

ORIGINAL ARTICLE

Isotretinoin, Acne and Depression: A Prospective Controlled Study

Isotretinoína, Acne e Depressão: Um Estudo Prospectivo Controlado

Received/Recebido
2020/03/02Accepted/Aceite
2021/07/04Published/Publicado
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ABSTRACT – Introduction: Acne and isotretinoin, one of its treatment, have been linked to the occurrence of depression. Our aim was to study if isotretinoin is associated with depression in a sample of acne patients followed for 6 months comparing them with acne patients under other treatment modalities and control patients without acne.

Methods: One hundred individuals were included: 50 controls and 50 with acne (24 using and 26 not using isotretinoin). Patients and controls answered the Beck Depression Inventory (BDI) and the 12 Item-Short Form Health Survey for quality of life (SF-12). Acne patients repeated this evaluation in 90 and 180 days.

Results: No differences were found between controls and acne patients regarding BDI results but controls performed worse in the SF-12 mental domain ($p=0.004$). No differences were found within the acne group between those treated and not treated with isotretinoin in the comparison of the BDI and SF-12 (mental and physical domains) in days 0, 90 and 180 (all with $p>0.05$).

Conclusion: In this small sample isotretinoin treatment showed to be safe regarding the occurrence of depression.

KEYWORDS – Acne Vulgaris/drug therapy; Depression/chemically induced; Isotretinoin/adverse effects.

RESUMO – Introdução: Depressão tem sido atribuída à acne e a um dos seus tratamentos, a isotretinoína. O nosso objetivo foi estudar se o uso da isotretinoína está associado com a depressão numa amostra de pacientes com acne acompanhados por 6 meses, comparando-se os com pacientes com acne sem este tratamento e com indivíduos de um grupo controle, sem acne.

Métodos: Cem indivíduos foram incluídos: 50 controles e 50 com acne (24 usando e 26 não usando isotretinoína). Pacientes e controles responderam ao Inventário de Depressão de Beck (IDB) e ao SF-12 (12-Item Short-Form Health Survey ou Forma curta com 12 questões do questionário de Pesquisa de Saúde). Pacientes com acne repetiram estes questionários após 90 e 180 dias.

Resultados: Indivíduos controles e pacientes com acne não mostraram diferenças quando os valores do IDB foram comparados, mas os controles tiveram um pior desempenho no SF-12 - domínio mental ($p=0,004$). Também não foi possível verificar diferenças entre os grupos de acne tratados e não tratados com isotretinoína quanto ao IDB e ao SF-12 nos dias 0, 90 e 180 (todos com $p>0,05$).

Conclusão: Nesta pequena amostra o tratamento com isotretinoína se mostrou seguro no que concerne à ocorrência de depressão.

PALAVRAS-CHAVE – Acne Vulgar/tratamento farmacológico; Depressão/induzida quimicamente; Isotretinoína/efeitos adversos.

INTRODUCTION

Acne vulgaris is a chronic inflammatory disease that affects the pilosebaceous unit. It results from androgen-induced augmented sebum production (seborrhoea), follicular hyper keratinization, bacterial colonization (mainly by *Cutibacterium acnes*) and local inflammation.¹ It is more common in the face, neck, chest, and back, affects 80% of teenagers² and leads to facial scarring in up to 20% of them.¹ This may cause distortion of body self-image bringing negative effects on self-esteem.¹

Acne has been connected with isolation, troubles in interpersonal relationships, depression and even with suicidal behavior.³ A study in New Zealand on 9567 young individuals has shown that

39.9% of those with self-rated severe acne reported suicidal ideation and 12.9% tried suicide.⁴

One of the mainstay treatments of moderate to severe acne is oral isotretinoin,⁵ a synthetic oral retinoid. Among other side effects, this drug has been associated with psychiatric problems such as depression, psychotic behavior and suicidality. Similarly, experimental studies with animal models pointed out that isotretinoin may be associated with a depressive like behavior.⁶

However, clinical studies in humans have shown conflicting results. While Vallerand *et al*⁷ in their systematic review of 11 trials showed that this medication increases the frequency of psychiatric adverse events, Huang *et al*⁸ in a meta-analysis including 31 studies observed that isotretinoin could improve depressive signs.

Another meta-analysis by Li *et al*⁹ observed that the risk of depression was seen in retrospective studies but that it did not appear in prospective studies and their overall results suggested that isotretinoin improved depression in patients with acne.

Using a drug that may cause depression in a disease that, by itself, is associated with depression could further worsen the problem. So, it is very important to clarify the role of isotretinoin in this context.

Herein we studied a sample of patients with acne using isotretinoin to see the risk of depression and quality of life comparing them with acne patients without this treatment and control subjects.

METHODS

This is a prospective study approved by local Committee of Ethics in Research (approved by the Committee of Ethics in Research from Evangelic Mackenzie School of Medicine under protocol number 98305418.0.0000.0103 from September 18th, 2020). All participants signed an informed consent. We included 100 individuals: 50 with acne (24/50 or 48% using isotretinoin and 26/50 or 52% without this treatment) and 50 age and gender matched individuals as a comparison group. All included patients were from a single Dermatology Center and had moderate or severe acne diagnosed by a dermatologist.

All acne patients receiving isotretinoin had grade III or grade IV acne and isotretinoin was used at a daily dose 1-2 mg/kg/day according to guidelines from the local dermatology service¹² and did not suffer any influence from the authors. Other acne patients, with acne grade III or IV were treated according the local protocol with topical retinoids, topical antibiotics and systemic antibiotics as appropriate and in according with patients characteristics.¹² Controls were healthy individuals from family of patients with acne and other individuals without acne.

This is a convenience sample that included all acne patients that came for regular consultations from November 2018 to September 2019 and that agreed to participate in the study.

Epidemiological data (age, gender, auto-declared ethnic background, duration of acne, marital status, income and years of formal education) were obtained from the charts or upon direct questioning.

Patients and controls answered a questionnaire that included familial history of depression, previous history of psychiatric/psychological consultation and a question on if they believed that they need a psychiatric or psychological evaluation. They also answered the Beck Depression Inventory (10) and 12-Item-Short Form Health Survey for quality of life (SF-12) (11). The Beck Depression Inventory is a 21-item self-reporting questionnaire for evaluating the severity of depression in normal and psychiatric populations. For each question answers are rated between 0 and 3. According to the sum of points in the 21 questions, depression symptoms can be classified as minimal (0-9), light (10-16), moderated (17-29) and severe (30-63).¹⁰

The SF-12 is a questionnaire with 12 items that evaluates the physical and mental domains of quality of life that goes from 0 to 100; high values are associated with better quality of life.¹¹

All patients and controls answered the Beck depression inventory and SF-12 on day 0. Acne patients (using isotretinoin or not) also answered the same instruments on day 90 (3 months after isotretinoin treatment) and on day 180 (6 months after isotretinoin treatment).

Acne patients and controls were compared at day 0. Acne patients using isotretinoin or not were compared at days 0, 90 and 180. We also compared data on acne patients obtained at day 0 with those obtained at day 90 and day 180.

Frequency and contingency tables were used to collect data. Data distribution was judged by Shapiro Wilk's test. Comparison of nominal data was done using Fischer and chi-squared tests. To compare numeric data of controls and acne patients and acne patients with and without isotretinoin we used unpaired t tests and Mann Whitney. To compare results of Beck and SF-12 questionnaire in days 0, 90 and 180 of acne patients we used the ANOVA or the Friedman tests. To compare Beck and SF-12 questionnaire at days 0 and 180 paired t test and Wilcoxon tests were used. The adopted significance was 5%.

RESULTS

We studied 50 acne patients (35 females/15 males) with median age of 20 years (IQR = 17 to 27 years) suffering from the disease for a median of 4 years (IQR = 3.0 -9.2), of whom 24 (14 females/10 males) with median age of 19.0 (IQR = 17.0 to 21.0) were under treatment with isotretinoin and had a median disease duration of 4 years (IQR= 3.0 to 8.5) (Table 1). As controls we included 50 healthy individuals without acne (35 females and 15 males) with a median age of 23.0 years (IQR=21.0 to 33.0). More than 90% patients in both groups of acne patients, as well and the control group had more than 8 years education and previous history of psychiatric evaluation or self-perceived need for it was respectively 31.1% and 25% for acne patients vs 46% and 50% for controls (Table 1). The self-perceived need for psychiatric evaluation but not the previous history of psychiatric evaluation was higher in controls than acne patients with $p=0.01$ and 0.13 respectively.

The comparison of socio-demographic data in acne patients using and not using isotretinoin was similar and therefore should not interfere in the results of the instruments used to measure quality of life and depression.

2. Comparison of SF-12 and Beck inventory between acne patients at day 0 and controls:

Comparing of Beck DI between acne/non-acne patients at Day 0, acne patients had similar scores in this instrument as controls (median value of 7.0 with IQR = 3.7 to 14.0 vs median of 10.5 with IQR = 4.5 to 16.2). When the Beck inventory was studied in categories more controls showed mild and moderate depressive symptoms (30% and 20% respectively) than acne patients (12% and 14% respectively) although this difference was not statistically significant (Table 2). Table 2 also shows that the mental domain of SF-12 instrument for quality of life was worse in controls than in acne patients without treatment (mean values of 39.1 ± 9.7 in controls vs 45.2 ± 11.1 in acne patients). No differences could be shown in the SF-12 physical domain.

3. Comparison of Beck depression inventory and SF-12 results between acne patients treated and not treated with isotretinoin

Acne patients were followed for a total of 180 days. The treatment was well tolerated with all included patients used the medications during the whole observation period (no dropouts).

Table 1 - Description of studied sample and comparison of acne patients with and without treatment with isotretinoin.

	Controls N=50	Total sample N=50	Acne with isotretinoin n=24	Acne without isotretinoin n=26	p (*)
Median age (years) (IQR)	23 (21-33)	20 (17.0-27.0)	19 (17.2-21.0)	21 (17.0-29.5)	0.29
Gender (n)					
Females	34/50 (68%)	35/50 (70%)	14/24 (58.3%)	21/26 (80.7%)	0.08
Males	16/50 (32%)	15/50 (30%)	10/24 (41.6%)	5/26 (19.2%)	
Formal education (years) (n)					
<8	3/50 (6%)	2/45 (4.4%)	0/24	2/21 (9.5%)	0.24
8-12	30/50 (60%)	25/45 (55.5%)	15/24 (62.5%)	10/21 (47.6%)	
>12	17/50 (34%)	18/45 (40%)	9/24 (37.5%)	9/21 (42.8%)	
Marital status (n)					
single	41/50 (82%)	41/50 (82%)	22/24	19/26	0.20
married	9/50 (18%)	8/50 (16%)	2/24	6/26	
other	-	1/50 (2%)	0	1/26	
Income (n of minimal wages)					
>3	17/39 (43.5%)	28/44 (63.6%)	16/23 (69.5%)	12/21 (57.1%)	0.20
3 to 5	17/39 (43.5%)	9/44 (20.4%)	4/23 (17.3%)	5/21 (23.8%)	
6 to 10	4/39 (10.2%)	3/44 (6.8%)	0	3/21 (14.2%)	
<10	1/39 (2.5%)	4/44 (9.0%)	3/23 (13.0%)	1/21 (4.7%)	
Median disease duration (years) (IQR)	-	4 (3.0-9.2)	4 (3.0-8.5)	4.0 (2.0-10.7)	0.85
Previous psychiatric /psychological evaluation (n)					
Yes	23/50 (46%)	14/45 (31.1%)	5/24 (20.8%)	9/21 (42.8%)	0.11
No	27/50% (54%)	31/45 (68.8%)	19/24 (79.1%)	12/21 (57.1%)	
"I need psychiatric /psychological evaluation" (n)					
Yes	25/50 (50%)	11/44 (25%)	6/23 (26.0%)	5/21 (23.8%)	0.86
No	25/50 (50%)	33/44 (75%)	17/23 (73.9%)	16/21 (76.1%)	

N=number; IQR= interquartile range;
 (*)- p refers to comparison of patients using with patients not using isotretinoin.

Table 2 - Comparison of acne patients (total sample) with controls.

	Acne patients n=50	Controls n=50	p
Median Beck Depression inventory (IQR)	7.0 (3.7-14.0)	10.5(4.5-16.2)	0.20
Beck Depression Inventory - categorical			
Minimal symptoms (<10) – (n)	34/50 (68%)	23/50 (46%)	0.08
Mild symptoms (10 to 16) – (n)	6/50 (12%)	15/50 (30%)	
Moderate symptoms (17-29) – (n)	7/50 (14%)	10/50 (20%)	
Severe symptoms (>29) – (n)	3/50 (6%)	2/50 (4%)	
Formal education (years) (n)			
<8	0/24	2/21 (9.5%)	0.24
8-12	15/24 (62.5%)	10/21(47.6%)	
>12	9/24 (37.5%)	9/21 (42.8%)	
Mean SF-12 mental domain (SD)	45.2 ± 11.1	39.1 ± 9.7	0.004
Mean SF-12 physical domain (SD)	48.7 ± 7.7	45.9 ± 6.8	0.06

n=- number; QR= Interquartile range; SD= standard deviation, SF-12=12 Item-Short Form Health Survey for quality of life.

The comparison of the results in the Beck depression inventory and of SF-12 (mental and physical domains) between the two acne groups (with and without isotretinoin) at days 0, 90 e 180 is presented on Table 3. Using the Beck inventory there was no significant difference between

groups at baseline (median value of 5.0 with IQR = 3.0 to 14.0 in the treatment group vs median value of 7.0 with IQR = 4.0 to 15.7 in patients not treated with isotretinoin), at 3 months (median values of 4.0 with IQR=4.0 to 15.7 vs 8.0 with IQR 2.7 to 16.2) and at 6 months

Table 3 - Comparison of Beck Depression Inventory and 12 Item- Short Form Health Survey for quality of life between acne patients with and without isotretinoin.

	Acne with isotretinoin N = 24	Acne without isotretinoin N = 26	p
Median BDI day 0 (IQR)	5.0 (3.0-14.0)	7.0 (4.0-15.7)	0.49
Median BDI day 90 (IQR)	4.0 (4.0-15.7)	8.0 (2.7-16.2)	0.82
Median BDI day 180 (IQR)	6.5 (1.5 -13.7)	6.0 (2.7 - 19.0)	0.48
Mean SF-12 MD- day 0 (SD)	44.7 ± 11.9	45.7 ± 10.4	0.74
Mean SF-12 MD -day 90 (SD)	43.8 ± 10.7	43.5 ± 9.8	0.93
Mean SF-12 MD day 180 (SD)	43.8 ± 12.07	41.4 ± 10.3	0.44
Mean SF-12 PD day 0 (SD)	49.4 ± 7.6	48.0 ± 7.9	0.51
Mean SF-12 PD day 90 (SD)	48.6 ± 6.5	46.5 ± 7.3	0.31
Mean SF-12 PD day 180 (SD)	49.0 ± 6.5	48.5 ± 7.6	0.79

N= number; IQR= interquartile range, SD= standard deviation, BDI= Beck Depression Inventory; SF-12= 12 Item-Short Form Health Survey for quality of life; MD= mental domain; PD= physical domain.

of treatment (median value of 6.5 with IQR = 1.5 to 13.7 vs 6.0 with IQR= 2.7 to 19.0).

The comparison of Beck Depression Inventory at baseline, days 90 and 180 in those using isotretinoin showed $p=0.72$; the comparison of SF-12 mental domain showed $p=0.86$ and of SF-12 physical domain, $p=0.85$.

The same has happened with control: the comparison of Beck Depression Inventory in days 0, 90 e 180 in those not using isotretinoin showed $p=0.86$; the comparison of SF-12 mental domain showed $p=0.08$ and of SF-12 physical domain, $p=0.34$.

When the results of Beck inventory in day 0 were compared to results at day 180 in acne patients using isotretinoin, no differences were found ($p=0.79$), as observed in acne patients not using isotretinoin ($p=0.97$).

The comparison of SF-12 mental domain in day 0 and 180 in acne patients treated with isotretinoin showed $p=0.68$ and in those not treated $p=0.71$. Likewise, the comparison of SF-12 physical domain in day 0 and 180 in acne patients treated with isotretinoin showed $p=0.82$ and in the group not treated $p=0.10$.

These results demonstrated that no changes in the mental or physical quality of life neither in the depression scores of Beck inventory were noted with the duration of the isotretinoin treatment.

DISCUSSION

The present results point out that patients, even with moderate to severe acne, have mostly a minor effect on the depression with 16/50 (32%) of them scoring more than 10 at Beck inventory. Moreover, no differences were found in the depression indicators between the acne group and controls, with controls having a worse performance of SF-12 mental domain and recognizing to need psychiatric/psychological monitoring than acne patients. This data is in disagreement with previous results and this may have been caused by differences in social and cultural aspects. Valorization of body-image, presence of alternative forms to improve self-esteem and social acceptance may differ according to the studied society.

We also did not find differences in patients treated and not treated with isotretinoin (this is only important to see if it changes after isotretinoin, not at the onset of treatment). Clarifying if isotretinoin is or not causing depression and suicidal ideation is important because of the existing concern that acne itself may be associated with considerable psychiatric morbidity.¹³

Acne is a disease not always considered to have important repercussions in daily practice, but emotional problems, anxiety, depression, suicidal ideation have been linked to it.¹³ So, aggressive treatment should be indicated in order to avoid such morbidity. Nevertheless, if isotretinoin, one of the backbones of this treatment is associated, per se, with psychiatric complications, its use could bring more complications.

One of the proposed explanations for psychiatric morbidity associated with isotretinoin use is a reduction in hippocampal volume seen in animal studies. Mice treated with this drug have decrease in hippocampal neurogenesis and reduction of hippocampal volume that could be an explanation for the mood disorder induced by isotretinoin.¹⁴ Hypervitaminosis A, a paradigm of retinoid side effects, is another possible explanation for the problem as it is linked to psychiatric symptoms including depression.¹⁵ Another possible explanation is the effect of retinoids on brain dopamine systems.¹⁶

Presently, we could not prove that isotretinoin changed the depression parameters either for better or for worse. Our patients were followed for 6 months. According to Kontaxakis *et al*⁶ the depression appearance has been described as early as 1 day and up to 4 months after starting the treatment with this medication. So, the present observation period was adequate to analyze its occurrence.

Although prospective and controlled, this study is limited by the small number of participants in the different groups. In addition, many healthy controls were family members of acne patients that could have been affected in their psychological health by their relative's problem. Therefore, this study needs replication to confirm the present results. Nevertheless, our results point to safety of isotretinoin use regarding depression occurrence.

Conflicts of Interest: The authors have no conflicts of interest to declare. **Financing Support:** This work has not received any contribution, grant or scholarship. **Confidentiality of Data:** The authors declare that they have followed the protocols of their work center on the publication of data from patients. **Protection of Human and Animal Subjects:** The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki). **Provenance and Peer Review:** Not commissioned; externally peer reviewed.

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho. **Fontes de Financiamento:** Não existiram fontes externas de financiamento para a realização deste artigo. **Confidencialidade dos Dados:** Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes. **Proteção de Pessoas e Animais:** Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsinquia da Associação Médica Mundial. **Proveniência e Revisão por Pares:** Não comissionado; revisão externa por pares.



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