The efficacy and tolerability of 10mg and 20mg/day isotretinoinin the treatment of acne vulgaris in Iraqi patients

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Abstract

Back ground: Oral isotretinoin is recommended for sever nodulocystic acne in the doses 0.5-2mg/kg/day which is usually associated with higher incidence of adverse effects. To reduce the incidence of side-effects and to make it more cost-effective, the lower dose regimen of isotretinoin has been used.

Aim: To compare the efficacy and tolerability of oral isotretinoin 10mg and 20mg/day in acne vulgaris.

Methods: one hundred and twenty patients with acne vulgaris were randomized into two treatment regimens each consisting of 60 patients. The first was treated with 10mg/day and the second group with 20mg/day for 24 weeks. Fifty five patients from the first group and 47 patients from the second group who continued the study for 24 week and 8 weeks after cessation of therapy. The response rate was recorded in the form of acne load and acne grade initially, during treatment and after 8 from stopping treatment. Side effects were also recorded in both groups.

Results: The response rate in both groups was comparable in mild, moderate, and severe acne vulgaris patients. Frequency and severity of treatment-related side-effects were significantly higher in the second group as compared to the first group.

Conclusion: 10mg/dayisotretinoin can be used in the treatment of mild, moderate and severe acne with less side effects as compared to 20mg/day.

Keywords: Acne, isotretinoin, 10mg/day

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Introduction

Acne vulgaris is a multifactorial, self−limited, chronic disorder of the pilosebaceous unit that is seen primarily in adolescents. The clinical picture can vary significantly, from mild comedonal acne to fulminant systemic disease.[1]Although the course of acne may be self-limiting, the sequelae can be life long, with pitted or hypertrophic scar formation.[2]

Acne is distributed mainly over the face, upper back, chest and upper arms.[3]

According to the severity of acne, there are various treatment modalities. They include both topical and systemic therapy. In systemic therapy the commonly used drugs are oral antibiotics, hormonal therapy and isotretinoin.[1]

Isotretinoin(13−cis retinoic acid) represents the single most important advance in acne therapeutics. Isotretinoin is given in a dosage of 0.5 − 1.0mg/kg/day after meals in sever nodulocystic acne and the treatment is continued till a cumulative dose of 120 – 150 mg/kg is achieved.[4]Interestingly, low−dose isotretinoin was attempted initially for severe acne also with or without combination with other agents. In severe acne, lower doses of 0.3 mg/kg/day proved to be equally effective as the standard 1 mg/kg/day,[5,6] but the high relapse rate were instrumental in discarding its use in severe acne. Recent studies have reinforced the view that low−dose isotretinoin is useful for mild to moderate acne with less side effects (cutaneous, systemic and laboratory based) as compared with standard regimen.[4,6,7,8,9,10]

To compare the efficacy and tolerability of tow therapeutic regimens (10mg/day and 20mg/day) of oral isotretinoin in acne vulgaris, the present prospective study was undertaken.

Methods

This is prospective study of comparative efficacy and tolerability of 2 therapeutic regimens (10mg/day and 20mg/day) of oral isotretinoin in acne vulgaris. A total number of 120 patients with acne were included in the study from the out-patient dermatology department of Al-kindy teaching hospital during the period from January 2012 till December 2012. Pregnant women, married women desiring to get pregnant and patients having personal and or a familial history of hyperlipidemia

were excluded from the study. All patients were included after written informed consent. After recording detailed demographic data (which included age, gender, age of onset and duration of disease) the patients were examined under good illumination and were finally graded into mild, moderate and sever on the basis of severity as described below.[11]

• Mild disease: several to many papules/pustules with no nodules.

• Moderate disease: several to many papules, pustules with few to several nodules.

• Sever disease: numerous and/or extensive papules/pustules with many nodules.

Total acne load was measured on the basis of Definition Severity Index[12] which was calculated as follows:

•Noninflamed comedones, opened and closed (no erythema) : 0.5

•Comedones/papules with surrounding erythema: 1

•Superficial pustules < 2mm with no or little erythema : 1

•Pustules with a diameter>2mm : 2

•Pustules with significant erythema : 2

Deep infiltrates with or without pustules/ nodules/ isolated cyst : 3•

Total acne load is calculated by multiplying the total number of each type of lesion with its severity index and adding them all together.

Only face and neck were selected to determine acne grade and acne load.

Serum lipid profile and liver function tests carried out initially and repeated after 4, 12, and 24 week of therapy. The criteria for discontinuation of therapy was a blood test rising above the following values : triglycerides > 400mg/dL, cholesterol> 300mg/dL, alkaline phosphatase> 264/UL(female), > 500/UL(male), ALT(Alanine transaminase)> 62/UL, AST(Aspartate aminotransferase)> 80/UL.[13]

Patients were randomized into tow treatment regimens each consisting of 60 patients [figure 1]. One group was given 10 mg/day and the other group 20mg/day for 24 week.

Body weight for patients in both groups was ranging between 50-60kg, so the daily dose for the first group was ranging between 0.17-0.2mg/kg/day and the daily dose for the second group was 0.33-0.4mg/kg/day. The total cumulative dose at the end of the study was 28.59-33.6mg/kg and 55.44-67.2mg/kg for the first and the second group respectively. Along with oral isotretinoin, all patients were also given oral dexamethasone 0.5mg at night for 10 days, and advised to apply topical 1% clindamycin phosphate solution twice daily. Patients were followed up at 2, 4, 8, 16 and 24 week of treatment, and 8 weeks after treatment cessation. Improvements were recorded by measuring total acne load at each visit. Sideeffects were recorded at each visit which includecheilitis, dry skin, mouth, nose and eyes, dermatitis epistaxis, facial redness, hair loss, photosensitivity, nail changes and systemic side−effects like fatigue, bone/ joint pains, muscular cramp.

All the findings were analyzed by Pearson Chi-square test.

Results

A total of 120 patients with acne vulgaris were divided into 2 groups: first group was treated with 10 mg/day and the second group was treated with 20mg/day for 24 week. Each group was followed at 2, 4, 8, 16, 24 during and 8 weeks post treatment.

Regarding demographic data of both groups, most of the patients were below 20 years (60% first group and 40.4% second group). No statistical significant differences regarding age and gender between both groups. (table1, figure1)

Eighteen patients were lost from the study, 5 from the first group and 13 from the second group, so 55 patients continued the study from the first group and 47 patients from the second group.

There was statistical significant difference between the two groups of patients who discontinued the study (5 patients from the first and 13 from the second).

For disease grading which was for both groups mild and moderate (41.8%, 40% for the first group and 42.6% and 40.4% for the second group), there was no statistical significant difference between both groups initially and 8 weeks after stopping treatment regarding acne grading. (table 2)

Acne load was measured initially and at 2, 4, 8, 16, 24 week of treatment and 8 weeks after stopping treatment for each group. There was no statistical significant difference between both groups regarding changes in acne load but the response rate for each individual group was significant after starting therapy and even 8 weeks after stopping isotretinoin if compared to start point i:e pretreatment and even the relapse of the disease after the 8 weeks of discontinuation was very slow and acne load never reach the starting point (table3, 4 and figure2)

Regarding side effects cheilitis, dry skin and hair fall were the most common side effects noticed during the study. for the second group, cheilitis(78.7%) and dry skin(36.2%) were more common, appear earlier and increased in severity gradually if compared with the first group which was 45.5%, 18.2% respectively and it is statistically significant. Hair fall was 27.3% for the first and 42.5% for the second which is not statistically significant. Other uncommon side effects like asteatotic dermatitis, dry nose, eyes, and facial redness also were more common in the second group, but the P value cannot be calculated because of the small sample size. Serum triglyceride was elevated in one patient in the second group, and no psychological problems were recorded. Thus the incidence of side-effects was high with the second group. All the side-effects were successfully managed.(table5)

In our study few relapses were recorded after 8 weeks from discontinuation of therapy but still the acne load much lower than before treatment

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Figure 1: Flowchart of patients participating in the study

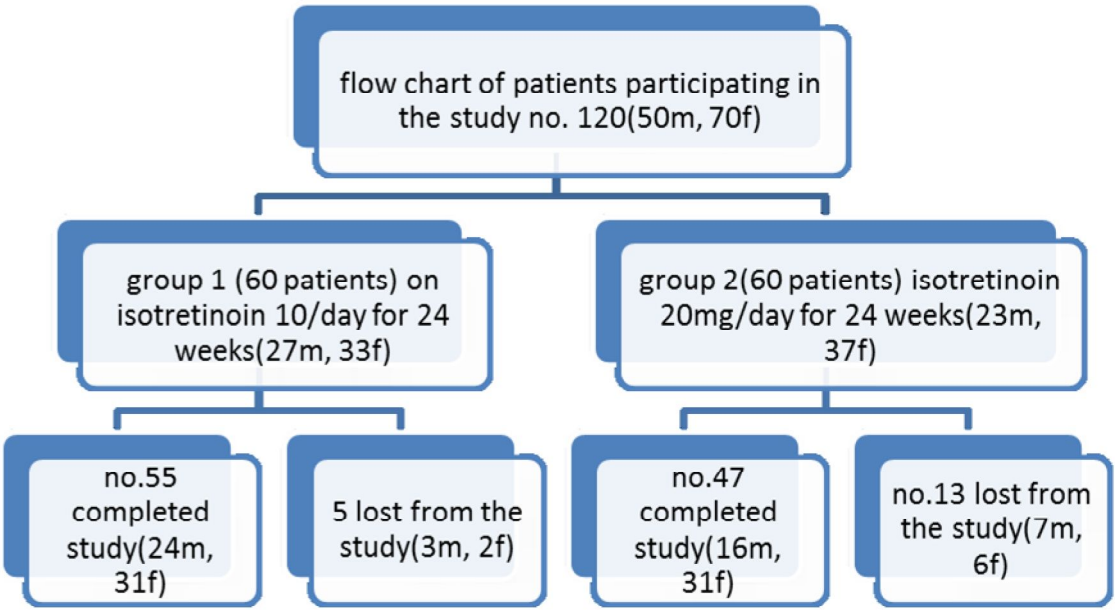

Table :1 showing age, gender and lost patients from both group

		Isotretinoin 10mg/day (n=55)		Isotretinoin 20mg/day (n=47)		P value
		No	%	No	%	
Age (years)	<20	33	60.0	19	40.4	0.088
	20--24	17	30.9	18	38.3	
	=>25	5	9.1	10	21.3	
	Mean±SD(Range)	19.9±4.0	(16-33)	21.6±4.7	(16-34)	
gender	Males	24	43.6	16	34.0	0.323
	Females	31	56.4	31	66.0	
Lost patient from follow up		5	8.3	13	21.7	0.041*

*Significant using Pearson Chi-square test at 0.05 level

Table:2 showing acne grade initially and after 8 weeks from stopping treatment

		Isotretinoin 10mg/day (n=55)		Isotretinoin 20mg/day (n=47)		P value
		No	%	No	%	
Acne grade initially	No	-	-	-	-	0.988
	Mild	23	41.8	20	42.6	
	Moderate	22	40.0	19	40.4	
	Severe	10	18.2	8	17.0	
Acne grade 8 weeks after cessation of therapy	No	4	7.3	7	14.9	0.458
	Mild	48	87.3	38	80.9	
	Moderate	3	5.5	2	4.3	
	Severe	-	-	-	-	

*Significant using Pearson Chi-square test at 0.05 level

Table-3- showing acne load of both group

	Isotretinoin 10mg/day (n=55)		Isotretinoin 20mg/day (n=47)		P value (t-test for two independent means)
Acne load at start	42.7±13.7	(20-73)	38.2±14.4	(20-70)	0.118
2 week	39.2±13.2	(20-70)	34.1±13.8	(16-70)	0.063
4 week	23.0±9.6	(7-55)	20.0±8.4	(9-40)	0.101
8 week	8.8±5.1	(0-30)	8.1±4.3	(1-20)	0.464
16 week	2.8±2.4	(0-13)	2.4±2.0	(0-8)	0.299
24 week	1.7±1.4	(0-5)	1.6±1.5	(0-6)	0.674
8 week after stop drug	7.8±5.2	(0-25)	6.3±5.6	(0-30)	0.164
P value (Paired t-test)	0.0001*		0.0001*		

*Significant at 0.05 level

Data presented as Mean±SD (Range)

Figure-2- showing the response rate in both group

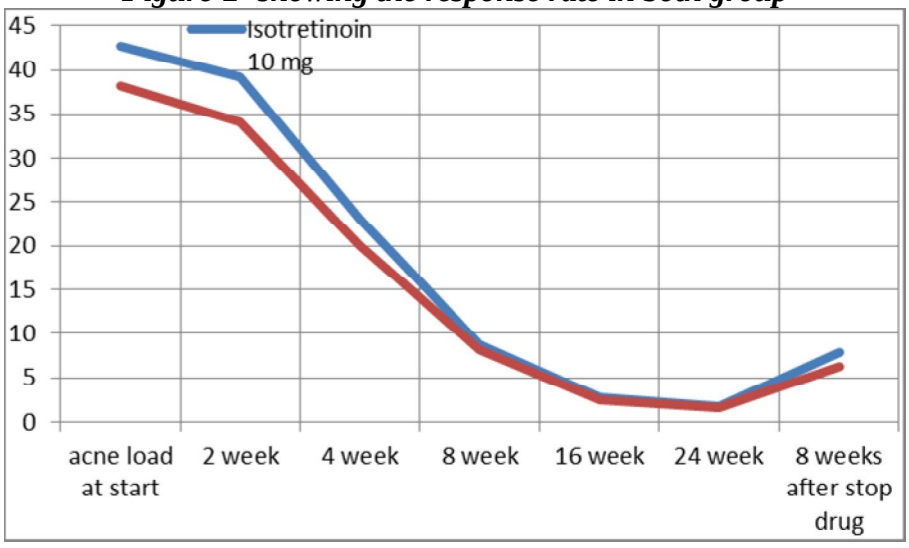

Table-4- showing side effects of both groups
Significant using Pearson Chi-square test at 0.05 level*

Discussion:

Isotretinoin is a quit, useful, FDA approved drug for the treatment of severe cases of nodulocystic acne. It has been recommended for sever nodulocystic acne in a dose of 0.5-2mg/kg/day for 16-20 weeks. However lower daily doses given over a longer period of time, with a total cumulative dose of 120-150mg/kg have been shown to reduce the relapse. This cumulative dosage can be reached over a period of 4-5 months with 1mg/kg/day. In patients with markedly inflammatory acne, lower starting doses may be indicated to prevent the induction of sever flares during the first month of treatment[1], while using this treatment protocol, the incidence of side-effects is quite high and requires regular monitoring including a watch on the serum lipid profile. It has been debated whether isotretinoin should be reserved for sever nodulocystic acne only or it can be used for mild and moderate acne also. To decrease the incidence of side-effects and to make the therapy protocol simpler, the lower dose regimen has been tried by various authors. Most of these studies have found that low-dose and intermittent regimens of isotretinoin are effective in moderate to severe acne with a lower incidence and severity of side effects.[10,14]

Although we gave the patients 0.5 oral dexamethasone for 10 days in hop to reduce side effects and flares and it did so for most of the patients, unfortunately 18 patients discontinued the study, those from the second group was twice as that of the first group (13, 5respectivly) which is statistically significant; and that because they developed more side effects and more flare-up of disease, so they want to change their medication.

In the present study we have tried to compare two doses of oral isotretinoin simultaneously (10mg/day and 20mg/day) and have also tried to correlate treatment response not only with total acne load but also with severity of the disease for the period (24 week) and after 8 weeks from stopping treatment. Most of the patients were selected in mild and moderate grade (41.8% and 40% for the first group and 42.6% and40.4% for the second group respectively). It was found that the first group with 10mg/day shows slightly slower response from the beginning of therapy till 2 weeks than the second group but after 8 weeks the same results were obtained with both groups till the end of 24 week of therapy, and even the relapse rate

was nearly similar in both groups after 8 weeks of discontinuing therapy.

The development of side effects was less with the first group. These side effects were quite lower than other studies with the conventional dose regimen (hyperlipidemia in 20-35% and elevated liver enzyme in approximately 4-10% of cases)[6,7] in this study only one patient from the second group developed elevated triglyceride level. None of the patients developed elevated liver enzyme. So we can repeat the therapy after a period of time because we are not exceeding the total cumulative dose which is 120-150mg/kg.

Considering the above findings, the use of isotretinoin should be considered in mild, moderate and severe acne in a low dose 10mg/day seems to be effective and safe treatment option in such cases.

Conclusion:

The gold standard for therapy in severe acne vulgaris is isotretinoin in a dose of 1mg/kg/day. In this study we compared the efficacy and tolerability of 10 and 20mg/day isotretinoin in mild, moderate and severe acne vulgaris and the result was comparable in both groups, but the side effects were more with 20mg regimen. Thus 10mg isotretinoin can be effectively administered in patients with acne vulgaris.

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