EVALUATION OF AZITHROMYCIN IN TREATMENT OF ACNE VULGARIS COMPARED WITH DOXYCYCLINE

A Thesis submitted
By

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Dedication

TO WHO IS FLASH IN OUR LIFE AND GONE

TO THE SPIRIT OF MY LOVELY SON...AHMED

ACKNOWLEDGEMENT

I would like to thank Dr. Sania Shaddad for her all

advice and effort to help me make this study as

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Also I am very grateful to my wife and my daughters
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ملخص الدراسة

يعتبر مايعرف بحب الشباب من اكثر الامراض الجلدية التى تصيب الانسان فى مرحلة المراهقة، ولاتكاد تمر هذه المرحلة من دون ان يصاب ببعض الذؤان والبثور. ويعتبر العلاج ضروريا فى تلك المرحلة لكى نمنع ماقد تحدثه من ندبات على الوجه مما يؤدى الى بعض حالات الاضطراب النفسى والاكتئاب.

وبالرغم من ان هنالك كثير من الادوية المعالجة لحب الشباب ولكن أصبحت هنالك تحديات متزايدة لفعالية هذه الادوية بسبب وجود فصائل متزايدة من بكتيريا حب الشباب المقاومة للمضادات الحيوية .

كما أن العلاجات الفموية التى تستخدم حاليا مثل الدوكسيسايكلين والارثرومايسين والتى تخفف الحالات الالتهابية للمرض تتطلب جرعات متعددة ولفترات طويلة حتى تؤدى مفعولها وترتبط كذلك بأعراض جانبية غير مريحة للمريض، ناتجة من قلة راحة المريض للعلاج .

مؤخرا تم طرح عقار جديد فى السودان من عائلة الماكرولايد وهو الازيثرومايسين يتوقع ان ياتىبنتائج جيدة فى هذه الحالة وذلك بناء على مميزاته المتفردة فى الحرائك الفارماكولوجية والدينماكية ومقدرته الاختراقية للانسجة. وقد أجريت هذه الدراسة لتقييم فعالية الازثرمايسين على مرض حب الشباب.

هذه الدراسة تم اجراءها فى مستشفى امدرمان التعليمى _ قسم الامراض الجلدية والغرض الاساسى من هذه الدراسة هو تحديد مدى فعالية علاج الازثرومايسين الفموى فى علاج حب الشباب وذلك بمقارنته مع اكثر العلاجات استخداما وهو الدوكسيسايكلين.

أجريت هذه الدراسة المقارنة على عينة عشوائية من (30) مريض تم تقسيمهم الى مجموعتين، مجموعة تناولت عقار الازثرومايسين وفق جرعات محددة وعددهم (15) والمجموعة الاخرى تناولت عقار الدوكسيسايكلين وفق الجرعة العلاجية المعتادة وعددهم (15).

اظهرت النتائج المستخلصة ان علاج الازيثرومايسين الفموى بمقارنته مع الدوكسيسايكلين انه لايوجد ختلاف معنوى أحصائى بين العقارين من ناحية المفعول بعد 22 اسبوعا من المعالجة.

اما فيما يخص انقاص حدة المرض اظهرت الدراسة ان الانقاص العام لمرضى مجموعة الازثرومايسين افضل من مجموعة الدوكسيسايكلين عند المقارنة مع الحالة المرضية قبل العلاج (83% مقابل 50%).

وبتقييم الاعراض الجانبية ونسبة الذين تساقطوا عن الدراسة نجد ان النسبة العالية كانت فى مجموعة الدوكسيسايكلين (33.3%) مقابل (6.66%) فقط من مجموعة الازثرومايسين.

وباخذ رأى المرضى المعالجين كاحدى معايير الدراسة أكد معظم المرضى من مجموعة الازثرومايسين بانهم يشعرون بتحسن واضح مقارنة مع ماتم تداوله من قبل من ادوية من ضمنها الدوكسيسايكلين.
تم أجراء دراسة صغيرة تكميلية للدراسة السابقة لمعرفة مدى فعالية مستحلب الازثرومايسن على المرضى فى حالة استخدامه كعلاج موضعى للجلد لحب الشباب وذلك بتجريبه على 10 مرضى من حالات حب الشباب الخفيف والمتوسط ولكن النتائج المستخلصة كانت غير مشجعة فى الاستمرار وذلك للاعراض الجانبية من تحسس الجلد الناتج عن الحامل المستخدم.
أوضحت الدراسة الحالية ان عقار الازثرومايسين الفموى يمكن ان يشكل علاج فعال وامن يضاف الى الخيارات المتاحة حاليا وتمتد ايضا فعاليته لاستخدامه للمرضى الذين لايستجيبون للعلاجات المستخدمة .
اما فيما يختص بعلاج الازيثرومايسين الموضعى فانه يتطلب اجراء مزيد من البحث ودراسات اوسع لتحديد المستحضر المناسب الذى يمكن ان يعطى نتائج واضحة يمكن ان تكون له مزايا افضل عن المستحضرات المستخدمة حاليا.

Abstracts

Acne vulgaris is the most common dermatological disorder in adolescence.

As a matter of fact no individual transit through adolescence with out a few comedones and papules. Treatment is essential to prevent physical and psychological effects scarring occurred; acne is frequently associated with profound emotional aspects and depression.

Although many treatments for acne are available, effective management has become increasingly challenging with the emergence of antibiotic-resistant strains of *Propionibacterium acnes.* Also systemic antimicrobial agents currently used such as doxycycline and erythromycin to reduce the inflammatory acne they require frequent administration for a long term therapy and some times associated with uncomfortable side effects contributing mainly to a decrease in compliance.

Of-late, newer macrolide azithromycin circulated in Sudan market expected to show promising results in this condition due to its unique pharmacokinetic profiles and high thermodynamic properties and penetrative potentials . This study was conducted to evaluate the role of azithromycin in treatment of acne vulgaris.

The present study was conducted in Omdurman teaching hospital – department of Dermatology. The main aim of this study is to evaluate the efficacy of oral azithromycin in acne by comparing it with most common therapy used for acne; doxycycline.

An opened label randomized comparative study was carried out in (30) patients of moderate to sever acne vulgaris divided them into two groups, group (A) administered

azithromycin capsules (15) in a specified and scheduled dose regimen and group (B) administered doxycycline tablets (15)as a usual regimen of therapy.

The results obtained from oral azithromycin therapy when compared with oral doxycycline show that statistically there is no difference between the two drugs in response at end of 22 weeks. The overall efficacy rated in terms of reduction of the severity of condition is up to 83% with azithromycin compared to 50% with doxycycline

In assessment of adverse effects and dropped-out rates the higher dropped- out rate found in doxycycline group (33.3%) while only (6.66%) for azithromycin group.

Also the patients opinion as an outcome measures most of them confirm that they feel much better with azithromycin rather than doxycycline.

Another minor complementary trial was adopted and we tried a topical formulation of azithromycin emulsion in 10 patients of mild to moderate acne but the results didn't encourage us to continue due to the skin irritation from the vehicle used.

The conclusion from the present study that oral azithromycin provides additionally effective and safe treatment option to the patients, and benefits may be further extended to those patients not responding to available antibiotic therapy.

For the topical application of azithromycin the trial suggests that the need for further investigation and larger studies to find out a suitable vehicle and stable formulation for azithromycin to be applied topically and to determine whether it will give any significant results and have any advantages over the currently used topical formulations.

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INTRODUCTION & LITERATURE REVIEW

بسم الله الرحمن الرحيم

1. INTRODUCTION

1.1 ACNE VULGARIS

1.1.1 Overview

A. Definition:

Acne vulgaris, or common acne, is a skin disorder of the pilosebaceous unit,

mainly of the face, chest and back that generally develops in adolescence and

improves in adulthood. The lesions usually start as open or closed comedones

and evolve into an inflammatory papules and pustules that either resolve as

macules or becomes secondary pyoderma, which results in various squeal.

Effective treatment, is essential to prevent physical and psychological scarring.

B. Importance:

Acne vulgaris is usually self-limiting, however, the condition is significant to

adolescents because of heightened self consciousness about appearance.

A great majority of people does not consult a physician for treatment of acne

therefore a pharmacist can play a significance role.

1.1.2 Epidemiology:

Acne vulgaris is the most common skin disease of adolescence; it affects about

90% of adolescents it affects primary adolescents in junior high and senior high,

then decrease in adulthood.

Age: 10 to 17 years in females, 14 to 19 in males; may appear first at 25 years or

older, acne may persist to age 35 or older.

Sex: More sever in males than in females.

Race: lower incidence in Asians and blacks, rare in China.

(Thomas *et al .,* 1998)

1.1.3 Etiology and Pathophysiology of Acne:

To help in understanding of skin lesions, it is necessary to be acquainted with

various descriptive terms used to characterized the lesions of acne vulgaris, the

important not only for defining the skin lesions in a given case but also help in

physical examination, diagnosis and assessment of the severity of the case :

Macule:

It is a flat colored lesion less than 2 cm in diameter, which is not raised above

the surface of surrounding skin.

Papule:

It is a small solid lesion with diameter less than 1 cm, raised above the surface of

the surrounding skin, and hence it can be palpated, (Figure 1.1-D) .

Nodule:

It is raised lesion larger than 1 cm, which is firm and therefore easily palpable.

It differs from a papule only in size.

Vesicle:

It is a small fluid-filled lesions less than 1 cm in diameter. Such lesion is often

translucent.

Pustule:

It is a vesicle filled with leucocytes (Figure 1.1-E).

Bulla:

A raised lesion , more than 1 cm in diameter and with fluid.

Cyst:

A soft, raised, encapsulated lesion 1-4 cm in diameter, which contains semisolid

or liquid material.

Wheal:

Raised erythematous papule, which is usually short-lived dermal edema.

Patch:

A maculae, larger than 2 cm.

Pimple:

Nonspecifically refers to whiteheads, blackheads, papules and pustules.

(Thomas *et al*., 1998).

The pathogenesis of acne vulgaris involves 3 events:

A. **Increased sebum production**

1. Sebum secretion is regulated primary by androgens, which are actively secreted in both sexes beginning at puberty.

2. One of these androgens testosterone is converted to dihydoteseosterone (DHT).

3. (DHT) levels induce the sebaceous glands to increase the size and activity resulting in increased amounts of sebum.

B. Abnormal clumping of epithelial horny cells within the pilosebaceous unit

1/ Normally keratinized horny cells are sloughed from the epithelial lining of the pilosebaceous duct in the hair follicles and are carried to skin surface with a flow of sebum. Figure 1.1- A.

2/ In the patient with acne the kertinization process is abnormal, characterized by increased adherence and production of follicular epithelial cell.

Earliest changes in the hair follicle occur when the follicular canal becomes blocked with abnormally keratinized desquamating cells, this process called retention hyperkeratosis and it results in obstruction of the outflow of pilosebsebaceous unit and plugging of the hair follicle with abnormally cohesive

desquamated cells. This plug starts above the opening of the sebaceous gland

into the follicular canal and causes gradual expansion of cells and sebum within

the canal.

C. **Presence of bacteria (*Propionibacterium acnes)* within sebum**.

1/ Increased sebum alone does not cause acne. Bacteria, most importantly

Propionibacterium acnes are present in increased numbers in persons who have

acne. So people with acne have skin colony counts of *Propionibacterium acnes*

that are significantly higher than the counts without acne.

2/ *Propionibacterium acnes* (gram-positive anaerobic bacteria) produces several

enzymes, including lipases, that break down sebum triglycerides to short – chain

free fatty acids, which are irritating cause comedones and result in inflammation .

(Leon *et al.*, 2000 ; Brown & Shalita, 1998)

Sequence of acne lesion development:

a. Mechanical blockage of a pilosebaceous duct by clumped horny cells

results in a closed comedo (whitehead) Figure 1.1-B.

b. When a closed comedo develops, it can form either a papule or open

comedo (blackhead) Figure 1.1-C.

The color is attributed to melanin or oxidized lipid and not to dirt.

c. With increased sebum production, obstruction and bacterial colonization, the

follicular unit ruptures, spilling its contents into the dermis. The neutrophils

inflow the lesion enlarge and fill with pus and becomes a pustule. Figure 1.1-D.

d. In more sever cases of acne papules may develop into nodules or cysts, due to

continuation of severe inflammation.

e. Scarring occurs to some degree in almost every patient. Scars may show

increased collagen (hypertrophic scars and keloid) or be associated with loss of

collagen (i.e. ice-pick scars, depressed fibrotic scars, superficial and deep, soft

scar and macular atrophy).

(Leon *et al*., 2000 ; Leyden JJ 2001).

1.1.4 Clinical Features:

1. Location: Acne vulgaris usually occur on the face, neck chest, upper back, and

shoulders. Any or all types of lesions may be seen on a single patient.

2. Shape: Round; nodules may coalescence to form linear mounds or sinus tract.

3. Arrangements: Isolated single lesion (e.g. nodule) or scattered discrete lesions

(papules, cysts, nodules).

4. Duration of lesions: Weeks to months to years.

5. Seasons: Often worse in fall and winter.

6. Signs and symptoms: The physical signs of acne vulgaris are blackheads (open

comedone), white heads (closed comedone), papules, pustules, abscesses and

cysts. Seborrhea is a frequent association. The face is the commonest site

involved. shoulders, nape of neck and the upper trunk can also be affected.

It is not uncommon for acne vulgaris to localize in one particular area.

This condition is usually a symptomatic; however some patients may have

pruritis or pain if large, tender lesions are present.

(Thomas *et al*., 1998).

There are other variants types of acne with different signs and symptoms include:

(i) **Acne conglobata** - characterized by deep and painful papules and nodules

with cystic lesions. Grouped, multiple blackheads and extensive scarring are also

present.

(ii) **Acne fulminans** - a rare variant seen almost exclusively in adolescent boys.

The patient suddenly develops acute inflammatory lesions, which may become

necrotic with hemorrhagic crusting. There is associated fever, myalgia,

arthralgia, and even frank arthritis. The condition is immunologically mediated

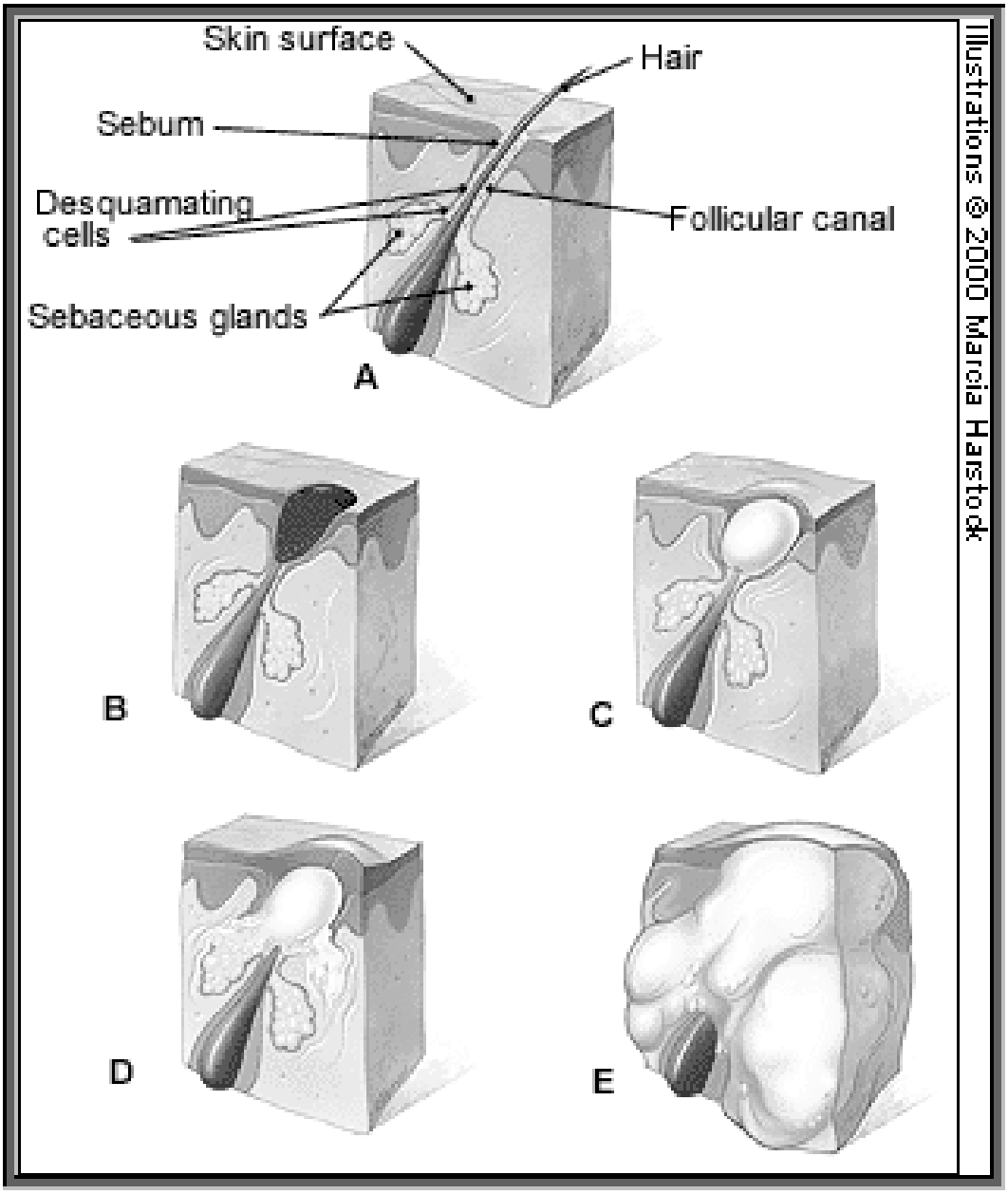
and requires treatment with systemic steroid.

(iii) **Acne excoriée** - this is a facial disorder secondary to an obsessional and

neurotic tendency to interfere with the skin. Acne lesions may be mild or even

absent and the physical signs are mainly unsightly excoriations and scarring.

(Kheng and Lee 1998 ; Thomas *et al.,* 1998).


Skin surface
Hair
Sebum
Desquamating cells
Follicular canal
Sebaceous glands
A
B
C
D
E
Illustrations © 2000 Marcia Harstock

1.1.5 *Complicating* factors

There are many factors have been implicated in exacerbation of acne such as:

1. Drugs and hormones:

Many topical and systemic medications (e.g. bromides, iodides, topical coal tar

products, androgens, phenytoin, lithium, corticosteroids) can be comedogenic and

can make acne worse or can induce acne-like eruptions (i.e., acneiform lesions).

2. Stress.

Despite rare individual exceptions, psychological stress is generally not though to

contribute to severity or exacerbation of acne.

3. Diet:

There is very little evidence to support a relationship between diet and acne.

Many difference food have been blamed for acne, from chocolates and sweets to

shellfish to nuts and other fatty food. Several studies have demonstrated that

chocolate does not affect acne. As general the patient of acne should be eating a

well-balanced diet, as with the most of other diseases, and as a matter of good

health, excess fats and carbohydrates should be avoided. The patient who think

that certain foods cause exacerbation of acne should probably avoid those foods.

4. Physical traumas or irritation:

These can promote the rupture of plugged follicles, which can produce

inflammatory reactions. Scrubbing the face, wearing headbands, cradling the chin

with the hand, and picking at the pimples can contribute to the primary

inflammation process.

Gentle regular washing with soap and water can be beneficial.

5. Cosmetics:

Some cosmetics bases and certain cosmetics ingredients are comedogenic (e.g.

lanolins, petroleum bases, coca butter) . Preparations such as cleansing creams

suntan oils, and heavy foundation should be avoided.

6. Menstrual cycle:

Some women may notice flare-up of acne during the premenstrual part of the

cycle. Fluctuations in the level of progesterone are the probable cause.

7. Environmental factors:

Very humid environments or heavy sweating lead to keratin hydration, swelling,

and a decrease in the size of the pilosebaceous follicle orifice, which results in

duct obstruction. The sun as well the artificial ultraviolet (UV) light can help

acne by drying and peeling the skin but both also can aggravate acne.

(Leon *et al.*, 2000).

1.1.6 Assessment of Acne:

Assessments of acne must be clone before setting the therapy and development of

a successful management strategy for acne depends on effective assessment.

In assessment of acne we have to take into consideration the following:

- Acne severity.
- The age of onset of lesions.
- The patient's age.
- Skin type.
- The presence of complicating factors.
- How much the patient cares about his acne?

The number and type of lesions that are present should be roughly determined

to asses further therapeutic responses.

(Leyden JJ 1997*).*

There are many ways of assessing therapy of acne vulagaris:

A- The Severity Index Method:

This method is adopted by Michaelsson and Lennart and Vahlquist in 1977.

The following procedures were undertaken for clinical evaluation of acne:

The number of open and closed comedones, pustules, infiltrates, and cystic

lesions in the face and submandibular regions were recorded. Separate counts of

lesions in areas other than the face. An estimation of total severity was made by

giving each type of lesions a severity index, which ranged from 0.5 for

comedones to 4 for cysts. Although the indexes where chosen arbitrarily, they

seemed to be reasonably close to reality. By multiplying the number of each type

of lesion with its severity index and adding each sum, we obtained a total score

that corresponded to the severity of the disease. The type of lesions and their

definition and corresponding severity index is shown in the following table 1.1 .

(Michaelsson *et al.,* 1977).

Table 1.1 Definitions of Acne Lesions and Their Severity Index

Type	**Severity index**	**Definition**
Comedones	0.5	Horny follicular plugs with incipient

		inflammatory changes and pinheaded size superficial follicular papules
Papules	1.0	Independent, infiltrated papules 2-8 mm in diameter; coalescent papules have been counted separately if possible.
Pustules	2.0	Pustules larger than 2 mm in diameter with surrounding inflammatory reactions.
Infiltrates	3.0	Nodules and infiltrates over 8 mm in diameter and coalescent papules where individual papules cannot be distinguished.
Cysts	4.0	Lesions where the infiltrates has broken down and formed a cyst with discharge.

B- The Leeds techniques:

These techniques adopted by Burke and Cunliffe in 1984 and they assessed acne

by two different methods:

1/ The Grading System Method:

This method is done by an overall assessment of acne in a particular area (face,

back and chest) and give a grade scale between 0 (No acne whatsoever) to 10

(the most sever acne). The grade from 0-2 is further subdivided into subscales

0.25, 0.5, 0.75, 1.0, 1.25, 1.5 and 1.75. Grades 0.25 to 1.0 represents patients with

physiological acne or (acne minor) where as grades 1.5 or mores represents

patients with clinical acne (acne major) and the grades from 1.5 to 10 subdivided

into 0.5 divisions .

2/ The Counting Method:

Lesions were divided into inflamed and non inflamed as follows:

a) Noninflammed were closed comedos, or whiteheads; and open comedos, or

blackheads, any intermediate lesion were counted according to their major

component. Prominent follicles, small milia or trichostatis spinulosa must be

roughly excluded they occur frequently and would badly skew the result.

b) Inflammatory acne lesions were either superficial (papules and pustules) or

deep (nodules, cysts and deep pustules). Each type of lesion is counted after

perfect examination under background of flourcent lightning divide the face into

right and left and count both sides.

(Burke and Cunliffe 1984)

C. Severity grading of inflammatory lesions :

This Adapted from Handbook of Nonprescription drugs 11 ed. Washington –

American Pharmaceutical Association 1996. And shown in table 1.2.

Table 1.2 The severity grading of inflammatory acne lesions:

Type of acne / Severity	Comedones	Papules/Pustules	Nodules

Mild	**Few to Numerous** **< 25**	**Few to several** **< 10**	**None**
Moderate	**Numerous**	**Several to many** **> 10**	**Few to several**
Sever	**Extensive**	**Numerous and/or extensive> 25**	**Many**

(Leon *et al.,* 2000).

1.1.7 Management of Acne Vulgaris:

General:

There may be great fluctuations in the natural course of acne and further more the

response to placebo therapy is considerable. (Thomas *et al.,* 1993).

Apart from general measures, topical treatment alone is usually adequate for

patients with mild acne. For more severe acne, combination of a topical agent

with an antibiotic, or with hormonal therapy for female patient, is indicated.

It is better to combine agents having different mode of actions - for example

a keratolytic with an antimicrobial. Even the most effective treatment programs

may take several weeks to produce any clinical improvement . People affected

with acne should avoid anything that seems to worsen the conditions (e.g.

cosmetics, clothing, cradling the chin with the hand).

For acne conglobata, isotretinoin is the treatment of choice.

This general aspect must be emphasized in the treatment.

(Leon *et al.,* 2000).

Acne can be classified into three categories for the purposes of treatment,

comedonal, inflammatory and nodulocystic.

1. Comedonal acne consists predominantly of open or closed comedones with

little or no accompanying inflammation (Figure 1.2). This type of acne typically

responds to topical keratolytic agents that decrease the cohesiveness of the

follicular cells.

2. Inflammatory acne characterize by erythematous papules and pustules, but

comedones may also be present (Figure 1.3). Topical agents alone may be

insufficient to treat inflammatory acne, which may benefit from systemic

antibiotics.

3. Nodulocystic acne may consist of comedones and inflammatory lesions, as

well as deeper nodules and cysts (Figure 1.4). Although a six-month course of

systemic antibiotics may be effective, nodulocystic acne frequently requires

treatment with isotretinoin .

(Betty and Jullia 2000).

1.1.7.1. Cleansing recommendation:

a. Because many acne patients have oily skin, gentle cleansing two to three times

daily is recommended for removing excess oil.

b. Acne lesions cannot be scrubbed away. Compulsive scrubbing may actually

worsen the acne by disturbing the follicular walls and , thus, setting the stage for

inflammation.

c. Mild facial soaps, such as Dove, Neutrogena could be used to clean the skin.

d. Medicated soaps containing sulfur, resorcinol, or salicylic acid are of little

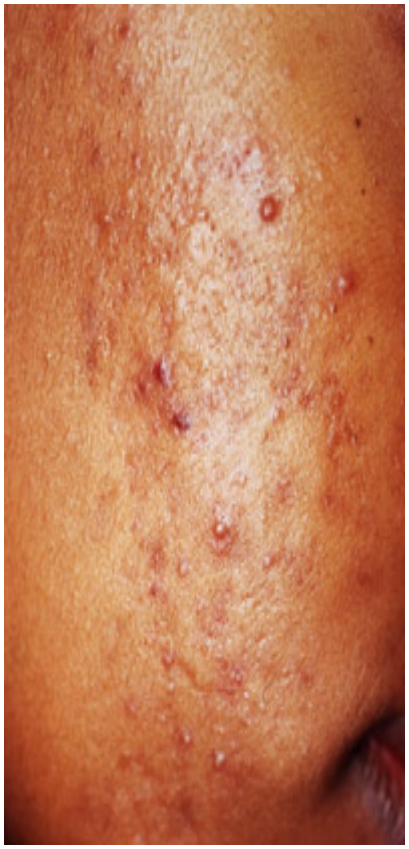
value because the medications rinsing away rather than penetrating the follicle.

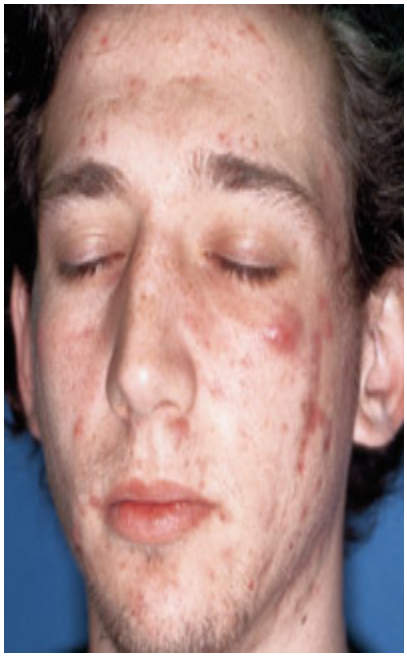
e. Patients with mild comedonal acne might find benefit from cleansers

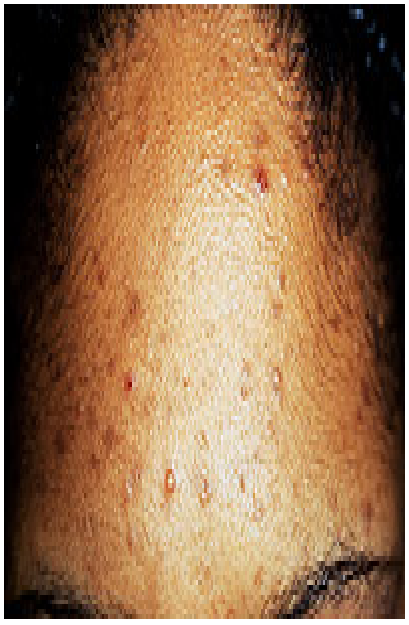
containing pumice, polyethylene, or aluminum oxide particles. However patients

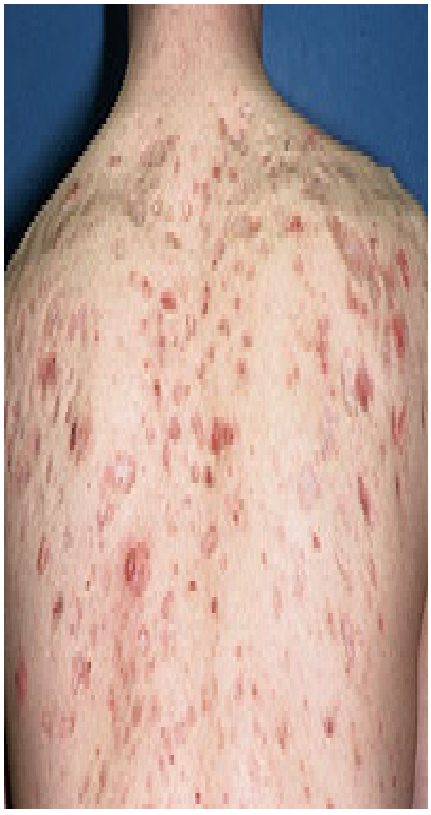
with inflammatory acne or sensitive skin should avoid these products.

(Leon *et al.*, 2000).









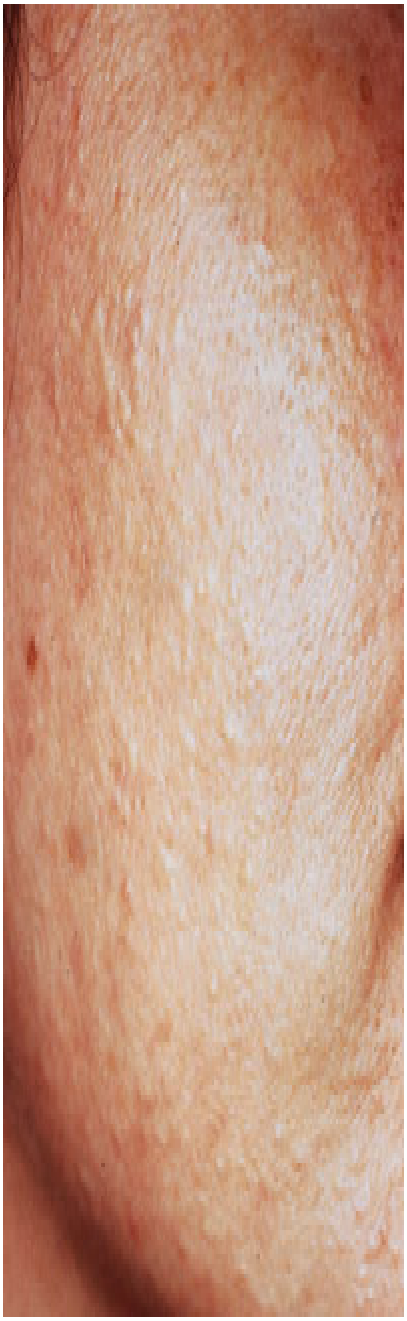


FIGURE1. 2 Comedonal acne. Closed comedones (whiteheads), a mass of desquamated cells plugs the follicular canal above the opening of the sebaceous gland. Sebum accumulates within the follicular canal and results in a white papule visible at the skin surface.

FIGURE1. 3 *(Top and bottom)* Inflammatory acne. The follicular wall ruptures, releasing sebum, cells and bacteria into the surrounding tissue, causing inflammation and redness.

FIGURE1. 4 *(Top and bottom)* Nodulocystic acne. Extensive tissue inflammation results in the formation of nodules, cysts or abscesses.

In open comedones (blackheads), when the opening of the follicular canal dilates, the plug protrudes from the canal and turns a dark color.

1.17.2. Treatment and care: (Leon *et al*., 2000).

Approaches to treatment depend on the severity of the condition. Although acne

cannot be cured, most cases can be managed successfully with topical treatment

alone based on the pathogenesis of the condition, potential methods include:

a. Unblocking of the sebaceous ducts so that the contents can be easily expelled.

b. Decreasing the amount of sebum that is secreted.

c. Changing the composition of the sebum to make it less irritating by decreasing

the population of *Propionibacterium acnes*.

1/ Nonprescription Topical medication:

a. Benzoyl Peroxide:

This medication has been traditionally recognized as the most effective topical

OTC agent for acne and many OTC products contain it. However the final

monograph from the FDA changed the status of benzoyl peroxide from Category 1

(generally recognized as safe and effective) to Category III , indicating that more

data are needed to prove its safety with regards to long-term photocarcinogenic

effects .Benzoyl peroxide has irritant, drying, peeling, comedolytic, and

antibacterial effects. The clinical response shows only minimal differences

among the 2.5%, 5% and 10% concentrations. A beneficial effect should be

noticed within 2 weeks, but the usual length of a therapeutic trial is 6-8 weeks.

Mechanism of action:

Benzoyl peroxide is act by decomposes to release oxygen, which is lethal to the

Propionibacterium acnes anaerobe. As an irritant, it increases the turnover rate of

epithelial cells, resulting in increased sloughing and promoting of resolution of

comedones. Thus benzoyl peroxides has a dual mode of action, that is it

effective against both inflammatory and noninflammatory acne.

The vehicle for benzoyl peroxide is also important in its overall activity.

The alcohol gel Vehicle tends to be more effective than the lotion or cream

formulations.

Application :

The affected area should be washed with mild soap and water, then gently patted

dry, the product should massaged gently into the skin avoiding the eyes, mouth,

lips and inside of the nose. The product can be applied at night left for 15 or 20

minutes to test the sensitivity and then washed out. If no excessive irritation

develops apply once daily for the first few days. If drying, redness, or peeling

does not occur in 3 days increase the application to twice daily. If patients have

to use benzoyl peroxide during the day, advise them to use a sunscreen and

avoid unnecessary sun exposure.

Adverse effects:

Benzoyl peroxide may cause a burning or stinging sensation, which gradually

disappears. Most of the adverse effects from this agent relate to its therapeutic

effect of irritating and drying the skin. For this reason the lowest concentration

available should be chosen initially.

From 1% - 3% of patients may be hypersensitive to benzoyl peroxide. Benzoyl

peroxide can discolor certain types of fabric or clothing material and can also

bleach hair.

b. Salicylic acid:

This an irritant keratolytic agent results in increased turnover of the epithelial

lining, through this effect salicylic acid probably promotes the penetration of

other acne products. It is used in a concentration range 0.5% - 2%.

c. Sulfur:

Sulfur is a keratolytic agent and has antibacterial actions. Sulfur traditionally has

been recognized as a less desirable product because it may be acnegenic with the

continued use, and it has offensive color and odor. Concentration is 3% - 8%

combined with resorcinol 2% or resorcinol monoacetate 3%.

d. Resorcinol:

It is also a keratolytic agent that has been recognized to be as effective agent

against acne when the agent is combined with sulfur.

2/ Prescription Medications:

Include both topical and systemic agents:

(i)Topical prescription agents:

a. Tretinoin:

It is retinoic acid, increase the turnover rate of nonadhering horny cells in

follicular canal which result in comedo clearing and inhibits new comedo

development. It is best used for noninflammatory cne. Tretinoin also may be

effective in combination with antibiotics or benzoyl peroxide for management of

severe inflammatory acne. It is probably the most effective topical agent for acne

especially acne characterized by comedones.

Application:

The cream formulation of tretinoin, which is less irritating than the gel forms

(which in turn less irritating than the solution form), should be used initially.

Because of the irritating properties tretinoin should be applied 30 minutes after

washing; initially it should applied every other day, then daily. Other irritating

substance such as strong a abrasive cleanser and stringent should be avoided

during treatment with tretinoin.

Side Effects:

Because of its irritant properties, tretinoin can cause excessive irritation,

erythrema, peeling and increased risk for severe sunburn. There may be an initial

exacerbation of the acne, and a total of 12 weeks may be necessary to fully assess

treatment efficacy.

b. Adapalene:

it is a topical retinoid-like compound that is dosed once daily. It appears to cause

less irritation than tretinoin and to be more effective. Therapeutic results should

be noticed in 8-12 weeks.

Same precautions apply to tretinoin apply for adapalene.

c. Azelaic acid 20% cream:

A topical agent that appears to be as effective as benzoyl peroxide or tretinoin for

treatment of mild to moderate inflammatory acne. This agent has both

antibacterial and antikeratinizing activity, it inhibits the growth of

Propionibacterium acnes and has an antipoliferative effect on kerratinocytes.

Side effects:

It seems to be less irritating than benzoyl peroxide or tretinoin. Stinging,

burning, tingling, pruritis, and erythema have been reported in a low number of

patients. It is also decreases pigmentation in the areas of increased pigmentation

but apparently does not affect frecklets, nevi, or normal skin. Because of it is

dual action, it can be used as a single product options in the treatment of mild to

moderate acne.

d. Topical Antibiotics:

Tetracycline ointment, Erythromycin solutions (2% & 4%) and Clindamycin

lotion are Examples of topical antibiotics used for treatment of mild to moderate

acne vulgaris.

Mechanism of Action:

The mechanism of action apparently involves suppression of the *P. acne* ,

which in turn minimizes the inflammatory response due to the acne.

Applications:

These antibiotics are applied directly to acne sites, thus minimizing serious side

effects from oral administration.

Side effects:

There are minimal side effects to these topically applied antibiotics. Mild burning

or irritation may occur. Tetracycline may discolor the skin and fluorescence in

black light. Clindamycin can be absorbed to result in pseudomembranous colitis.

(ii) Systemic prescription agents:

a. Systemic Oral Antibiotics

Although topical therapy is generally adequate for comedonal acne, control of

inflammatory acne usually requires systemic antibiotics. Antibiotics in acne act

by inhibition of the follicular bacterium, *P. acnes*. An antibiotics do not affect

existing lesions, but also prevent future lesions through this effect. *P. acnes*

resistance has been observed with tetracycline and erythromycin , but most

strains remains sensitive. The antibiotics that have proved to be most effective

include tetracycline, doxycycline, minocycline and erythromycin. These drugs

penetrate the follicle and sebaceous gland well and decrease colonization by

Propionibacterium acnes. They also have an anti-inflammatory effect

independent of their antimicrobial properties. Antimicrobials should be given for

6 months to exert its full effect, despite that noticeable improvement may be

observed earlier . If the response to one antibiotic is not satisfactory another one

can be tried. If successful, any of these drugs can safely be continued on a long-

term basis. The patients should be made to understand that treatment is only

suppressive and not curative, and relapse may follow withdrawal of the

drug. A pustular folliculitis of the face due to Gram-negative superinfection is a

rare complication of long-term antibiotic therapy and should be looked out for in

case of 'resistance' to treatment. Culture of the pustules should be done in case of

doubt. Although rare hypersensitivity reactions have been reported, the safety

profile of these antibiotics is, in general, excellent, making routine laboratory

monitoring in the asymptomatic, healthy patient unnecessary.

(Driscoll *et al.*, 1993).

1. Tetracycline:

It is extremely inexpensive. It is a bacteriostatic agent which acts mainly by reducing the acne bacteria population on the skin.

Dosage:

The usual dose is 1 gm/day in divided dosage gradually reduced to maintaince dose of 250mg per day, and should be taken with an empty stomach. Milk and diary products should be avoided.

Side effects:

Include GIT upset, drug eruption (especially fixed drug eruption). Also may cause other adverse effects, including vaginal yeast infections and dyspepsia (rarely, esophagitis with esophageal ulcerations). Other rare adverse effects include photosensitivity and pseudotumor cerebri. This group of antibiotic is absolutely contraindicated in pregnancy and extra caution should be taken in prescribing it to young female patients. Tetracycline may cause discoloration of forming teeth and should not be given to pregnant women or to children younger than 13 years unless all permanent teeth have erupted. Although the tetracyclines have a long track record of safety, instances of single-organ

dysfunction (most commonly, severe cutaneous reaction) have been reported, as

well as a few cases of hypersensitivity reaction and serum sickness like reaction.

Tetracycline therapy should be avoided in patients with renal or hepatic disease.

(Shapiro *et al*., 1997)

2. Doxycycline:

Is the most frequently used oral antibiotics for acne. It is a tetracycline derivative

that exhibits excellent penetration into follicles and sebaceous glands because it

is more lipid soluble. It is better tolerated than tetracycline and may be taken

with food.

Dosage:

Can be given as a single daily dose (100 mg/day) or in a divided twice daily

dosage .

Side effects:

Of the tetracycline derivatives, it is the one most likely to cause photosensitivity.

Other adverse effects are similar to those of tetracycline.

(Shapiro *et al.*, 1997)

3.Minocycline:

Is considered the most effective of the tetracycline derivatives, possibly because

preexisting minocycline resistance is rare.

Dosage:

50mg – 200mg daily and it can be taken with food.

Side effects:

Unlike the other tetracycline's, only infrequently causes photosensitivity. Most

adverse effects of minocycline are similar to those of the other tetracycline.

However, minocycline may cause cutaneous hyperpigmentation in scars,

dizziness vertigo and headache. In rare instances, the development of a lupus-

like syndrome. Minocycline is also associated with a higher frequency

of hypersensitivity reactions than the other tetracyclines. Although

hyperpigmentation is slow to fade, the other reactions usually resolve promptly

with discontinuation of therapy.

(Shapiro *et al.,* 1997; Leon *et al.,* 2000).

4. Erythromycin:

This is as effective as Tetracycline but resistance develops more rapidly. It is

inexpensive. Erythromycin 2% and 4% topically is also used for mild to

moderate cases. However, *Propionibacterium acnes* resistance to erythromycin

develops more frequently (in as many as 60 percent of isolates) than with the

other systemic antibiotics.

Dosage:

Range from 500mg-2000mg per day in divided doses.

Side effects:

Often causes dyspepsia or abdominal discomfort even when taken with meals.

The drug is safe in pregnancy, and is preferred to tetracycline for married

woman.

(Leon *et al.,* 2000).

5. Trimethoprim-sulfamethoxazole:

Has been used successfully in patients with acne resistant to erythromycin or

tetracycline's.

b. Isoretinoin :

It is a vitamin A derivatives indicated for sever recalcitrant nodules acne.

A single course of therapy can result in complete and prolonged remission

period.

Mechanism of action:

Although the exact mechanism is unknown, isoretinoin decrease sebum

production and keratinization, and it reduces the population of

Propionibacterium acnes.

Dosage:

Doses range from 0.5 mk/kg/day to 2 mg/kg/day given twice daily for 15 – 20

weeks.

Side effects:

(i) **Mucutaneous dryness**. Cheilitis (i.e., inflammation of the lips), dryness of the

nasal mucosa, and facial dermatitis may occur with isoretinoin use. These effects

can be treated with topical lubricants. Dryness of the eye can occur so people

using isoretinoin should never wear contact lenses.

(ii) **Elevated serum level**. Isoretinoin may elevate serum triglycerides and

cholesterol, as well as liver enzymes.

(iii) **Birth defect**. Isoretinoin is a potent teratogen and should not be given to

pregnant women.

(iv) **Depression**. There have been reports of depression, psychosis, and rarely

suicidal ideation and suicidal attempts, and suicide. This must have been taken in

the context that teenagers with acne may often be depressed related to their

appearance.

(Orfanos CE, Zouboulis CC. 1998).

c. Antiandrogens and hormones:

(1) Estrogen can decrease sebum production through an antiandrogenic effect.

(2) Some progestin agent in oral contraceptives (e.g. norethinderone, norgesterol)

have an androgenic activity that can stimulate sebum secretion resulting in acne.

One of the progestins**, noregestinate**, is minimally androgenic, and when it

combined with ethinylestadiol as a triphasic combination oral contraceptive

agent, it is effective in the treatment of moderate acne in some women and is

FDA approved for such.

(Shaw JC. *1*996)

(4) Corticosteroids. Although corticosteroids as a causing acne, they also can be

used to treat severe acne, intralesional injection of triamcinolone and systemic

corticosteroids have been used for severe inflammatory acne and severe cystic

acne respectively. Predinsolone (or its equivalent) in doses of 20 mg per day or

higher may be used for a short period of time to quickly improve acne for

important event like a weeding. Topical corticosteroids are not effective.

(Leon *et al.,* 2000).

(5) Spiranolactone. Is androgen antagonist that may be used on a limited basis.

(Leon *et al.*, 2000).

Treatment for severe acne

If treatment fails with systemic antibiotic therapy and other anti acne perpetrations, two clinical entities must be considered:

1/ **Antibiotic resistance** :

Although many treatments for acne are available, effective management has become increasingly challenging with the emergence of antibiotic-resistant strains of *Propionibacterium acnes*. Resistance to *Propionibacterium acnes* is reported to have increased from "extremely rare to occasional" in the mid 1980s to 62% in referral centers in 1996.

(Cooper 1998; Espersen 1998).

‘‘Antibiotic therapy has been a backbone in the management of acne for many decades and probably will continue to be in the future, although, with the development of less-sensitive strains, the predictability of antibiotic therapy can

no longer be assumed," stated James J. Leyden, MD, who is Professor in the Department of Dermatology at the University of Pennsylvania. (Leyden 2001)

2/ **Folliculitis** related to overgrowth of gram-negative Enterobacteriaceae**,** Staphylococci or Malassezia yeasts. Aerobic and anaerobic cultures and sensitivity determinations should be used to decide on appropriate antibiotics.

Gram-negative folliculitis is frequently treated with ampicillin, less commonly with trimethoprim-sulfamethoxazole and, occasionally, with isotretinoin.

The addition of topical benzoyl peroxide, a broad-spectrum antimicrobial agent, may also be beneficial in many patients who have folliculitis related to either bacteria or yeast. (Eady *et al.,* 1998).

Nodulocystic acne, if left untreated, may cause physical and emotional scarring.

This form of acne is unlikely to respond to topical therapy. Initially, patients should be prescribed an oral antibiotic. If the acne fails to respond after six months of conventional therapy, treatment with isotretinoin should be considered.

Adjuvant therapy with other agents may be considered during isotretinoin treatment. Topical antibiotics may be beneficial, but use of topical keratolytics and drying agents should be discontinued because concomitant use

may lead to extensive dryness. Occasionally, oral erythromycin or prednisone is

used at the beginning of isotretinoin therapy to control the initial acne flare-up.

None of the tetracyclines should be used for this purpose because the

combination of a tetracycline and isotretinoin increases the likelihood of

pseudotumor cerebri development.

In patients with more severe acne, the addition of another agent (estrogen, anti-

androgen, spironolactone, or isotretinoin) may be necessary to control sebum

overproduction.

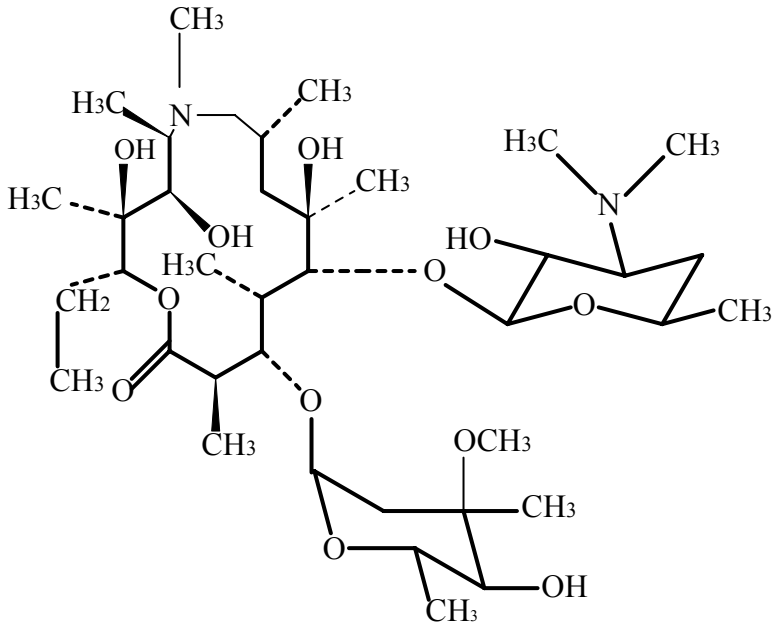
(Leyden JJ *et al*., 1997).

1.2 AZITHROMYCIN .

1.2.1 Chemical and physical properties:

Azithromycin (N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A) is an azalide antimicrobial agent, structurally related to macrolide antibiotic erythromycin. Azithromycin maintains the basic macrolide structure with a methyl substituted nitrogen in place of the carbonyl at the 9α position at the aglycon ring, blocking the internal dehydration pathway, this providing increased acid stability. (Richard and Harry 1993).

Chemical Structure of Azithromycin



(2R, 3S, 4R,5R, 8R, 10R, 11R, 12S, 13S, 14R)-13-[(2,6-dideoxy-3-C-methyl-3-O

-mehy -[[alpha]]-L-ribo-hexopyranosyl]oxy]-oxy]-1-oxa-6-azacyclopentadecan

-15-one

Azithromycin as the dihydrate is a white crystalline powder with a molecular formula of C38H72N2O12*2H2O and a molecular weight of 785.0. Good stability of Azithromycin has been demonstrated in the presence of low pH of stomach ,it is more active at pH ≥7.4.

(The Merk index 1989).

Azithromycin is a basic drug, poorly soluble in water but highly lipid soluble. Azithromycin is stable below 40°C, preferably stored between 15 and 30 °C in a well closed container. Decomposition of Azithromycin occurs primarily by acid -catalyzed hydrolysis of the ether bond to the neutral cladinose sugar.

(Drug information for the health care professional 1999).

1.2.2 Indications

Azithromycin is used in the **treatment** of:

1. Bacterial exacerbation of chronic bronchitis or acute otitis media due to *Haemophilus influenzae, Moraxella catarrhalis, or Streptococcus pneumoniae.* However, Azithromycin is not recommended as the first line of therapy for otitis media.
2. Cervicitis gonococcal.
3. Cervicitis nongonococcal.
4. Urethritis gonococcal.
5. Urethritis nongonococcal.

Azithromycin is used in the treatment of cervicitis or urethritis due to *Chlamydia trachomatis* or *Neisseria gonorrhoeae*.

6. Chancroid (Genital ulcer disease in men due to Haemophilus

ducreyi).

7. Pelvic inflammatory disease due to Chlamydia trachomatis, Mycoplasma hominis, or Neisseria gonorrhoeae.
8. Pharyngitis, or Tonsillitis due to Streptococcus pyogenes.
9. Community-acquired peuemonia due to Chlamydia pneumoniae, Haemophilus influenzae, Legionella pneumophilia, Moraxella catarrhalis, Mycoplasma pneumoniae, Staphylococcus pneumoniae, or Streptococcus pneumoniae.
10. Uncomplicated skin and soft tissue infections due to Staphylococcus aureus, Streptococcus agalactiae, or Streptococcus pyogenes.

Azithromycin is also used in the **Prophylaxis** of Disseminated MAC disease in patients with advanced human immunodeficiency virus HIV infection.

(Drug information for the health care professional 1999).

1.2.3 Pharmacokinetics:

1.2.3.1 Absorption:

Following oral administration of Azithromycin the bioavailability is about 40% of the dose is, so it is rabidly absorbed. (Martindale 1993). Absorption is reduced by food intake; food decreases peak serum concentration (C_{max}) values by approximately 52% and AUC by approximately 43%. After 500 mg loading dose on day one, then 250 mg once a day on other 4 days, the peak plasma concentration (C_{max}) on day one is approximately 0.41 mcg/ml for healthy young adults and 0.24 mcg/ml on day five. T_{max} for oral dosage forms is attained at 2.1 to 3.2 hours in healthy adult subjects.The pharmacokinetic modeling of Azithromycin is characterized by a multicompartment model following

oral absorption. Azithromycin undergoes first order oral absorption with a mean K_a of 0.76 h^{-1} following a lag time of 1.2 hour. (Guy *et al* 1991).

1.2.3.2 Distribution:

Azithromycin is rapidly and widely distributed throughout the body, it concentrates intracellular, resulting in tissue concentration 10 to 100 times higher than those found in plasma or serum. It is highly concentrated in phagocytes and fibroblasts; very low concentration (∠ 0.01mcg per ml) has been detected in the cerebrospinal fluid of human with non-inflamed meninges, higher concentration found in brain tissue in animal studies.

(Drug information for the health care professional 1999).

Extensive distribution has been demonstrated in a variety of body tissues and fluids including, middle ear exudates, bronchial secretion, prostatic tissue, and bone. This extensive tissue distribution prolongs $T_{1/2}$ and enables shorter duration of therapy so more patient compliance. Azithromycin is highly lipid soluble, with volume of distribution of approximately 23L/Kg.

Serum protein binding is low, with 50% binding observed at a serum concentration of 0.05 mg/L, and only 12% binding at 0.5 mg/L. This protein binding occurs primarily to α and β globulins, and not to albumin. Protein binding of Azithromycin also correlates to α_1 acid glycoprotein. Patients with elevated levels of α_1 acid glycoprotein may have up to a 5-fold increase in protein binding compared with controls. **(Richard & Gallis 1999).**

Table 1.3 selected Tissue concentrations to Plasma/Serum Concentrations Ratios:

Tissue or Fluid	Time after Dose (h)	Tissue or Fluid Concentration (µg/ml)	Corresponding plasma or serum level (µg/ml)	Tissue (Fluid) / Plasma (Serum) Ratio
Skin	72-96	0.4	0.012	35
Lung	72-96	4.0	0.012	> 100
Sputum	2-4	1.0	0.64	2
Sputum	10-12	2.9	0.1	30
Tonsil	9-18	4.5	0.03	> 100
Tonsil	180	0.9	0.006	> 100
Cervix	19	2.8	0.04	70

(Adopted from PDR 1999)

1.2.3.3 Metabolism:

Most of the absorbed dose of Azithromycin remains un- metabolized within the body, when metabolism does occur hepatic demethylation is the primary route. There are many metabolites in the bile but with no significant activity. When Azithromycin accumulates in the liver this will increase azithromycin demethylase activity, but no evidence of hepatic cytochrome P450 induction or inactivation . (Nestar & Morris 1993.)

1.2.3.4 Elimination:

Biliary concentration of Azithromycin is greater than serum concentration suggesting biliary excretion. More than 50% of the drug related material in the bile is un- changed parent drug. The feces are also important route of elimination. Urinary excretion of un-changed

drug is minor route of elimination (∠6%within one week after oral administration). About 20% of the drug that reaches the systemic circulation is excreted unchanged in urine. Renal clearance is in a range of 6-11.34L/h.Serum elimination occurs in a polyphasic manner. The initial rapid decline in drug plasma concentration implies a rapid redistribution phase into tissue, followed by a second component of distribution and elimination. When $T_{1/2}$ is measured between 8-24 hours after a single oral dose of 500 mg, it is found to be 11-14 hours. The average tissue half life is between 2 and 4 days..

(Nestar & Morris 1993.)

1.2.4 Dosing:

Usual adult and adolescent dose:

Bronchitis, bacterial exacerbations or Pharyngitis, streptococcal or Pneumonia, due to *Streptococcus pneumoniae* or *Haemophilus influenzae*, or, Skin and soft tissue infections, uncomplicated, due to *Staphylococcus aureus*, *Streptococcus agalactiae,* or *Streptococcus pyogenes* or Tonsillitis, streptococcal:

Adults and adolescents 16 years of age and older: Oral, 500 mg as a single dose on first day, then 250 mg once a day on the other 4 consecutive days.

Cervicitis, nongonococcal or Urethritis, nongonococcal-

Adults and adolescents 16 years of age and older: Oral, 1000 mg as a single dose. Adolescents up to 16 year, safety and efficacy have not been established.

(Drug information for the health care professional 1999).

1.2.5 Adverse effects: The main side effects shown in Table 1.4

Table 1.4 :The main side effects of azithromycin:

Adverse Effects	Frequency
Gastrointestinal disturbances (abdominal pain; diarrhea; nausea; vomiting).	Less frequently
Headache.	Rarely
Dizziness	Rarely
Allergic reactions such as: anaphylaxis and angioedema	Rarely

(Drug information for the health care professional 1999).

1.2.6 Contraindications & Precautions:

Azithromycin is contraindicated in patients with known hypersensitivity to azithromycin or any of the macrolide antibiotics. Because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be co-administered. Since azithromycin is principally eliminated via the liver,. Allergic reactions, including angioedema, anaphylaxis and dermatological reactions have been reported rarely in patients on azithromycin therapy. There is a possible interaction between azithromycin and following drugs:Antacids, Carbamezapine, Cyclosporine, Digoxin. Theophylline and Warfarin.

1.3 DOXYCYCLINE

(National Committee for Clinical Laboratory Standards 1990)

1.3.1 Chemical and Physical Properties:

Doxycycline is a broad-spectrum antibiotic synthetically derived from

oxytetracycline and is available as doxycycline monohydrate; doxycycline

hyclate; doxycycline hydrochloride hemiethanolate hemihydrate; and

doxycycline calcium for oral administration. It is also available as doxycycline

hyclate for intravenous use as well as coated hyclate pellets.

The molecular formula of doxycycline monohydrate is $C_{22}H_{24}N_2O_8 \cdot H_2O$ and a

molecular weight of 462.46. The chemical designation for doxycycline is

4-(Dimethylamino)-1, 4, 4a, 5, 5a, 6, 11, 12a-octahydro-3,5,10,12,12a-

pentahydroxy-6-methyl-1, 11-dioxo-2-naphthacenecarboxamide monohydrate.

The molecular formula for doxycycline hydrochloride hemiethanolate

hemihydrate is $(C_{22}H_{24}N_2O_8 \cdot HCl)_2 \cdot C_2H_6O \cdot H_2O$ and the molecular weight is

1025.89. Doxycycline is a light-yellow crystalline powder. Doxycycline hyclate

is soluble in water, while doxycycline monohydrate is very slightly soluble in

water. Doxycycline has a high degree of lipid solubility and a low affinity for

calcium binding. It is highly stable in normal human serum.

1.3.2 Indications:

Doxycycline is indicated for the treatment of the following infections:

1- Rocky mountain spotted fever, typhus fever and the typhus group, Q fever,

rickettsialpox, and tick fevers caused by Rickettsiae.

2- Respiratory tract infections caused by *Mycoplasma pneumoniae.*

3. Lymphogranuloma venereum caused by *Chlamydia trachomatis.*

4. Psittacosis (ornithosis) caused by *Chlamydia psittaci.*

5. Trachoma caused by *Chlamydia trachomatis*, although the infectious agent is

not always eliminated as judged by immunofluorescence.

6. Inclusion conjunctivitis caused by *Chlamydia trachomatis.*

7. Uncomplicated urethral, endocervical or rectal infections in adults caused by

Chlamydia trachomatis.

8. Nongonococcal urethritis caused by *Ureaplasma urealyticum.*

9. Relapsing fever due to *Borrelia recurrentis.*

Doxycycline is also indicated for the treatment of infections caused by the

Following, gram-negative microorganisms:

10. Chancroid caused by *Haemophilus ducreyi.*

11. Plague due to *Yersinia pestis* (formerly *Pasteurella pestis).*

12. Cholera caused by *Vibrio cholerae* (formerly *Vibrio comma)*.

13. Campylobacter fetus infections caused by *Campylobacter fetus* (formerly

Vibrio fetus).

14. Brucellosis due to *Brucella* species (in conjunction with streptomycin).

15. Bartonellosis due to *Bartonella bacilliformis.*

Prophylaxis: Doxycycline is indicated for the prophylaxis of malaria due to *Plasmodium falciparum*in short term travelers (4 months) to areas with chloroquine and/or pyrimethamine-sulfadoxine resistant strains. Because many strains of the following groups of microorganisms have been shown to be resistant to doxycycline, culture and susceptibility testing are recommended.

Doxycycline is indicated for treatment of infections caused by the following gram-Negative microorganisms, when bacteriologic testing indicates appropriate susceptibility to the drug:

Escherichia coli., *Enterobacter aerogenes* (formerly *Aerobacter aerogenes)*. *Shigella* species., *Acinetobacter* species (formerly *Mima* species and *Herellea* species). Respiratory tract infections caused by *Haemophilus influenzae.*

Respiratory tract and urinary tract infections caused by *Klebsiella* species.

Doxycycline is indicated for treatment of infections caused by the following

gram- positive microorganisms when bacteriologic testing indicates appropriate susceptibilityto the drug:

Upper respiratory tract infections caused by *Streptococcus pneumoniae*

(formerly *Diplococcus pneumoniae)*.

When penicillin is contraindicated, doxycycline is an alternative drug in

the treatment of the following infections:

Uncomplicated gonorrhea caused by *Neisseria gonorrhoeae.*

Syphilis caused by *Treponema pallidum.*

Yaws caused by *Treponema pertenue.*

Listeriosis due to *Listeria monocytogenes.*

Anthrax due to *Bacillus anthracis.*

Vincent's infection caused by *Fusobacterium fusiforme.*

Actinomycosis caused by *Actinomyces israeli.*

Infections caused by *Clostridium* species.

In acute intestinal amebiasis, doxycycline may be a useful adjunct to

amebicides.

In severe acne, doxycycline may be useful adjunctive therapy.

1.3.3 Pharmacokinetics:

Doxycyclines are readily absorbed and are bound to plasma proteins in

varying degree, they are concentrated by the liver and bile. Excreted in the

urine and feces at high concentrations and in a biologically active form.

Doxycycline is virtually completely absorbed after oral administration.

Following a 200 mg dose, normal adult volunteers averaged peak serum

levels of 2.6 mg/ml of doxycycline at 2 hours decreasing to 1.45 mg/ml at

24 hours. Excretion of doxycycline by the kidney is about 40%/72 hours in

individuals with normal function (creatinine clearance about 75 ml/min.)

This percentage excretion may fall as low as 1-5%/72 hours in individuals

with severe renal insufficiency (creatinine clearance below 10 ml/min.).

Studies have shown no significant difference in serum half-life of

doxycycline (range 18-22 hours) in individuals with normal and severely

impaired renal function.

1.3.4 DOSAGE AND ADMINISTRATION:

Adults: The usual dose of oral doxycycline is 200 mg on the first day of

treatment (administered 100 mg every 12 hours) followed by a

maintenance dose of 100 mg/day. The maintenance dose may be

administered as a single dose or as 50 mg every 12 hours. In the

management of more severe infections (particularly chronic infections of

the urinary tract), 100 mg every 12 hours is recommended.

The therapeutic antibacterial serum activity will usually persist for 24 hours following recommended dosage. When used in streptococcal infections, therapy should be continued for 10 days. Administration of adequate amounts of fluid along with capsule and tablet forms of drugs in the tetracycline class is recommended to wash down the drugs and reduce the risk of esophageal irritation and ulceration. If gastric irritation occurs, it is recommended that doxycycline be given with food or milk. The absorption of doxycycline is not markedly influenced by simultaneous ingestion of food or milk.

Studies to date have indicated that administration of doxycycline at the usual recommended doses does not lead to excessive accumulation of the antibiotic in patients with renal impairment.

Uncomplicated gonococcal infections in adults (except anorectal infections in men):

100 mg, by mouth, twice a day for 7 days. As an alternate single visit dose, administer 300 mg stat followed in one hour by a second 300 mg dose. The dose may be administered with food, including milk or carbonated beverage, as required.

Uncomplicated urethral, endocervical, or rectal infection in adults caused by *Chlamydia trachomatis:* 100 mg by mouth twice a day for 7 days.

Nongonococcal urethritis (NGU) caused by *C. trachomatis or U.urealyticum:*

100 mg by mouth twice a day for 7 days.

Syphilis-early: Patients who are allergic to penicillin should be treated with doxycycline 100 mg by mouth twice a day for 2 weeks.

Syphilis of more than one year's duration: Patients who are allergic to Penicillin should be treated with doxycycline 100 mg by mouth twice a day for 4 weeks.

Acute epididymo-orchitis caused by *N. gonorrhoeae:*

100 mg, by mouth, twice a day for at least 10 days.

Acute epididymo-orchitis caused by *C. trachomatis:*

100 mg, by mouth, twice a day for at least 10 days.

Dosing: Acne Vulgaris Doxycycline 100-200 mg/day in divided doses

For prophylaxis of malaria: For adults, the recommended dose is 100 mg daily. For children over 8 years of age, the recommended dose is 2 mg/kg

given once daily up to the adult dose. Prophylaxis should begin 1-2 days

before travel to the malarious area and for 4 weeks after the traveler leaves

the malarious area.

1.3.5 Adverse effects:

Due to oral doxycycline's virtually complete absorption, side effects of the

lower bowel, particularly diarrhea, have been infrequent. The following

adverse reactions have been observed in patients receiving tetracyclines:

Gastrointestinal: anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia,

enterocolitis, and inflammatory lesions (with monilial overgrowth) in the

anogenital region.

Hepatotoxicity has been reported rarely. These reactions have been caused by

both the oral and parenteral administration of tetracyclines.

Rare instances of esophagitis and esophageal ulcerations have been reported

in patients receiving capsule and tablet forms of the drugs in the tetracycline

class.Most of these patients took medications immediately before going to

bed.

Skin: maculopapular and erythematous rashes. Exfoliative dermatitis has

been reported but is uncommon, also Photosensitivity .

Renal toxicity: rise in BUN has been reported and is apparently dose related.

Hypersensitivity reactions: urticaria, angioneurotic edema, anaphylaxis,

anaphylactoid purpura, serum sickness, pericarditis, and exacerbation of

systemic lupus erythematosus.

Blood: Hemolytic anemia, thrombocytopenia, neutropenia, and eosinophilia

have been reported.

Other: bulging fontanels in infants and intracranial hypertension in adults

When given over prolonged periods, tetracyclines have been reported to

produce brown-black microscopic discoloration of the thyroid gland.

No abnormalities of thyroid function studies are known to occur.

1.3.6 CONTRAINDICATIONS & PRECAUSIONS

This drug is contraindicated in persons who have shown hypersensitivity to any

of the tetracycline. As with other antibiotic preparations, use of this drug may

result in overgrowth of nonsusceptible organisms, including fungi.

If superinfection occurs, the antibiotic should be discontinued and appropriate

therapy instituted.

Doxycycline others substantial but not complete suppression of the asexual blood

stages of *Plasmodium* strains. Doxycycline does not suppress *P. falciparums*

sexual blood stage gamocytes. Subjects completing this prophylactic regimen

may still transmit the infection to mosquitoes outside endemic areas.

The use of drugs of the tetracycline class during tooth development (Last half of

pregnancy, infancy childhood to the age of 8 years) may cause permanent

discoloration of teeth (Yellow-gray-brown). This adverse reaction is more

common during long-term use of the drugs, but it has been observed following

repeated short-term courses. Enamel hypoplasia has also been reported.

Tetracycline drugs, therefore, should not be used in this age group unless other

drugs are not likely to be effective or are contraindicated. All tetracyclines form

a stable calcium complex in any bone-forming tissue. A decrease in fibula

growth rate has been observed in premature given oral tetracycline in doses of 25

mg/kg every 6 hours. This reaction was shown to be reversible when the drug

was discontinued. Results of animal studies indicate that tetracycline cross the

placenta, are found in fetal tissues, and can have toxic effects on the developing

fetus (often related to retardation of skeletal development). Evidence of embryo

toxicity has also been noted in animals treated early in pregnancy.

If any tetracycline is used during pregnancy or if the patient becomes pregnant

while taking this drug, the patient should be apprised of the potential hazard to

the fetus.

Photosensitivity manifested by an exaggerated sunburn reaction has been

observed in some Individuals taking tetracyclines. Patients exposed to direct

sunlight or ultraviolet light should be advised that this reaction can occur with

tetracycline drugs, and treatment should be discontinued at the first evidence of

skin erythema.

1.3.7 DRUG INTERACTIONS

Because tetracyclines have been shown to depress plasma prothrombin activity,

patients who are on anticoagulant therapy may require downward adjustment of

their anticoagulant dosage.

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin,

it is advisable to avoid giving tetracyclines in conjunction with penicillin.

Absorption of tetracycline is impaired by antacids containing aluminum,

calcium, or magnesium, and iron-containing preparations, and bismuth

subsalicylate.Barbiturates, carbamazepine, and phenytoin decrease the half-life of

doxycycline.The concurrent use of tetracycline and Penthrane (methoxyflurane)

has been reported to result in fatal renal toxicity. Concurrent use of tetracycline

may render oral contraceptives less effective.

1.4 Comparison between Azithromycin and Doxycycline:

Refer to the scientific background above comparing between azithromycin

and doxycycline in their characteristics we could find the following:

Table 1.5 shows a comparison between Azithromycin and Doxycycline:

Characteristics	Doxycycline	Azithromycin
Chemical properties	Structurally doxycycline is derived from tetracycline.	Structurally azithromycin is derived from erythromycin.

Physical properties	doxycycline is very slightly soluble in water, has a high degree of lipid solubility than tetracycline.	Azithromycin have a methyl group instead than the hydroxyl group make a basic drug, poorly soluble in water but highly lipid soluble
Pharmacokinetics	It is highly stable in normal human serum. Doxycycline will not degrade into an epianhydro form.	high lipid solubility render it to be rapidly and widely distributed throughout the body, so it is have large volume of distribution (Vd) and thus Prolong T½. also more Penetrative to soft tissues.
Dosing	The usual dosage and frequency of administration of doxycycline (100-200 mg/day) differ from that of other tetracycline (1-2 g/day make it more compliance for the patient.	prolongs T½ enables shorter duration of therapy so more patient compliance and it is given in abase of once a day dosage for a period of three days treatment. Rather than 4 times /day for erythromycin.

Spectrum of activity	Doxycycline primarily bacteriostatic and are thought to exert their antimicrobial effect by the inhibition of protein synthesis & have broad spectrum against wide range of gram positive and gram negative bacteria.	Azithromycin & other macrolides are bacteriostatic and bactericidal in their action depending on concentration, and are thought to exert their antimicrobial effect by the inhibition of protein synthesis & have broad spectrum against wide range of gram positive and gram negative bacteria
Side effects	Less than tetracycline	Rare and less than erythromycin Especially in GIT upset.
Contraindications & Drug interactions	It is absolutely contraindicated During pregnancy and nursing Period. And also to children. Has many interactions with other Drugs, impaired its absorption.	Safe in pregnancy and lactation. Has a few drug – drug Interactions.

A unique Pharmacokinetic properties of azithromycin include better absorption

and more extensively distribution into tissue also a high concentration within

cell (including phagocytes), these attributes result in a much greater tissue or

secretion drug concentration compared to simultaneous serum concentration

compare to doxycycline. Also in comparison side effects profile and drug

interactions doxycycline has many limitation in use in females who are pregnant

or planning a pregnancy or nursing a child and has higher toxicity than

azithromycin especially acne treatment required long term of treatment (6 months

and above).

From the comparison above between azithromycin and doxycycline rise a

question did azithromycin could be effective in treatment of acne vulgaris

patients like doxycycline.

Many studies have been done to evaluate azithromycin alone and others compare

it is efficacy in acne vulagris with tetracyclines and other antibacterial .

(Gruber *et al.*, 1999) conduct an open study in 72 outpatients with acne vulgaris,

to compare the clinical efficacy and tolerability of azithromycin and minocycline.

Azithromycin was administered as a single oral dose (500 mg/day) for 4 days in

four cycles every 10 days and minocycline was administered 100 mg daily for 6

weeks. Improvement was assessed 6 weeks after initiation of treatment with a

four-graded scale. A satisfactory clinical response was observed in 75.8% of the

patients treated with azithromycin and in 70.5% of those treated with

minocycline. There were no significant differences between these two acne

treatments in terms of reduction of the number of lesions ($p > 0.05$). Both agents

were well-tolerated and mild side effects were reported in 10.3% of azithromycin

and 11.7% of minocycline treated patients.

(Fernandez 2000) perform a study in inflammatory acne in 79 patients treated

with oral antimicrobial agents were studied retrospectively over a period of 46

weeks. Patients were treated with tetracycline, erythromycin, minocycline, and

doxycycline, the most commonly prescribed oral antimicrobials used to treat

acne. Individuals that were unable to tolerate this therapy or had failed

conventional therapy were treated with the azalide antibiotic azithromycin, given

in a single oral 250-mg dose three times a week. The other agents were

administered daily in divided doses as is current practice. Patients were also on

topical care.The efficacy and reported side-effects were examined for all agents.

Significant improvement was noted in 4 weeks. All agents were effective in

reducing inflammatory lesions and improving acne. Azithromycin produced a

slightly higher percentage of patients with a greater than 80% reduction in their

inflammatory acne lesions (85.7%) vs. an average of 77.1% for all other agents.

All differences observed were not statistically significant the results show that

azithromycin is a safe and effective alternative in the treatment of inflammatory

acne with few side-effects and good compliance, and suggest the need for further

investigation with a clinical trial that will compare the long-term efficacy and

tolerability.

(Parasad D *et al.,* 2001) conduct a randomized comparative study in 60 patients

with moderate to sever acne were randomly assigned to two groups A&B.

Group A received 100mg doxycycline daily in addition to topical 0.05%

tretinoin cream, whereas patients of group B were given 500mg azithromycin

once a day for four days per month along with topical 0.05% tretinoin cream,

for a total of 12 weeks. Of the 60 patients, 22 in group A and 28 of group B were

evaluated.The monthly dose of azithromycin was found to be as effective as daily

doxycycline on a pure protocol basis and statistically significantly better than

doxycycline by intention to treat analysis.

(Singhi *et al.,* 2003) conduct a comparison of oral azithromycin pulse therapy

of 500mg daily in 3 consecutive days in a 10-day cycle against daily 100mg

doxycycline in 2 groups of 70 patients, both groups combined their therapy with

topical erythromycin, their findings suggest a combination of azithromycin and

topical erythromycin was significantly better (77.76%) than doxycycline and

topical erythromycin (63.74%0) in treatment of inflammatory acne vulagaris.

The incidence and severity of side effects were also lower with azithromycin.

Bruce Sylvester & Italian researchers reported in - February 16, 2004 - at the

American Academy of Dermatology 62nd Annual Meeting that Pulse therapy with

azithromycin is Efficacious and safe for the treatment of acne:

"On the basis of these results, azithromycin had the desired effects in a

percentage of patients ranging from 75% to 80% (e.g., the same or even more

than the percentage reached by the use of other oral antibiotics)," the

investigators reported. The study was open-label, and enrolled 65 Caucasian

subjects in 2 groups. In Group 1, 40 young men and women, aged 18-25

years, diagnosed with papulopustolar acne underwent oral azithromycin therapy

at 500mg/day administered after the evening meal for 3 consecutive days over a

course of 4 weeks. In Group 2, 25 young men and women, aged 18-25, diagnosed

with papulopustolar acne, underwent the same treatment regimen for 6 weeks.

The pharmacokinetics of the drug determined the scheduling of treatment.

Subjects were not allowed to concurrently use any other topical or systemic

drugs.The investigators recorded the number of inflammatory lesions

appearing before and after the course of treatment. A "good/excellent" result was

deemed as greater than or equal to 50%; a "moderate" result was 20-50%; and

>20% was deemed as "no result." For Group 1, the researchers reported

good/excellent results for 40% of subjects, moderate results for 35%, and no

result for 25%. "On the whole, a partial or complete remission was observed in

75%," the researchers wrote.For Group 2, the researchers reported

good/excellent results for 56% of subjects, moderate results for 24%, and no

result for 20%. "On the whole, a partial or complete remission was observed in

80% of patients. We had, with the 6-week regimen, an improvement of the

percentage of positive results, from 75% to 80%,"the investigators wrote.

As for adverse events, the researchers reported that 6 patients developed

gastralgia and 1 left the trial. "No other side effects were reported or observed," it

was noted.(WASHINGTON, DC - February 16, 2004).

(Naseema & Abu Talib 2004) done an open- label, non comparative study for 12

weeks at the outpatient clinics of Aga Khan University Hospital, Abassi Shaheed

Hospital. 35 adolescent and post adolescent patients with moderate to sever

papulopustular acne vulgaris were enrolled.

All patients completed the study. Azithromycin, 500mg orally thrice weekly for

12 weeks, was used . After the baseline visit patients were scheduled to return at

four weekly intervals for 12 weeks. Efficacy was gauged by the percentage

clearance of papulopostular acne lesions.Safety assessments included the

monitoring of adverse events, and compliance was checked at the four - weekly

regular visits up to 12 weeks. The results obtained that (82.9%) showed

remarkable improvement in the first 4 weeks with 60% reduction of their

inflammatory papulopostular lesions. Maximum clerance (80%) was observed at

12 weeks. Adverse effects,such as heartburn reported by four patients (11.4%).

All patients completed the 12-weeks study period.

(S. Kus *et al.,* 2005) done a randomized, investigator-blinded study to compare

the efficacy of azithromycin with doxycycline. Fifty-one patients were

randomized to receive either azithromycin 500 mg/day on 3 consecutive days per

week in the first, on 2 consecutive days per week in the second, and on 1 day per

week in the third month. The other group was given doxycycline twice a day for

the first month and once a day for the second and third months. Clinical

assessment was made at baseline, at the end of first, second, third, and post-

treatment first and second months. Side effects were recorded. Statistically

significant improvement for the facial lesions were obtained with both drugs.

Neither drug was shown to be more effective than the other. The beneficial effect

continued until 2 months after treatment. In the azithromycin group three patients

had diarrohea, while photosensitivity was seen in two patients using doxycycline.

CHAPTER (2)

OBJECTIVES

2. OBJECTIVES

Since tetracycline, doxycycline and erythromycin are the antibiotics effective in

treatment of acne vulgaris, However there is increasing evidence of development

of tetracycline's and erythromycin resistant strains of *Propionibacterium acnes*

from both the topical and systemic use; As the treatment involves long term

therapy with antibiotics, there is need for a newer antibiotics to be tried .

A new agent introduced to Sudan market with a long half life such as

azithromycin could be tried in treatment of acne . It will be more compliant ;

if it shows effectiveness .

Since doxycycline gives good results over tetracycline we expect also

azithromycin to give us better results over erythromycin and comparative to

doxycycline.

Topical formulations such as erythromycin 2% and 4% have been a major

clinical therapy for acne. To date, no topical solution of azithromycin is available

for the treatment of acne vulgaris.

The objectives of this study:

1. The main aim of this study is to compare and evaluate the clinical efficacy of

oral azithromycin in treatment of acne vulgaris with oral doxycycline.

2. Formulate a suitable topical preparation of azithromycin and evaluate it s

effect in treatment of acne vulgaris.

CHAPTER (3)

MATERIAL & METHOD

3.1 Material

Materials used in this study are the following drugs for each group:

Table 3.1 Materials used for each group:

GROUP	DRUG	SOURCE
A	Azithromycin capsules 250 mg (AZITROLYD)	Alfares Pharmaceutical- SYRIA
B	Doxycycline tabs 100 mg (DOXYCYCLINE)	General medical corporation - SUDAN

3.2 METHOD

To evaluate the role of azithromycin and compare it with doxycycline, we conducted this opened label randomized comparative study.

3.2.1 Subject area:

This study have been carried on Omdurman Teaching Hospital, Dermatology Department. This clinic is one of the main dermatology clinics in Sudan served an average of 350 outpatients per week.

3.2.2 Subject inclusion criteria:

The criteria for a patient to be included in the study any patient, male or female complain from inflammatory acne vulgaris aged between 16-40 years.

3.2.3 Subject exclusion criteria:

- Patients less than 16 years.

- Females who were pregnant or nursing a child.

- Patients with a history of hypersensitivity to teteracyclines or macrolides antibiotics.

3.2.3 Sampling Population and Study Design:

This study was carried as prospective, randomized, controlled, and single centre trial, during the period from March 2003 to September 2003.

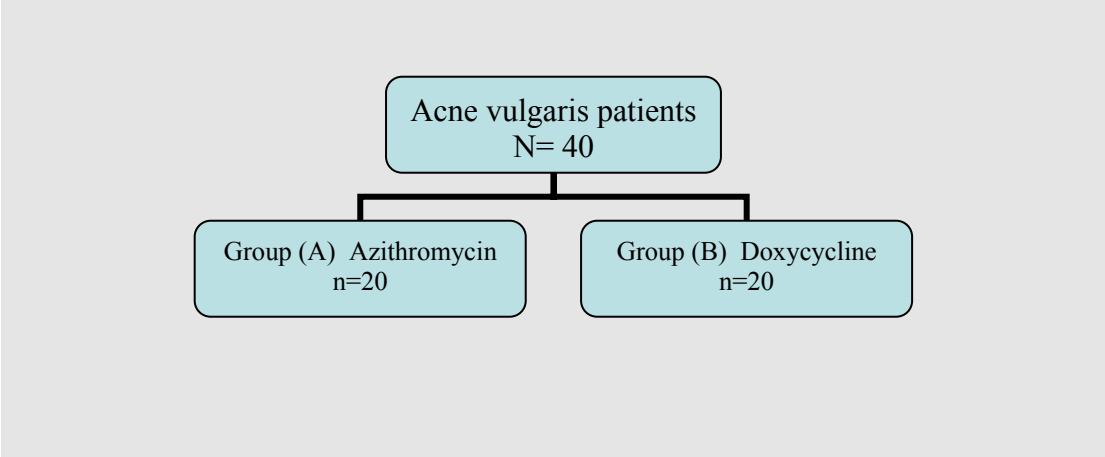
A sample of 40 adolescent and post- adolescent patients from patients suffering from inflammatory acne vulgaris and who are coming to the dermatology clinic looking for the treatment have been selected randomly to participate in this study

Patients randomly assigned to two groups; A and B each group of patients have a line of treatment. Figure 3.1 shows the numbers and distribution of each assigned group.

Patients of group (A) received azithromycin caps,

Patients of group (B) received doxycycline tablets.

Figure 3.1 The numbers and distribution of each group:



3.2.4. Data Collection:

All patients are going to be subjected to:

A. Interview and questionnaire

Data were collected via a questionnaire after face to face interview and the

following background and dependent variables & data were recorded in each

patient questionnaire & assessment card:

1/ Serial number .

2/ Name of the patient.

3/ Age of the patient

4/ Sex

5/ Occupation

6/ Residence

7/ Habits: By habits we mean that does the patient customs to use or apply any

cosmetics creams or cleansing agent preparations or others on their faces.

8/ Age of the onset of lesion

9/ Severity of the case.

10/ Previous treatment (If any).

B/ Assessment of acne severity:

Clinical examination to assess the severity of acne were done for each patient by

specialized dermatologist (Dr. Osman Suleiman Khalifa Co- Supervisor) .

Assessment of severity grading whether; Mild; Moderate; Sever by observing

each type of facial lesion and how it spread in face, chest and back.(as per the

severity grading method, shown in table 1.2.(Leon, *et al.*, 2000).

This primary assessment of severity will be considered as a baseline at the first

visit and each visit for severity reduction. Each patient severity grade is given a

code in order to be processed and analyzed later as shown in Table 3.2

Table 3.2 The code given for severity grade:

Severity	Code
Mild	**1**
Moderate	**2**
Sever	**3**

C/ Drug administration policy:

Each group of patients are going to administer the corresponding drug therapy

according to the following dose regimen :

- Group (A) planned to receive azithromycin capsules as 250mg daily for 3

weeks, then 250mg every other day for 5 weeks then 250mg every 4 days for 2

months, then 250mg once a week. (Walter and Shelly 2001).

- Group (B) received doxycycline tablets 100mg daily as the usual acne treatment

D/ Response evaluation and outcome measures:

After administration of each group the prospective drug therapy, follow up of the

patients have been done every 2 weeks visit to evaluate the response in

comparison to the baseline assessment. Assessment of improvement was

evaluated in each scheduled visit for the face, chest and back (when affected),

global assessment was evaluated at week 22 (visit 11) using 4 point scales and

abbreviations as shown in table 3.3:

Abbreviation	Scale	Explanation

R.R	**-1**	Relapse Response and means that the case is relapsed after improvement or worsen and there is exacerbation in the quantitative assessment of lesions.
N.R	**0**	No Response and mean that acne shows no change.
W.R	**1**	Weak Response and mean that there is slight improvement in quantitative assessments of lesions.
G.R	**2**	Good Response and indicate that there is a clear improvement in quantitative assessment of lesion or no lesions.

Table 3.3 explanation of abbreviation and corresponding scales:
Others outcome measures used in the study in addition to acne response, acne

severity reduction , considered for the assessment of effectiveness such as;

- ❖ Adverse drug reactions and drop out rates.
- ❖ Patient's opinion:

The patient's opinion of the improvement since the beginning of treatment

was registered at each visit as follows; much better, better, somewhat

better, no change or worse and relapsed.

- ❖ Patient's Photographs:

Color photographs are required from some patients to compare the

response before and after treatment.

3.2.5 Data analysis and treatment:

Data was stored and analyzed using spreadsheets of Microsoft Excel 2000. The

results of background and demographic variables presented as Tables and

graphs. The comparisons between two groups for the efficacy results is analyzed

statistically using SPSS software program version 11 using the student' *t*-tests to

compare between the mean of two groups, assuming the null hypothesis that

there is no significance difference between azithromycin and doxycline groups in

treatment of acne vulgaris.

CHAPTER (4)

RESULTS

4. RESULTS

4.1 Demographic Data of study population & Baseline Characteristics:

Of 40 patients enrolled in the study 18 patients of group (A) and 15 patients of

group (B) could be evaluated. Two patients of group (A) and five patients of group (B) loss to follow up and discontinued for non obvious reasons and therefore dropped out from efficacy results but involved in the baseline characteristics.

Figure 4.1: Diagram of numbers of patients continued and discontinued:

Diagram showing numbers enrolled and percentage of drop out of the study:

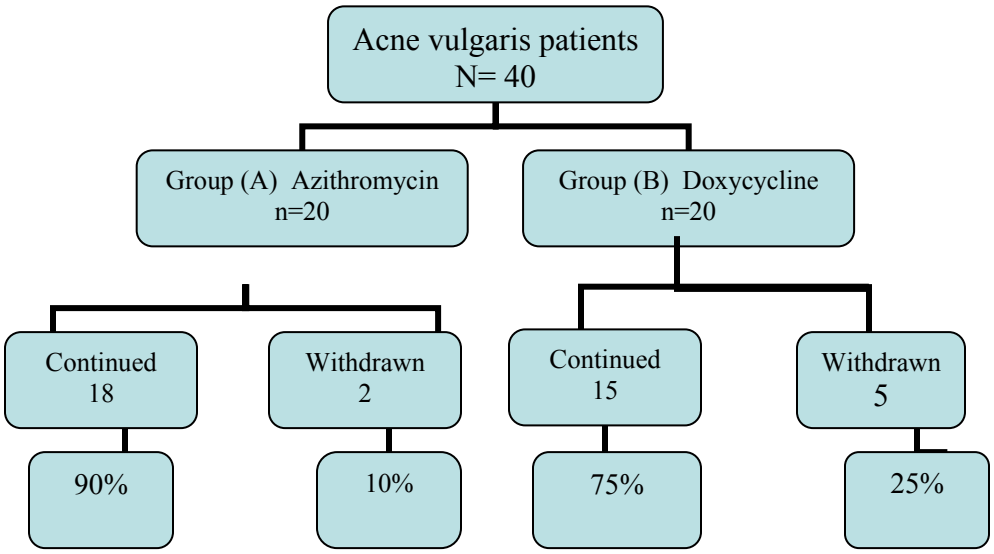
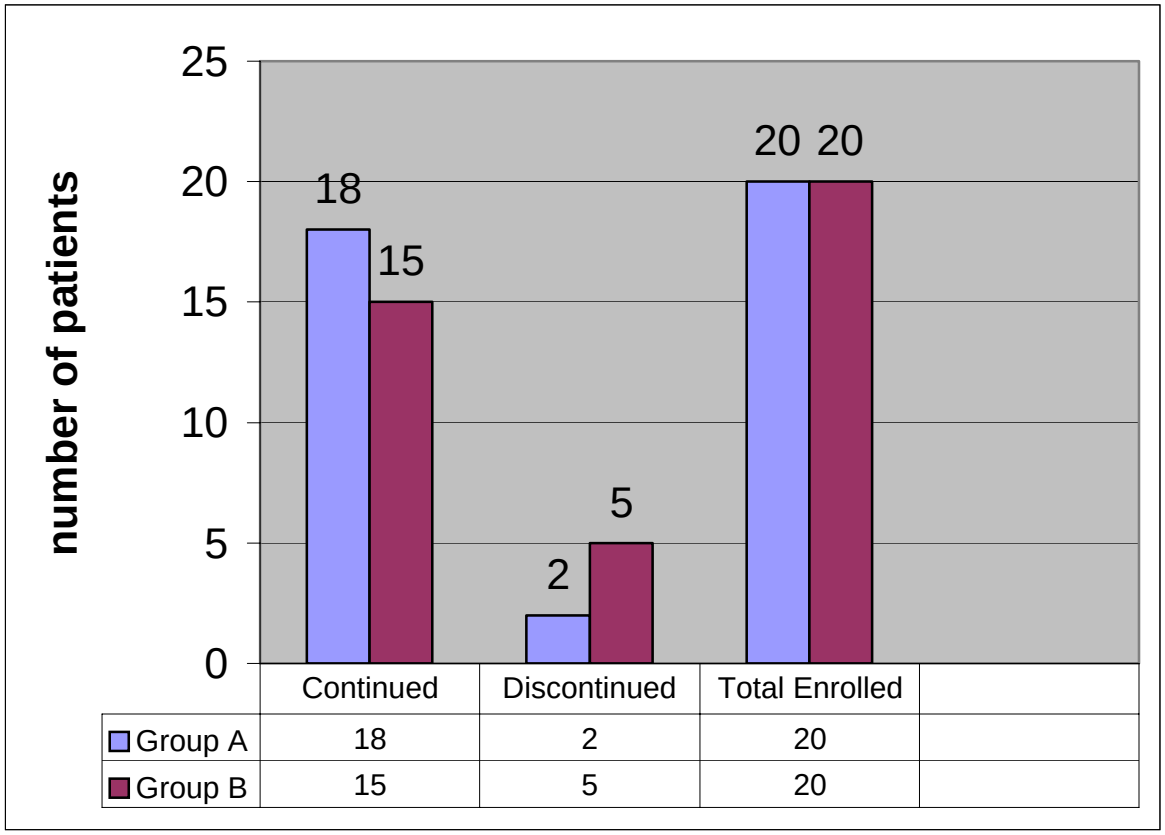
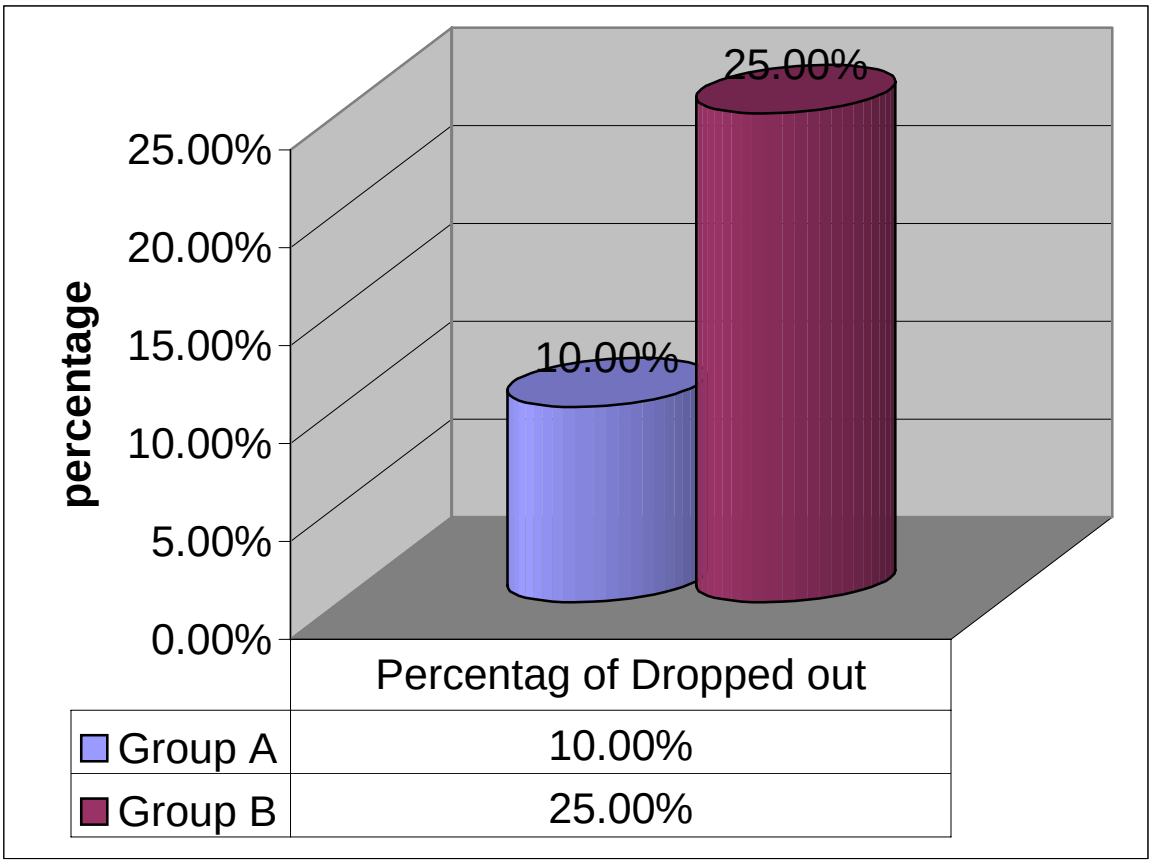


Figure 4.2: Graph of numbers of patients continued and discontinued per each group:



	Continued	Discontinued	Total Enrolled	
Group A	18	2	20	
Group B	15	5	20	

Figure 4.3 percentages of patients droped out per each group:



80% (32 patients) from study population enrolled basically are females and 20%

(8 patients) are males. This percentages is also applied for each group, that is

each group is composed from 16 females (80%) and 4 males (20%). This

presented in table 4.1 and figure 4.4. We observe that the numbers of females are

significantly higher than males, and this may attributed to that female are more

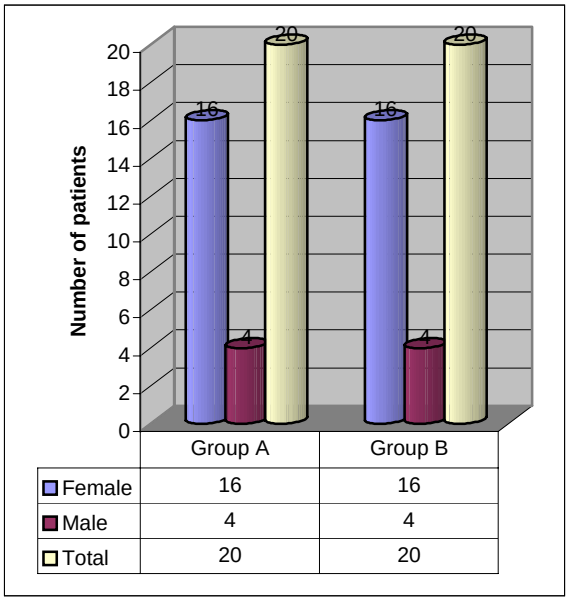
cares about their appearance than males and we feel that from the study they are

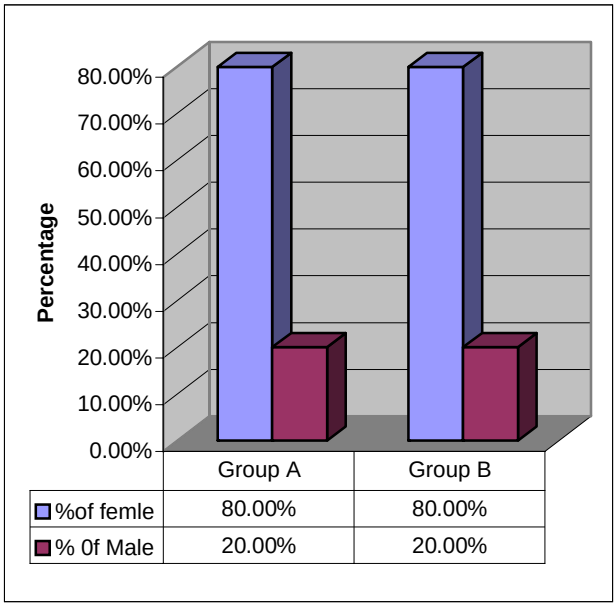
more worried about their faces therefore seeking for the treatment and at the same time more interested to follow up .

T able 4.1 distribution of male and female between each group.

	Female	Male	Total
Group A	16	4	20
Group B	16	4	20

Figure 4.4 number and percentage of male and female per each group





65% (26 patients) of the patients enrolled in the study are in the age range 16-25

years, and about 32.5% fall in the age range 26-30 years, only one patient (2.5%) in the range 31-40 years of age. Table 4.2 and figure 4.5 shows the distribution of patients according to the age range, figure 4.6 shows the percentage of distribution of patients according to the age range.

Table 4.2 distribution of patients according to the age range:

Age range (years)	**Number of Patients**	
	Group (A)	**Group (B)**
16 - 20	5	5
21 - 25	8	8
26 - 30	6	7
31 - 35	0	0
36 - 40	1	0
Total	20	20

Figure 4.5 distribution of patients according to the age range between each group:

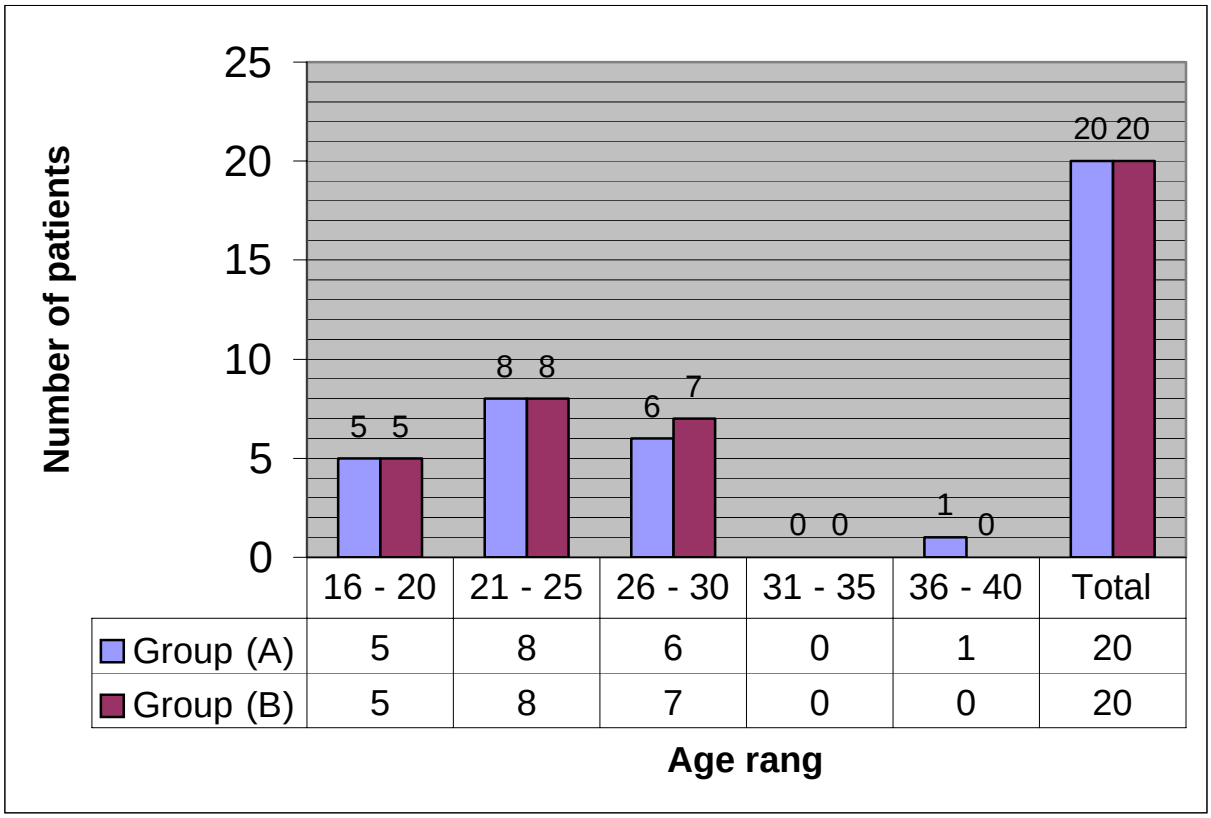


Figure 4.6 percentage of distribution of patients according to the age range:

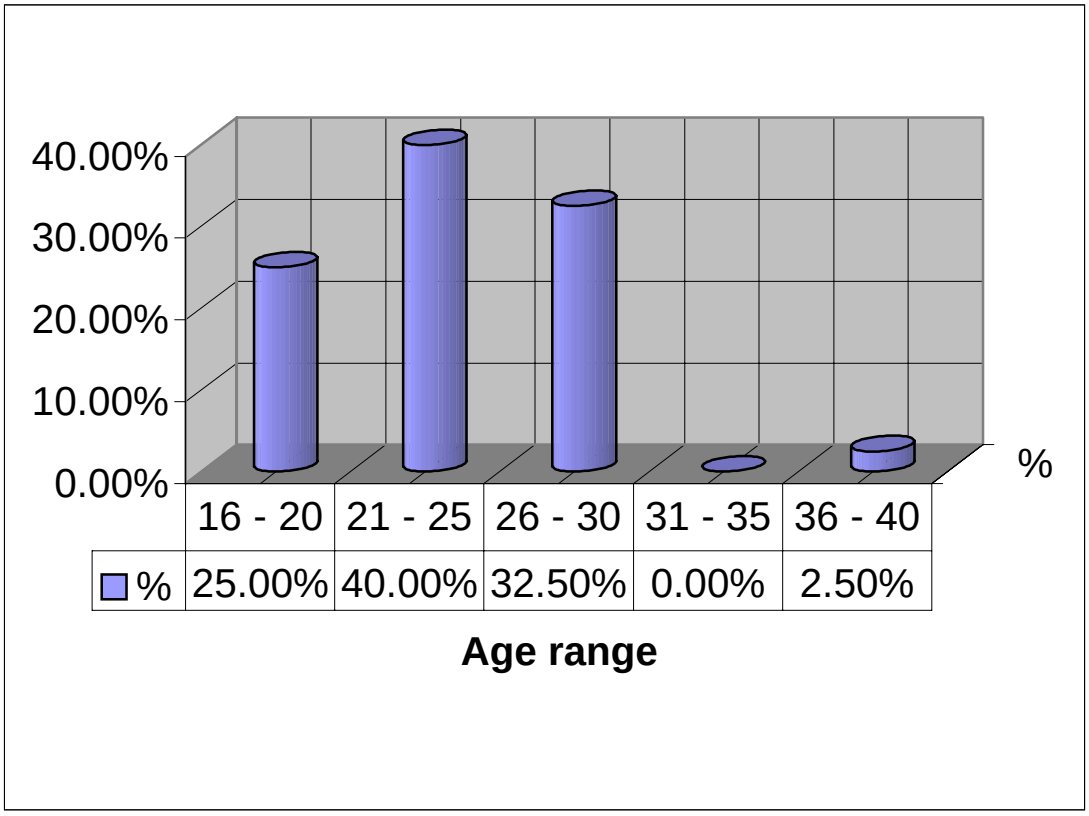


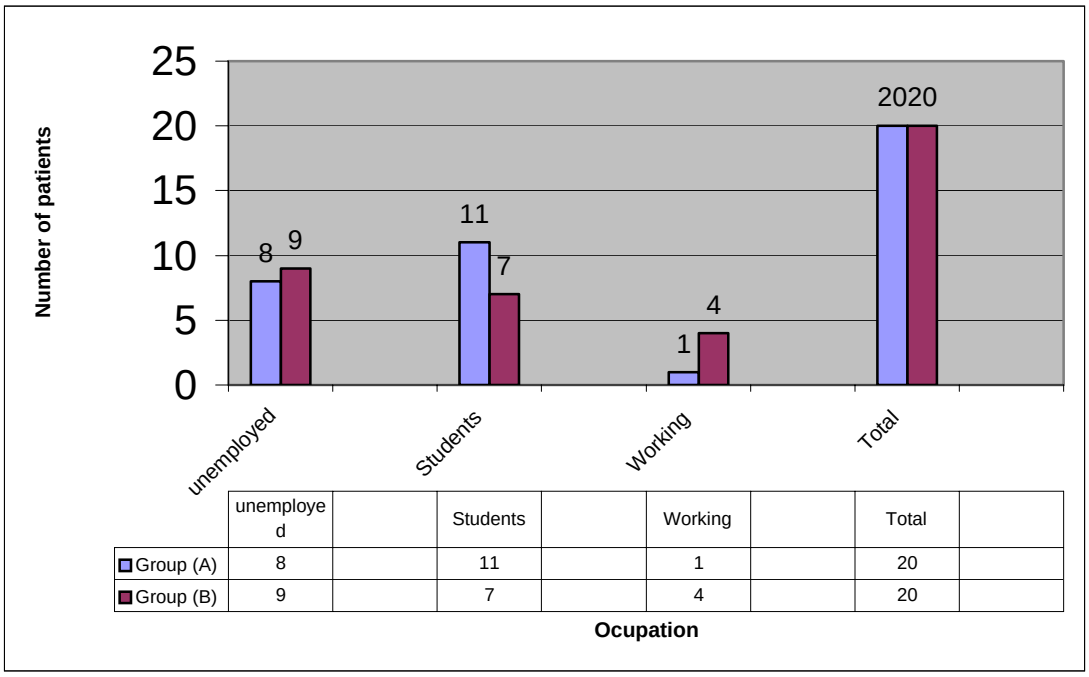
Table 4.3 Shows the occupation of study population, 45% (18 patients) are students and about 42.5% (17 patients) are unemployed , the remaining 12.5%

(5 patients) working in different jobs.

Table 4.3 occupation of study population:

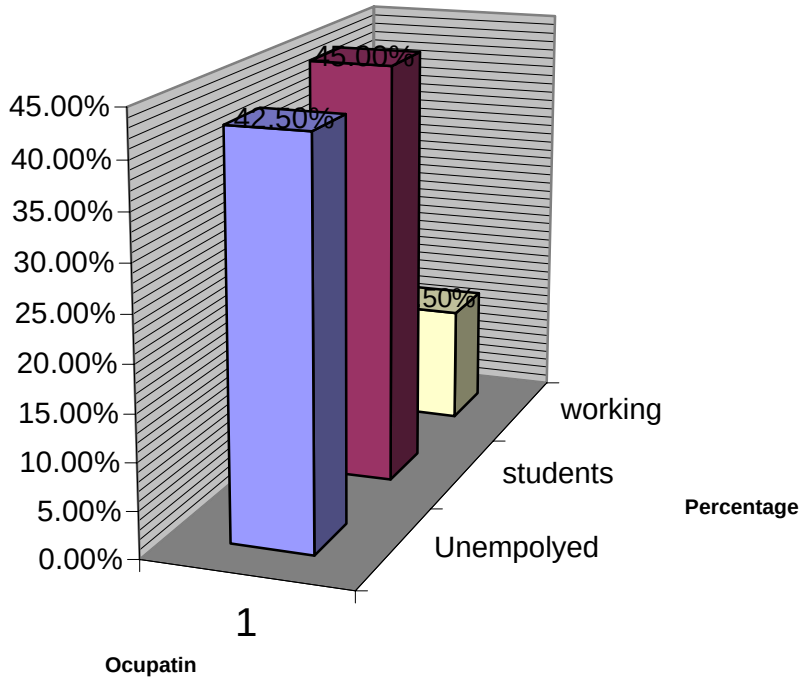
	Number of Patients	
Occupation	**Group (A)**	**Group (B)**
Students	11	7
unemployed	8	9
Working	1	4
Total	20	20

Figure 4.7 number of patients according to their occupation :



	unemployed		Students		Working		Total	
Group (A)	8		11		1		20	
Group (B)	9		7		4		20	

Figure 4.8: percentage of distribution according to the occupation:



	1
Unempolyed	42.50%
students	45.00%
working	12.50%

The residence of the majority of patients is Omdurman city 77.5% (31 patients)

the remaining 22.5% are from out of Omdurman city (9 patients) and four patients of them are from out of Khartoum district. Table 4. 4 shows the distribution of patients according to their residence between each group.

Table 4.4 Distribution of patients according to their residence:

Residence	**Number of Patients**	
	Group (A)	**Group (B)**
Omdurman	13	18
Khartoum	2	0

Khartoum North	1	2
Eldoium	2	0
Shendi	1	0
Elshemalia	1	0
Total	20	20

Figure 4.9 number of patients according to their residence per group:

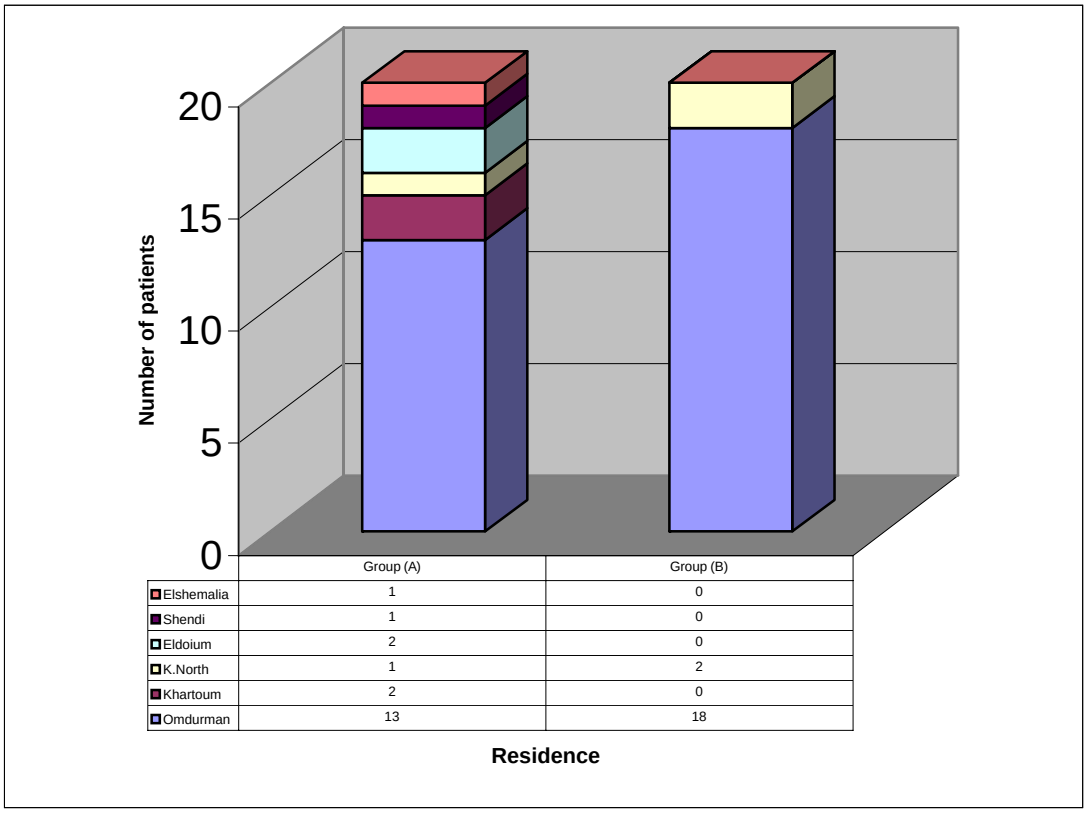
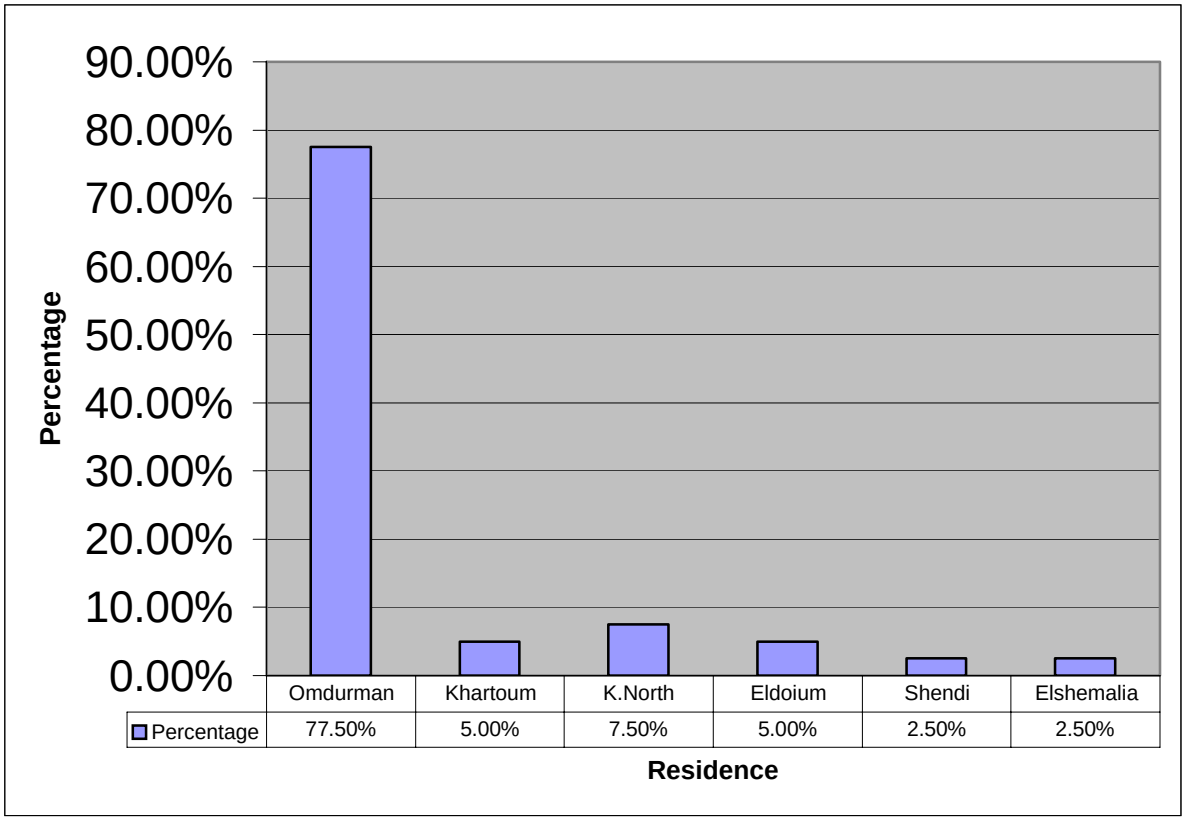


Figure 4.10 percentage of patients according to their residence:



More than 50% (21) of the patients have different habits of applying different

creams on their faces, the purpose of this application is also different, (especially

in females, Boys are not in the habit of putting things on the face) some of them

apply such preparation as a cosmetics, and others as they claimed for whitening

the face and skin, also they use this preparation as cleansing agents.

In most cases they are costumed to apply more than one preparation on their

faces when we ask about the details of the preparation used we surprise that the

majority of this preparations are steroidal products and most of the patients

confirm that this preparations become either initiative factors or complicating

factors for acne vulgaris .
The details of this preparation shown in the table 4.6 and Figure 4.13

Table 4.5 distribution of patients according to habits:

	Have a Habit	No Habit
Group A	8	12
Group B	13	7

Table 4.6 Details of dermatological preparations applied by patients as a habit:

Preparation	**Purpose for use by the patients**	**%**
Betamethasone cream (Betnovate cream, Betaderm cream)	Whitening cream	8%
Dexamethasone cream (Dermovate cream)	Whitening cream	8%
(Lecucid-R) Hydroquinone + Tretinoin	Whitening cream	12%
Trimisolone + Nemoycin + Nystatin (Kenacomb cream)	Whitening cream	4%
Topigel cream -Steroid preperation	Whitening cream	6%
Diana cream	Cosmetics	18%
Kelly cream	Cosmetics	21%
Rose cream & Rose soap	Cosmetics	13%
Cleartone & skin success	Cleansing agents	10%

Figure 4.11 distribution of patients according to habits:

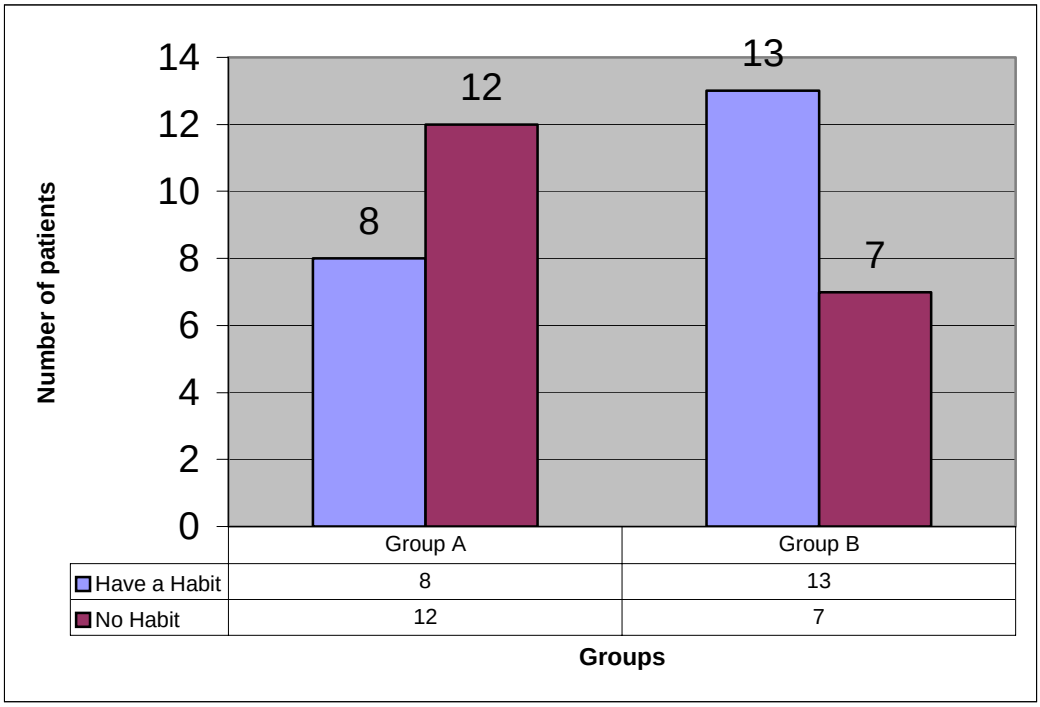
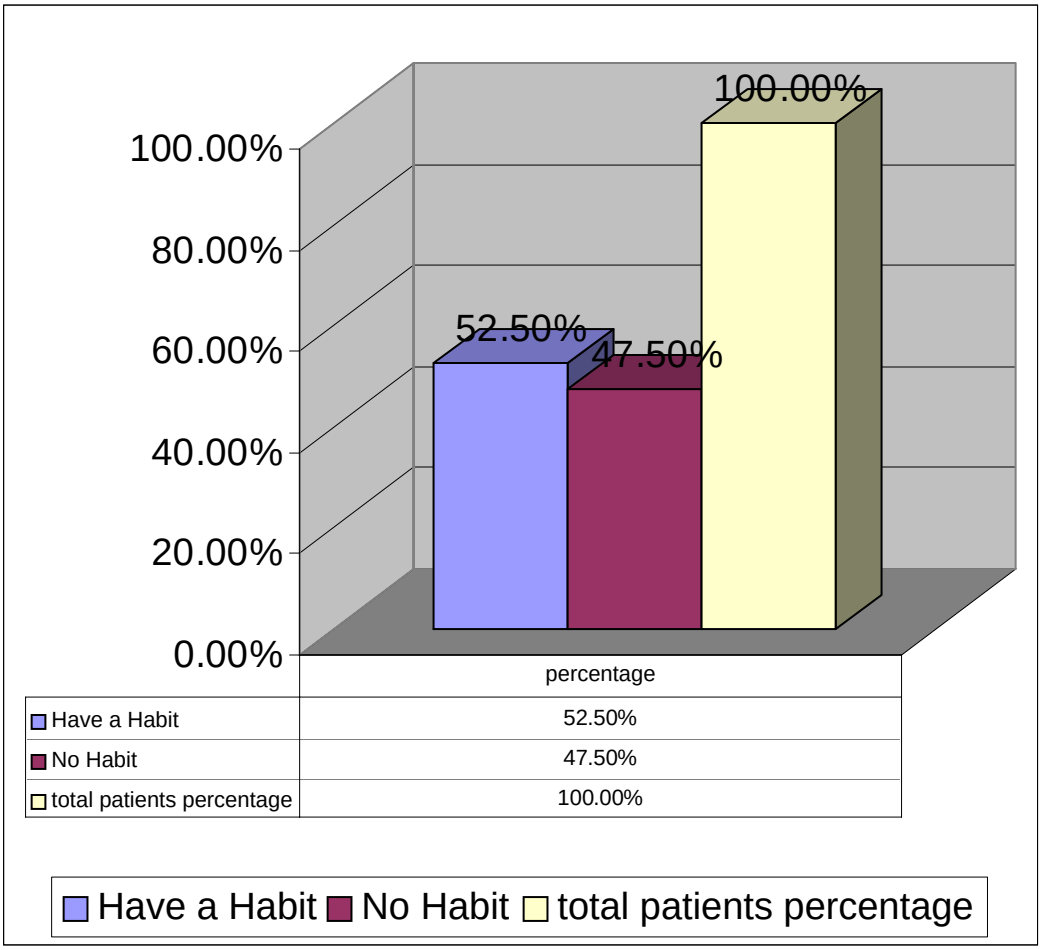


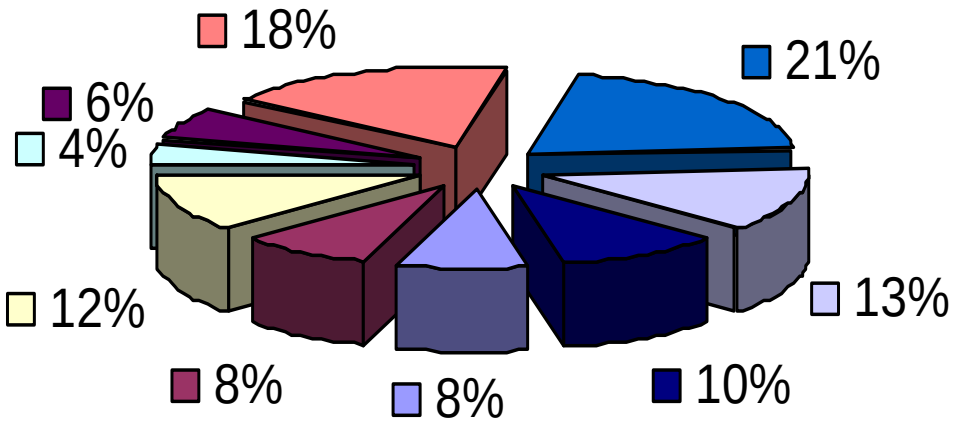
Figure 4.12 percentage of patients according to habits:



	percentage
Have a Habit	52.50%
No Habit	47.50%
total patients percentage	100.00%

Figure 4.13 Details of dermatological preparations applied by patients as a habit:

details Percentage of preperation used



- Betamethasone
- Dexamethasone
- Lecucid-R
- Trimisolone
- Topigel
- Diana
- Kelly
- Rose
- Clear tone

Table 4.7 and Figure 4.14 and Figure 4.15 shows the number and percentage of

patients, according to the age of lesions. 77.5% (31) of patients their lesion's age

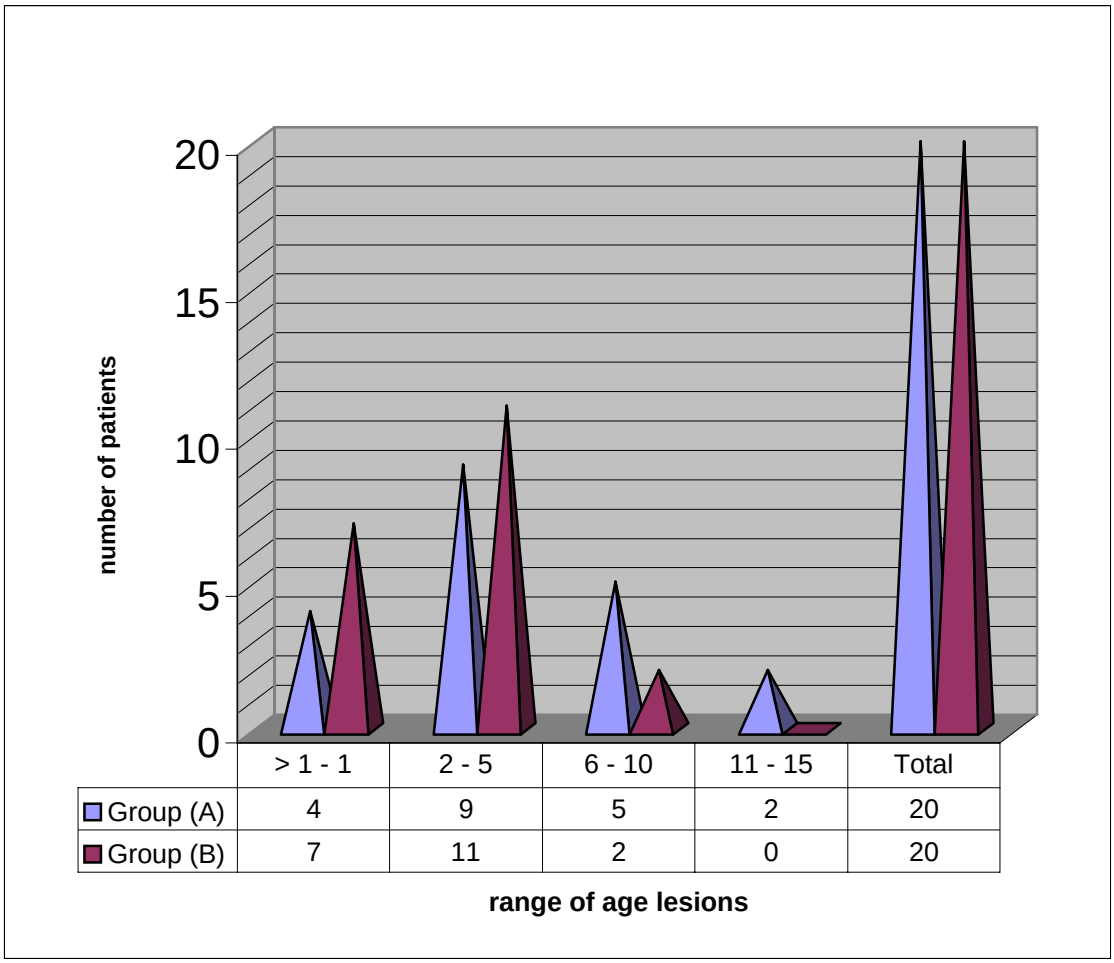
are between the range of > 1 year – 5year. The remaining 22.5% (9patients) have

an age of lesion range of 6 – 15 years.

Table 4.7 distribution of patients according to age of lesions between each group:

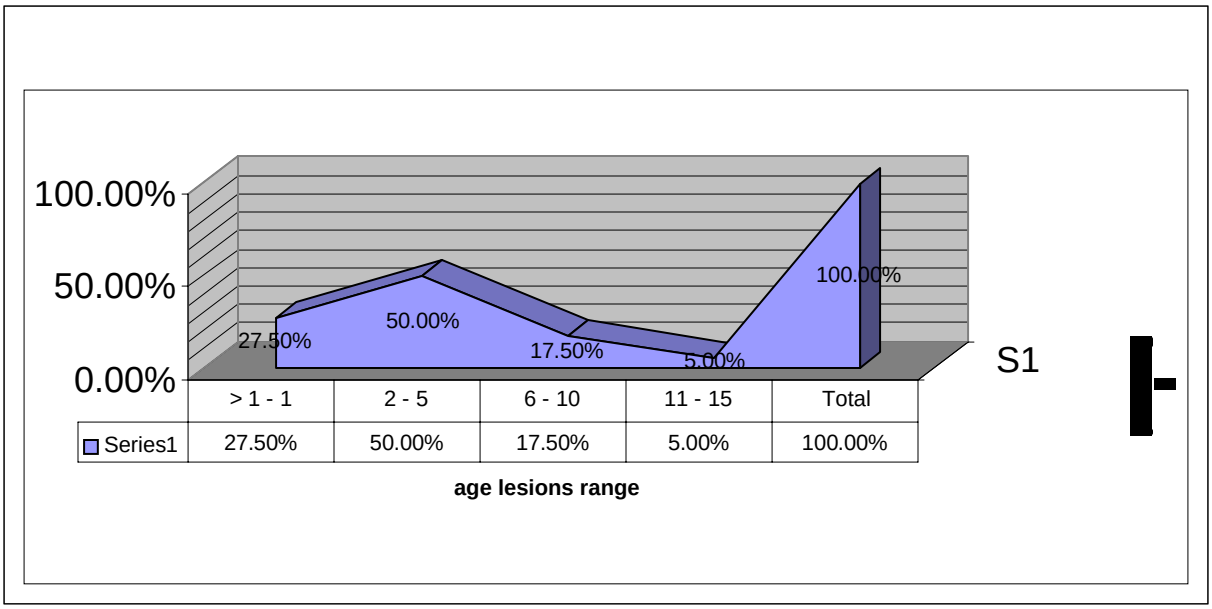
Age of lesions range (years)	**Number of Patients**	
	Group (A)	**Group (B)**
0 - 1	4	7
2 - 5	9	11
6 - 10	5	2
11 - 15	2	0
Total	20	20

Figure 4.14 number and distribution of patients according to age of lesions:



	> 1 - 1	2 - 5	6 - 10	11 - 15	Total
Group (A)	4	9	5	2	20
Group (B)	7	11	2	0	20

Figure 4.14 percentage of patients according to age of lesions:



Analysis of the data according to the severity of the acne lesions among the

patients show that 50% (20 patients) of the cases are sever and 25% (10 patients)

cases are moderate and 25% (10 patients) are of mild cases. The majority of cases

within group (A) are sever acne lesions 70%, while the majority of group (B) are

of mild & moderate cases (35%.each).

Table 4.8 shows the distribution of patients according to the severity of the case:

Severity grade	**Number of Patients**	
	Group (A)	**Group (B)**
Mild	3	7
Moderate	3	7

Sever	14	6
Total	**20**	**20**

Figure 4.16 shows the distribution of patients according to the severity of the case:

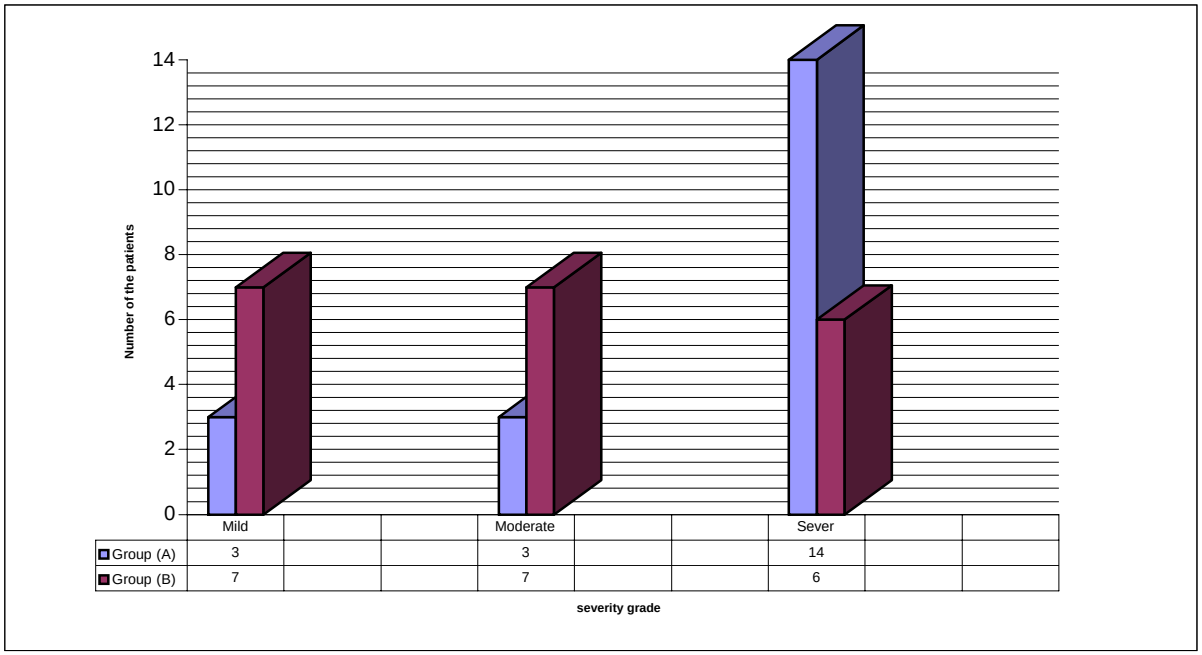
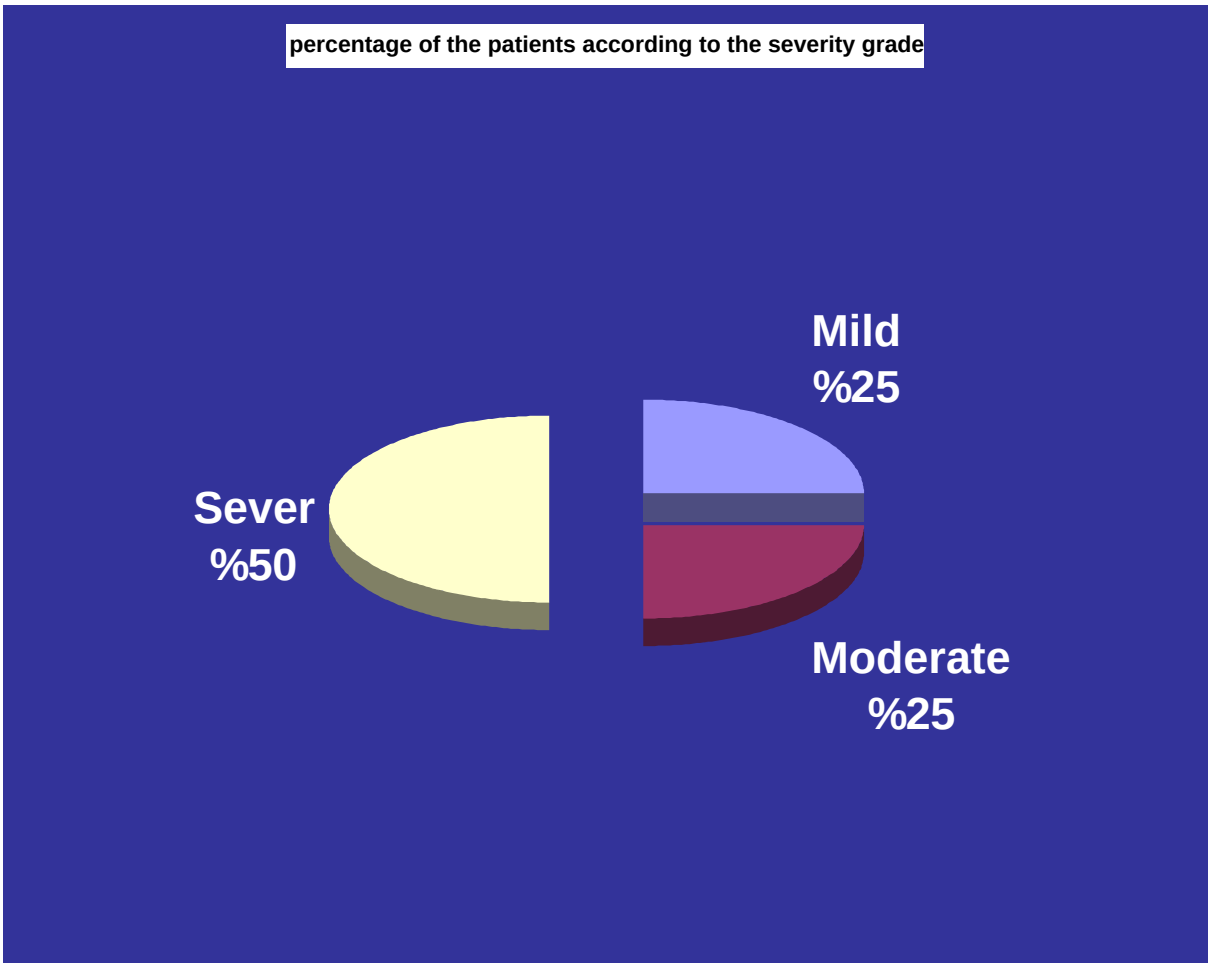


Figure 4.17 Percentage of the patients according to the severity grade:



From the total patients enrolled in the study (40), only (8) patients 20% did not

take any treatment before they enrolled in the study. 80% (32) have taken a

previous treatment and still complain and looking for other or new treatment.

When we ask about the details of the previous treatment and its effect on their

cases, we find that most of them take more than one treatment (i.e. combination

of systemic and topical treatment). The response is also different; some of them

feel a slight improvement others say there is no improvement, a few of them

claimed that there is an irritation and exaggeration in their cases after starting the

treatment.In order to take more reliable results we advise the patients to stop any

previous treatment and didn't take any concomitant treatment.

Table 4.9 Distribution of patients according to the previous treatment between

each group of therapy:

Previous treatment	**Number of Patients**		
	Group (A)	**Group (B)**	**Total**
Yes	16	16	32
No	4	4	8
Total	20	20	40

Table 4.10 Shows the details of previous medications in a percentages:

Previous medications	**Percentage**

Medicated Soaps	23%
Oral antibiotics (mainly Doxycycline)	22%
Retinoic acid cream	11 %
Benzoyl peroxide lotion	10%
Topical antibiotic applications (mainly erythromycin solution)	9%
Topical steroid preparations	8%
Keratolytic agents (salicylic acid and sulphur topical applications)	5%
Anti-irritant topical formulations (Calamine lotion, Zinc oxide paste)	4%
Cleansing preparations	3%
Hormones	2%
Antihistamines	2%
Oral steroids	1%

Figure 4.18 shows the distribution of patients according to the previous treatment:

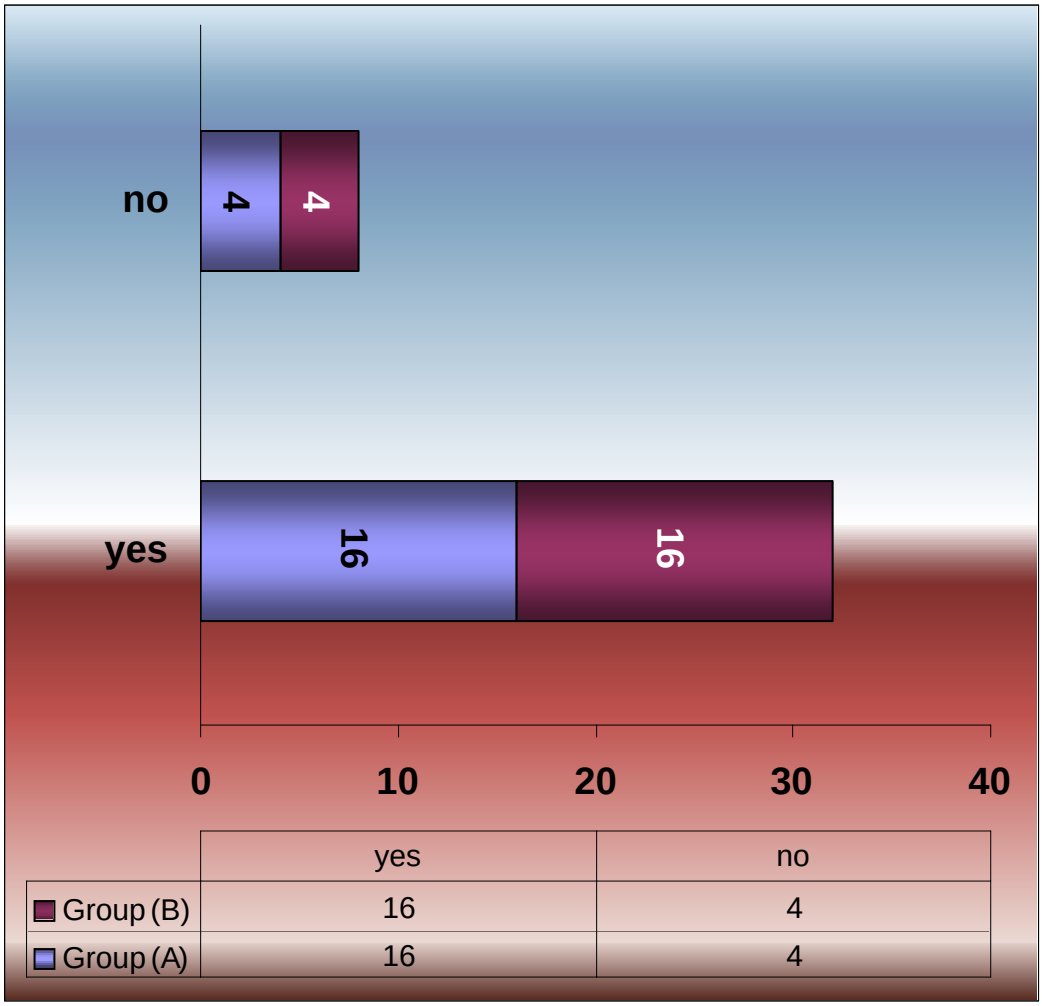
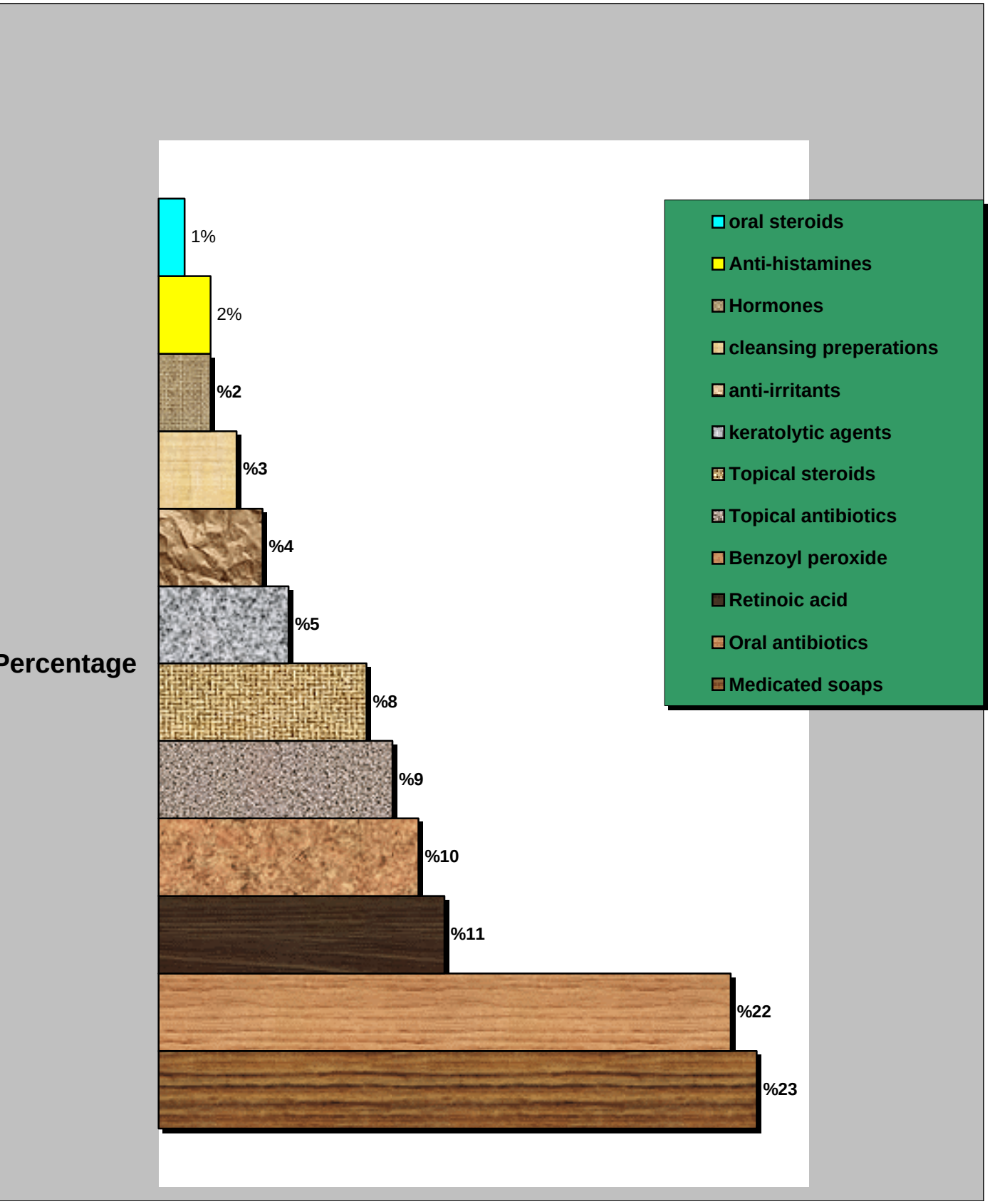


Figure 4.19 shows the percentage of medications used as a previous treatment:


Percentage
1%
2%
%2
%3
%4
%5
%8
%9
%10
%11
%22
%23
oral steroids
Anti-histamines
Hormones
cleansing preperations
anti-irritants
keratolytic agents
Topical steroids
Topical antibiotics
Benzoyl peroxide
Retinoic acid
Oral antibiotics
Medicated soaps

4.2 Efficacy Results:

4.2.1 Assessment of the response:

Comparing the means of responses for each group per each visit individually

(11 visits - 2 weeks interval between each visit) for the both groups we obtained

the result shown in the table 4.11.

Table 4.11 shows the comparison between means of response for each group per

Visit (from visit 2 - visit 12):

	Mean Values Of response	
Visit	***Group (A)***	***Group (B)***
2nd visit	1.33	1.25
3rd visit	1.16	1.43
4th visit	1.39	1.57
5th visit	1	1.8
6th visit	1.58	1.75
7th visit	0.9	1.67
8th visit	1.6	1.67
9th visit	1.66	1.33
10th visit	1	2
11th visit	1.56	0.5

12th visit	2	1

(The 1st visit the visit of baseline or assessment of severity of the disease visit).

When presenting the above values of Table 4.11 on a graph we get the Figure

4.20 shown under, which could indicate the mean values for response of

group (A) is more comparable with that is observed for group (B) at some

visits (visit 2,4,6 &8) and less comparable at other visits (3,5,7,9&10).

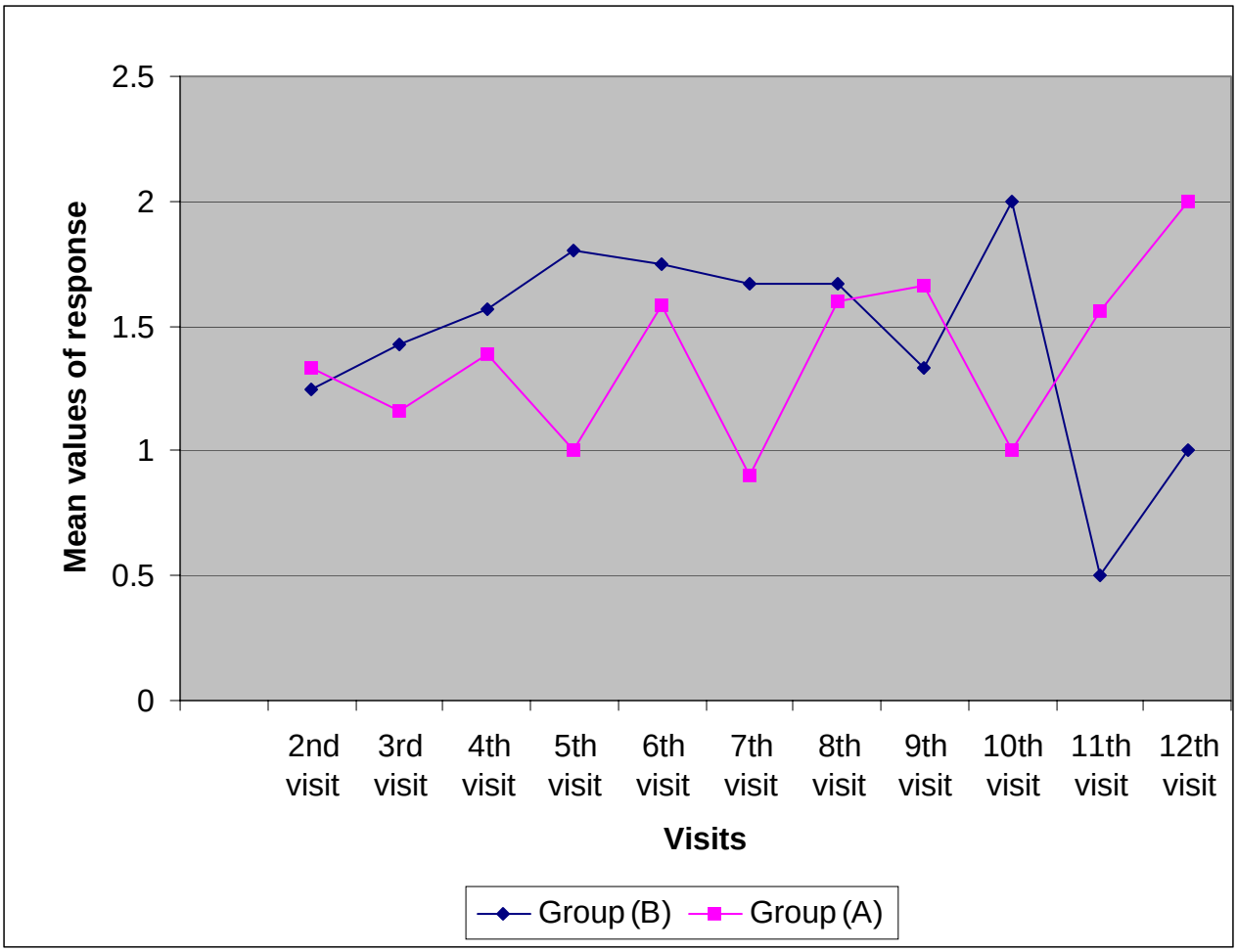
The graph is going smooth for group (B) from visit 2 to 10) while it is not so

for group (A). The mean response is increased for group (A) at the end of the

Visits (visit 11 & 12) while decreased for group (B) at the same visits.

Figure 4.20 Comparison of mean values of response distribution between two

groups per each visit:



The data processed and analyzed statistically by SPSS software program version

11 using the student' *t*- tests to compare between the mean of two groups we

obtained the following results from computer:

T – Test

Paired samples statistics

		Mean	N	Std Deviation	Std Error Mean
Pair 1	Group (A)	1.3709	11	0.3425	0.1033
	Group (B)	1.4518	11	0.4226	0.1274

Paired Samples Correlations

		N	Correlations	Sig.
Pair 1	Group (A) & Group (B)	11	- 0.544	0.084

Paired Samples Test

		Paired Differences							
					95% Confidence Interval of the Difference				
		Mean	Std. Deviation	Std Error Mean	Lower	Upper	*t*	df	Sig. (2-tailed) (P-value)
Pair 1	Group (A)- Group (B)	- 8.09E -02	0.06733	0.2030	- 0.5332	0.3714	*- 0.399*	10	*0.699*

From the statistically results above:

- The computed *t* value of – 0.339 doesn't fall in the critical region .

- The level of significance $P > 0.05$ and we fail to reject the null hypothesis,

that is mean we can not reject the claim there is no significance difference

between two treatment groups (azithromycin and doxycline groups) in treatment

of acne vulgaris.

4.2.2 Assessment of the severity grade improvement:

The efficacy was also determined from the severity grade improvement.

We compare between the reductions in the mean of global severity grade from

baseline to visit 12 for 18 patients in group (A) and 15 patients in group (B).

The data processed and analyzed statistically by SPSS software program version

11 using the student' *t*- tests to compare between the reductions in mean of two

groups we obtained the following results from computer:

T – Test

Paired samples statistics

		Mean	N	Std Deviation	Std Error Mean
Pair 1	Group (A) Baseline	1.3908 2.46	18 18	0.3765 0.66	0.1044 0.18
Pair 2	Group (B) Baseline	1.4970 2.20	15 15	0.4165 0.63	0.1317 0.2

Paired Samples Correlations

		N	Correlations	Sig.
Pair 1	Group (A) & Baseline	18	- 0.015	0.961
Pair 2	Group (B) & Baseline	15	- 0.019	0.959

Paired Samples Test

		Paired Differences							
					95% Confidence Interval of the Difference				
		Mean	Std. Deviation	Std Error Mean	Lower	Upper	*t*	df	Sig. (2-tailed) (P-value)
Pair 1	Group (A)- Baseline A	- 1.0708	0.7649	0.2121	- 1.5330	- 0.6085	*- 5.047*	17	*0.01*
Pair 2	Group (B)- Baseline B	- 0.7030	0.7637	0.2415	- 1.2493	-0.1567	*- 2.911*	14	*.017*

- Mean = (decrease or reduction)
From the statistically results above, when we make the difference in

the mean between each group and its baseline we get the mean of

severity reduction. The severity in both groups decreased significantly

from the baseline to the visit 12 ($P< 0.05$). However highly statistically

significant decrease in severity grade is more in group (A) ($P =0.01$),

than observed in group (B) ($P= 0.017$).

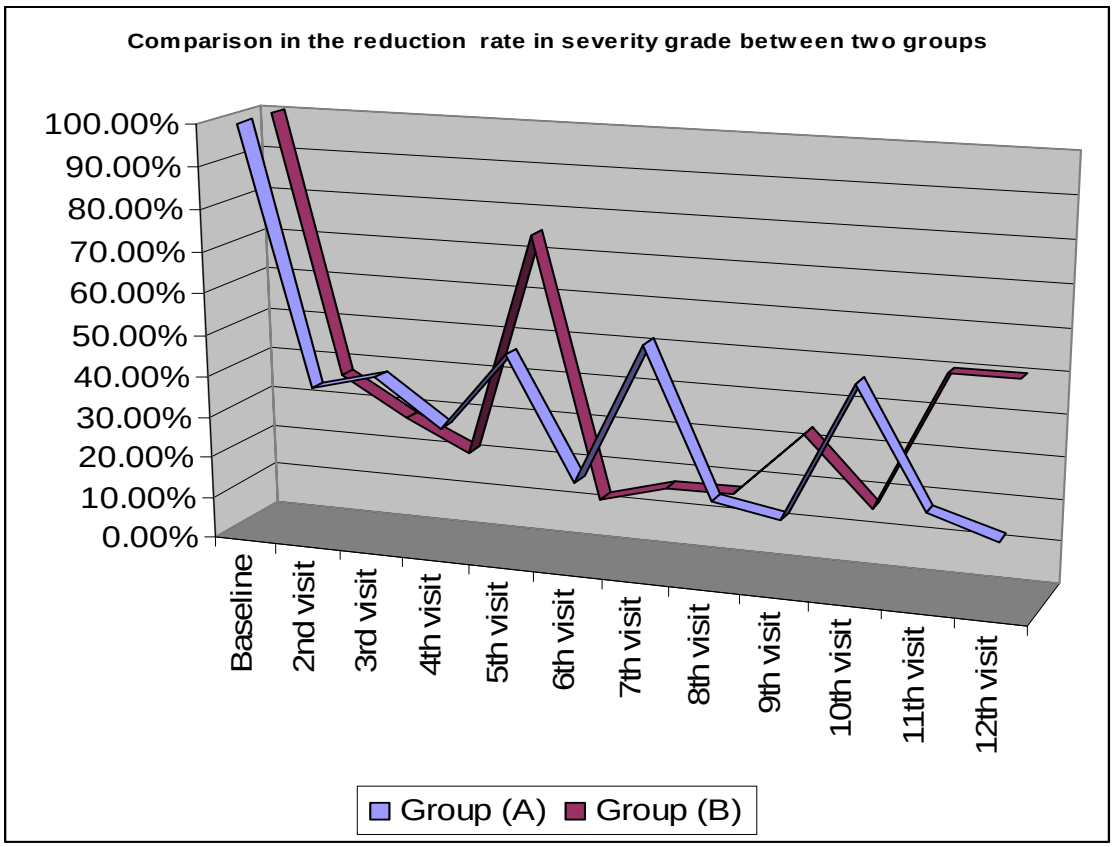
Figure 4.21 shows comparison between two groups in the reduction rate from

baseline to 12^{th} visit in the severity grade we could observe a decrease in the

reduction rate for both groups, but the decrease in group (A) at the 12^{th} visit is

more pronounced (from 100% to 17%) than group (B) (from 100% to 50%).

Figure 4.21 Comparison between two groups in the reduction rate in severity grade:



4.2.3 Adverse effects and drop-out rates assessments:

1/ One patient from the continued azithromycin group (5.6%) complained from

gastritis, and one patient from continued doxycycline group (6.7%) complained

from nausea and vomiting, but both of them continue the study.

2/ Refer to the figures 4.1, 4.2 & 4.3 we observe the higher percentage rate of

drop-out in doxycycline group comparatively to the azithromycin group (25% &

10% respectively).

4.2.4 Patient's opinion:

The patient's opinion of the improvement was recorded at each visit. During the

visits and up to the week 24 there was a higher percentage of patients in

azithromycin treated group than doxycycline treated group who reported a

distinct degree of improvement after beginning such therapy.

Five patients in the azithromycin group had previously responded unsatisfactory

to treatment with doxycycline feel that they are much better with azithromycin

treatment.

There special cases had a very sever acne vulgaries for a period more than 10

years and tried many treatments during this period even hormones and steroids

but their condition did not improved , were then treated with azithromycin they

consider the results after treatment with azithromycin to be definitely superior to

those obtained with the previous treatment. One of them had an excellent

response with a clear or no lesion for a long period.

Many patients from azithromycin group have a period of relapse after

improvement, and this mainly occur upon the change from one dose regimen to

another (this due to the tapering dose regimen adopted for azithromycin in this

study which is difficult comparatively than doxycycline) and could lead to

missed doses and gap in the treatment , when we feel that we advise the patient to

return to the previous dose regimen period until we feel the improvement return

again we shift carefully to the new regimen period.

4.2.5 Evaluation of photographs:

Color photographs required from some patients pre-treatment and after the end of

The study for both groups in order to compared and evaluate the response of the

Treatment therapy. Figure 4.21 and Figure 4.22 shows an example of color

photographs for two different patients from group (A) and group (B) respectively

pre and after treatment, but unfortunately it is not easy to govern that there is a

clear response pre and after treatment for each group.

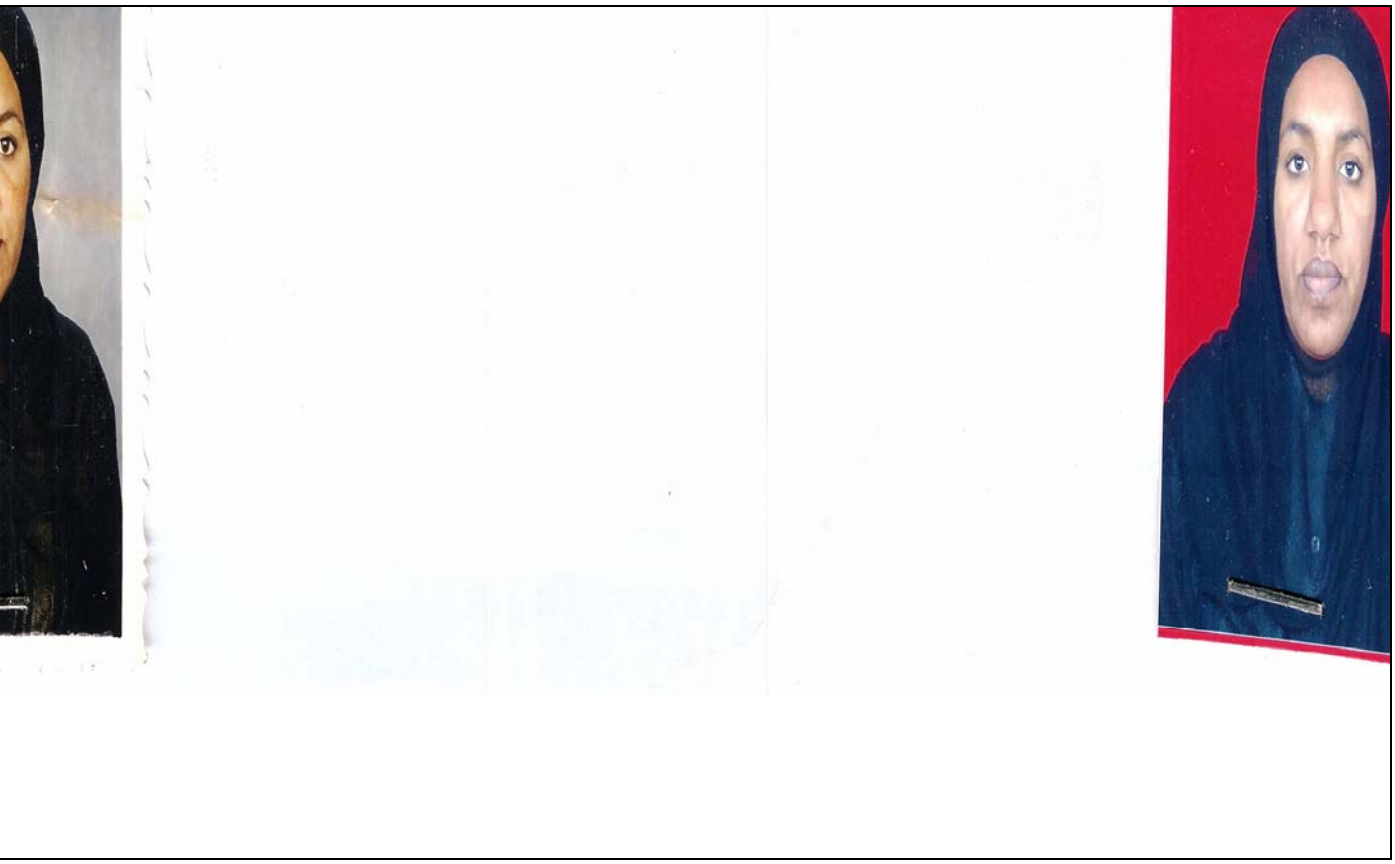
However there is some reduction in the severity grade pre and after treatment for

both group therapy especially in group (A) as judged independently by more than

one observer unaware of the type of treatment prescribed. The weak results

obtained from photos did not encourage us to continue use it as outcome measure.

Figure 4.21 Two photographs for a patient of group(A) comparing pre and after treatment



Pre-Treatment ***After treatment***

Figure 4.22 Two photographs for a patient of group(B) comparing pre and after

treatment

Pre-treatment ***After treatment***

CHAPTER (5)

DISCUSSION

5 Discussion

From the demographic results the incidence of acne patients are mainly between

the age of adolescence and post adolescence (16-30 years) and a few of them

over 30 years (2.5%).

(Acne vulgaris is the most common skin disease of adolescence; it affects about

90% of adolescents it affects primary adolescents in junior high and senior high,

then decrease , acne may persist to age 35 or older).

(Thomas *et al* ., 1998).

Many cosmetics bases and topical preparations used are complicating factors for

acne, most preparations are steroids compounds used in creams and ointments

bases .

(Many topical and systemic medications -e.g. bromides, iodides, topical coal tar

products, androgens, phenytoin, lithium, corticosteroids- can be comedogenic and

can make acne worse or can induce acne-like eruptions , i.e., acneiform lesions.

Some cosmetics bases and certain cosmetics ingredients are comedogenic - e.g.

lanolins, petroleum bases, coca butter- . Preparations such as cleansing creams

suntan oils, and heavy foundation should be avoided.

(Leon *et al.,* 2000).

Duration of lesions: Weeks to months to years. (Thomas *et al* ., 1998).

And the study confirm that some about quarter of the patients have an acne lesion

age from weeks to months and half of them have and acne lesion age from 1-5

years the remaining quarter have an acne lesion age more than 5 years.

The main aim of this study is to evaluate the effect of oral azithromycin antibiotic

in the treatment of acne vulgaris by comparing its effect against doxycycline oral

antibiotic which is the most widely and traditionally used .

The efficacy results of the study show that through different outcome measures

there is a significant improvement observed during the study period.

The outcome measure of the response assessment show azithromycin found to be

effective as doxycycline in improving acne state.

The overall efficacy measured in terms of reduction of the severity of condition

at the end of 22 weeks, is up to 83% with azithromycin compared to 50% with

doxycycline .

In spite we are faced by some problems such as lack of consistent common

outcome measures and endpoint due to inadequacy of acne trial in general.

In addition to the small size of the sample population and increased number of

missed visits result in some statistical errors.

The other outcome measures of adverse effects and drop out rates and patient

Opinion confirm that azithromycin is safe and effective in inflammatory acne

with few side effects and good compliance. But it is difficult to ascertain that

the relative risk of adverse effects is the main reasons of high rate of drop out

from doxycycline group or there other reasons.

Also no clear recommendation can be made concerning the appropriate dose of

azithromycin in treatment of acne vulgaris that should be used in order to

decrease the relapse state of acne and recurrence in changing the dose regimen.

And this observed clearly when comparing between the graph of doxycycline and

azithromycin in figure 4.20 we noticed that the graph of doxycycline is more or

less smooth while of azithromycin is not that and this due to scheduled tapering

dose used in azithromycin dosage policy adopted for this in compare with the

constant dosage of doxycycline all over the period of the study for group (B)

The photography out measure is of poor quality and it is difficult to rely on it as a

strict analytical method for assessment of the severity of the case and to evaluate

the response of treatment therapy.

(Cook *et al*., 1979) confirmed that photography has three drawbacks, in

assessment of acne severity and response, first there is a technical problem,

constant lightening, constant distance between the patient and camera and

constant developing procedures are essential and difficult to maintain accuracy.

Second photographs will never adequately detect the small non-inflamed lesions.

Third photography is two dimensional; it never replaced palpitation, and errors in

distinguishing deep lesions from active superficial lesions or macules will occur.

Defining pharmacological efficacy and clinical outcome in acne management is

difficult, declared Dr. Leyden JJ (1997), because “we really do not know what

concentration any antibiotic can achieve in sebaceous follicles. So we do not have the luxury of being able to look at minimum inhibitory concentrations and relate them to known concentrations of drugs, the way one can, for example, in septicemia or meningitis." Instead, he stated, "We have to resort to indirect methods because most laboratories are not going to culture for *Propionibacterium acnes*.." .

Similar results to our study were obtained by many researchers work in this field,

(Fernandez *et al.,* 2000) who gave azithromycin 250mg per day for 3 days in a week, after 4 weeks he found 85% reduction in acne lesions compared with 77% for other antibiotics (doxycycline, tetracycline, Monocycline).

(Parasad D *et al.,* 2001) found doxycycline 100mg daily to be as effective as azithromycin 500mg for 4 days in a month on a pure protocol basis .

(Singhi M K *et al.,* 2003) in a comparison of oral azithromycin pulse therapy of 500mg daily in 3 consecutive days in a 10-day cycle against daily 100mg doxycycline both groups combined their therapy with topical erythromycin, their findings suggest a combination of azithromycin and topical erythromycin was significantly better (77.76%) than doxycycline and topical erythromycin

(63.74%0) in treatment of inflammatory acne vulagaris. The incidence and

severity of side effects were also lower with azithromycin.

(Gruber *et al.,* 1999) compared azithromycin 500mg for 4 days for 10 days

against monocycline 100mg daily for 6 weeks period therapy and observed a

satisfactory clinical response (70%-75%) and well toleration with both drugs.

(Toda *et al .,* 1999) report from the annual meeting of the American Academy of

dermatology " The pulsed dosing scheduled may represent convenient regimen

than that with tetracycline and it is derivatives in addition azithromycin can be

taken with or without meals, teyeracyclines must be taken 1 hour before or 2

hours after meals"The pulsed consisted of 500mg on day 1 followed by 250mg

per day on days 2-5 on the begging of each month.*)*

(Naseema *et al .,* 2004) conclude that azithromycin 500mg thrice weekly for 12

weeks is safe and effective treatment of acne vulgaris with excellent patient

compliance.

Bruce Sylvester & Italian researchers reported in - February 16, 2004 - at the

American Academy of Dermatology 62nd Annual Meeting that Pulse therapy with

azithromycin is efficacious and safe for the treatment of acne:

"On the basis of these results, azithromycin had the desired effects in a

percentage of patients ranging from 75% to 80% (e.g., the same or even more

than the percentage reached by the use of other oral antibiotics," ..

(S. Kus *et al.,* 2005) done a randomized, investigator-blinded study to compare

the efficacy of azithromycin with doxycycline, neither drug was shown to be

more effective than the other.

The beneficial effect continued until 2 months after treatment.

CHAPTER (6)

CONCLUSION

6 Conclusion

As a conclusion from this study, azithromycin is likely to be an effective

alternative treatment for moderate to sever inflammatory acne vulgaris which is

resistant to doxycycline therapy, but this study found no reliable evidence to justify continued use as first line therapy if doxycycline still effective and no resistant developed for it by the patient especially given the price difference between the two products.

That is to say azithromycin provides additionally effective and safe treatment option to the patients and benefits may be further extended to those patients not responding to available antibiotic therapy.

CHAPTER (7)

A PILOT RUN FOR TOPICAL AZITHROMYCIN IN TREATMENT OF ACNE VULGARIS

7.1 INTRODUCTION

A number of inorganic compounds and antibiotics are used topically in treatment

of mild and moderate acne vulgaris. Erythromycin is one of the common

antibiotics therapy of acne vulgaris, topical formulation available is erythromycin

solution in concentrations of 2% and 4%. The problem about the topical

formulations antibiotics such as erythromycin is the development of resistant by

Propionibacterium acnes.

In one of the clinical study Eady EA *et al* (1994) observed that one of the four

patients attending the outpatients clinic carried a resistant propino- bacteria in the

facial skin.

Topical therapy is employed for mild acne and as maintenance treatment.

Of-late, newer macrolides such as oral Azithromycin have shown promising

results in this condition. To date no topical solution formulation of azithromycin

is available for treatment of acne vulgaris. Azithromycin is characterized by a

unique activity and higher penetrative power to the tissue at the same time have

an antiacne potential against bacteria induced acne. If it is formulated in a

suitable topical preparation with a known concentration/s it could be a good

options for the resistant cases of acne. Also azithromycin is highly lipophilic and

thus concentrates inside the lipid-rich sebaceous follicle, where its antibacterial

action can target *Propionibacterium acnes*..

7.2 OBJECTIVE

Erythromycin has a good solubility in water and alcohol and so it could be

miscible and stable with this two solvents, methylation of 9α carbonyl position

azithromycin decrease water solubility and stability and increase lipid solubility .

(Ritchard & Gallis *et al* .,1999 *)* & (Drug information for the health care

professional *et al.,* 1999).

So azithromycin can not be easily formulated as erythromycin in a solution since

it will be poor soluble and less stable and a suitable vehicle for lipid soluble

products have to be adopted.

Emulsions are known to have high stability and ability to incorporate a range of

drugs of varying physicochemical properties.

The objective of the present investigation is to prepare a stable topical emulsion

of azithromycin and to find a suitable concentration/s which could be used in a

trial to determine the efficacy of topical azithromycin in treatment of subjects

with acne vulagaris.

7.3 MATERIAL & METHOD

7.3.1 Material:

Table 7.1: Shows the material used in topical formulation

Material used	Manufacture	Source
Azithromycin Dihydrate raw material (10 gm)	DR. REDDY's - INDIA	Alfares Pharmaceuticals - SYRIA
Castor Oil	Locally made	Indonesia
Paraffin Oil	Locally made	Indonesia
Emulsifying Wax	Locally made	Germany
Empty Containers	Locally made	Egypt

Mortar & Pestle		England

7.3.2 Method:

7.3.2.1 Study area:

This study was conducted in Omdurman Teaching Hospital – Department of

Dermatology as a continuation for the study of evaluation of oral azithromycin

therapy in acne vulgaris from August to September 2003. More details about the

hospital given in Chapter (3).

7.3.2.2 Inclusion and Exclusion criteria:

Patients of mild to moderate acne vulgaris as new cases and patients who are

previously treated with oral azithromycin and had a good reduction in the severity grade observed (from sever to moderate or mild) are included in this study.

Patient exclusion is of sever acne vulgaris who are needed start with oral antibiotic therapy.

7.3.2.3 Study procedure and design

Formulation of Azithromycin Emulsion

(I) Preparation of emulsion:

- 500 ml of emulsion was prepared using the following quantities of ingredients:-

Castor Oil ……25 ml

Liquid paraffin……100 ml

Emulsifying wax.....…….15 ml

Distilled water to……..……500 ml

- Mineral oils and the emulsifying agent warmed to 60 C and transferred to mortar.

- Water is added gradually to the mixture of oils with a continuous stirring with

pestle until cooled and an oil in water (O/W) emulsion is obtained.

(II) Incorporation of azithromycin powder:

- We divided the obtained 500 ml emulsion into 5 portions each portion is of 100

ml.

- each portion is added each time to a pre-weighted amounts of azithromycin raw

material of 0, 1, 2, 3 and 4 gm with a continuous and homogenous mixing in

order to obtained different azithromycin emulsion concentrations 0%, 1%, 2%,

3% and 4%.

- Again each portion we divided it into two containers of 50 ml and tightly closed

and "external use only" label is stickled to each container and the concentration

of azithromycin is written to the label.

Sampling and application of azithromycin emulsion:

10 patients were selected for the study 5 of them from the old cases pre-treated

with oral azithromycin capsules and improved from sever to mild or moderate

and the other 5 are new cases of mild and moderate acne vulgaris. Each one of

the group given a container of different concentration. Table 7.2 shows the

number of patients and corresponding concentration of topical Azithromycin

emulsion application.

Table 7.2 Number of patients and corresponding concentration of azithromycin

emulsions:

Concentration	Number of new cases	Number of old cases
0%	1	1
1%	1	1
2%	1	1
3%	1	1
4%	1	1
Total	5	5

We request from each patient to apply the topical preparation two times a day in

the morning and evening.

7.3.2.4 Data collection:

Data for response is collected through weekly face to face interview .

The response of each concentration is observed visually by counting the number

of lesions decreased or increased after treatment and also taking the opinion of

patients about the response and side effects and the data evaluated and assessed

from the second week to the fourth week of the trial (First week started apply the

preparation).

7.4 RESULTS

Second week:

We observe that most of the patients complained from the new and old cases

complained from irritation after application of the preparation, this irritation

mainly occur when applied the preparation at the morning and subjected to

sunlight exposure.

Some of the patients of the old cases feel that as if there is relapse to their cases

and there is increase in the number of lesions. The patients of the new cases feel

that there is no response or improvement in their case. Even the control patients

of 0% azithromycin the same irritation which suggest that the skin irritation

occurred mainly influenced by the vehicle rather than the azithromycin itself.

We ask the patients to continue apply the preparation but we advise them to apply

it once daily at the evening instead of morning and evening.

Third week:

One patient from the old patient who are using the 3% concentration his lesion

start to subside after relapse, also one patient from the new cases respond to 3%

concentration, but still the remaining complain from irritation.

Fourth week:

Still the problem of irritation exist and some of the patients of the old cases

stopped the treatment by themselves afraid that their cases may worsen after

improvement result from oral therapy , we advise the patients to stop the

treatment we put the old cases again in the azithromycin oral therapy as the last

scheduled therapy and the new cases given the suitable therapy.

Finally we decided to discontinue the trial according to the result obtained.

7.5 DISCUSSION

It seems that the vehicle of emulsion and the mineral oil specifically may cause

the adverse effect of skin irritation and flare rather than azithromycin since even

the patients that apply blank preparations suffering from the same problem.

This suggest that more much work is needed to find out a suitable vehicle other

than emulsion such as gel to incorporate azithromycin without causing irritation,

and a trial with much more sample size.

Some cosmetics bases and certain cosmetics ingredients are comedogenic (e.g.

lanolins , petroleum bases, coca butter) . (Leon, *et al.,* 2000).

A trial similar to this published in Indian Journals of Pharmaceuticals Sciences

made by (Kale 2002) its conclusion as follows:

Transparent, optically isotropic, and thermodynamically stable microemulsions

could be formulated for topical application for azithromycin . Microemulsions

exhibited good physicochemical properties. Primary skin irritation studies

indicated the safety of microemulsions for human use. From microbiological

assay, it is evident that microemulsions could serve as the best vehicle for topical

application of antiacne moiety, azithromycin. Antiacne formulation containing

azithromycin was successfully formulated using microemulsion as the drug

delivery system.

Another later study done by (Mc Hugh *et al* ., 2004*)* conclude that:

A 2% azithromycin in 60% ethanol/water solution can be prepared and is stable

for at least 6 months at room temperature. The methodology and power of the

study were adequate to identify improvement in acne vulgaris and rosacea.

It appears the formulation of topical azithromycin was at least comparable with

topical erythromycin. No significant adverse events were identified in the 20

patients of acne group. From 20 patients with rosacea, transient irritation

occurred in five.

7.6 SUGESSTIONS

The trial suggest the need for further investigation and larger studies to find out

a suitable vehicle and stable formulation for azithromycin to be applied topically

and to determine whether it will give any significant results and have any

advantages over the currently used topical formulations.

CHAPTER (8)

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STUDY QUTIONNARE FOR AZITHROMYCIN CAPSULES COMPARE TO DOXYCYCLINE IN ACNE VULGARIS TREATMENT

بسم الله الرحمن الرحيم

ial No:……

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cupation:- ……..

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its:- …….

e of onset of lesion:- ……..

ns & symptoms & severity of the case :-……..

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vious treatment (If any) :- ……
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ient group & regimen of treatment:-

1- Azithromycin	2- Doxycycline	3- Placebo

previations terms of the results:-
R - (No Response)
R - (Weak Response)
- (Good Response)

sults / date	1st visit	2nd visit	3rd visit	4th visit	5th visit	6th visit	7th visit	8th visit	9th visit	10th visit	11th visit	12th visit

Literature review :-

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Findings:-

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Conclusions:

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Recommendation:

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STUDY QUTIONNARE OF AZITHROMYCIN TOPICAL APPLICATION IN TREATMENT OF ACNE VULGARIS

بسم الله الرحمن الرحيم

No: ……

of the patients:- …….

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(No Response)
(Weak Response)
(Good Response)

Results Date	**1st visit**	**2nd visit**	**3rd visit**	**4th visit**	**5th visit**	**6th visit**	**7th visit**	**8th visit**	**9th visit**	**10th visit**	**11th visit**	**12th visit**

Literature review :-

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Findings:-

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Conclusions:

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