

**Outcome of Adapalene and Isotretinoin in the treatment of acne vulgaris**

ABSTRACT

Topical application of **Isotretinoin** and **Adapalene** has proved effective in treating acne vulgaris. Both drugs demonstrate therapeutic advantages and less irritancy over tretinoin, the most widely used treatment for acne. The objective of this study was to compare the efficacy and tolerability of **Adapalene** cream 0.1% and Isotretinoin cream 0.05% in the treatment of acne vulgaris.

Hundred patients were enrolled and were instructed to apply Adapalene cream 0.1% (50 patients) or Isotretinoin cream 0.05% (50 patients) once daily over a 6-week treatment period. Efficacy determination included non-inflammatory and inflammatory lesions count by the investigator and global evaluation of improvement.

Cutaneous tolerance was assessed by determining erythema, scaling, burning and pruritus. Adapalene and Isotretinoin creams were highly effective in treating acne vulgaris. However Adapalene was found significantly more effective than **Isotretinoin**. Adapalene has faster onset of action of, which reflects on patients psychologically in term of improvements, comforts and good appearance. Significantly lower skin irritation was noted with **Adapalene**, indicating that **Adapalene** may begin a new era of treatment with low-irritant retinoids. It seems

24 that, **Adapalene** treatment is a good choice for topical treatment of acne vulgaris  
25 with less side effects and high efficacy. Adapalene should be described as first line  
26 for treatment of acne vulgaris.

## 27 **INTRODUCTION**

28 Acne is an extremely common skin disease, and thus, individuals have various  
29 beliefs and perceptions about its treatment methods. In a recent community- based  
30 study, 68% of male and 66.8% of female teenage participants were reported to  
31 have acne <sup>(1)</sup>.

32 Although less frequently encountered than in adolescence, a significant number of  
33 adults, and 20 years of age or older, also have acne <sup>(1)</sup>. In many cases, acne is  
34 regarded as a physiologic phenomenon, which is likely to regress spontaneously  
35 after adolescence. However, in **some individuals**, acne persists and substantially  
36 increases the likelihood of scarring <sup>(2)</sup>. Because acne is a common skin condition, it  
37 has a great impact on quality of life. Thus, a detailed understanding of its more  
38 general aspects is important <sup>(3)</sup>. Numerous clinical research studies have been  
39 undertaken on its epidemiology in western countries <sup>(1,4,5)</sup>. However, comparatively  
40 few have been undertaken in African and Asian populations <sup>(6,7)</sup>.

41 Acne is usually diagnosed by the patient. The physician needs to  
42 determine if the condition is non-inflammatory (open and closed comedons),

43 inflammatory (papules or pustules) or a mixture of both, the most common  
44 situation.

45 Topical treatment is sufficient in most patients with acne, but systemic  
46 therapy is required in patients who have acne nodules and cysts <sup>(4)</sup>. Topical  
47 retinoids such as Tretinoin, Isotretinoin, or Adapalene are effective in many  
48 patients with comedonal acne.

49 Adapalene is a topical retinoid derived from naphthoic acid with a selective effect  
50 on the epidermis. It is indicated for treatment of acne vulgaris, alone or with other  
51 anti-actinic topicals. It displays comedolytic and anti-inflammatory activities.

52 Topical retinoids are comedolytic and anti-inflammatory. They normalize follicular  
53 hyperproliferation and hyperkeratinization. They reduce the numbers of  
54 microcomedones, comedons, and inflammatory lesions and may be used alone or  
55 in combination with other acne medications. The most commonly prescribed  
56 topical retinoids for acne vulgaris include Adapalene, Tazarotene, and Tretinoin.  
57 These retinoids should be applied once daily to clean, dry skin, but they may need  
58 to be applied less frequently if irritation occurs <sup>(9)</sup>. Skin irritation with peeling and  
59 redness may be associated with the early use of topical retinoids. Alternate-day  
60 dosing may be used if irritation persists. Topical retinoids thin the stratum  
61 corneum, and they have been associated with sun sensitivity. So patients should be  
62 instructed about sun protection <sup>(8)</sup>. Retinoids are used in the treatment of many

63 diverse diseases and are effective in the treatment of a number of dermatological  
64 conditions such as inflammatory skin disorders, skin cancers, disorders of  
65 increased cell turnover as psoriasis, and photoaging<sup>(9)</sup>.

66 Adapalene is a third-generation topical retinoid primarily used in the treatment of  
67 mild-moderate acne and is also used (off-label) to treat keratosis pilaris as well as  
68 other skin conditions<sup>(10)</sup>.

69 Adapalene has been shown to enhance the efficacy of topical clindamycin,  
70 although adverse effects are also increased<sup>(11)</sup>. Application of Adapalene gel to  
71 the skin 3–5 minutes before application of clindamycin enhances penetration of  
72 clindamycin into the skin, which may enhance the overall efficacy of the treatment  
73 as compared to clindamycin alone<sup>(12)</sup>.

74 Unlike tretinoin (Retin-A), Adapalene has also been shown to retain its efficacy  
75 when applied at the same time as benzoyl\_peroxide due to its more stable chemical  
76 structure<sup>(8,9)</sup>. Adapalene in small concentrations is a moderator of cellular  
77 differentiation, keratinization, and inflammatory processes. It has both exfoliating  
78 and anti-inflammatory effects. The exact mode of action of Adapalene is  
79 unknown.

80 Adapalene is applied topically to the skin, and its absorption into the blood  
81 through this medium is very low. Only trace amounts of Adapalene have been  
82 found in the plasma of chronically treated patients<sup>(13)</sup>.

83

84           Tretinoin is all-trans stereoisomer of retinoic acid, used topically for  
85 treatment of cases of acne vulgaris in which comedons, pustules, and papules  
86 predominate; it prevents comedons formation and suppresses keratin synthesis;  
87 common adverse effects are erythema and desquamation. It is also administered  
88 orally in treatment of acute <sup>(13)</sup>.

89 In a Pakistani clinical study conducted by Iftikhar et al **Adapalene** cream 0.1%  
90 was compared against **Isotretinoin** 0.05% in the treatment of acne vulgaris. The  
91 study targeted comparing efficacy and tolerability of **Adapalene** cream 0.1% and  
92 **Isotretinoin** cream 0.05% in the treatment of acne vulgaris <sup>(14)</sup>.

93 Both **Adapalene** and **Isotretinoin** demonstrated comparable efficacy. However,  
94 significantly lower skin irritation was noted with Adapalene.

95           The only frequent adverse event is a mild skin irritation during the first two  
96 weeks of treatment.

## 97   **Objective**

98           The present study was undertaken to compare the efficacy and tolerability of  
99 Adapalene cream 0.1% and Isotretinoin cream 0.05% in the treatment of acne  
100 vulgaris of the face.

## 101   **Materials and Methods**

102

103           This is an observational, cross-sectional hospital-based study included the both

104 genders attended Khartoum Teaching Dermatology Hospital with acne vulgaris  
105 from September 2010 to September 2011. Pregnant women, breast feeding  
106 women and patients on a previous treatment have been excluded

107 **Sample size:**

108 According to the Equation:

109 
$$N = Z^2 (PQ)/D^2$$

110 Where:

111 N= Sample size.      Z = constant 1.96 2

112 P = Prevalence = 10% Q = (1-P).

113 D = allowable error = 4%

114 It was determined to be 90 patients, but 100 patients of mild to moderate  
115 acne irrespective of age, sex and social status were enrolled. After an informed  
116 consent, a detailed history was taken and scrupulous physical examination was  
117 performed in each patient.

118 Patients were randomized into two groups A and B (fifty patients for each).  
119 The randomized process was conducted by asking the patient to take folded  
120 paper contained the A or B letter and then the patient would be enrolled in  
121 Adapalene or Isotretinoin group. Patients in group A applied Adapalene cream  
122 0.1% and group B used Isotretinoin cream 0.05% once daily at night for 6  
123 weeks. Quantity of cream remained the same i.e. equivalent to size of half a  
124 pea.

125 All patients were clinically diagnosed. Efficacy variables included non-  
126 inflammatory, inflammatory lesions and total lesion counts; global grade; and  
127 global assessment of improvement in acne severity. Skin tolerability variables  
128 that were known to be associated with topical retinoid derivatives included  
129 erythema, desquamation (scaling), dryness, pruritus, and stinging/ burning, thus  
130 the presence of any of them during the course of treatment have been accounted  
131 as a drug intolerability indicator. During period of follow-ups we encouraged  
132 our patients to mention any symptoms concomitant with our regular

133 reexaminations. Demographic data collected by direct interviewing to the  
134 intended subjects and clinical examination was done according to the attached  
135 questionnaire.

136  
137 Data was analyzed by Statistical Package for Social Sciences (SPSS),  
138 version 10, t- test used to compare quantitative variables ( score of nonmedical  
139 treatment according to socioeconomic status) . Analysis of variance ANOV A  
140 was used to compare score of nonmedical treatment according to education  
141 level.

142 Chi-squared test was used to determine the statistical significances of  
143 association between qualitative variables. Test was considered significant, when  
144 P. value is less than 0.05.

145

## 146 RESULTS

147 Fifty patients were treated with Adapalene and fifty were treated with  
148 Isotretinoin. The means age of Adapalene and Isotretinoin groups were  
149  $27.42 \pm 10.15$  and  $24.28 \pm 7.92$ .

150 The gender distribution of Adapalene and Isotretinoin groups, in both groups  
151 the percentage of males was 22 % and female 78%. Among Adapalene group  
152 the mild cases were 36% and moderate cases were 64%, while among  
153 Isotretinoin group, the mild cases were 18% (9) and the moderate were 82 %.

154 Cases with inflammatory lesions were 62% of Adapalene groups, while 76  
155 % were of Isotretinoin groups.

156 Analysis indicated that Adapalene cream was significantly ( $P < 0.01$ ) more  
157 effective in treating acne than Isotretinoin gel after 3 and 6 weeks from  
158 treatment. After 3 weeks of treatment with Adapalene 2% was cured, 94 %  
159 were improved and 4 % were not improved, while within Isotretinoin group 2%

160 was cured, 46 % were improved and 52 % were not improved. After 6 weeks of  
 161 treatment with Adapalene 90% was cured and 10 % were improved, while  
 162 within Isotretinoin group 8% was cured, 50 % were improved and 42 % were  
 163 not improved. After 6 weeks of treatment with Adapalene 28 % of cases had  
 164 lesions, while among Isotretinoin group they were 84 %.

165 The adverse drug reactions on skin based on scaling, erythema, burning  
 166 sensation, pruritus and other assessment were significantly (P<0.001) high  
 167 among Isotretinoin group than Adapalene one. The percentages were 20 %  
 168 scaling, 28 % erythema, 10 % burning sensation, 10 % pruritus and 6% other  
 169 of Adapalene group and 74 % scaling, 48 % erythema, 42 % burning  
 170 sensation, 32 % pruritus and 12% (+) others of Isotretinoin group.

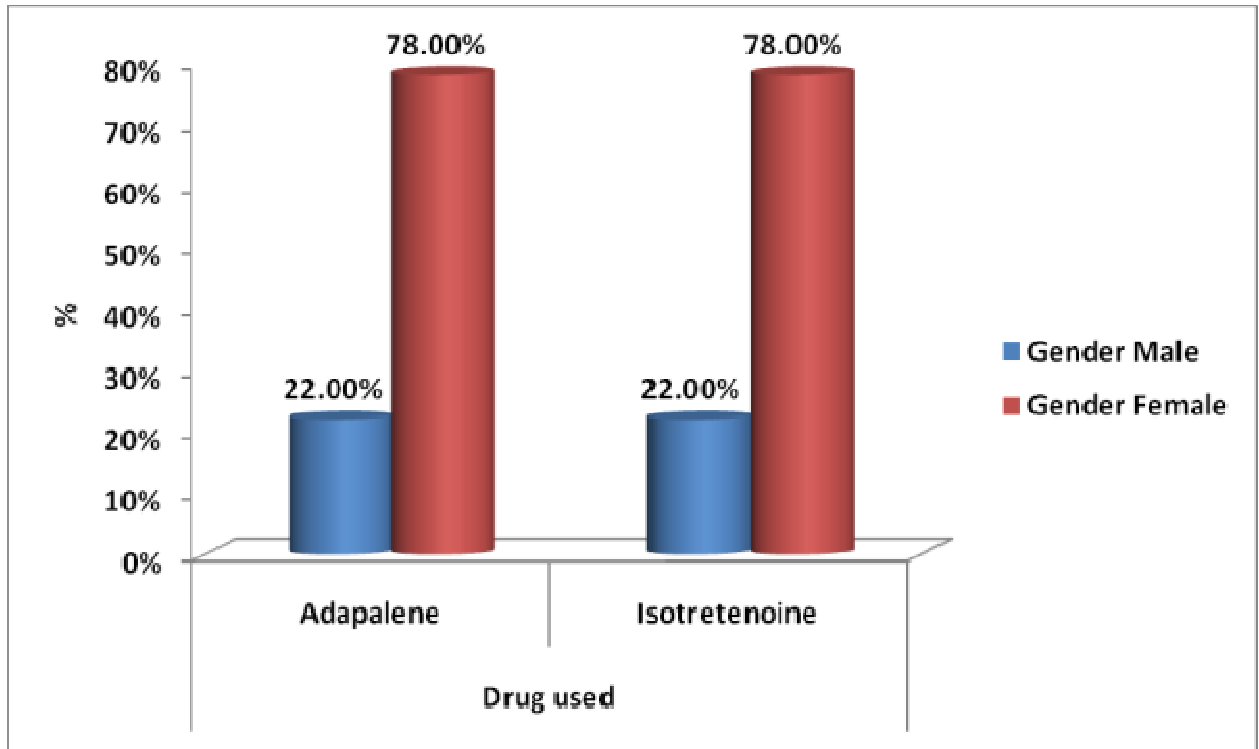
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174 Table 1: The mean age of Adapalene and Isotretinoin groups

Drug used	Age		
	N	Mean	Std. D.
Adapalene	50	27.42	10.15
Isotretinoin	50	24.28	7.92

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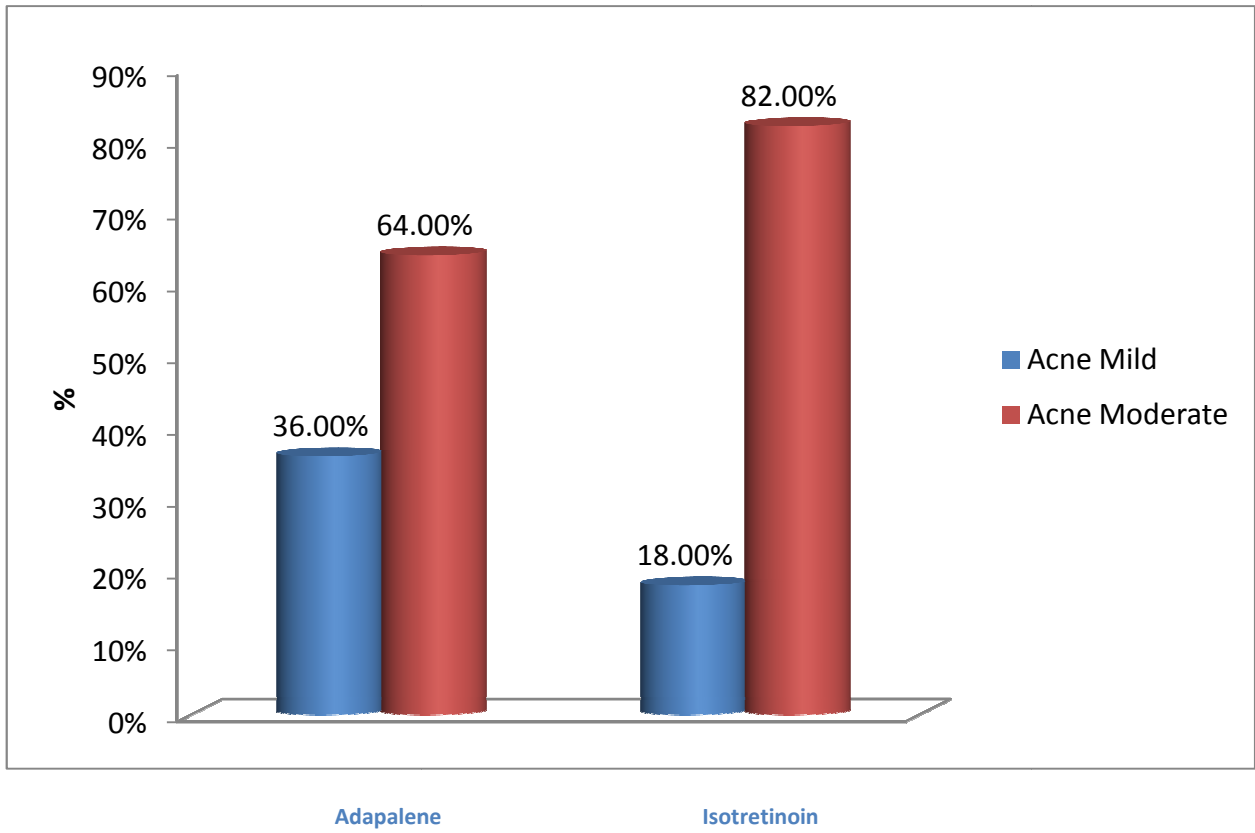


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Figure 1: The gender distribution of Adapalene and Isotretinoin groups

182 Table 2: Distribution of type of drug used according to acne severity and  
183 inflammatory

		Drug used			
		Adapalene		Isotretinoin	
		N	% of Total N	N	% of Total N
Acne	Mild	18	36.00%	9	18.00%
	Moderate	32	64.00%	41	82.00%
Inflammatory	Yes	31	62.00%	38	76.00%
	No	19	38.00%	12	24.00%



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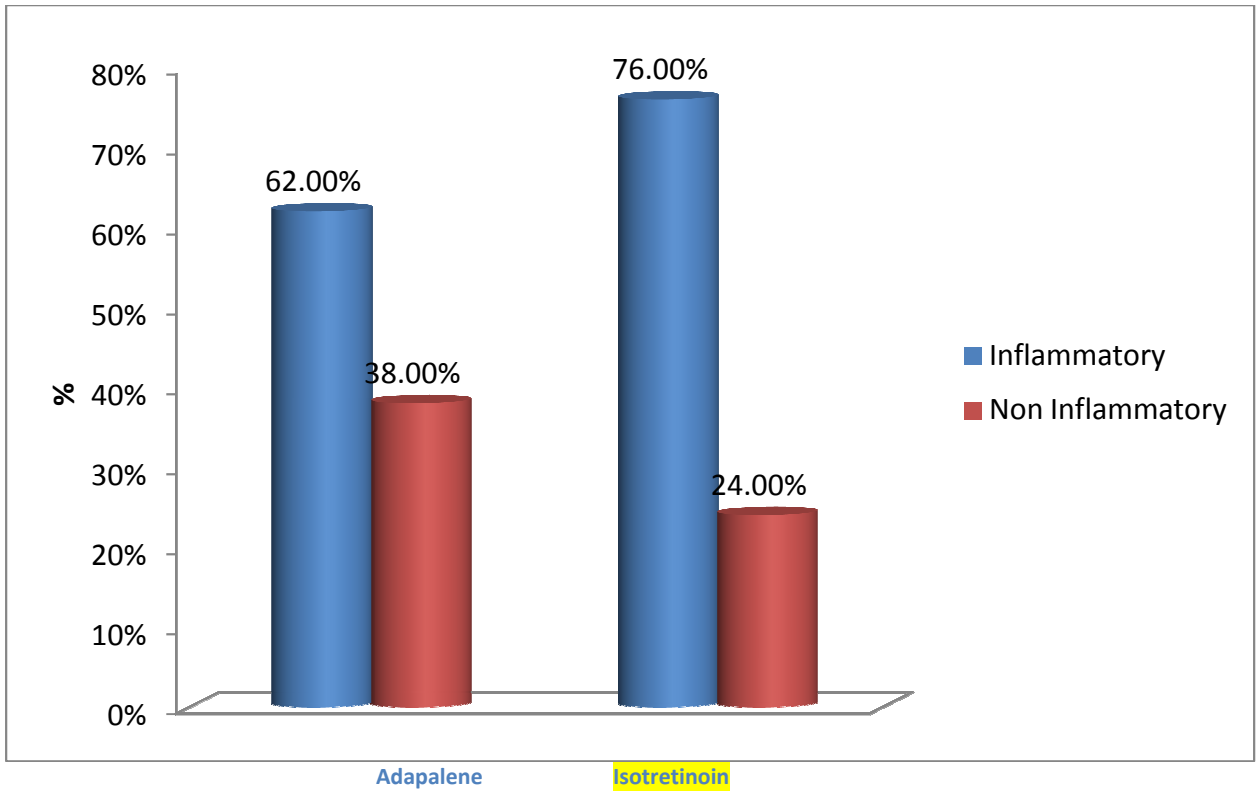
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Figure 2: Distribution of type of drug used according to acne severity



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192 Figure 3: Distribution of type of drug used according to Inflammatory.

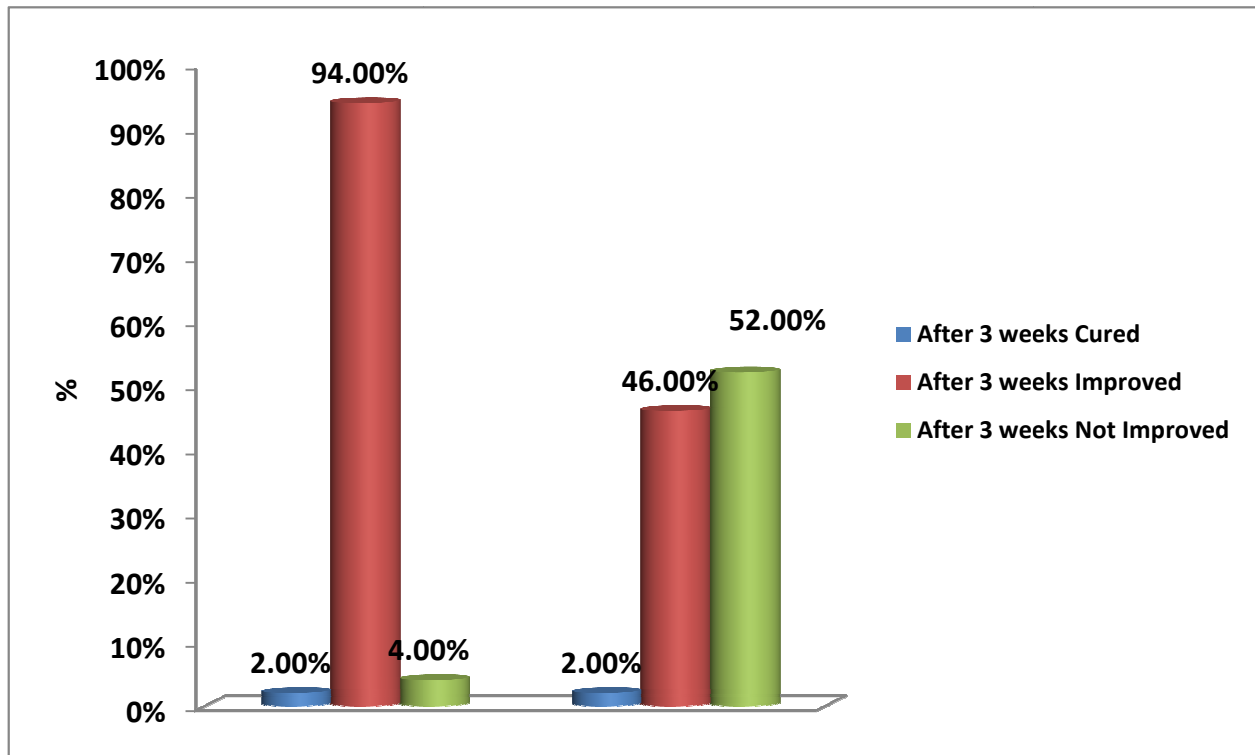
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194 Table 3: Acne improvement according to type of drug used and duration of  
195 treatment

196

Improvement		Drug used			
		Adapalene		Isotretinoin	
		N	% of Total N	N	% of Total N
After 3 weeks	Cured	1	2.00%	1	2.00%
	Improved	47	94.00%	23	46.00%
	Not Improved	2	4.00%	26	52.00%
After 6 weeks	Cured	45	90.00%	4	8.00%
	Improved	5	10.00%	25	50.00%
	Not Improved	0	0.00%	21	42.00%

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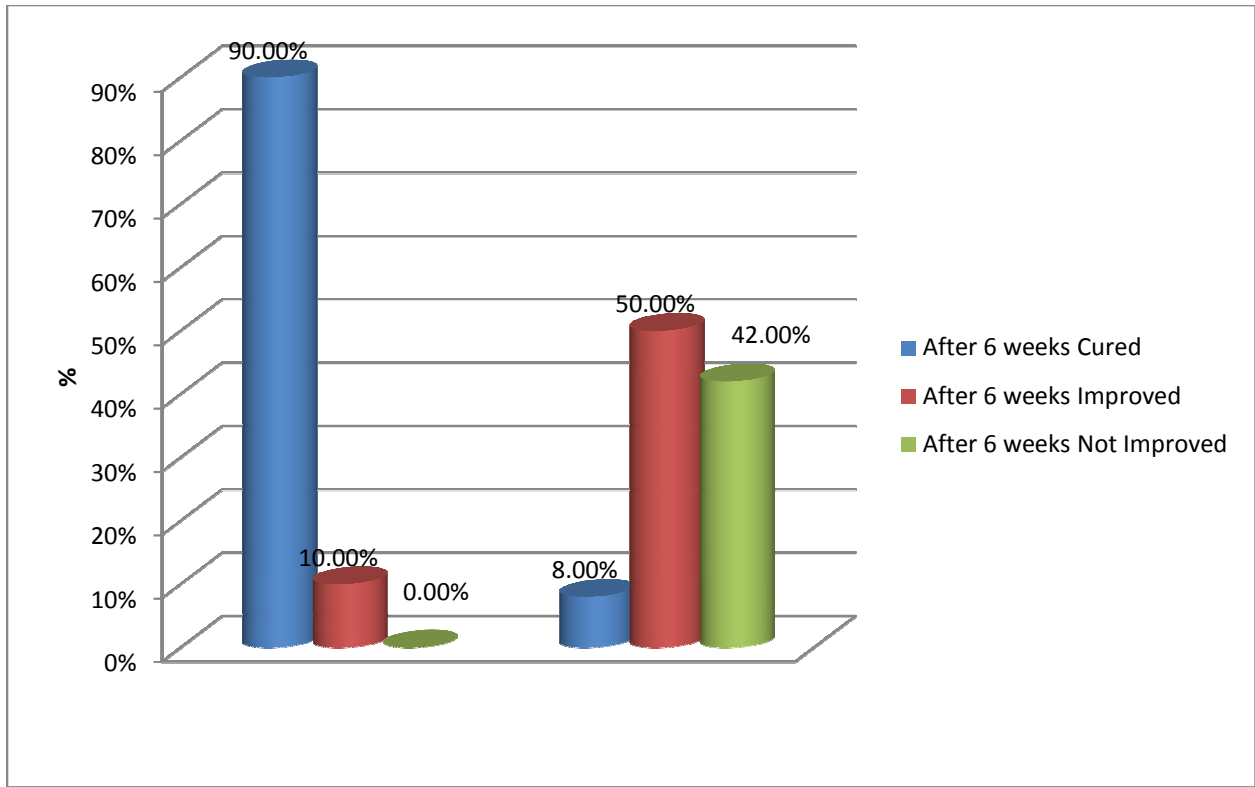


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Figure 4: Acne improvement according to type of drug used after 3 weeks



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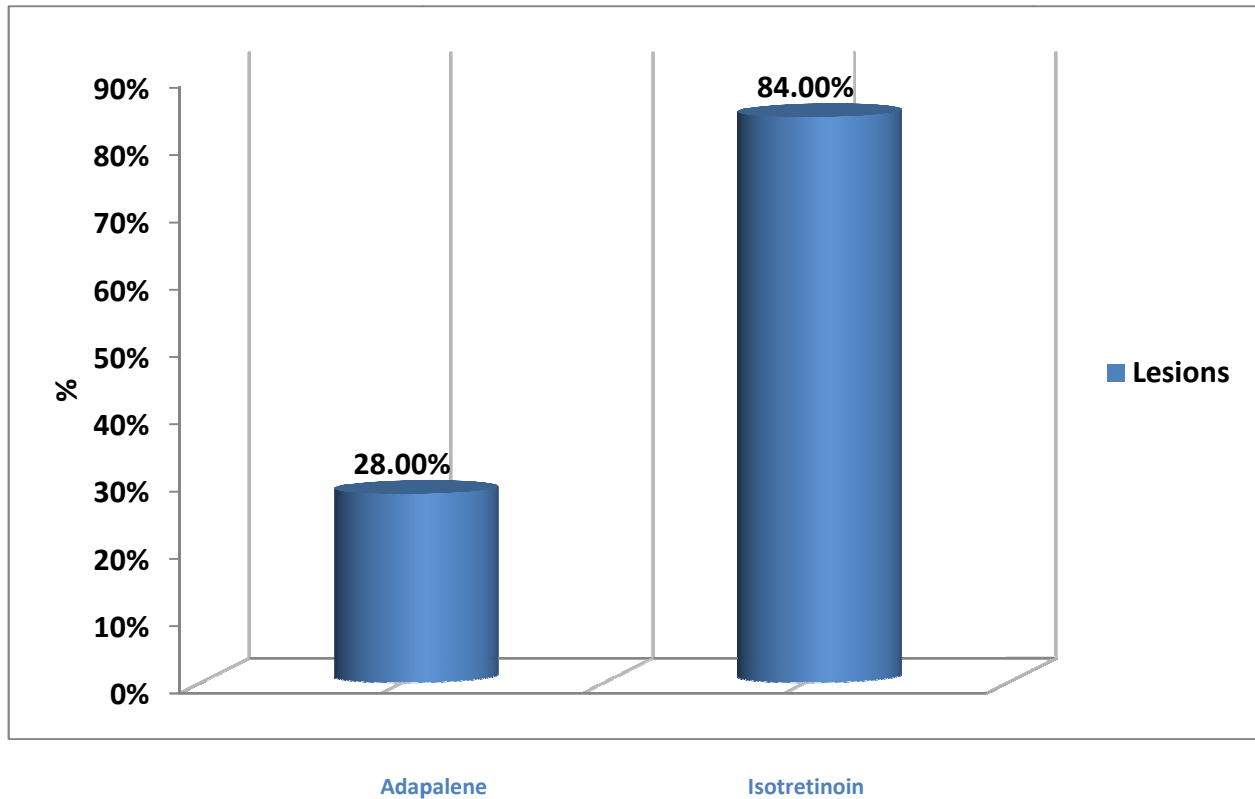
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Figure 5: Acne improvement according to type of drug used after 6 weeks



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208 Figure 6: Lesions after treatment among Adapalene and Isotretinoin group

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210

**Table 4 Adverse drug reactions according to type of drug used**

Adverse drug reactions	Drug used			
	Adapalene		Isotretinoin	
	N	% of Total N	N	% of Total N
Scaling	10	20.00%	37	74.00%
Erythema	14	28.00%	24	48.00%
Burning sensation	5	10.00%	21	42.00%
Pruritus	5	10.00%	16	32.00%
Others	3	6.00%	6	12.00%

211

212

213 DISCUSSION

214 Acne vulgaris is a chronic, inflammatory disease of the pilosebaceous unit, that  
215 affects seborrhoeic areas like face, back, and chest and characterized by comedons,  
216 papules, pustules, nodules, cysts, and scars. Almost every individual has some  
217 degree of acne during puberty with spontaneous resolution occurring in early adult  
218 life. Occasionally, the disease persists into the fourth decade or even remains a  
219 lifelong problem. Because of the involvement of the face with considerable  
220 cosmetic problems, acne is a major psychosocial problem for many teenagers and  
221 young adults<sup>(15-17)</sup>.

222 The treatment of acne vulgaris is not curative. The purpose is to reduce  
223 discomfort due to inflamed lesions, to improve the appearance, and to prevent  
224 scars. Acne management is a long-term treatment and requires patience. The  
225 patient should be informed on the issue<sup>(15, 18)</sup>.

226 Topical treatment of acne vulgaris has changed over the years. Agents  
227 containing sulphur or resorcinol were used in especially first part of 20<sup>th</sup> century.  
228 Salicylic acid which is a keratolytic agent was popular in some time. Nowadays,  
229 the most popular topical agents were retinoids, benzoyl peroxide, azelaic acid, and  
230 topical antibiotics<sup>(19)</sup>.

231 Topical application of Isotretinoin and Adapalene has proved effective in  
232 treating acne vulgaris. Both drugs demonstrate therapeutic advantages and less  
233 irritancy over tretinoin, the most widely used treatment for acne. They both act as

234 retinoid agonists, but differ in their affinity profile for nuclear and cytosolic  
235 retinoic acid receptors.

236 The objectives of this study were to compare the efficacy and tolerability of  
237 Adapalene cream 0.1% and Isotretinoin cream 0.05% in the treatment of acne.

238 Result indicated that both Adapalene cream 0.1% and Isotretinoin are effective in  
239 treating acne. However Adapalene was found significantly more effective than  
240 Isotretinoin, After 6 weeks of treatment all patient (Mild and Moderate) treated  
241 with Adapalene were either cured or improved, while among Isotretinoin group  
242 42% of patients were not improved and 50% improved. Patients remained with  
243 lesions after 6 weeks of treatment among Adapalene group were significantly  
244 lesser than among Isotretinoin group. This result with agrees with previous studies  
245 by Ioannides *et al* and Ahmed *et al*<sup>(20,21)</sup>. All these studies ensured the efficacy of  
246 Adapalene in comparison with other different retinoids.

247 The study demonstrated that Adapalene has faster effect than Isotretinoin. After  
248 3 weeks of treatments 96 % of patients treated with Adapalene were either cured  
249 or improved, while among Isotretinoin group the percentage was 48 %.The faster  
250 onset of action of Adapalene was also recorded by considering the safety and  
251 tolerability and like many previous studies<sup>(20,21)</sup> Adapalene showed significantly  
252 higher safety and tolerability concomitant with Iftikar<sup>(14)</sup>.The safety and tolerability  
253 was assessed depending on the degree of scaling, erythema, burning sensation and



254 pruritus. This anti-inflammatory effect is due to inhibition of the lipooxygenase  
255 activity and also to oxidative metabolism of arachidonic acid. These mechanisms  
256 may be the reason for decreased risk of irritation with **Adapalene**. Adapalene has a  
257 very low percutaneous absorption once the drug has penetrated the stratum  
258 corneum, so that it becomes entrapped in the epidermis and hair follicle, which are  
259 targeted areas. Only trace amounts (0.25 ng/ml) of parent substance have been  
260 found in the plasma of acne patients following chronic topical application of  
261 Adapalene in controlled trials. Excretion appears to be primarily by the biliary  
262 route. Erythema, peeling, dryness and burning are the most frequent encountered  
263 side effects accorded with Millikan results<sup>(22)</sup>.

264

## 265 **CONCLUSIONS**

266 The purpose of treatment of acne vulgaris is to reduce discomfort due to  
267 inflamed lesions, to improve the appearance, and to prevent scars. Both **Adapalene**  
268 cream 0.1% and **Isotretinoin** are effective in treating acne, however **Adapalene** was  
269 found significantly more effective than Isotretinoin. Adapalene has faster onset of  
270 action of, which reflect on patients psychologically in term of improvements,  
271 comforts and good appearance. Significantly lower skin irritation was noted with  
272 Adapalene, indicating that **Adapalene** may begin a new era of treatment with low-  
273 irritant retinoids.

## 274 **RECOMMENDATIONS**

275           Adapalene treatment is a good choice for topical treatment of acne vulgaris  
276 with less side effects and high efficacy. Adapalene should be described as first line  
277 for treatment of acne vulgaris.

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