

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

24 retinoids. It seems that, **Adapalene** treatment is a good choice for topical treatment
25 of acne vulgaris with less side effects and high efficacy. Adapalene should be
26 described as first line 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⁽¹⁾.

32 Although less frequently encountered than in adolescence, a significant number of
33 adults, and 20 years of age or older, also have acne⁽¹⁾. 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⁽²⁾. 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⁽³⁾. Numerous clinical research studies have been
39 undertaken on its epidemiology in western countries^(1,4,5). However, comparatively
40 few have been undertaken in African and Asian populations^(6,7).

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⁽⁴⁾. Topical retinoids
47 such as Tretinoin, Isotretinoin, or Adapalene are effective in many patients with
48 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⁽⁹⁾. 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 corneum,
61 and they have been associated with sun sensitivity. So patients should be instructed
62 about sun protection⁽⁸⁾. Retinoids are used in the treatment of many diverse

63 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⁽⁹⁾.

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⁽¹⁰⁾.

69 Adapalene has been shown to enhance the efficacy of topical clindamycin,
70 although adverse effects are also increased⁽¹¹⁾. Application of Adapalene gel to the
71 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⁽¹²⁾.

74 Unlike tretinoin (Retin-A), Adapalene has also been shown to retain its efficacy
75 when applied at the same time as benzoylperoxide due to its more stable chemical
76 structure^(8,9). 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⁽¹³⁾.

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⁽¹³⁾.

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⁽¹⁴⁾.

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
$$N = \frac{Z^2 (PQ)}{D^2}$$

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 intolerance 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 ± 10.15 and 24.28 ± 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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 173

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

175

176 **Table 2: The gender distribution of Adapalene and Isotretinoin groups**

Gender	Drug used		Total
	Adapalene	Isotretenoin	
Male	11	11	22
	22.00%	22.00%	22.00%
Female	39	39	78
	78.00%	78.00%	78.00%

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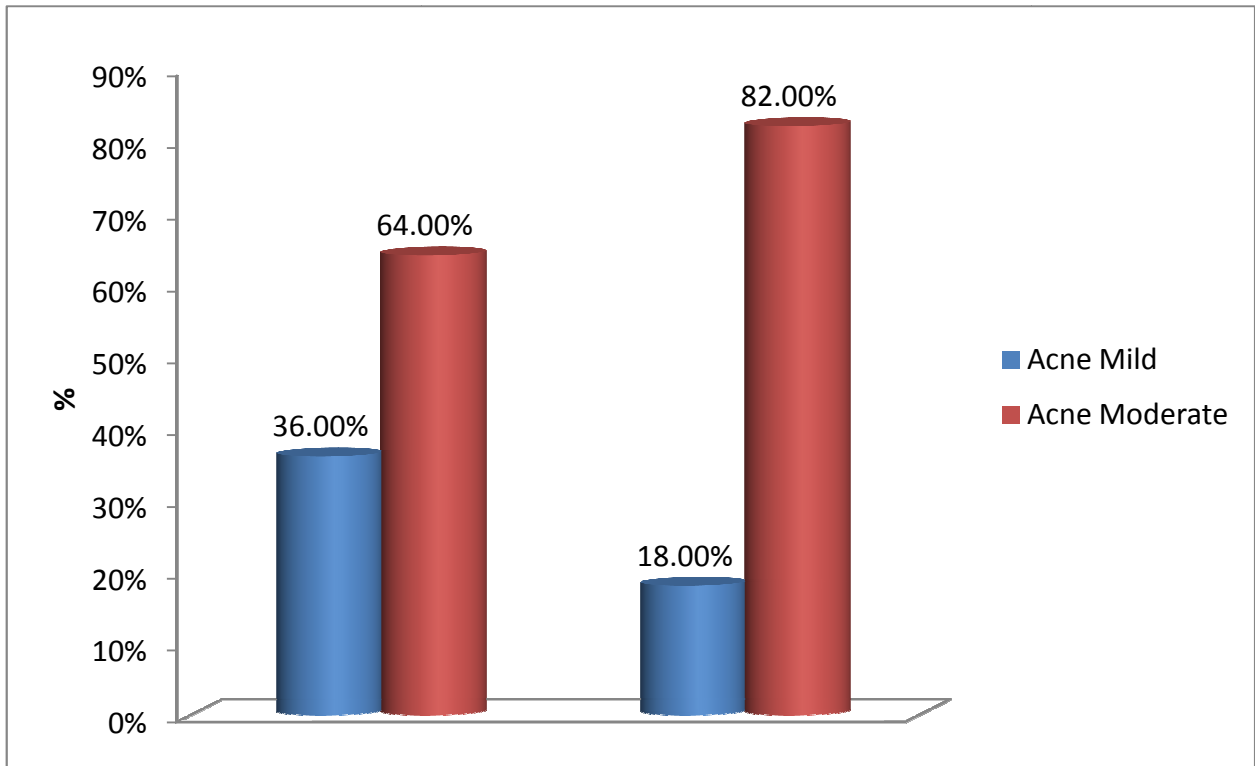
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181 Table 3: Distribution of type of drug used according to acne severity and
 182 inflammatory

		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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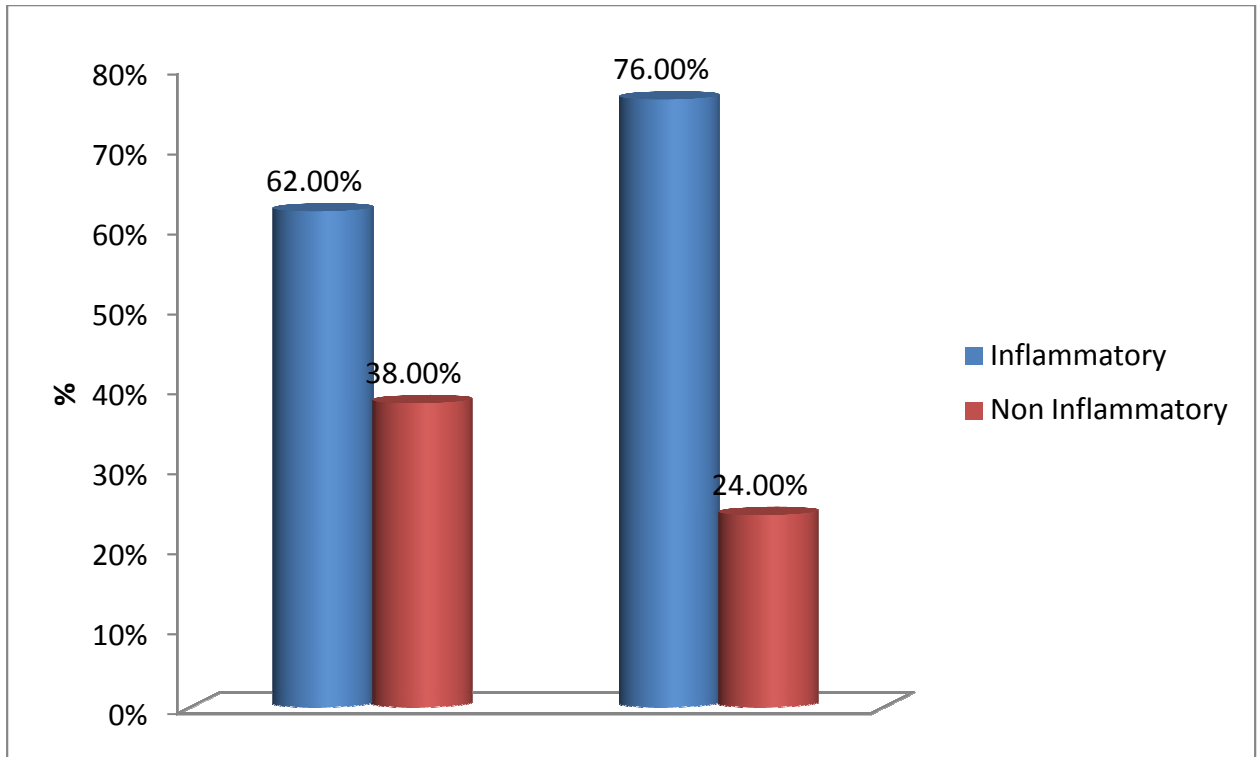
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185 [Adapalene Isotretinoin](#)

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187 Figure 1: Distribution of type of drug used according to acne severity

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Adapalene Isotretinoin

191 Figure 2: Distribution of type of drug used according to Inflammatory.

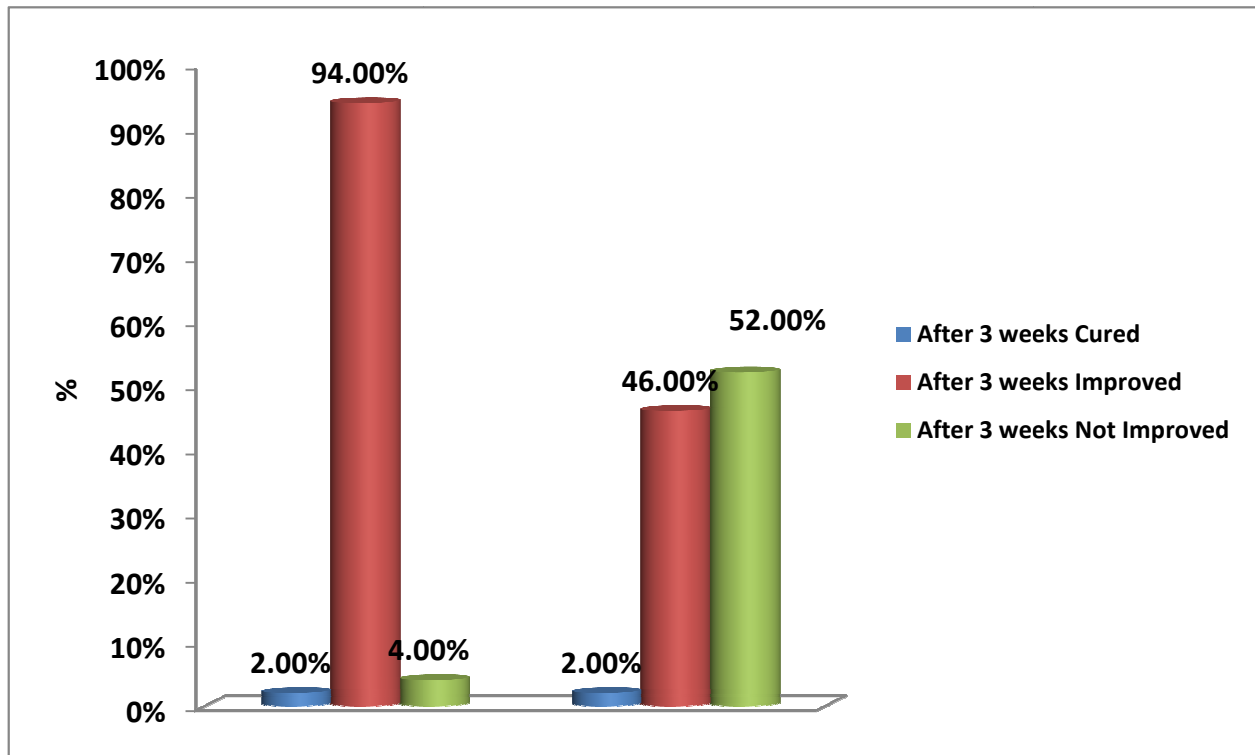
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193 Table 4: Acne improvement according to type of drug used and duration of
194 treatment

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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%

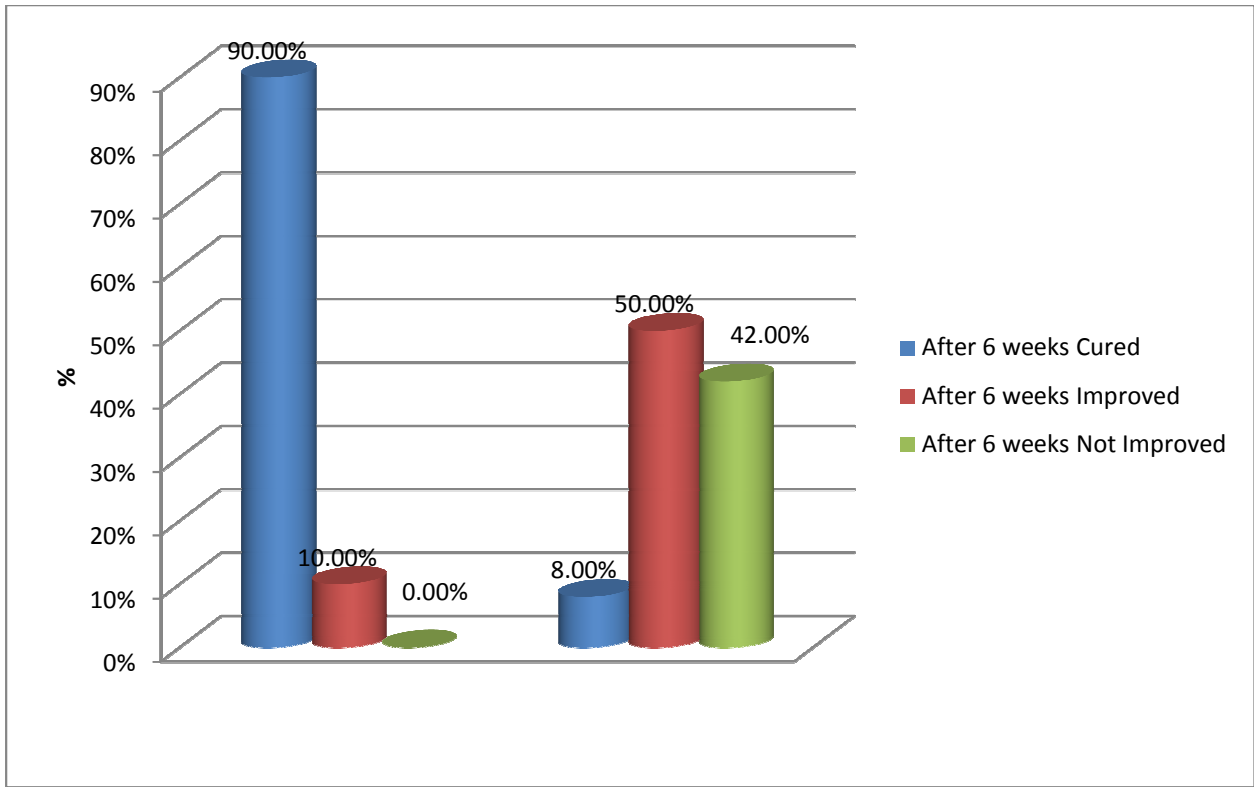
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198 **Adapalene Isotretinoin**

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



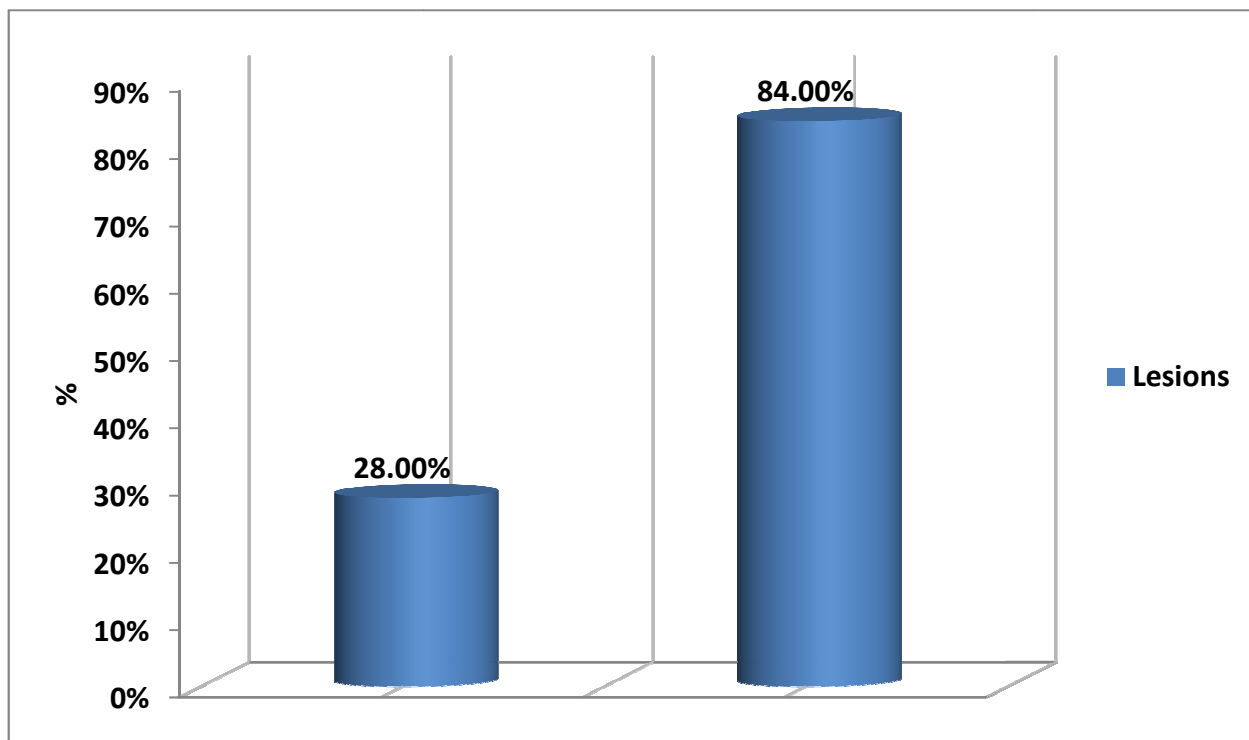
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201 Adapalene Isotretinoin

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203 Figure 4: Acne improvement according to type of drug used after 6 weeks

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206 **Adapalene Isotretinoin**

207 Figure 5: Lesions after treatment among Adapalene and Isotretinoin group

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209 **Table 5 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%

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211

212 DISCUSSION

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

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

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

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

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

235 The objectives of this study were to compare the efficacy and tolerability of
236 Adapalene cream 0.1% and Isotretinoin cream 0.05% in the treatment of acne.
237 Result indicated that both Adapalene cream 0.1% and Isotretinoin are effective in
238 treating acne. However Adapalene was found significantly more effective than
239 Isotretinoin, After 6 weeks of treatment all patient (Mild and Moderate) treated
240 with Adapalene were either cured or improved, while among Isotretinoin group
241 42% of patients were not improved and 50% improved. Patients remained with
242 lesions after 6 weeks of treatment among Adapalene group were significantly
243 lesser than among Isotretinoin group. This result with agrees with previous studies
244 by Ioannides *et al* and Ahmed *et al*^(20,21). All these studies ensured the efficacy of
245 Adapalene in comparison with other different retinoids.

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

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

263

264 **CONCLUSIONS**

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

273 **RECOMMENDATIONS**

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

277 REFERENCES

- 278 1. Collier CN, Harper JC, et al . The prevalence of acne in adults 20 years and older.
279 JAm Acad Dermatol2008; 58: 56 9.
- 280 2. Layton AM, Henderson CA, Cunliffe WJ. A clinical evaluation of acne scarring
281 and its incidence. Clin Exp Dermatol1994; 19: 303-8.
- 282 3. Smithard A, Glazebrook C, Williams HC. Acne prevalence, knowledge about acne
283 and psychological morbidity in mid-adolescence: a community-based study. Br J
284 Dermatol2001; 145: 274-9.
- 285 4. Goulden V, Stables GI, Cunliffe WJ. Prevalence of facial acne in adults. J Am A
286 cad Dermatol1999; 41: 577-80.
- 287 5. Cunliffe WJ, Gould DJ. Prevalence of facial acne vulgaris in late adolescence and
288 in adults. Br Med J 1979; 1: 1109-10.
- 289 6. Yeung CK, Teo LH, Xiang LH et al. A community-based epidemiological study
290 of acne vulgaris in Hong Kong adolescents. Acta Derm Venereol 2002; 82: 104-7.
- 291 7. Tan HR, Tan A W, Barkham T, et al. Community-based study of acne vulgaris in
292 adolescents in Singapore. Br J Dermatol2007; 157: 547-51.
- 293 8. Kang S, Voorhees JJ. Topical retinoids. In: Fitzpatrick's Dermatology in General
294 Medicine, 7th ed, Wolff, et al (Eds), McGraw Hill, 2008. p.2106.
- 295 9. Stefanaki C, Stratigos A, Katsambas A (June 2005). "Topical retinoids in the
296 treatment of photoaging". *J Cosmet Dermatol*4 (2): 130–4. doi:10.1111/j.1473-
297 2165.2005.40215.x. PMID 17166212.
- 298 10. Rolewski S (2003). "Clinical review: topical retinoids". *Dermatol Nurs* 15 (5):
299 447–50, 459–65.

- 300 11. Wolf JE, Kaplan D, Kraus SJ, et al. (2003). "Efficacy and tolerability of combined
301 topical treatment of acne vulgaris with Adapalene and clindamycin: a multicenter,
302 randomized, investigator-blinded study". *J Am Acad Dermatol* 49 (3 Suppl):
303 S211–7.
- 304 12. Jain GK, Ahmed FJ (2007). "Adapalene pretreatment increases follicular
305 penetration of clindamycin: in vitro and in vivo studies". *Indian J Dermatol*
306 *Venerol Leprol* 73 (5): 326–9. doi:10.4103/0378-6323.34010. PMID 17921613.
- 307 13. Martin B, Meunier C, Montels D, Watts O (October 1998). "Chemical stability of
308 Adapalene and tretinoin when combined with benzoyl peroxide in presence and in
309 absence of visible light and ultraviolet radiation". *Br J Dermatol* 139 Suppl 52: 8–
310 11. doi:10.1046/j.1365-2133.1998.1390s2008.x. PMID 9990414.
- 311 14. Ahmed I, Sarwar M. Topical Adapalene cream 0.1% v/s Isotretinoin 0.05% in the
312 treatment of acne vulgaris: a randomized open-label clinical trial. *Jof Pakistan*
313 *Assoc. of Dermatol* 2009; 19: 23-26.
- 314 15. Cunliffe WJ, Poncet M, Loesche C, et al. 1998. A comparison of the efficacy and
315 tolerability of Adapalene 0.1% gel versus tretinoin 0.025% gel in patients with
316 acne vulgaris: a meta-analysis of five randomized trials. *Br J Dermatol*,139 Suppl
317 52:48–56.
- 318 16. Strauss JS, Thiboutot DM. 1999. Diseases of sebaceous glands. In Freedberg MI,
319 Eisen AZ, Wolff K, Austen KF, Goldsmith LA, Katz SI, Fitzpatrick TB, eds.
320 *Dermatology in general medicine*. 5th ed . New York: McGraw Hill Co. p 769–84.
- 321 17. Braun-Falco O, Plewig G, Wolff HH, et al. 2001. *Dermatology*. 2nd ed. Berlin:
322 Springer-Verlag.
- 323 18. Oberemok SS, Shalita AR. 2002. Acne vulgaris, II: treatment. *Cutis*, 70:111–4.
- 324 19. Bergfeld WF. 1998. The evolving role of retinoids in the management of
325 cutaneous conditions. *Clinician*, 16:1–32.
- 326 20. Ioannides D, Rigopoulos D , Katsambas A. 2002. Topical Adapalene gel 0.1% vs.
327 Isotretinoin gel 0.05% in the treatment of acne vulgaris: a randomized open-label
328 clinical study. *Br J Dermatol*, 147:523–27.

- 329 21. Ahmed I, Sarwar M. Topical Adapalene cream 0.1% v/s Isotretinoin 0.05% in the
330 treatment of acne vulgaris: a randomized open-label clinical trial. Journal of
331 Pakistan Association of Dermatologists 2009; 19: 23-26.
- 332 22. Millikan LE. 2000. Adapalene : an update on newer comparative studies between
333 the various retinoids. Int J Dermatol, 39:784–8.

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