

Comparative Efficacy of Three Low - dose Isotretinoin Regimens in Treatment of Mild to Moderate Acne Vulgaris on the Face in Tertiary Care Institute

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Abstract

Background: Acne is a disease that affects almost 100% of the population. The clinical presentation ranges from comedones, papules, pustules and nodules. Various systemic treatment modalities like oral antibiotics, retinoids, hormonal therapy and corticosteroids, are available with varied benefits and side effects. **Aims:** To study and compare the efficacy and safety profile of three low dose isotretinoin regimens in the treatment of mild to moderate acne vulgaris. **Methods:** 75 patients having mild to moderate acne vulgaris were randomized into three different low dose isotretinoin regimens. Each was consisting of 25 patients. Group A was prescribed 5 mg, Group B 10 mg and Group C 20 mg isotretinoin for 4 months. Clinical improvement and side effects were recorded. **Results:** All regimens showed clinical improvement in 4 months of therapy. Isotretinoin 20 mg was found to be superior in later half of therapy. But isotretinoin 10 mg and 20 mg both were statistically equally efficacious in mild to moderate acne vulgaris. Side effects were higher in Group C as compared to Group A and B. **Conclusion:** We conclude that all three low dose regimens were efficacious in mild to moderate acne vulgaris. Isotretinoin 10 mg was found to be an effective and safe treatment option in such cases.

Keywords: Acne, Isotretinoin, Low Dose

1. Introduction

Acne vulgaris is one of the most common dermatological disorder¹. It is a chronic inflammatory disease of the pilosebaceous units that is seen primarily in adolescents with significant psychological and social impact. The pathogenesis of acne is multifactorial.

Most cases of acne present with a pleomorphic variety of lesions mainly over the face, upper back, chest and upper arms².

According to the severity of acne, there are various treatment modalities. Isotretinoin is the key component of anti-acne therapy. Isotretinoin is a first generation synthetic retinoid.

Isotretinoin is a FDA approved drug for the treatment of severe cases of nodulo-cystic acne. Its conventional recommended dose is 0.5-1.0 mg/kg body weight per day for 16-32 weeks, with a maximum cumulative dose of 120 mg/kg. This regimen is known to produce good results; however, it might cause several dose-dependent muco-cutaneous and systemic side effects. In an end to surmount this limitation and to make the regimen cost-effective, low-dose regimens for mild to moderate grades of acne have been advocated³. As the side effects are dose related, the idea of low dose isotretinoin therapy for acne is attractive, but little data exist on the safety and efficacy of this strategy³⁻⁵.

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There are no reports observing the safety and efficacy of these three low doses of isotretinoin in the treatment of mild to moderate acne vulgaris. Hence, we conducted the present study to compare the efficacy and side effects of three low dose isotretinoin regimens.

2. Methods

The present comparative case study was carried out in the department of Dermatology Venereology and Leprology of a tertiary health care institute. A total 75 patients of ≥ 14 yrs. having Global Acne Grading Score (GAGS) score < 31 were included in the study. Approval of institutional ethical committee was taken.

Exclusion criteria: Participants with history of hypersensitivity or allergic reactions to isotretinoin, concomitant use of any over-the-counter products, past treatment with systemic retinoids, having family and/or personal history of diabetes, abnormal lipid profiles, significant hepatic/renal dysfunction or an underlying psychiatric disorder. Females who are pregnant, breast feeding or planning a pregnancy during the proposed study period. Written informed consent including consents from parents in case of minor was taken. 3 groups were formed Group A, B & C by sequential method of randomization. Subject's demographic data (age, sex, address etc.) and clinical data included symptoms, duration, severity, site of acne such face, trunk were gathered and compiled. The initial assessment of acne was done using GAGS by the investigator. The baseline as well as the periodic assessment of acne by GAGS was performed by a single investigator to avoid bias. The baseline investigations included complete blood cell counts; serum glutamate pyruvate transaminase, serum triglycerides, and urine pregnancy test were done before the study. Female participants were advised to start treatment only after their next menstrual period to ensure that they were not pregnant at the time of initiation of the treatment.

Group A received 5 mg, Group B 10 mg and group C received 20 mg of oral dose. Isotretinoin once a day for four months. Followed up at one-month interval and investigations such as complete blood cell counts, serum glutamate pyruvate transaminase, serum triglycerides were done only at the end of 1 month and 4 months. Improvement assessed by clearance of acne lesions by a dermatologist (MS). Very good response - $>80\%$ clearance of lesions, good response - 50% to 80% clearance, fair response - 30% to 50% clearance and poor response - $<30\%$ of clearance.

After the completion of study period, subjects of persistent acne vulgaris were managed accordingly. The study had no financial support from any outside agency.

3. Results

Out of 75 patients enrolled, 7 patients were dropped out. Total 68 patients observed in the study. Out of those 24 in group A, 23 in group B and 21 in group C.

Table 1. Age and Sex wise distribution of study sample

Age	Sex				Total	%
	Male	%	Female	%		
14-18	16	23.53%	9	13.24%	25	36.77%
19-23	23	33.82%	13	19.12%	36	52.94%
24-28	6	8.82	0	0.00%	6	8.82%
29-33	0	0.00	1	1.47%	1	1.47%
Total	45	66.18%	23	33.82%	68	100.00%

Table 1, there was no statistically significant difference between age and sex distribution.

Table 2, shows relation of sex distribution and severity of GAGS score on visit 1.

There was more reduction in mean GAGS score seen in 20 mg group rather than other groups (Table 3). The percentage wise mean GAGS score reduction was seen

Table 2. GAG score and sex-wise distribution of study sample

Gag score (visit 1)	Sex				Total	%
	Male	%	Female	%		
1-18 (mild)	31	45.59%	14	20.59%	45	66.18%
19-30 (moderate)	14	20.59%	9	13.24%	23	33.82%
Total	45	66.18%	23	33.82%	68	100.00%

Table 3. Mean GAGS score reduction in all visits in all groups

Visits	Group A	% Reduction	Group B	% Reduction	Group C	% Reduction
Visit 1	16.292	100%	15.826	100%	15.476	100%
Visit 2	14.125	86.70%	13.130	82.96%	11.143	72%
Visit 3	10.208	62.66%	9.000	56.87%	7.952	51.38%
Visit 4	6.625	40.66%	5.030	31.78%	4.476	28.92%
Visit 5	3.458	21.22%	2.043	12.91%	1.238	8.00%

Table 4. Independent T test for Comparison between group A and group B of GAGS scores

GAGS score on visit	Group Statistics				Std. Deviation	Independent T test statistic		
	Groups	N	Mean			t	Sig. (2-tailed)	Significance
Visit 1	A	24	16.292	5.544	0.286	0.776	Not Significant	
	B	23	15.826	5.606				
Visit 2	A	24	14.125	5.705	0.619	0.539	Not Significant	
	B	23	13.130	5.286				
Visit 3	A	24	10.208	4.384	0.939	0.353	Not Significant	
	B	23	9.000	4.442				
Visit 4	A	24	6.625	3.048	1.79	0.08	Not Significant	
	B	23	5.044	3.007				
Visit 5	A	24	3.458	2.449	1.983	0.053	Not Significant	
	B	23	2.044	2.440				

Table 5. Independent T test for comparison between group B and group C of GAGS scores

GAGS score on visit	Group Statistics				t	Sig. (2-tailed)	Significance
	Groups	N	Mean	Std. Deviation			
Visit 1	B	23	15.83	5.61	0.228	0.821	Not Significant
	C	21	15.48	4.45			
Visit 2	B	23	13.13	5.29	1.397	0.17	Not Significant
	C	21	11.14	3.99			
Visit 3	B	23	9.00	4.44	0.829	0.412	Not Significant
	C	21	7.95	3.89			
Visit 4	B	23	5.04	3.01	0.635	0.529	Not Significant
	C	21	4.48	2.91			
Visit 5	B	23	2.04	2.44	1.164	0.251	Not Significant
	C	21	1.24	2.12			

as 79%, 87% and 92% in group A, group B and group C respectively as per comparison of GAG score in first visit.

Table 4 shows there was no statistical difference between mean GAGS scores on any visit in group A and

B. It suggests that 5 mg and 10 mg isotretinoin are equally efficacious in mild to moderate acne vulgaris.

Table 5 shows there was no statistical difference between mean GAGS score in group B and C on any visit.

Table 6. Independent T test for comparison between group A and group C of GAGS scores

GAGS score on visit	Group Statistics			Std. Deviation	Independent T test statistic		
	Groups	N	Mean		t	Sig. (2-tailed)	Significance
Visit 1	A	24	16.29	5.54	0.539	0.593	Not Significant
	C	21	15.48	4.45			
Visit 2	A	24	14.13	5.71	2.003	0.051	Not Significant
	C	21	11.14	3.99			
Visit 3	A	24	10.21	4.38	1.814	0.077	Not Significant
	C	21	7.95	3.89			
Visit 4	A	24	6.63	3.05	2.41	0.02	Significant
	C	21	4.48	2.91			
Visit 5	A	24	3.46	2.45	3.228	0.002	Significant
	C	21	1.24	2.12			

Table 7. Combined side effects of all 3 groups

Side effects	Group A (n=24)		Group B (n=23)		Group C (n=21)	
	Frequency	%	Frequency	%	Frequency	%
Cheilitis	15	62.5%	21	91.30%	21	100%
Xerosis (Dryness of skin)	4	16.67%	5	21.74%	8	38.10%
Dryness of mouth	0	00.00%	1	4.34%	1	4.76%
depression	0	00.00%	0	00.00%	0	00.00%
Dry, rough hair	0	00.00%	1	4.34%	2	9.52%
Scaling over palms	0	00.00%	0	00.00%	0	00.00%
Dandruff	0	00.00%	0	00.00%	3	14.28%
Hair loss	0	00.00%	0	00.00%	1	4.76%
Erythema over face	0	00.00%	0	00.00%	1	4.76%
Abnormal SGPT	1	4.17%	2	8.70%	2	9.52%
Abnormal S.TG	0	00.00%	4	17.39%	5	23.81%

It suggests that 10 mg isotretinoin and 20 mg isotretinoin are equally efficacious in mild to moderate acne vulgaris.

Table 6, shows there was no difference between mean GAGS score on visit 1, visit 2 and visit 3 in group A and C. But there was statistical difference between mean GAGS score on visit 4 and visit 5 in group A and C. It suggests that 20 mg isotretinoin is superior than 5 mg isotretinoin in mild to moderate acne vulgaris.

Cheilitis was the most common side effect observed in our study. It was seen in 62.5%, 91.30% and 100% in group A, B and C respectively. Xerosis was seen in 16.67%, 21.74% and 38.10% in group A, B and C respectively. While, dryness of mouth seen in 4.34% and 4.76% in group B

and group C. 4.34% and 14.28% patients had complained of dry rough hair in group B and C respectively. 14.28% patients had dandruff, 4.76% had hair loss and 9.52% had complained of erythema over face in group C. Most of these adverse events were transient in nature and resolved with symptomatic management. Dryness of mouth, depression, dry rough hair, scaling over palms, dandruff, hair loss and erythema over face was not seen in group A. Abnormal serum glutamate pyruvate transaminase was seen in 4.17%, 8.70% and 9.52% in group A, B and C respectively, whereas abnormal serum triglycerides was seen in 17.39% and 23.81% in group B and group C. It was not deranged in group A (Table 7).

Table 8. Comparison of different low-dose isotretinoin studies

Name of protocol	Authors	No. of pt	Treatment dose (mg/kg/day) and duration (weeks)	Degree of resolution (%)/ relapse	Conclusion
Low dose	Hermes et al. (1998) ⁷	94	0.43 (35)	99.8/33	Response was very good in 62.8% and good in 31.9% patients
Low dose v/s 0.5-1 mg/kg/d	Lefaki et al. (2003) ⁸	32	0.15-0.4 (24)	69	Adverse effects low, beneficial effect on preexisting scarring and relapse rate
Low dose	Amichai et al. (2006) ³	638	0.3-0.4 (24)	93.7/5	Good efficacy, low incidence of severe adverse effects and lower cost than higher doses
Inter-mittent and daily	Akman et al. (2007) ⁹	66	0.5 (24)	90/15	Effective in moderate acne, less adverse effects
Low dose, 20 mg alternate day	Sardana et al. (2009) ¹⁰	305	0.15-0.28 (24) + 1% clindamycin	87.64/ 16.35	Almost equal efficacy, less adverse effects
Different regimens	Agarwal et al. (2011) ²	120	0.4 – 1.0 (16)	93-96	Almost equal efficacy in mild to moderate acne
Low dose	De et al. (2011) ¹¹	70	0.3 (16) + pulsed oral zithromycin	93.9/11.3	Therapy found to be effective in severe acne, acceptable side effects
20 mg/d v/s 20mg bd x 7 days/ month	El-sherif NA et al. (2013) ¹²	55	0.4-0.7 (16)	84.78/22-39	Equal efficacy in moderate acne, intermittent regimen may be cost effective alternative
Low dose, 20 mg/day	Rao et al. (2014) ¹³	60	0.4 (12)	90/4	Found to be effective in moderate to severe acne, low incidence of side effects

4. Discussion

Recommended dose of isotretinoin is 0.5-1.0 mg/kg body weight per day for 16-32 weeks, till maximum cumulative dose of 120 mg/kg. But a dose-ranging study of isotretinoin demonstrated a low daily dose (0.1 mg/kg/day), intermediate daily dose (0.5mg/kg/day), and high daily dose (1 mg/kg/day) administered over 20 weeks cleared the vast majority of patients⁶.

The side effects are dose dependent, higher doses cause several dose dependent side effects. To overcome this limitation and to make the regimen cost-effective, low-dose isotretinoin for mild to moderate grades of acne have been advocated.

There are various studies showing low dose isotretinoin (0.1-0.5 mg/kg/day) is effective in acne with a low incidence of severe side effects and at a lower cost (Table 8).

In our study we observed at the end of two months of therapy the mean reduction of GAGS score was 37%, 43%

and 48% in group A, B and C respectively, which was not statistically significant. There was significant reduction of GAGS score during third and fourth months of therapy. The mean reduction of GAGS score at the end of four months therapy in group A, B and C was 79%, 87% and 92% respectively. As per our study 20 mg isotretinoin is more effective than 5 mg and 10 mg in view of clinical improvement. But there was no statistically significant difference in mean GAGS score reduction between the 10 mg and 20 mg isotretinoin therapy for 4 months.

Among these 3 groups, patients in group C have developed more side effects than other two groups. The side effects were cheilitis (100%), xerosis (38.10%), dryness of mouth and dry, rough hair (4.76%), dandruff (14.28%), erythema over face and hair loss (4.76%), elevated liver enzyme (9.52%) and elevated serum triglycerides (23.8%) which was similar to previous studies^{3,10,13-16}.

We did not consider the follow up period in this study due to lack of time period. The anti Acne therapy was

continued in subjects after 4 months of study as per latest GAGS score.

5. Conclusion

All three doses of isotretinoin 5 mg, 10 mg and 20 mg are effective in mild to moderate acne vulgaris but considering all aspects, we recommended 10 mg isotretinoin in view of clinical efficacy as well as side effects as compared to 5 mg and 20 mg dose. It has good tolerability and response to treatment among Indian patients. The only pitfall is the long duration of treatment in order to achieve the cumulative dose.

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