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CAN LOW DOSE OF ISOTRETINOIN CAUSE DEPRESSION

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Abstract

Background: Depressive symptom may associate with daily recommended dose of Isotretinoin for nodulocystic acne. Does reducing the dose will reduce the incidence of depressive symptoms is still not clearly understood.

Study objective: To compare the types and frequency of depressive symptoms among patients with nodulocystic acne receiving three different low doses of isotretinoin (10mg daily, 20mg every other day, and 20mg daily).

Study design: Open randomized clinical trial.

Study setting: Dermatology clinic at Ibn Sina teaching hospital

Patients & methods: 169 patients with severe nodulocystic acne were randomly assigned to one of three isotretinoin regimen groups as follows: 10 mg daily (n=46), 20mg alternate day (n=58), and 20 mg daily (n=65). After a month of treatment, patient assessed for degree of improvement of acne and incidence of depressive symptoms

Results: The frequencies of depressive symptoms irrespective to group were as follows: crying in 36 (21.3%), anger in 35 (20.7%), sleep disturbance in 32 (18.9%), isolation in 29 (17.1%), and sadness in 20 (11.8%) of patients. The frequency of crying, anger and sadness were significantly rose with increase dose of isotretinoin from 10mg to 20mg daily (p-value equal to 0.02, 0.02, and 0.001 respectively).The summated depressive symptoms rose from (0.52 symptoms) in 10 mg daily to (1.19 symptoms) in 20 mg daily dose and the difference was statistically significant.

Conclusion: Depressive symptoms increased gradually with increase dose of isotretinoin and reducing the dose to least effective dose is mandatory.

Key Words: isotretinoin, dose regimen, depression, nodulocystic acne.

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INTRODUCTION

Isotretinoin is an efficacious and widely-used systemic therapy for severe recalcitrant nodulocystic acne lesions[1]. But the proverb "no rose without thorn" is applicable to it. Early after its release on the market, isotretinoin use was linked to wide ranges of adverse effects at the recommended daily dose (0.5-1 mg/ kg)[2].

One of these adverse effects was the psychiatric symptoms[3]. Since the 90s of last century many case reports, short case series studies, reports from the Adverse Drug Event Reporting Systems (ADERS) linked depression and suicidality to the use of isotretinoin have been accumulated in US Food and Drug Administration (FDA)[4]. But, later larger studies and meta-analysis reports revealed considerable controversy regarding a proposed causal relationship between isotretinoin and depression[5]. Now a day there is marked debate among researchers regarding presence [6] or absence of this association [7]. Even those who support the presence of this relation vary in explaining its relation to the dose. Some suggest dose-dependent relation, while other considered as idiosyncratic relation. These controversies prompt us to conduct this study aiming to elaborate incidence and types of depressive symptoms in acne patients using three different small doses of isotretinoin.

Study objective:

To compare the types and frequency of depressive symptoms among nodulocystic acne patients receiving three different low doses of isotretinoin (10mg daily, 20mg every other day, and 20mg daily).

Patients and methods

The study was conducted as open randomized clinical trial. All patients with recalcitrant, extensive and nodulocystic acne who attended to dermatology clinic at Ibn Sina teaching hospital during Jan. 1 - April 30, 2018 were asked to participate in the study. One hundred sixty nine patients were eligible and accept to participate in the current study. Baseline screening tests of liver, kidney and lipid profile was done to the all patients. Furthermore, pregnancy test was done to married female patients. The recruited patients were randomly assigned into one of three treatment regimen groups. The first group used Isotretinoin 10mg daily, the second group used Isotretinoin 20mg every other day, and

the last group used Isotretinoin 20 mg daily. After a month of treatment, patient assessed for outcome measures. The data collected include (severity of acne, degree of xerosis, chelititis, and presence or absence of depressive symptoms. Data were processed by the use of statistical package SPSS Ver 18 (SPSS Inc., Chicago, Ill). Different descriptive statistical methods were used to summarize and tabulate the data. A chi square test was used assess difference in frequency of depressive symptoms among three treatment groups. The difference in sum of depressive symptoms among three groups were compared using Kruskall Wallis test. A p-value <0.05 was considered statistically significant.

RESULTS

One hundred sixty nine patients with severe nodulocystic acne participate in the study. Their age range from 14- 27 years with mean (SD) of 19.5 (2.0) years. They are consisted of 42 (24.9%) males and 127 (75.1%) females. Each patient was allocated into one of the three schedules of the study. Table 1 shows the distribution of demographic characteristics of the participants in each group. Results reveal small but not significant differences among three groups regarding age, weight and gender (p-value 0.08, 0.09. 0.07 respectively).

***Table 1**. Comparison of demographic characteristics of patients with nodulocystic acne among the three isotretinoin doses and schedules groups*

Characteristic	Isotretinoin doses & schedules			P-value
	10 mg daily N= 46	20 mg alternate day N=58	20mg daily N=65	
Age, mean (SD)	21.73 (1.79)	19.06 (2.04)	20.35 (1.94)	0.08
Weight, mean (SD)	59.68 (11.52)	61.13 (16.39)	58.75 (11.54)	0.09
Gender, No. (%)				
Male	11 (13.05%)	20 (34.5%)	16 (24.6%)	0.07
Female	40 (87.0%)	38 (65.5%)	49 (75.4%)	

Table 2. Comparison of frequencies of depressive symptoms among different isotretinoin doses and schedules regimen for severe nodulocystic acne

Depressive symptoms	Isotretinoin doses & schedules			Total N=169	P-value
	10 mg daily N= 46	20 mg alternate day N=58	20mg daily N=65		
Crying	4 (8.7%)	14 (24.1%)	18 (27.7%)	36 (21.3%)	0.02
Isolation	4 (8.7%)	12 (20.7%)	13 (20.0%)	29 (17.1%)	0.1
Sleep disturbance	6 (13.0%)	12 (20.7%)	14 (21.5%)	32 (18.9%)	0.5
Anger	8 (17.4%)	8 (13.8%)	19 (29.2%)	35 (20.7%)	0.02
Sadness	2 (4.3%)	4 (6.9%)	14 (21.5)	20 (11.8%)	0.001

The frequencies of depressive symptoms reported by the patients are shown in Table 2. The result reveal that most frequent depressive symptom reported by the patient irrespective to dose they received was the unexplained bout of crying reported by 36 (21.3%) of patients, while the least frequent symptom was feeling of sadness reported by 20 (11.8%) of patients. In general the frequencies of depressive symptoms in descending manner were as follows: crying episode, recurrent bout of anger, sleep disturbance, feel isolated and lastly, feel sadness. Taking the dose of isotretinoin in consideration reveal that doubling the dose from 10mg daily to 20 mg daily yield: tripling the frequency of crying episode, doubling frequency of feeling isolated, one and half times raise in suffering from sleep disturbance and anger bout, and lastly, five times more frequency of feeling sad. The frequency of crying, anger and sadness were significantly rose with increase dose of isotretinoin (p-value equal to 0.02, 0.02, and 0.001 respectively).

Figure 1 depicts the average and 95% CI of summated depressive symptom in each study group. The result show gradual raises in mean of summated depressive symptom with increase dose of isotrtinoin. The average summated symptom was (0.522 symptoms) in 10 mg daily dose which rose to 0.862 (symptoms) in 20 mg alternate day schedule to reach its peak (1.196 symptoms) in 20 mg daily dose.

Analysis of variance shows a significant difference in average summated depressive among three group of the study (p-value = 0.05). A post hoc analysis to determine the non-homogenous group shows significant difference between 10 mg daily dose and 20 mg daily dose. The rest of differences between groups were statistically not significant.

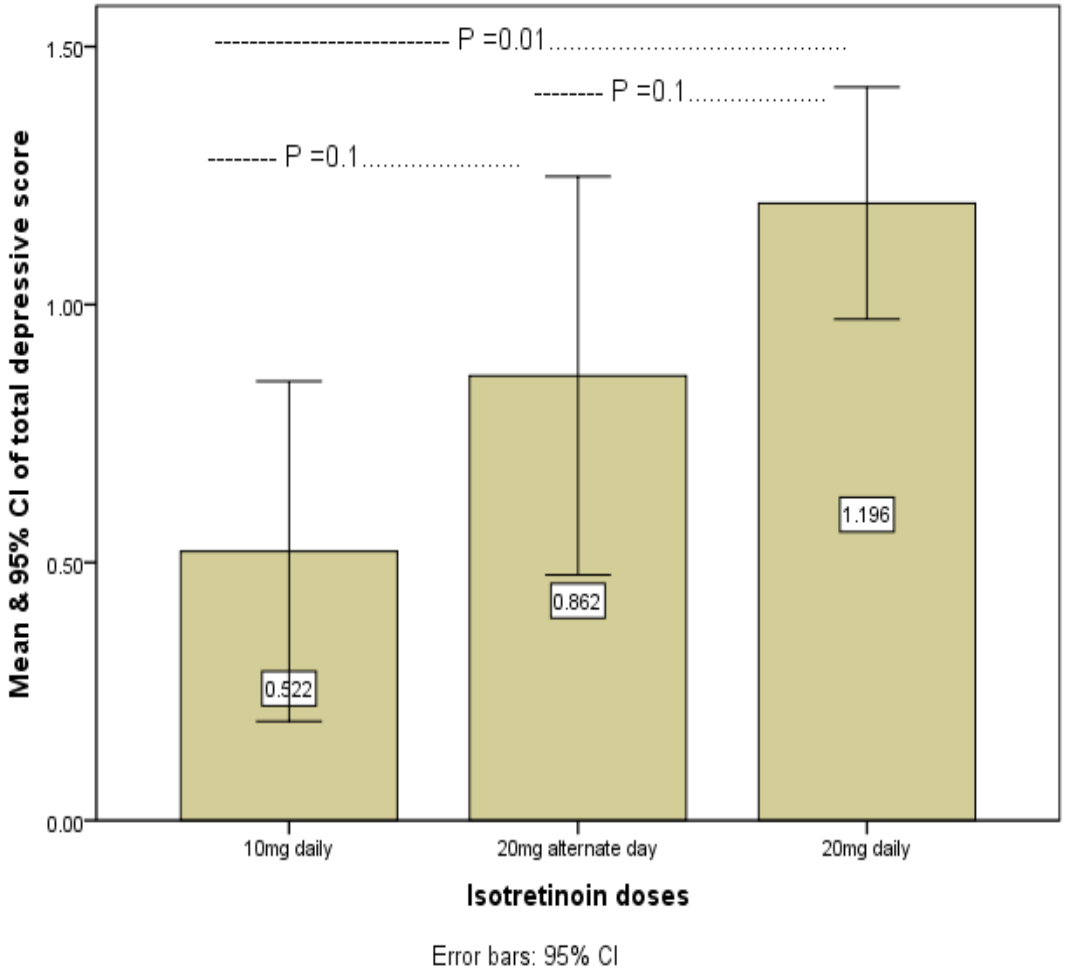

***Fig 1**. Comparison of mean and 95% CI of summated depressive symptoms among different isotretinoin doses and schedules regimen for severe nodulocyctic acne*

DISCUSSION

Isotretinoin is very effective treatment of acne and disorders of keratinization in the routine clinical dose[8]. The result of this open trail revealed that lowering the dose of isotretinoin below 0.5 mg/ kg/day like 10-20mg daily can preserve the effectiveness of isotretinoin. This finding is consistent with conclusion of recent randomized trial that reports minor non-significant difference in effectiveness of isotretinoin in conventional (0.5 mg/kg/day), low-dose (0.25mg/kg/day) and or intermittent (0.5mg/kg daily for one week every four weeks) oral dose in the treatment of acne[9].

In this series of 169 acne patients, 75% of them were adolescent females. Although this is not properly conducted epidemiological study, but the adolescent female preponderance in this series tells us two things: first, there is a general misconception that "acne only affects teenagers". Significant proportion of adults continues to be plagued by acne well beyond the teenage years particularly women[10]. Second, Community trend and media massage push more females to seek medical attention and help to get rid of acne[11].

This study provides new evidence for nature of interrelation between using small dose of isotretinoin and occurrence psychological adverse reaction. Among all groups about one quarter of the patients suffered from episodic attack of crying and anger. This result is in agreement with the conclusion of Al-Suhaibani recent study which conducted on 202 Saudi patients (age from 18-25 years) with severe acne treated by oral isotretinoin. Twenty seven percent of participant suffered crying episode during the treatment[12]. The current study also revealed that incidence of unexplainable crying episode rose three times with doubling the dose (10mg to 20mg daily). The result supports the causal link between isotretinoin administration and development of psychiatric adverse reactions. This finding is consistent with recent large systematic review of literatures conducted Bremener et[13] al in 2012. Reviewing literatures revealed the following sound and scientifically plausible findings that support this link: The fat-soluble nature of isotretinoin allow easy crossing blood-brain barrier[14]; Functional MRI shows increase activity of hippocampal and frontal orbital areas during isotretinoin

administration[15]; Retnoic acid increase activity of dopaminergic and serotonergic systems[16]; animal study show that chronic administration of isotretinoin increase depression-related behavior in mice[17]. Contrary to previous literatures[18,19], none of current series of patients has suicidal ideation or attempt. In fact, the authors of these papers specified that severe acne is an independent risk factor for attempted suicide. Furthermore, they reported that an additional risk may be present, but can't be established with certainty. Magin et al conduct extensive search in the MEDLINE, EMBASE and PsychINFO databases and find numerous case reports linking isotretinoin to depression and suicidal ideation, there is, as yet, no clear proof of an association. They suggest the possibility of a relatively rare idiosyncratic adverse effect remains[20]. This conclusion is probably consistent with the current finding regarding suicide attempt. Regarding depressive symptom, the results of current study revealed gradual dose dependent increases in incidence of depression with the increasing dose of isotretinoin from 10mg daily to 20mg. In conclusion, current series provide new support to the role of isotretinoin in the occurrence of the depressive symptoms in patients with acne. Which make close observation of acne patients for neuropsychiatric side effects become mandatory during isotretinoin therapy? Furthermore, prescribing it should be limited only to those with severe acne, resistant or unresponsive to several courses of antibiotics.

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