Efficacy of oral doxycycline in treatment of red face syndrome subjects : A prospective noncontrolled case-series study

Usama Abdul-Jaleel[1] , Aqeel Agab Sarhan[2] and Safaa H. Ganduh[3]

الخلاصة

متلازمة الوجه الأحمر هي عباره احمرار و حرقان مزمن للوجه نتيجة وضع مستمر للستيروئيدات الموضعية لمنطقة الوجه و تمتاز بهيجان الحاله بعد اي محاوله لايقاف الستيروئيدات. وجد انها نتيجة فرط تجمع اوكسيد النتريك. مادة الدوكسيسايكلين تعارض الانزيم المكون لاوكسيد النتريك.

الهدف من البحث : لتقييم فعالية الدوكسيسايكلين و إيقاف استخدام الستيرويدات في علاج متلازمة الوجه الأحمر

اشتملت هذه الدراسة على 66 مريض مصاباً بمتلازمة الوجه الأحمر الناتج من الستروئيدات الموضعية، حيث تم تشخيصهم من قبل اختصاصي الجلديه العيادة الاستشارية في مستشفى الديوانية التعليمي للفترة من تموز 2011 إلى تشرين الثاني 2011 ، و تم إيقاف استخدام الستيروئيدات الموضعية وإعطائهم علاج الدوكسيسايكلين فمويا بجرعة 100 ملغم مرتين يوميا (كبسولة واحدة صباحا و مساءً) ولمدة أربعة أسابيع متبوعة ب100 ملغم مرة واحدة يوميا ولمدة أربعة أسابيع أخرى وتم تسجيل كل المعلومات الخاصة بكل مريض حيث تم متابعة الأعراض والعلامات على المرضى في كل زيارة.

اظهر تحليل البيانات تأثيراً ذا قيمة واضحة لعلاج الدوكسيسايكلين فمويا في تحسن العلامات والأعراض والتي تشمل الاحمرار، الحطاطة، الحرقة، والشد، بعد أربعة أسابيع من العلاج ومع ذلك أظهرت تحسنا ملحوظا في الوذمة بعد مرور ثمانية أسابيع من العلاج، بينما توسع الشعيرات الدمويه بقيت دون تحسن بعد استكمال العلاج.

في ضوء النتائج التي أفرزتها هذه الدراسة يمكننا استنتاج ما يلي:

قد يكون الدوكسيسايكلين فمويا فعال في علاج العلامات والأعراض المرتبطة بمتلازمة الوجه الأحمر الناتج من استخدام الستروئيدات الموضعية.

Abstract

Background: Red face syndrome is a chronic burning erythema of the face that occurs after prolonged application of topical corticosteroid and characterized by flare-ups after trial of corticosteroid withdrawal.It is mediated by nitric oxide overproduction. Doxycycline was found to inhibit inducible nitric oxide synathase .

Objective: to assess the efficacy of oral doxycyline and corticosteroid withdrawal in hastening the resolution of red face syndrome

Methods : In this prospective non-controlled case series study, 68 patients were identified as having red face syndrome by dermatologist in Al-Diwanyia Teaching Hospital , from July 2011 to September 2011 and they have been treated with oral doxycycline and corticosteroid withdrawal.

[1]: Department of Dermatology, Al-Qadissiya College of Medicine ,Al- Diwanyia , Iraq.

[2,3]: Department of Clinical Pharmacy, College of Pharmacy, University of Baghdad , Iraq.

Results : 66 patients completed the study while 2 patients stopped treatment because of severe gastric upset .Oral doxycycline was significantly able to decrease the total score of the clinical complaints after 4 weeks treatment (7.3 ± 0.46) compared to baseline (12 ± 0.32) (P<0.05) in patients with further significant decrease in the total scores at 8 weeks (3.9 ± 00.49) compared to baseline (12 ± 0.32) (P<0.05).
Conclusion : oral doxycycline seems to be effective in treatment of red face syndrome
Key words : doxycycline, nitric oxide, red face syndrome.

Introduction

Since 1980, when Marvin Rapaport initiated peculiar red skin syndromes,various syndromes have been named in the literature for what is purported to be distinct clinical problems. It is believed that they are all related corticosteroid addiction (Table 1)[1-2].

Table 1. Erythema syndromes

Red face syndrome
Status cosmeticus
Red scrotum syndrome
Vulvodynia
Perianal atrophoderma
Chronic recalcitrant eczema

Modified from Rapaport and Rapaport (2006)[2].

Red face syndrome was the most common steroid addiction. The condition started by application of corticosteroids for dry face ,mild acne or melasma, irritation from windy conditions, irritation from eye make-ups or nonspecific pruritus. The rash progressed and worsened as more steroids were used, with larger areas of the face erupting but often sparing the nose and the upper lip ('the headlight sign'). As the problem worsened, edema of the eyelids and vesiculation of the cheeks occurred, associated with a more severe erythema. [2,3].Histologic findings are non specific : the epidermis may exhibit variable spongiosis and atrophy, and the dermis shows mild telangiectases with sparse to mild superficial perivascular and interstitial lymphocytic infiltrate [2,3,4,5].

It has been believed that this syndrome is a form of corticosteroid addiction mediated by nitric oxide (NO) overproduction in response to long-term topical corticosteroid use. This chemical which is released by the endothelium of blood vessels as endothelium-derived relaxing factor, is a natural dilator. It is profoundly inhibited by glucocorticoids. When a vessel is constricted with the use of topical corticosteroids various metabolites, including nitric oxide, build up to counteract this constriction. Because of this build up, when the corticosteroid has worn off and the vessels are allowed to return to their normal size, they actually dilate to a size larger than their original diameter. With the daily use of topical corticosteroids of mlid or moderate strength, the vessels are constantly being constricted and a continual build up of natural dilators occurs. Instead of returning to their normal size after corticosteroid cessation, the vessels begin to remain dilated for longer amounts of time. This potentiates the erythema, burning and itching [6] .

Doxycycline and minocycline are members of the tetracyclines family of broad-spectrum antibiotics. Tetracyclines inhibit iNOS activity not via a direct inhibition at the enzyme level but also through an inhibition of NOS mRNA expression, which leads to the decrease in protein expression and NOS activity[7].

Hence, the hypothesis assumed that doxycyline in oral form could help in improving the signs and symptoms of red face syndrome due to topical corticosteriod. To the best of our knowledge no attempts have been made to evaluate the efficacy of doxycycline alone in red face syndrome in Iraq.

Aim of the study

To assess the efficacy of oral doxycycline 100mg twice a day and corticosteroid withdrawal in the treatment of red face syndrome

Patients and methods

Study design

Open labeled (prospective uncontrolled) therapeutic trial was done on sixty eight consecutive outpatients seeking treatment for red face syndrome were assessed by dermatologist in the outpatient clinic of the Department of Dermatology in Al-Diwanyia Teaching Hospital, Diwanyia, Iraq , from July 2011 to September 2011. This study was in agreement with the ethics of Al-Diwanyia Teaching Hospital.

Patients

The patients were diagnosed clinically by a dermatologist in Al-Diwanyia Teaching Hospital as a red face syndrome. Questions covered age, sex, duration of treatment with topical corticosteroid, and reason for using of topical corticosteroid as shown in patient information sheet (table 2). Patients

were asked to completely stop the use of topical corticosteroids before starting the treatment. All patients started on oral doxycycline 100 mg twice daily for 4 weeks then once daily until complete resolution of the associated signs and symptoms that assumed for extra 4 weeks[8].

Patients inclusion criteria

The inclusion criteria included confirmation of the diagnosis of red face syndrome by clinical history and manifestations.

Patients exclusion criteria

The exclusion criteria were patients younger than 18 years old, pregnancy or breastfeeding and severe gastric disorder.

Evaluations

`Evaluation of clinical symptoms and complaints pretreatment and after initiation of treatment with oral doxycycline was quantified using a calculated score: clinical score for steroid dermatitis developed by (Liu & Du 2008)[9]as shown in (table2)

The evaluation was performed by same dermatologist at week 0, 4 and 8 weeks after the initiation of the treatment with oral doxycycline.

Table 2

Parameters	Absent(0)	Mild(1)	Moderate(2)	Sever(3)
Erythema				
Papule				
Edema				
Dryness				
Telangiectasia				
Itching				
Burning				
Sensation of tightness				

For assessing patients, clinical symptoms and complaints were graded as absent, mild, moderate, or severe. These grades were scored as 0, 1, 2 and 3, respectively[9].

Data analysis

Statistical analysis was carried out using the SPSS statistical package version 16 (SPSS Inc. USA). The statistical significance ($P<0.05$) was determined by one way analysis of variance (ANOVA) followed by LSD test.

Results

Sixty-eight patients entered the current study. Two patients were later excluded as they stopped treatment because of severe gastric upset after initiation of the treatment with oral doxycycline. The demographic data and baseline characters of those patient were illustrated table 3.

Table(3) showed that mean age of the patients was 33.59± 6.30 (18-40) years. There were 54 (81.8%) females and 12 (18.2%) males. The duration of the corticosteroid use ranged from 2 month to 5 years, with a mean 23.72 months. The types of corticosteroids used were 40 (60.6%) clobetasole propionate 0.05%, 14 (21.2%) betamethasone valerate 0.1%, 8 (12.15%) mixtures containing steroid and 4 (6.1%) hydrocortisone acetate 2.5%.

The main reasons for using these topical corticosteroids included 45 (68.2%) whitening of skin.15 (22.7%) melasma, 4 (6.1%) mild facial acne and 2 (3%) mild facial dryness .

Table (4) and figure(1) showed that treatment with oral doxycycline was significantly able to decrease the total score of the clinical complaints and symptoms which are associated with red face syndrome after 4 weeks treatment (7.3± 0.46) compared to baseline (12 ± 0.32) (P<0.05) in patients enrolled in this study. Also oral doxycycline was able to decrease the total scores significantly after 8 weeks (3.9 ± 00.49) compared to baseline (12 ± 0.32) (P<0.05). Collectively, the percentage of change was increased with the progressing of treatment with doxycycline 38% and 69% in 4 weeks and 8 weeks, respectively.

Table 3 Demographics and baseline characteristics

Parameters	**Demographics**
Mean age, years (range)	33.59± 6.30 (18- 40)
Sex females	54 (81.8%)
Males	12 (18.2%).
Mean duration of steroid use (months)(range)	32.72 (2-60)
Topical corticosteroid used	
Clobetasole propionate 0.05%	40 (60.6%)
Betamethasone valerate 0.1%	14 (21.2%)
Mixture containing corticosteroid	8 (12.1%)
Hydrocortisone acetate 2.5%	4 (6.1%)
Reason for using of topical corticosteroid	
Skin whitening	45 (68.2%)
Melasma	15 (22.7%)
Mild facial acne	4 (6.1%)
Mild facial dryness	2 (3%)

Table 4 Effects of doxycycline treatment on the total scores in 4 weeks and 8 weeks in patients with red face syndrome and the percent of change of mean of the scores compared to baseline.

Period / Clinical signs and symptoms	Baseline (week 0)	Week 4	Percent of change (baseline vs week4)	Week 8	Percent of change (baseline vs week 8)
Total scores	12 ± 0.32	7.3 ± 0.46#	39.2%	3.9 ± 0.49*	67.5%

Values are presented as mean ± SEM; N=66;
Significantly different compared to baseline level (P<0.05).
* Significantly different compared to baseline level (P<0.05).

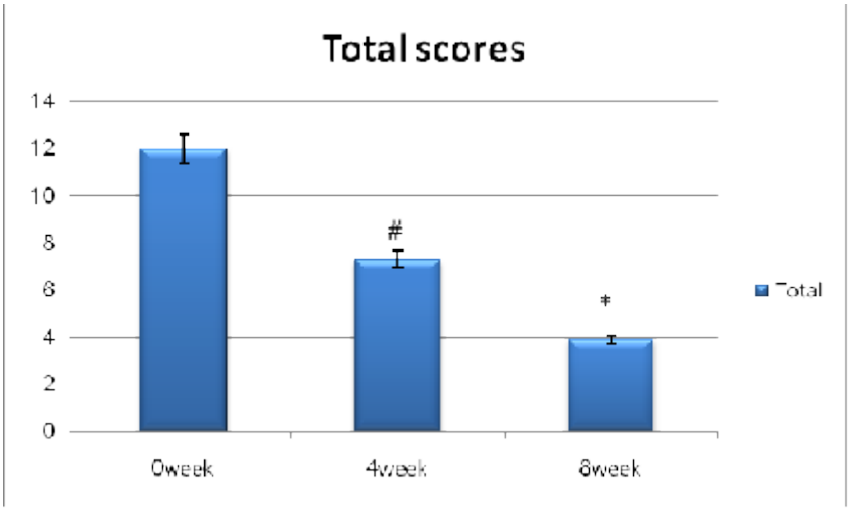


Figure 1 The effects of doxycycline (100 mg, twice daily, in 4 weeks and 8 weeks) on the total scores of the signs and symptoms of red face syndrome. Each bar represent mean rank ± standard error of mean (n= 66).

\# Significantly different from week 0 (p<0.05).
* Significantly different from week 0 (P<0.05).

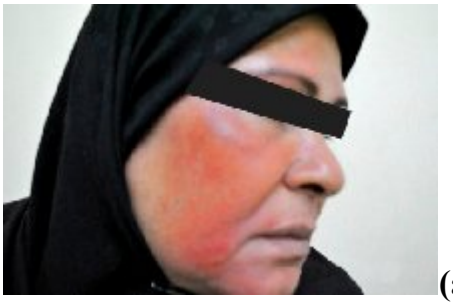
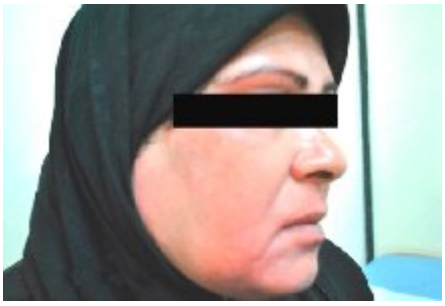

(a)

(b)

Figure 2 (a) Diffuse erythema before treatment. (b) The skin lesion resolved after the end of treatment

Discussion

It has been considered that red face syndrome is a form of "corticosteroid addiction" mediated by nitric oxide overproduction in response to long term topical corticosteroid use[2,4,10]. Treatment of the symptoms associated with this syndrome is demanding and involves discontinuation of topical corticosteroids which can result in a dramatic flare up that is frequently complicated by steroid withdrawal symptoms including burning, erythema and edema[2,3,4]. Topical steroids, antibacterials, antifungals, antipruritics (menthol, camphor, doxepin) and metronidazole and systemic antibiotics (erythromycin, penicillins), antifungals (griseofulvin, ketoconazole) and antihistamines have been reported to be ineffective [3,4].

Tetracyclines were found to inhibit inducible NO synthase ,mRNA expression, this unique property of tetracyclines makes them promosing candidate as safe and acceptable modulators of NO for various pathological conditions[7]. Moreover, Abbas *et al* 2008 have suggested that doxycycline may be effective in the treatment of red scrotum syndrome[8]..

Regarding the patients demographics data in this study, it was found that the mean age of the patients enrolled in this study was 33.59 ranging from 18-40 years old. This was probably because people, at this age, start to take care of their appearance.

In this study, most of the patients were female 81.8% while the male 18.2%. Also, the results showed that the mean duration of using topical corticosteroids was 32.72 months ranged from 2 months to 5 years. This seems to be acceptable where the addictive phase of topical corticosteroids usually took 4 months to develop[2]. However, this is not a rule where another study revealed that addiction sets after 4-6 weeks of frequent usage[4]. Unfortunately, the results found that most of the topical corticosteroids used were classed as potent or very potent.

Flare of the facial dermatitis (e.g. erythema, itching, burning and dryness) after trial of the patient to discontinue the use of corticosteroid was also very important reason to increase the amounts and potency of topical corticosteroid, so patients were unable to stop the topical corticosteroids. Rapaport *et al* (1999 a) strongly believed that this just perpetuated the problem and did not allow for a full recovery[4].

In this study, the main reason of using topical corticosteroids was skin whitening as the topical corticosteroids act as skin lightener owing to their potent bleaching effect[11,12]. Also this explains the predominance of females in this study which may satisfy their desire.

In the current study, the results showed that doxycycline was able to improve the signs and symptoms that are associated with the red face syndrome which results from corticosteroid addiction. During follow-up periods the majority of the patients noticed flare up of erythema and burning after the patients stopped corticosteroid application and started with doxycycline treatment. After which the patients reported significant improvement of the erythema, papule, dryness, burning sensation, itching and tightness for the skin ($P<0.05$) between pretreatment and after 4 weeks. All the patients had complete resolution of symptoms and signs mentioned above at 8 weeks. Edema was not improved in all patients after 4 weeks of treatment with doxycycline while after 8 weeks of treatment, edema deceased significantly. Telangiectasia was the most recalcitrant feature without any significant improvement after 4 and 8 weeks treatment. However, after 8 weeks of treatment with doxycycline total scores of all the signs and symptoms decreased significantly compared to pretreatment and week 4.

We believe that oral doxycycline hastened recovery in our patients. In fact, this quick recovery cannot be accounted for by abstinence from corticosteroids alone as this usually takes a much longer period of time–reaching up to 18 months [8].

Conclusions

From this study, one can conclude that doxycycline therapy in oral form may be considered as an effective treatment for patients with red face syndrome .

Drawbacks of this study were.(1) Lack of a control group ,(2) there was no study of serum level of nitric oxide in patient with red face syndrome before and after treatment to shed some light on the mechanism by which doxycycline exert its effects,(3) Limited follow-up of the patients.

Refrences

1. Rapaport MJ, Rapaport V. (1999 a). Eyelid dermatitis to red face syndrome to cure: clinical experience in 100 cases. *J Am Acad Dermatol, 41*, 435-442.

2.Rapaport MJ, Rapaport V. (2006). The red skin syndrome: corticosteroid addiction and withrrawal. *Expert Rev.Dermatol* .1 ,547-561.

3. Fisher BK (1997). The red scrotum syndrome. *Cutis*. 60:139–41.

4. Rapaport MJ, Lebwohl M (2003). Corticosteroid addiction and withdrawal in the atopic: The red burning skin syndrome.*Clin Dermatol*. 21:201–14.

5. Rapaport M (2007). Rebound vasodilation from long-term topical corticosteroid use. *Arch Dermatol*. 143:268–9.

6. Rapaport MJ, Rapaport V. (1999 b). Prolonged erythema after facial laser resurfacing or phenol peel secondary to corticosteroid addiction. *Dermatol Surg., 25*, 781-784.

7-Amin AR, Attur MG, Thakker GD, Patel RN, Pranav RV, Patel RN (1996). A novel mechanism of action of tetracyclines: Effects on nitric oxide synthases. *Proc Natl Acad Sci USA*, 93: 14014–14019.

8. Abbas O, Kibbi AG, Chedraoui A, Ghosn S. (2008). Red scrotum syndrome: Successful treatment with oral doxycycline. *Journal of Dermatological Treatment,* 1, 1-2.

9.Liu ZH, Du XH. (2008). Quality of life in patients with facial steroid dermatitis before and after treatment. *Journal European Academy of Dermatology and Venereology,* 22, 663-669.

10.Rapaport MJ, Rapaport VH. (2004). Serum nitric oxide levels in ‘‘red’’ patients: separating corticosteroid-addicted patients from those with chronic eczema. *Arch Dermatol*, 1013-1014.

11.Mahe A *et al* (2003). Skin diseases associated with the cosmetic use of bleaching products in women from Dakar,Senegal. *British J. of Dermatol.,* 148(3):493-500.

12.Godlee F. (1992). Skin lighteners cause permanent damage *Br. Med. J. 305*, 333.