



**COMPARISON BETWEEN THE METRONIDAZOLE GEL 0.75% AND PERMETHRIN CREAM 2.5% IN THE TOPICAL TREATMENT OF ROSACEA**

\*<sup>1</sup>Dr. Noor J. Mahdi, <sup>2</sup>Dr. Ali H. Hafedh and <sup>3</sup>Dr. Wesam A. Jawad

<sup>1,2,3</sup>Al- Kindy Teaching Hospital/ Ministry of Health/Baghdad/Iraq.

\*Corresponding Author: Dr. Noor J. Mahdi

Al- Kindy Teaching Hospital/ Ministry of Health/Baghdad/Iraq.

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**ABSTRACT**

A comparative clinical study was conducted to evaluate the efficacy and safety of metronidazole gel 0.75% and permethrin cream 2.5% in the treatment of rosacea at the Department of Dermatology and Venereology in Al-Kindy teaching hospital during the period from July 2016 to March 2017. Sixty-six patients, who diagnosed to have rosacea on clinical ground, were enrolled in this study. Patients randomly divided into two groups: The first group included 36 patients subjected to treatment with metronidazole gel and the second group included 30 patients subjected to treatment with permethrin cream. All patients were instructed to use the treatment twice daily for 2 months. Results revealed that the patients treated with metronidazole gel showed a significant improvement in the inflammatory lesions counts after 2 weeks of treatment. The improvement of the Erythem was slight which indicated the need of a longer time to show significant response. Effect of metronidazole gel on telangiectasia is mild, show slight improvement. Concerning the Patients treated with permethrin cream results showed an improvement in the inflammatory lesions counts and erythema but statistically not significant. It had no effect on telangiectasia. In conclusion: However, metronidazole gel and permethrin cream can be used for treatment of rosacea, but the metronidazole gel 0.75% is more effective and safe than permethrin cream 2.5% and has infrequent side effects.

**KEYWORDS:** Metronidazole permethrin rosacea.

**INTRODUCTION**

Rosacea is a relatively common disease, especially in fair-skinned people of Celtic or Northern European heritage (Plewig and Jansen 1999). It affects approximately 13 million Americans (Cuevas, 2001., Bikowski, 2000). It is rarer in the dark skinned people, particularly the American and African blacks (Logan and Griffiths, 1984; Jansen and Plewig, 1997).

Although women are more often affected than men in earlier stages (3:1 ratio), men develop the grotesque tissue and sebaceous gland hyperplasia that lead to rhinophyma much more frequently, and although rosacea tend to be milder in women, it can lead to severe emotional distress owing to its chronic course (Plewig and Jansen 1999; Hirsch and Weinberg 2000).

A descriptive study conducted by Feldman et al., (2001), based upon data on rosacea visits (1990-1997) obtained from the National Ambulatory Medical Care Survey revealed that; there were 1.1 million outpatient visits for rosacea annually in the United States. Most rosacea outpatients were Caucasian (96%). Most visits were by women (69%) and the mean age of the patients was

(50±17SD) years. Visits to dermatologist accounted for 78% of visits

Although the precise aetiology of rosacea remains a mystery, various factors have been suspected of contributing to this condition such as genetic predisposition, gastrointestinal factors, Drugs, food, Alcohol, Sunlight, and psychological factors (Plewig and Jansen 1999; Abell, 1997). Rosacea is a chronic disease that is difficult to treat, and cure is often not possible. It usually responds to treatment, but patients must be warned that improvement will be gradual, and perseverance is required. Caring for rosacea patients requires a dedicated clinician and compliant patient (Greaves, 1983; Plewig and Jansen 1999). Several types of the topical treatments were used to treat patients for instance: Metronidazole, Permethrin, Antibiotics, Imidazoles, Azeliac acid, Retinoids, and Tacrolimus (Nielsen, 1983; Plewig and Jansen 1999, Nally and Berson, 2006) Because of rosacea is a chronic disease with period of remission and exacerbation, many medications has been used to control the activity of the disease, therefore, this study was carried out to evaluate the efficacy and safety of metronidazole gel 0.75% and permethrin cream 2.5% in the treatment of rosacea.

## PATIENTS AND METHODS

### Patients

Open comparative therapeutic clinical study was conducted to evaluate the efficacy and safety of metronidazole gel 0.75% and permethrin cream 2.5% in the treatment of rosacea. This study was conducted at the Department of Dermatology and Venereology in Al-Kindy Teaching Hospital in a period between July 2016 to March 2017. A total number of 66 patients (45 Females and 21 males) with female to male ratio 2.1:1 were enrolled in this study. Their ages ranged from 26-66 years.

Full history was taken from each patient, including the name, age, sex, social status, job, history of the disease itself, the age of onset, duration, complaint of the patient, family history of the same disease or any other skin diseases, drug history (topical and systemic), presence of other skin diseases, other systemic diseases such as hypertension, diabetes or others, involvement of other systems such as eye involvement, gastrointestinal problems. Exacerbating factors (sun exposure, heat and psychological factors....ete), and habits (smoking, alcohol). Patients were instructed to stop any other medications at least one month before starting the therapy. Physical Examination of the patients and assessment of their disease was done according to the disease severity score, which includes: severity of erythema, number of the papules, pustules and telangiectasia, (Table 1). The severity of erythema was determined according to a color chart.

Patients with subtypes I and II, were included in this trial. Patients with phymatous rosacea, ocular rosacea, those with severe steroid-induced rosacea, and pregnant women, were excluded. Patients were divided randomly into two groups: Group A: Patients who treated with metronidazole gel 0.75%, their numbers were 36 patients (9 males and 27 female). Their ages ranged from 26-66 years. Each patient instructed to use the gel topically twice daily for 2 months and Group B: Patients who treated with permethrin cream 2.5%, their numbers were 30 (12 males and 18 female) 15 of them (3 males and 12 females) default from the beginning of the study because of irritation. Their ages ranged from 35-55 years.

Each patient instructed to use the cream topically once daily for 2 months. Clinical evaluation was done for the two groups at week 2 and week 6 of treatment. The assessment carried out by observing the severity of erythema and counting the numbers of papules, pustules and telangiectasia and recording any side effect

### Statistical analysis

Data were analyzed by using (SPSS) program version 17 and MINITAB V 16 Means were compared by t tests and p-value of  $\leq 0.05$  considered statistically significant.

**Table (1): Disease severity score.**

Score	0	1	2	3
Erythema	Absent	Mild	Moderate	severe
Papule	0	<5	5-10	>10
Pustule	0	<5	5-10	>10
Telangiectasia	Absent	<5	5-10	>10

## RESULTS

The duration of the disease ranged between 1 month and 10 years. Positive family history was found in 16(31.3%) patients. Gastrointestinal problems were found in 18 (32.7%) patients in the form of gastritis (Table 2).

**Table 2: Description of the study group.**

	Patients information.	Patients No.	(%)
1.	Family history	16	31.3%
2.	GIT involvement	18	35.2%
3.	Systemic diseases		
	Hypertension	15	29.4%
	Diabetes	5	9.8%
4.	Habits		
	Smoking	7	13.7%
	Alcoholism	1	1.9%

The age of onset in our study range from (26-66) years, with the most affected age group were (46-55) compromised 21(41%) of patients (Table 3).

**Table 3: Distribution of age group among 51 patients.**

age/ year	No
15-25	0
26-35	2
36-45	19
46-55	21
56-65	8
66-75	1

The presenting symptoms of the patients were: burning in 48 of the patients, stinging in 46 patients, itching in 24 patients, dry appearance and scale in 27 patient and most patients had more than one complaint (Table 4).

The sites of the lesions were in the cheek 51 patients, nose in 49 patients, forehead in 33 patients and chin in 24 patients and most patients have more than one site (Table 5).

**Table 4: Complain of 51 patients, most patient have more than one complain.**

Complain	No. of the patients
Burning	48
Itching	24
Dry appearance or scale	27
Stinging	46

**Table 5: Site of lesions in 51 patients most patients have more than one site.**

Site	No. of the patients
Cheek	51
Nose	49
Forehead	33
Chin	24

Sun exposure was the major aggravating factor in 49% of patients (Table 6).

**Table 6: Aggravating factors among 51 patients.**

Aggravating factors	No. of the patients
Sun	49
Psychological	41
Heat	10

The results obtained that the patients treated with metronidazole gel showed an improvement in inflammatory lesion count (papules and pustules). This improvement statistically significant, ( $p=0.001$  for papules,  $p=0.002$  for pustules). (Table 7; Fig 1) The improvement of the erythema was slight which indicated the need of a longer time to show significant response.

**Table 7: Effect of metronidazole gel on severity of disease.**

Metronidazole	Week 0	Week 2	Week 6	p
Erythema	3	1	0	0.174
Papule	12	4	0	0.001
Pustule	12	6	0	0.002
Telangiectasia	18	18	15	0.838

The results of Group B showed that the effect of permethrin cream 2.5% on inflammatory papules and pustules and erythema was mild. However there was an improvement but statistically was not significant ( $p=0.178$  for papules), ( $p=0.061$  for pustules), ( $p=0.178$  for erythema). Table (8) illustrated that no improvement was detected regarding the telangiectasia. The number of patients who showed relapsing of the disease was 9(58%) (Table 9; Fig. 2, 3).

Side effects of permethrin were severe and could not be tolerated by the most of the patients, skin irritation was the main complain, it include burning sensation, itching and swelling. Because of these side effect, 50% of the patients default from the study.

**Table 8: Effect of permethrin cream on severity of disease.**

Permethrin	Week 0	Week 2	Week 6	p
Erythema	6	4	1	0.178
Papule	3	1	0	0.174
Pustule	6	4	0	0.061
Telangiectasia	6	6	5	0.943

**Table 9: Relapse rate in both groups**

Relapse	Positive	Total	%
Metronidazole	16	36	42
Premethrine	9	15	58



(A) (B)



(A) (B)

**Picture (1): Two patients with rosacea before (A) and after (B) treatment with metronidazole.**



(A) (B)

**Picture 2: Patient with rosacea, (A) before treatment, and (B) skin irritation after use permethrin cream.**



(A) (B)

**Picture 3: Patient with rosacea, (A) before, and (B) after treatment with permethrin cream.**

**DISCUSSION**

The present study showed that the age of onset in our study range from (26-66) years, with the most affected age group were (46-55) compromised 21(41%) of

patients. This was in agreement with other reported epidemiological data (Blount and Pelletier, 2002).

Family history was positive in 16 (31.3%) of our patients, which was similar to a study where 30% of patients reported positive family history (Rebora, 1993).

Gastrointestinal symptoms found in 18 (35.2%) of patients, this less than that reported in another study (Bhattarai *et al.*, 2012).

Most common affected sites by rosacea were cheeks and nose, and the main complain of our patients was burning sensation, these data similar to other study (Bhattarai *et al.*, 2012).

Sun exposure was the major aggravating factor in 49% of patients this corresponding to other study (Lazaridou *et al.*, 2010).

Because of rosacea is a chronic disease with period of remission and exacerbation, many medications has been used to control the activity of the disease.

In our study, the number of facial inflammatory papules, pustules and erythema score show improvement in both groups of patients, but the effect of metronidazole gel statistically significant, while the effect of permethrin cream was statistically not significant. In contrast to Turkish study, which showed that permethrin cream was effective as metronidazole gel and superior to it in reducing *D. folliculorum* (Kock *et al.*, 2002).

Erythema need longer time to show a significant response. The improvement in the erythema started to become statistically significant after 6 weeks of treatment with metronidazole gel. This result is similar to result of a study which showed that the use of metronidazole gel in rosacea result in reduction of inflammatory lesions and erythema score (Van Zuuren *et al.*, 2005, 2007).

Regarding telangiectases, there is mild improvement in severity in group A. Two studies show the effect of metronidazole gel on telangiectases, Two studies reported no benefits were noticed in the telangiectases severity (Van Zuuren *et al.*, 2005, 2007), while, other study showed an improvement of telangiectasia score as well as erythema and inflammatory lesions using 1% metronidazole cream with SPF 15 (Tan *et al.*, 2002).

In group B, no improvement observed in the telangiectasia sore, similar to other studies (Kock *et al.*, 2002; Swenor, 2003).

Relapse was determined by a clinically significant increase in the intensity of erythema or in the numbers of papules and pustules to a point that was intolerable to the patient, prominence of telangiectasia and dryness were also observed.

We noticed in our study that 16(42%) of 36 patient receiving metronidazole gel show relapse of disease after 3 months after stopping treatment, which is greater than what reported in another study (Mark *et al.*, 1992), this is may be due to short period of study.

9 (58%) of 15 patients receiving permethrin cream 2.5% show relapse, no other study show relapse rate of permethrin cream in rosacea.

The side effects associated with topical metronidazole therapy was infrequent, mild, and tolerated by the patients, mild itching and burning sensation was noticed at the early course of the treatment which were reduced with subsequent treatment. No evidence for causing phototoxic or photoallergic reaction. This similarly reported by another studies (Mark *et al.*, 1998 Mark; Van Zuuren *et al.*, 2007).

While side effects of permethrin cream could not be tolerated by half of the patients. The main of these side effects was skin irritation and burning sensation, in contrast to another study which reported mild side effects of permethrin cream (Kock *et al.*, 2002).

The result of our study shows that topical metronidazole gel 0.75% was effective and safe in controlling rosacea with mild and transient side effects and it is considered superior to permethrin cream 2.5%.

## CONCLUSION

Metronidazole gel 0.75 is an effective and safe therapeutic option in rosacea, it show significant superiority over using permethrin cream 2.5% in improving principal sings of rosacea (inflammatory lesions and erythema), with mild and tolerable side effects and it is effective in preventing relapsing of rosacea and maintains remission.

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