method than the regular blood transfusions for the patients, families, health workers, and insurance systems.

Aspirin is a nonsteroidal anti-inflammatory drug (NSAID), but differs from most others in the mechanism of action, since only low-doses of aspirin (75-100 mg/day) exert protective vascular effects (28). Although aspirin and other salicylates have similar effects (analgesic, antipyretic, and anti-inflammatory) with the other NSAIDs and inhibit the same enzyme cyclooxygenase (COX), aspirin does so in an irreversible manner and, unlike others, affects more the COX-1 than the COX-2 variants of the enzyme. It inhibits the production of thromboxane, which is significant for building of a patch over damaged blood vessels. Because the patch can become too large and block blood flow extensively, aspirin is also used at low-doses to prevent heart attacks, strokes, and other thromboembolic events. Additionally, low-doses of aspirin are usually given just after a heart attack to reduce the risk of progression or development of others. A review of data regarding aspirin use for secondary prevention of acute coronary syndromes demonstrated that low-doses of aspirin are consistently favored for short- and long-term use due to the lack of a dose-response relationship between increasing the dose and improved efficacy, and a higher incidence of gastrointestinal bleeding with increasing the dose (28,29). Women aged 65 years and older without any established cardiovascular disease, women of any age with established cardiovascular disease, and women of any age with an estimated 10-year risk of cardiovascular disease of 10% or higher are likely to experience a benefit from low-doses of aspirin (30). Low-doses of aspirin have been shown to be effective in prevention of one-fifth of thromboembolic events (non-fatal myocardial infarction, non-fatal stroke, or vascular death) in a meta-analysis of 16 secondary prevention trials in patients with previous myocardial infarction, stroke, or transient cerebral ischemia. This corresponds to an absolute reduction of about 10-20 per 1,000 patients in the yearly incidence of non-fatal events, and to a smaller, but still definite, reduction in vascular death (31). So the benefits of antiplatelet therapy substantially exceed the risk for secondary prevention (31), and use of low-doses of aspirin reflects good clinical practice and is encouraged in current guidelines (29).

As a conclusion, SCDs are chronic inflammatory processes on endothelium mainly at the capillary level and there was a highly significant association between PLT count and severity of the SCDs. So low-dose aspirin will probably be beneficial for patients with the SCDs.

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Adaptive Support Control Volume (ASV) and Early weaning of Ventilator in Intensive Care Unit

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ABSTRACT

Aim: To demonstrate the role of choosing the mode of ventilator in the patient's outcome and therefore early weaning from ventilators.

Method: After obtaining the acceptance of our ethical committee this study was done.

One hundred and twenty six patients were randomly taken in this study, in two groups; sixty four patients in group (A) using the synchronized intermittent mandatory volume (SIMV), and the other sixty two patients (B) group using an adaptive control volume (ASV) as another mode.

Result: We found that patients who were on adaptive support volume (ASV) group (B) had faster process of weaning and early extubation, and showed better arterial blood gases with easier management, which lead to early discharge from the ICU.

Conclusion: Training to use the new mechanical ventilators modes like adaptive support ventilation (ASV) is advisable, in some patients to wean and extubate early in comparison with the (SIMV) mode with best arterial blood gases and early discharging from the intensive care unit.

Key words: Mode, Weaning, Mechanical Ventilators. SIMV, ASV

Introduction

This study was conducted in a our busy intensive care unit (ICU) of King Hussein medical city in the period between November 2012 to September 2014, which includes forty nine beds; all our beds are occupied most of the time. Each one is fully equipped with standard international tools and monitors.

Most of the admitted patients are in need to be on ventilator for different etiologies, and they are ventilated, by using the traditional mode already included in standard ventilators, and watching the results of arterial blood gases for each one in provision of early starting of weaning and then extubation.

A new mode (which is called intelligent mode) included in new ventilators, was optionally started to be used in some patients. Results were analyzed to prove the benefit of this new mode, adaptive support ventilation (ASV) for early weaning from ventilator.

Most seriously ill lung patients were selected to be on ASV mode. We start weaning of the patient since intubated by using this mode, because the work of breathing (WOB) is minimal and the loop is closed; the time of ventilation was observed to be shorter than in the other previously used mode (SIMV). It has become a recommended way to early extubate and then discharge of the patients from the intensive care unit; it also a safe way of weaning (1) which decreases the hospitalization of patients with less use of resources, cost, morbidity and mortality (2-6).

Adaptive support ventilation (ASV) was introduced internationally in 1994 as an intelligent mode of ventilation which contains the measurement of respiratory mechanics and algorithm of closed loop pressure control for maintaining the proper minute volume.

Patients and Method

After the approval of the ethics committee of royal medical services was obtained, one hundred and twenty six patients were taken randomly in this study; they were taken in two groups A and B. as shown in Table 1 below.

An ordinary intubation was done for all critically ill patients by using Popofol or Ketamine in sleeping dose upon the patient's blood pressure and suxamethonium chloride in intubating dose. They were randomly assigned to be in one of our two studied groups (A or B) then connected to ventilator and putting the setting reasonable for each one upon his/her condition. Sedation was given to both groups which consisted of two to three milligrams of morphine sulphate as initial dose then two to three milligrams hourly infused, and increased or decreased as needed, for example giving either two or three milligrams when suctioning the endotracheal tube or inserting an intravenous line mainly in central veins. Vasopressors or anti-hypertensive drugs were prescribed as required for each case.

Group (A) the synchronized intermittent mandatory volume SIMV was selected. The setting installed is dependent on the patients' arterial blood gases, and body weight, seven to ten milliliter per each kilogram body weight tidal volume (TV), fractional inspired oxygen (FIO₂), positive end expiratory pressure (PEEP) and respiratory rate (RR) were chosen for each case respecting the saturation of oxygen (SPO₂), metabolic state and PCO₂. All these ventilator settings were fine tuned after obtaining the results of each arterial blood gas (ABGs) which were taken as routine, thirty minutes after first intubation or after attaching the patients to ventilator. If the patient admitted was already intubated, then ABGs were reviewed twice daily, early morning and afternoon, or upon any modification of the patient's condition all through the day.

All Group B patients were attached to ventilators by using ASV mode, which consists of three parameters only: ideal patient's body weight, percentage of theoretical value of minute ventilation desired based on nomogram of Radforf (7), and maximal inspiratory pressure tolerated after first four to five breaths taken from ventilator. The ventilator determines the compliance and resistance of the patient's airways and delivers a pressure controlled ventilation then optimizing inspiratory pressure and respiratory rate using the formula of Otis (8) which determines the respiratory rate with least work of breathing as a function of the expiratory time constant. As the patients start to take the breath by their own effort which is detected for each breath, the ventilator switches to inspiratory pressure support (IPS). This level of support is always adapted to patient's respiratory rate and tidal volume to achieve the preset minute ventilation using a comfortable breath pattern.

Harmful patterns like rapid shallow breathing, high dead space ventilation, breath holding and excessive large breath are all prevented by adjustments of inspiratory pressure and respiratory rate which means that the machine is continuously changing.

In both groups A and B the weaning protocol of our ICU was applied, and the end results of each group were analyzed by the attending intensivest to see in which of the selected ventilator modes (ASV versus SIMV) the early weaning and extubation occurred.

Results

The main interesting finding in this study was duration of weaning is shorter in group B in comparison with group A as showed above 5 to 14 hours, intubation time also was shorter, and then the stay length in ICU, and other parameters like respiratory rate which was found to be little bit lower in the ASV

Table 1: Differences between patients and their numbers in each group

No. of Patients in each group	Group (A) 64	Group(B) 62
Age	55 ±3 years	56±2
Sex (M/F)	33/31	32/30
Height(cm)	165±8	170±5
Weight	67±5	69±4
ICU stay length(days)	6±2	5±1

Table 2: The difference in all parameters in both groups

Group	SIMV (A)	ASV (B)
Duration in hours	14 h	5 h
Breath per minute RR	12/ min	14/min
Tidal volume TV(ml)	500ml/br.	525/br.
Paco ₂	44mmhg	40mmhg
Heart Rate (HR)	85/min.	83/min.
Mean arterial pressure (MAP)	88 mmhg	87 mmhg
Sedation Morphine total dose (mg)	6mg /h	2mg/h

mode, tidal volume was found somewhat higher in the ASV group in comparison with the SIMV, which reflects less PaCO₂ in the ASV.

Also vital signs were taken into consideration; the difference in both groups was watched, heart rate (HR) and mean arterial pressure (MAP) were shown to be minimally different in response to different concepts of ventilation during the weaning. Finally the total amount of sedative drugs, Morphine, was used in significant smaller doses in the ASV group (B), compared to the SIMV group (A); all these findings are shown in Table 2.

Discussion

This study shows that using different ventilator modes results in different variable outcomes in the weaning process, such as time of ventilation and then extubation which may differ from one mode to another. In this study we compared the most popular mode of ventilation used in the ICUs in our region, SIMV, with the new mode called (intelligent mode) ASV which was used in our ICU included in the new ventilator machine.

The great finding was observed in the group that used the ASV mode in whom the trachea was extubated earlier, with at least 6-24 hours than in the other group.

In ASV group (group B) this mode provides a ventilation in pressure support (pressure control ventilation) and automatic change from pressure control ventilation to inspiratory pressure support. This also leads to fast spontaneous ventilation; the patient-machine interaction was improved in comparison with the SIMV mode, and this leads to early weaning from the ventilator.

The ASV mode was possible in almost all types patients, including the moderate respiratory failure (PaO₂/FIO₂ ratio between 150-300mmhg) with appropriate inspiratory pressure.

The smooth weaning and extubation in ASV mode decreased the requirement of serial ABGs with its reducing the use of resources, nursing effort, and finally the total cost, and simplifying of the weaning trials.

The effect of different modes on ventilator and their safety and efficacy on patient outcomes is difficult to assess. (9,15)

Conclusion

Training to use the new mechanical ventilator modes like adaptive support ventilation (ASV) is advisable in some patients in order to be able to wean and extubate early in comparison with the (SIMV) mode with better arterial blood gases; therefore providing early discharge from the intensive care unit and less burden financially and human resources.

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Progressive Ataxia of Unknown Etiology

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Introduction

The hereditary ataxias are a heterogeneous group of diseases. Most attempts at classification have been based on pathologic findings and are not always useful for the clinicians. Many of these disorders are multisystem degeneration in which the underlying biochemical or other defect is usually unknown. The pathophysiology is correspondingly poorly understood. Hereditary ataxia can be divided into the hereditary congenital ataxia, the ataxia linked with metabolic disorder, and early onset ataxia of unknown etiology (1) (Table 1).

Table 1: Classification of Hereditary Ataxia

I.	Congenital Cerebellar Ataxia
II.	Ataxia associated with metabolic disorders
	a. Intermittent ataxia syndromes
	b. Progressive unremitting ataxia syndromes
	c. Ataxia disorders associated with defective DNA repairs
III.	Progressive ataxia disorders of unknown etiology.
	a. Early - onset cerebellar ataxia (onset usually before age 20)
	b. Late - onset cerebellar ataxia (onset usually after age 20)

Classification

The degenerative cerebellar and spinocerebellar disorders are a complex group of diseases, most of which are genetically determined. Tremendous confusion exists in classifying degenerative disorders causing ataxia, and there is no universally accepted system. These disorders can be divided into two main groups, depending on whether onset of symptoms is before or after the age of 20 years. Most of the early onset are autosomal recessive, and the later onset ones autosomal dominant (2). Most of these disorders are multisystem degenerations in which the underlying biochemical or other defect is usually unknown; the pathophysiology is correspondingly poorly understood. The differential diagnosis of ataxia is important since some of them are treatable if detected early. The discussion will concentrate on progressive ataxia of unknown etiology.

Progressive Ataxia Disorders of Unknown Etiology

These can be divided into two main groups, depending on whether onset of symptoms is before or after the age of 20 years. Most of the early onset disorders are autosomal recessive, and the later onset ones autosomal dominant (2).

A. Early Onset Cerebellar Ataxia

Friedreich's ataxia (FA)

Friedreich's ataxia is the most common of the early onset ataxia. It is one of the best defined and most common forms of hereditary ataxias of unknown etiology(1,2). In some large case series it comprises about 50% of the hereditary ataxia (2,3). It is transmitted in an autosomal recessive manner, with occasional sporadic cases, and usually appearing in childhood or in adolescence but rarely in old age (4). The disease usually progresses slowly without remission, affecting both the central and peripheral nervous system (4,5). The most frequent first symptom is ataxia of gait, although occasionally scoliosis or cardiac symptoms precede definite neurologic symptoms.

The epidemiology of Friedreich's ataxia is perplexing. The clinical features and diagnostic criteria were defined by the Quebec Cooperative Study of Friedreich's Ataxia (QCSFA) (6) and by Harding (1,2) (Table 2). Both authors regarded recessive inheritance, progressive ataxia of limbs and gait and lower limb areflexia as obligatory criteria. The onset, according to the QCSFA and Harding (2, 6), should never occur after the age of 20 years, and always before 25, according to Harding (2). A recent case was reported in the literature where symptoms started at a later stage (7). Both consider extensor plantar response, pes cavus, scoliosis and cardiomyopathy frequent, but not essential signs. Dysarthria, decreased lower limb deep sensation and weakness, obligatory signs for the QCSFA, are not considered essential for an early diagnosis by Harding (2). The diagnosis is made essentially on clinical grounds; CT scan of the brain may show mild cerebellar atrophy.

Table 2: FRIEDREICH'S ATAXIA : DIAGNOSTIC CRITERIA

Essential Criteria for Diagnosis: Present in More than 95% of Cases

Autosomal recessive inheritance
 Age at onset of symptoms before 25 y
 Progressive limb and gait ataxia
 Absent knee and ankle jerks
 Extensor plantar responses
 Motor nerve conduction velocity > 40m/s in upper limbs
 Small or undetectable sensory action potentials

Additional Criteria, Not Essential for Diagnosis: Present in More than 65% of Cases

Dysarthria*
 Pyramidal weakness of lower limbs
 Absent reflexes in upper limbs*
 Distal loss of joint position and vibration sense in lower limbs*
 Scoliosis
 Abnormal electrocardiogram

Other Features Present in 50% of cases or less

Nystagmus
 Optic atrophy
 Deafness
 Distal weakness and wasting
 Pes cavus
 Diabetes

The prevalence is known only for some populations (3, 8-11). The range is from 0.6 to 1.4/100,000 population. The incidence has been estimated to be approximately 1-2/100,000 (8,12).

In Southern Italy it ranges from 2.1 to 5.4 x 10⁻⁵ (13). Some studies revealed female preponderance (14,15); other series revealed that it occurred equally in males and females (10,16).

Friedreich's ataxia is characterized by degeneration of the spinocerebellar pathways, the dorsolateral columns, and the dentate nuclei (1). There are few changes in the cerebellar cortex itself (1). The cerebrospinal fluid is usually normal and the CT scan of the brain is either normal or shows mild cerebellar atrophy. The primary clinical signs include ataxia, most marked in the lower limbs and often accompanied by dysarthria, nystagmus is usually present in 70% and skeletal-muscle weakness (17). Optic atrophy and retinal pigmentation is usually present. Pes cavus and scoliosis almost always develop (18). Death is usually sudden and may be secondary to cardiac arrhythmias (17). Cardiac involvement is frequent occurring in some 50% to 90% of cases (19); most commonly concentric hypertrophic cardiomyopathy is found (19,20).

A dilated cardiomyopathy has been noted only rarely (21,22), and congestive heart failure is considered a late complication of the disease. There are suggestions that the increase in catecholamine release may contribute to the development of hypertrophic cardiomyopathy (23). Other authors contest this idea (24).

Multiple studies have shown that the small coronary arteries are abnormal in patients who have cardiac disease and Friedreich's ataxia (25,13). The functional significance of this has been challenged by Hewer (25). Biller, et al. (13) reported a prevalence of 1.5% of cerebral infarction in 131 patients. It occurred in half of the patients who developed atrial fibrillation or atrial flutter with underlying symptomatic cardiomyopathy (13). Speech disorder is common in FA (14).

Some dysarthric symptoms include: Sudden pitch changes (this was present in our patient), ataxic staccato, explosive elements, transient harshness, disturbances of respiratory and articulatory control, bradylalia, and dysdiadochokinesia (26,27).

Electrophysiological and pathological studies suggest that axon degeneration and secondary demyelination occur in peripheral sensory nerves (15).

Disease progression is a question open to discussion. It was suggested (28) that axon loss in the peripheral nerve may increase with age. In contrast, some believe (29) that axon loss does not progress during the disease and that further clinical worsening may result from progressive impairment of the cerebellar and corticospinal pathways (29).

Electrophysiological evaluation of FA patients usually includes determination of motor and sensory conduction velocities (MCV, SCV) and multimodal evoked potentials (30). The degeneration of peripheral sensory and somatosensory pathway

is usually measured by using nerve conduction studies and somatosensory evoked potential (SEPs) and brain-stem auditory evoked potentials (BAEPs) and the blink reflex (30).

Biochemical alterations observed in this disease include a reduced insulin receptor activity which leads to an insulin resistance state and a reduced glucose tolerance in about 40% of patients (31). Several lipid abnormalities have been noted as well, including a striking reduction in linoleic acid (21), low cholesterol levels with a total cholesterol reduction in serum and in the LDL and HDL fractions are described (21). At the cellular level, deficiencies in activity of the pyruvate dehydrogenase complex and alpha ketoglutarate dehydrogenase complex have been described (32).

The results of therapeutic trials in Friedreich's ataxia with a number of drugs, including choline chloride, lecithine, physostigmine, γ -vinyl aminobutyric acid, 5-hydroxytryptophan, benserazide and thyrotropin releasing hormone, have been inconsistent or unconfirmed in terms of producing functional neurologic improvement (2). It was found that the level of the dopamine metabolite, homovanillic acid (HVA) is low in the cerebrospinal fluid (CSF) of patients with either Friedreich's ataxia (FA) or olivopontocerebellar atrophies (31). Amantadine hydrochloride (AH) is known to stimulate dopamine release (34). The use of AH in FA and OPCA was recently tested (35). Both studies revealed an improvement in reaction time (RT) and movement time (MT). Surgery for foot deformity and scoliosis may be of benefit in well selected patients (36). It is essential to minimize perioperative bed rest. So there is no treatment known to influence the slowly deteriorating disease course. In order to minimize disability and prolong ambulation, strengthening and stretching exercises and functional retraining including aerobic endurance exercise are recommended (36).

Early - Onset Cerebellar ataxia with Retained Tendon Reflexes

The other early onset ataxias are listed in Table 3. They are usually rare, with the exception of early onset cerebellar ataxia with retained reflexes, which occurs at a frequency about one quarter of that of FA, is often confused with it, but is genetically distinct. The main clinical difference is that the tendon reflexes are normal or brisk in the disorder (23). It is important to distinguish between these two disorders, since the prognosis is better in the former, with patients losing the ability to walk on average 13 years later than in FA. In addition, severe skeletal deformity, heart disease, and diabetes do not occur (24).

Cerebellar Ataxia with Hypogonadism

The association of progressive ataxia with hypogonadotrophic hypogonadism is rare (2). Neurological symptoms usually develop in the third decade and hypogonadism is obvious at puberty. Neurological syndromes include dysarthria, nystagmus, progressive limb and gait ataxia, mental retardation, dementia deafness, choreoathetosis, retinopathy and sensory loss.

Cerebellar Ataxia with myoclonus

The association of cerebellar ataxia and myoclonus, is often referred to as the Ramsay Hunt syndrome. This is a very heter-

Table 3. EARLY - ONSET ATAXIC DISORDERS OF UNKNOWN ETIOLOGY**Friedreich's ataxia****Early-onset cerebellar ataxia with**

Retained tendon reflexes

Hypogonadism

Myoclonus (idiopathic Ramsay Hunt syndrome, progressive myoclonic ataxia)

Pigmentary retinopathy

optic atrophy + or - mental retardation

cataract and mental retardation (Marinesco-Sjogren syndrome)

Deafness

Extrapyramidal features

X-linked recessive spinocerebellar ataxia

TABLE 4: LATE-ONSET ATAXIC DISORDERS OF UNKNOWN ETIOLOGY**Autosomal dominant cerebellar ataxia (ADCA) with**

Ophthalmoplegia, dementia, optic atrophy, extrapyramidal features and amyotrophy may include Machado- Joseph disease) (ADCA type I)

ADCA with pigmentary retinopathy +/- Ophthalmoplegia and extrapyramidal features (ADCA type II)**Pure ADCA of later onset (after age 50) (ADCA type III)****Periodic ADCA****Other syndromes**

ogenous entity. Some of the identifiable causes include Baltic myoclonus, mitochondrial encephalomyopathy, and sialidosis (24). The rest of cases can be labelled as progressive myoclonic ataxia (24). Symptoms include the development of stimulus - sensitive myoclonus or generalized seizures at the end of the first decade of life. Ataxia and dysarthria develop a few years later with pyramidal signs in the limb. The myoclonic part of this syndrome may respond to clonazepam or valproate sodium with marked improvement in motor function.

B. Late Onset Cerebellar Ataxia

These disorders have proved the most difficult and controversial in terms of classification (Table 4). The pathological findings are heterogenous reflecting huge clinical variations in the dominant ataxia (2).

Autosomal Dominant Cerebellar Ataxia Type I (ADCA Type I).

The age of onset of symptoms in this syndrome ranges from 15 to 65 years but is most commonly in the third or fourth decade of life. Ataxia of gait is the most frequent presenting symptom; it usually involves the limbs and is invariably associated with dysarthria. Early onset usually predicts more progressive disability (37). Associated symptoms may include ophthalmoplegia, nystagmus, lid retraction and optic atrophy. Bulbar

symptoms are common during the later stages of disorder and predispose the patient to respiratory infection. Other common symptoms include dementia, extrapyramidal signs, wasting and fasciculation of the face and tongue.

Autosomal dominant cerebellar ataxia Type II (ADCA Type II).

This is clinically and genetically different from ADCA type I. It is characterized in all families having retinopathy. The age at onset is earlier than that of ADCA type I, most commonly occurring between 15 and 35 (2,38).

Autosomal Dominant Cerebellar Ataxia Type III

This is relatively pure cerebellar syndrome in which dementia, ocular or extrapyramidal features do not occur and onset of symptoms usually after the age of 50 years (39). Nystagmus and pyramidal signs in the limbs are quite common.

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It must be true: Accept your colour, stop hunting for skin whitening, black is beautiful

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ABSTRACT

Skin is the most voluminous structure of the body. It not only presupposes a physiological duty but embodies a 'social interface' among the individual and others. It occurs to be standing the most researchable constitution in the cosmetic business. Generally speaking there is an exponential interest both from the doctors as well as our patients seeking resolutions towards maintaining and attaining a perfect skin.

White skin is the dream of all Arab women with a particular attention in Libya and a fair skin is symbolized as a beauty sign. Libyan women tend in the summer time to shade themselves from the sun and deprive themselves from the benefit of sun and vitamin D for their big wedding day. Skin lightening cosmetics are widely used in most African countries including Libya where Libyan women are obsessed by it due to certain brands ruthlessly advertising fair and lovely skin, and it is a growing problem.

Use of cosmetic products to bleach or improve the skin texture and colour is a habit chiefly among dark-skinned Libyan women.

The concept of having white' skin complexion has been considered trendy and desirable.

The active ingredients in these cosmetic products are mainly hydroquinone, mercury and corticosteroids in higher concentrations. Several additives are used to enhance the bleaching achievement.

Since these products are used mostly for longer periods, on a large body surface area, and under hot moist circumstances, the per-cutaneous absorption is boosted. Thus the complications of these products are very detrimental and sometimes can be deadly (Table 2).

In many instance ladies who buy those products without any medical consultations or prescriptions will only present to professionals when drawbacks are incurred. Such patients have tried everything, both at home and also in other clinics - and on occasion spending what amounts to a fortune on products and treatments that have little or no effect at all.

Hyperpigmentation disorders and skin lightening treatments have a significant impact on the dermatologic, physiologic, psychological, economic, social, and cultural aspects of life. Raising patient's awareness is vital to avoid such irreversible complications.

To come to a close and sum up, it is mandatory to raise more knowledge and understanding on the occurrence and dangers of this misuse practice.

Key words: steroids, hydroquinone, depigmenting agents, skin bleaching, cosmetics.

Aim of this paper

The use of skin bleaching products for cosmetic purposes is a very popular practice in dark skinned women from Libya. The dermatologic complications associated with this practice have been comprehensively reported in the existing literature. The aims of this review paper is:

- 1- to shed light on the potential aspects of their complications in the long run and to
- 2- enlighten about the clinical practice and the proper advice to be given to patients who seek such medications
- 3- to increase the knowledge about the dermatological consequences of this practice in the Libyan community.

Introduction

Skin lightening (bleaching) cosmetics and toiletries are extensively applied in most African countries including by Libyan women in Libya (Figures 1-3). In fact, the use of cosmetic products to bleach or improve the skin texture and colour is an ordinary habit among dark-skinned Libyan women.

The usual active ingredients in these cosmetic products are mainly hydroquinone (strong oxidant), mercury and corticosteroids in higher concentrations (Figures 1 & 4 & 7 & 8). Some are unknown (Figure 11). Several additives are added to augment the bleaching effect. Hydroquinone is a melanocyte toxic product which combats melanogenesis (Table 1).

Since these products are used usually for long duration, with various concentrations, on a large body surface area, and under hot humid conditions, thus the per-cutaneous absorption is enhanced and subsequently complications occur (Dadzie & Petit 2009).

The history of practicing skin bleaching dates back over many years in diverse communities around the globe. In reality, in the early era around 1900s some American physicians proposed utilization of radiation as a skin bleaching agent (Dadzie & Petit 2009).

The complications of these products are very detrimental and sometimes can be deadly (Table 1). Some of the well known complications are allergic contact dermatitis, Steroid induced monomorphic acne (Mahé et al 2003, Nnoruka and Okoye O 2006, Poli 2007), exogenous ochronosis (Figure 1) (Gandhi et al 2012, Kombaté et al, 2012), skin thinning (papering) (figure 5&6&9&10), dyschromia (Mahé et al 2003) and hypo/hyperchromia (leucoderma) and prominent striae atrophy (Nnoruka and Okoye O 2006), bruise, echymosis, telangiectasias (figure 6), impaired wound healing, wound dehiscence, with inclination to infections, candidiasis and mycosis (Mahé et al 2003, Nnoruka and Okoye O 2006), tinea corporis, pyoderma, cellulitis, peri-oral dermatitis (Mahé et al 2003), erysipelas, facial hypertrichosis and macular hyperpigmentation of face/ macular hyperchromia (Nnoruka and Okoye O 2006), and some claimed scabies (Mahé et al 2003) and warts, mercurial nephropathy, peripheral neuropathy (Mahé and Perret 2005), cataracts, glaucoma, eye infections and blindness, steroid addiction syndrome, immunosuppression, lichenification, scarring, poikiloderma, brown nails, elastosis, roseacea, leucomelanoderma, vibices, burn, sun burn, eczema,

Diabetes mellitus (Nnoruka and Okoye O 2006), nephrotic syndrome (Tang et al 2013), and a broad spectrum of cutaneous and endocrinologic complications of corticosteroids, including suppression of hypothalamic-pituitary-adrenal axis resulting in systemic complications such as hypertension, hypercorticism (Pitché et al 2005, Dadzie & Petit 2009).

In that essence, there has been a report in the Medical Observer of Australia about a hypoadrenalism in a 24-year-old Sudanese woman who was referred for investigation of fertility problems and found to have low serum cortisol (Rouse 2015). Her GP noted she had a darker skin complexion; however her face was a lighter shade. On questioning her she revealed the use of two over-the-counter creams bought at a suburban store selling African commodities; those creams were fluocinonide 0.075% and hydrocortisone acetate 1% and were used for many years (Rouse 2015). The explanation of the suppression of the hypothalamic-pituitary-adrenal axis is simply the per cutaneous steroids systemic absorption. And in the existing literature, this has been confirmed (Perret et al 2001). Moreover cases of nephrotic syndrome have been reported in relation to the use of bleaching agents where the main culprit was mercury and such patients should be sent for assessing the blood and urine level of protein and mercury (Tang et al 2013).

The exogenous ochronosis is reported to occur with higher concentration of 8% and can be seen within 5 years of continuous application of hydroquinone products (Ly&Soko et al 2007). However Gandhi et al 2012 reported its occurrence with only 2% concentrations.

Moreover hydroquinone which is composed of benzene derivate is well known to be with carcinogenic properties and teratogenicity in vivo. Some few studies documented the associations between developments of cutaneous malignancy in relation to hydroquinone (type 2). This has been claimed to be postulated to be through its pro-carcinogenic effect or due to suppression of the natural photo-protection effect of melanin, however it is still a contradiction to prove and needs further studies to confirm (Dadzie & Petit 2009). Hydroquinone is well known with a photosensitizing effect in different concentrations, and has been hugely marketed for 50 years as a skin-lightening product and continues as the most customarily used whitening constituent in the assembly (Mahé & Perret 2005).

In the old days, hydroquinone and other cutaneous depigmenting products were broadly prescribed by dermatologists to combat pigmentary disorders, and in many instances it carries a variety of side-effects, including mercury poisoning. (Dadzie & Petit 2009).

Issues and apprehensions have been elevated regarding its impending dermatological and systematic side effects, which led to ban all hydroquinone products from the US market by the FDA on 29 August 2006 (Dadzie & Petit 2009). This has led the dermatology community to publish some papers in regard of this ban and address the FDA concerns and the risks around hydroquinone. However in the third world, including Libya, it is still considered, prescribed and used as a lightening agent.

Wood's lamp can be a helpful tool to assess the level of the hyperpigmentation.

Table 1: different bleaching agents and mode of action and side effects

Agent-active ingredients	Mode of actions	Side effects
Hydroquinone 1,4-dihydroxybenzene	strong oxidant melanocyte toxic. inhibitor of melanogenesis	Irritant and allergic contact dermatitis, with following post-inflammatory dyspigmentation, peripheral neuropathy, exogenous ochronosis Nail plate pigmentation
Corticosteroids clobetasol-containing agents	initial local vasoconstriction occurring when applied to the skin, giving an impression of an immediate reduction in pigmentation of the skin Inhibitory effect on epidermic melanogenesis.	> 3 weeks, especially on thin skin i.e facial and flexural, is associated; Striae, peri-oral dermatitis, rosacea-like eruption, acne vulgaris, telangiectasia, poor wound healing, easy bruising and hypertrichosis. Other side-effects; ophthalmic i.e (cataracts, glaucoma, eye infections & blindness) associated with the application of topical steroids to the face, especially the eyelids and aseptic osteonecrosis (personal observations). Cutaneous infections such as dermatophytosis, cellulitis, erysipelas, scabies and warts,
Mercury (salts) Currently skin lightening is also a cause of mercury toxicity (Hatters disease).	inhibition of melanin formation	Hatters disease= psychiatric (disturbance of recent memory, impairment of intellectual function, inattention and depression) and neurological (irritability, memory loss and neuropathies) problems renal impairment (minimal change or membranous glomerulonephritis), paradoxical increase in skin pigmentation, due to direct deposition of metallic mercury granules in the dermis
Kojic acid (KA) and glycolic acids (GA)	KA is tyrosinase inhibitor and an antioxidant. derived from various fungal-Aspergillus and Penicillium. GA is alpha-hydroxyl acids derived from sugar cane- At low concentrations; it has an epidermal discohesive effect, while at high concentrations it results in epidermolysis. Both lead to removal of the superficial epidermis thus a depigmenting effect when used for skin lightening. Additional possible depigmentation include rushing of keratinocytic turnover with a drop in their melanosome loading time.	Irritant contact dermatitis, with the risk of post-inflammatory hyperpigmentation (PIH).

Table 2: Briefing of Aesthetic complications

Trophic issues	Striae, skin atrophy and scarring
Pigmentary issues	Darkening, leucoderma, periorbital hyperpigmentation (spectacles), exogenous ochronosis, polikoderma, variegate appearance
Lichenoid issues	lichenfication
Vascular issues	Telangectasia and lilac redness of eyelids, bruise
Exoskeleton	Facial hirsutism and brown nails
Joints	dyschromia, including hyperpigmentation of the joints
Others	peritibial ichthyosis, purpura, Pigmented keratosis pilaris, erythrosis of the elbow

Figure 1: Ochronosis**Figure 2: Uneven complexion and requested for lightening products**

Figure 3: Post strong steroids cream



Figure 4: Hyperpigmentation from different treatment she used including strong steroids



Figure 5: Uneven colour with dark knuckle due to strong steroids application for 4 years



Figure 6: Thin skin and telangiectasia due to steroids

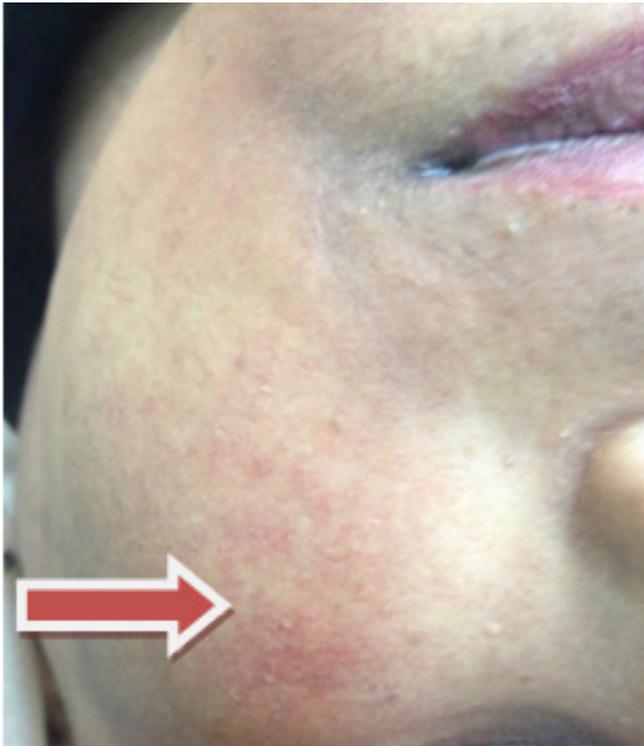


Figure 7: Black ladies favour this cream for whitening - clo-betasol



Figure 8: Patients are taken by the title WHITE CREAM



Figures 9 and 10: Post 4 years gamavate cream



Figure 9



Figure 10

Figure 11: A cream without ingredients listed



Libyan Traditional Ways to Lighten up their Skin

The cultural practice of skin bleaching to lighten normally dark skin (mostly Fitzpatrick skin photo-types IV to VI) is highly prevailing in Libya. The most common traditional modalities of the skin bleaching practice in Libya are: lemon, saffron and turmeric.

Some have gone far and do use different food herbs and spices such as 2 TSP saffron or turmeric powder with 1 TSP honey, 1 TSP rose water, 1 TSP cornstarch and then mixing them up with 1 TSP fresh lemon juice all of which is mixed and applied on face for one hour until it has dried up and then remove as a scrub to lighten up their skins. Another mix is pea's powder mixed with lemon juice in gauze and applied as a mask on the face. Another way is a cane milk mixed with fresh lemon juice. Also for the body, they mix henna powder with water and leave on the body with rose water. Also others would mix peas with honey and rose water and leave as a mask then peel off. Also mixing Tafal (green material paste) or Barouk (it's a white stones form to grind into a white powder, and to be mixed with rose water and applied on the face and it is called an instant bridal whitening complexion and well known in Tunisia) which is mixed with rose water and left on the face until dried up to give the whitish complexion of the face, also dried yeast granules mixed with water and left to ferment and then add rose water, as well as Felyia and cucumber water mix. Also in the old days they grind cinnamon in the mouth and then apply on the cheeks to give the red tint.

Libyan women did not stop at this level; however some sought the use of some creams by their peers, to attain the whitish complexion, as some go beyond on to using local strong steroids namely Gamavate and Decloban creams (clo-betasol, and fluocinonide) from OTC and I met some who think and strongly believe they are the beauty creams. The most common places where Libyan women tend to apply such agents on, is face, neck, dorsa of the hands, elbows, between thighs and knees in order. And the duration of the practice varied from 1 month to few years as most declared. Women tend to buy them without any medical prescription.

The high use of super potent steroids is reported to be alarming and striking (Mahé et al 2003). Libyan women find strong steroids application to be appealing as they are potent lighteners for their skin tone and complexion, and the most observed bleaching products among black women were the blind application of super-potent topical steroids class I which appeared to be the main culprits responsible for the observed skin complications in the clinical setting.

This fact is attributed to the easily accessibility to strong steroids which in many instances are free of charge at polyclinics in Libya and if not, they are available at low prices at private pharmacies.

From my observation, it seems the most concerning skin diseases motivating ladies visits to the dermatology clinic are complications of that misuse practice, i.e. pigmentation disorders or caustic effects of their own choices of applications (Mahé et al 2003).

In some cases the dermatological diagnoses were based mainly on clinical grounds; this reflects that the dermatological, where clinical accuracy or the diagnosis of common dermatoses appears good and perceived (Mahé et al 2003).

Also in many places where the products claimed to be a "natural" skin bleacher, was found to be containing higher concentration of hydroquinone or corticosteroids, or even both simultaneously (Mahé & Perret 2005). I recall in the old days, ladies were obsessed by Shirley cream and fair and lovely cream to have a lighter skin.

Discussion

Topical strong steroids have surfaced in the latest years as chief facial skin lighteners, due to their potent bleaching power, and perhaps also their anti-inflammatory activity that could limit the risks for dermatitis; nevertheless, they appeared here as the main cause to blame for the complications observed with ladies (Mahé et al 2003)

Nowadays in the last few years, the new trend is for promoting and advertising glutathione and others as antioxidants without any harmful agents, in the form of tablets and injections in different strengths, and they are marketed strongly without any proper monitoring, studies, inspection and legislations and patients are deceived by the description of it is magical results attained in a few months and in most cases patients are zealous and taking by such attractive commercials products and are willing to pay a fortune to achieve the ultimate wishes and yearning desire for a fair supple skin. This is because the white and pale skin is considered as a beauty sign and social privileges for better groom proposal and working chances. In Libya in many places, dark and black skin is still considered as a negative cultural perception and stigma. Moreover some far east people who have olive skin, and who are more working in the nurse field in Libya, such as Philipinos tends to use such products more as well to attain the white radiant skin. This phenomenon is sweeping Europe the other way around, where western women go to the tanning salon to acquire the dark glow.

There are many various wide varieties of different skin-lightening brands in the Libyan market which are being imported from overseas, and bearing the fact of the high demand to purchase such products for such skin-lightening products in this country make it a flourishing business.

The total sales volume of skin lighteners is high in Libya and there is no rough estimation due to the lack of registrations and records.

The most common excuses for such products encountered in the clinical settings are: to improve the skin before marriage, to get rid of blemishes on the face and other parts of the body, to attain a beautiful radiant skin, to even out the skin tone and some as a fashionable trend heard by their peers.

Also in the clinical setting I in many instances encountered a request for skin bleaching treatment by some patients to lighten up their complexion.

There is not any evidence based clinical trials yet on their safety, method of actions, nor the long run complications and consequences. Its temporary effects and need to be continuous as some medical colleagues declared from their patient's outcome, plus it is a means for a very lucrative business for many marketing companies.

Patient awareness of their risks is vital and thus it is critical for every practicing physician to be aware of these complications and raise awareness for those ladies who turn up in the clinic asking for them officially.

Skin lightening compounds, such as hydroquinone and topical corticosteroids, are often prescribed and used to treat hyper-pigmentation disorders; namely melasma, or lighten skin for cosmetic purposes. In spite of their recognized usefulness, huge dermatological and systematic complications have been linked with them. Authorized bodies have identified the drawbacks of skin lighteners and questioned the safety of this substance, and in fact it is nowadays forbidden in certain countries to sell such products. This has led to the possibility of exploring other alternatives to inhibit skin pigmentation such as retinoids, azelaic acid, arbutin, kojic acid, aleosin, mequinol, licorice extract, ascorbic acid, soy proteins, and N-acetyl glucosamine.

Dermatologists and users of such products should be attentive of the various components in bleaching compounds, and their potential impediments.

The management of the aesthetic complications of artificial skin whitening causes real problems, and the therapeutic means available are financially inaccessible to most patients living in developing countries. Trophic disorders, whether skin atrophy or striae atrophicae, are beyond any therapeutic resources.

The general state of welcoming bleaching and whitening in the Libyan community could arise from the inherent feeling of having a fair skin in the community which signifies beauty and attraction to the counterpart gender.

Conclusion

This article hints to a number of traditional bleaching methods that have a certain beauty and mystery for Libyan women's culture. This personal observation of high demand and use of super potent steroids is striking, as in fact most of such products are easily accessible through pharmacies without a prescription. The motivations of such patients to visit a doctor are the complications incurred of such practice.

The misuse of over-the-counter (OTC) cosmetic and bleaching agents must be banned and forbidden and there should be some legislation incurred on pharmacies onto not selling such products without a prescription, and emphasizing consulting a dermatologist beforehand. Usually patients in Libya attain such topical products by unregulated bodies including pharmacies.

Such patients usually presented particularly complex medical, social and emotional problems, where they are desperate for a solution and willing to pay anything.

Moreover in the dermatology communities, a discussion on the safety of bleaching agents including hydroquinone should offer a sole occasion to raise consciousness and understanding about skin bleaching risks and mandate careful consideration and selection.

Now with the introduction of the internet, some people's access to unscrupulous suppliers via the internet to avoid costs of professional consultation, and most of Libyan women have an access especially to the social media, like facebook where many marketers use it to promote their business solo and informally without any regulation and legislation; they just post and ask the client privately about the price and the delivery mode. Such marketing places an effective tempting post, where most women are taken in by and cannot resist, and especially single ones and they buy them without any prior consultation to attain that fairer skin for the big wedding day that she ever dreamt and wished for.

Self administration is dangerous and fraught, not least due to no safe information about the products name, exact formulations and safety, neither provided nor approved by the regulatory bodies.

The purchase of medications over the internet is utterly poorly unregulated and this poses an even greater problem that should be tackled and addressed. Moreover, Libyan women can easily obtain topical strong strength corticosteroids without any medical prescription.

Each case reported should be taken seriously and should be reviewed thoroughly and analyzed.

The breakdown by level of education and application was not explored among women but most of them state their peers applied it and advised about it.

Aesthetic complications associated with artificial bleaching and depigmentating products are common, but are rarely the reason for consulting a dermatologist. In the absence of suitable therapeutic agents, prevention, based on informing women of the damaging effects of artificial depigmentation, is the only way forward.

We need to educate ladies and men's with pigmentary problems to request early dermatological consultation for their dermatoses, rather than to self-medicate with over-the-counter or illegally obtained cutaneous depigmenting bleaches to avoid complications which would impact the patients at the sociological and psychological levels.

There is a need for appropriate public health prevention campaigns to raise awareness to combat such illegal trafficking of bleaching agents to implement.

There is a need for rigorous scientific studies, especially in the Arab world where such studies remain scarce, to critically evaluate the global burden and adverse health effects associated with skin bleaching.

In many instances, the aesthetic complications of artificial skin bleaching causes real problems and beyond any financial affordability, and any possible corrections and less than optimal, such striae atrophicae, skin atrophy, and exogenous ochronosis. Some claimed that Nd:Yag 1064-nm laser system is a bit effective in ochronosis.

There should be a form of protection, such as photoprotection, should be the rule. Any product to be used of those bleaching products must comply with the legislation in force.

The take home message and the general rule for such patients is to keep away from direct sun lights, as both UVA and UVB rays are responsible and both likewise accountable for deepening pigmentation. For instance, UVA rays penetrate deeper into the skin than UVB rays, and cause wrinkles and age spots. Thus in that instance “A” for ageing. While UVB rays are responsible for tanning. Thus “B” for burning. In order to combat pigmentation and prevent further damage and protect the skin, a sunscreen with a minimum protection of SPF30 is mandatory and essential. Also it is vital to increase awareness of the potential complication of cumulative body glucocorticoid excess syndromes and the consequences for secondary adrenal insufficiency are important to minimise problems.

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