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A topical gel of tea tree oil nanoemulsion containing adapalene versus adapalene marketed gel in patients with acne vulgaris: a randomized clinical trial

Roqya Najafi-Taher[1] · Aarefeh Jafarzadeh kohneloo[2,3] · Vahid Eslami Farsani[4] · Neda Mehdizade Rayeni[4] · Hamid Reza Moghimi[5] · Amirhooshang Ehsani[4] · Amir Amani[6,1]

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Abstract

Adapalene is used for treatment of acne vulgaris, a common dermatological disease. Nano-based carriers have been developed to improve solubility and bioavailability of adapalene and other acne treatment drugs. In our previous report, tea tree oil nanoemulsion containing adapalene gel (TTO NE + ADA Gel) showed appropriate physical and biological properties such as stability, viscosity, pH, size, morphology and biocompatibility in an animal model. The present study was designed to assess efficacy and safety of the TTO NE + ADA Gel in comparison with 0.1% adapalene marketed gel (ADA Marketed Gel). A total of 100 patients were randomized to receive TTO NE + ADA Gel or ADA Marketed Gel, once daily at night, for 12 weeks. Analysis for efficacy was conducted by acne lesion count (total, inflammatory and non-inflammatory) and acne severity index at weeks 4, 8 and 12 using generalized estimating equation along with the safety assessments in each measurement for assessing dryness, erythema, burning sensation and irritation. Significantly better reduction in total, inflammatory, and non-inflammatory acne lesions were reported for TTO NE + ADA Gel as compared to the ADA Marketed Gel overall and on each measurement occasion (p value < 0.001 for all). Mean acne severity index also reduced with TTO NE + ADA Gel significantly in comparison with ADA Marketed Gel (p value < 0.001). Dryness was the most common adverse effect reported in both groups and it was higher in TTO NE + ADA Gel group. In conclusion, TTO NE + ADA Gel compared to ADA Marketed Gel appears more effective in the treatment of acne vulgaris, with no important change in adverse effects.

Keywords Acne vulgaris · Adapalene · Tea tree oil · Nanoemulsion

✉ Amirhooshang Ehsani
ehsanih@sina.tums.ac.ir

✉ Amir Amani
a.amani@nkums.ac.ir

1 Department of Medical Nanotechnology, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran

2 Department of Epidemiology and Biostatistics, Tehran University of Medical Sciences, Tehran, Iran

3 Research Center for Rational Use of Drugs, Tehran University of Medical Sciences, Tehran, Iran

4 Department of Dermatology, Razi Hospital, Tehran University of Medical Sciences, Tehran, Iran

5 Department of Pharmaceutics and Nanotechnology, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran

6 Natural Products and Medicinal Plants Research Center, North Khorasan University of Medical Sciences, Bojnurd, Iran

Introduction

Acne vulgaris is a common dermatological disease which causes negative psychological consequences such as depression, lower self-esteem and influences on the quality of life of patients [1]. Increase in sebum production, colonization of Propionibacterium acnes and hyper keratinization of follicles are main causes of acne vulgaris [2]. Topical therapy is the main treatment in mild to moderate cases. It also plays a role of additional support in severe cases along with systemic therapy [3]. Combination therapy by different anti-acne agents which target several pathogenic factors improve efficacy of treatment and increase patient satisfaction. In this regards, combination of antimicrobial agents and topical retinoids is commonly considered as the first drug regime for almost all patients [4–6].

Improving drug efficacy, drug release control, increase of biological life time and capacity of delivering multiple

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pharmaceutical agents in a single carrier are advantages that are offered by nanostructures. In recent studies, various nanostructures in treatment of acne have been reported [7–14]. Among different nanostructures, nanoemulsions provide additional advantages like low viscosity, ease of preparation and more importantly, increased topical efficacy, which make them promising topical delivery carriers [15–20].

In our previous study, a combinational therapy including adapalene (a third generation retinoid) and tea tree oil (an antibacterial agent) in a nanoemulsion carrier showed a significant improvement in transdermal delivery of adapalene and anti-bacterial activity in-vitro as well as biocompatibility in animal model [21]. The present study was conducted to evaluate efficacy and safety of treatment with tea tree oil nanoemulsion containing adapalene gel (TTO NE + ADA Gel) in comparison with adapalene marketed gel (ADA Marketed Gel) in patients with mild to moderate acne vulgaris.

Materials and methods

A triple blind, randomized clinical trial was carried out at Razi hospital between May 2017 and July 2018. The study was approved by Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.REC.1396.2934) and registered at the Iranian Registry of Clinical Trials (IRCT2015090223864N1). Informed consent was also taken from each of the participating patients.

Patients

Sample size was measured based on another study, considering drop rate of 15%. It was predicted that a minimum of 50 patients would be essential in each group [22]. Patients of either gender, 15–40 years of age, with acne vulgaris were enrolled in the study. Patients with severe cases of acne (existence of nodules and cysts), diabetes mellitus, endocrine disorder or those who were taking acne creating drugs (such as oral or local steroids, spironolactone and finasteride) were excluded from the study. Exclusion criteria were pregnancy and lactation as well as patients younger than 15 years old. Patients were not permitted to take any other systemic or topical treatment for acne vulgaris concomitantly from two weeks' prior the initiation up to the end of the study.

Study procedures

Eligible patients were randomized using a centralized computer generating randomization schedule to receive treatment with TTO NE + ADA Gel or ADA Marketed Gel. Patients were trained to wash the entire face each night with a gentle skin cleanser, rinse immediately and pat the skin with a towel. A thin film of formulations was applied to affected areas once a day. Patients were instructed to avoid use of medications in eyes and lip areas, and also to minimize sun exposure. The duration of the study was 12 weeks and patients were followed-up on outpatient basis at weeks 4, 8 and 12 after initiation of the study.

To determine efficacy of treatment, number of non-inflammatory lesions (NILC) (open and closed comedones), inflammatory lesions (ILC) (papules, pustules) and total lesions count (TLC) were recorded. Acne severity index (ASI) was assessed by the following equation [23]:

$$\mathrm{ASI} = \mathrm{Papules} + (2 \times \mathrm{pustules}) + (\mathrm{comedones}/4)$$

Adverse events were documented on each of the scheduled visits. Details such as duration (date of onset and end), severity (mild (easily tolerated), moderate (discomfort without interfering normal daily activity) or severe (interfering with normal daily activity), treatment and final outcome were noted. The evaluator was unware of the medications. At the end of the study, the data were analyzed by a blind investigator and then the labels were revealed.

Statistical analysis

All statistical analyses were performed using SPSS 24.0 software for Windows (SPSS Inc, USA) and significance was set at p value less than 0.05. Demographic variables were analyzed between groups using Pearson's chi-square test and one sample T test for categorical and continuous data, respectively. To compare baseline disease characteristics of patients between groups, Mann–Whitney U test was used. To evaluate the significance of mean improvements in spot counts within each treatment group as well as between-groups, generalized estimating equations (GEE) model was used and adjustment was made for confounder. For tolerability evaluation, Pearson chi-square statistic was calculated.

Results

A total of 100 patients with acne vulgaris of the face were enrolled in the study. Fifty-three of them were randomized to receive TTO NE + ADA Gel, and 47 patients received treatment with ADA Marketed Gel.

Demographics and baseline characteristics

Patients enrolled in the TTO NE + ADA Gel and ADA Marketed Gel groups had similar age while proportion of both genders enrolled in each group were not similar (p = 0.032), therefore, sex was adjusted by GEE analysis as confounder. Table1 shows the details of demographic profile of the patients enrolled in the study. Baseline characteristics of the population are summarized in Table 2. Severity of acne at baseline was similar in both groups as reflected by a similar number of total, inflammatory, and non-inflammatory lesions as well as acne severity grades.

Efficacy evaluation

In a descriptive sense, as shown in Fig. 1, the TLC, ILC, NILC, and ASI scores showed better improvement in the TTO NE + ADA Gel group versus ADA Marketed Gel group. The amount of Inflammatory lesions showed a decreasing trend overall (within-group, $p < 0.001$) and prominently for the TTO NE + ADA Gel group ($\beta = -3.282 \pm 0.5989$ after 12 weeks; between-group, $p < 0.001$), non-inflammatory lesion count showed a decreasing trend overall and on each measurement occasion (-5.473 ± 1.1429 after 12 weeks, $p < 0.001$). The difference between the two groups, on each measurement, was overall significant for total lesion count (-8.832 ± 1.5189 after 12 weeks, $p < 0.001$). The ASI decreased significantly over time in both groups ($p < 0.001$). It decreased more in the TTO NE + ADA Gel group, and the decrement trend was found to be statistically significant ($\beta = -5.79 \pm 1.020$ after 12 weeks, $p < 0.001$ Table 3).

The change in the acne severity grades reported in each of the treatment groups during the course of the study is shown in Fig. 2. The decreasing trend was more obvious for the TTO NE + ADA Gel group after 12 weeks of treatment: acne severity grade of subjects in this group shifted significantly from moderate to mild, almost clear and clear grades. Based on the change in the acne severity index, 71.69% patients in the TTO NE + ADA Gel group achieved success in treatment as compared to 6.38% patients in the ADA Marketed Gel group. Furthermore, increase in acne severity grades was not observed in patients in any of the groups.

Tolerability evaluation

Severity of adverse events was 'mild' in all patients treated with both formulations while there was no 'serious' adverse event reported in any group. Topical adverse events were observed in both groups, more increased in the TTO NE + ADA Gel group compared to the ADA Marketed Gel (Fig. 3). Irritation at week 4 was significantly higher in TTO NE + ADA Gel compared to ADA Marketed Gel (43.4 vs 17%, p value = 0.005). However, in following visits, no statistically significant difference was observed between groups for irritation (22.6 vs 8.5% at week 8 and 7.5 vs 6.4% at week 12). Dryness was the most common adverse effect in both groups (68.8% in the TTO NE + ADA Gel group and 53.2% in ADA Marketed Gel at week 4). In the following visits as it can be seen from Fig. 3, percent of reporting of dryness is higher than patients in both groups at week 8 and

Table1 Demographic characteristics of patients

Characteristics	TTO NE + ADA Gel	ADA Marketed Gel	p value (significance)
Age (year)	26.72 ± 5.231 (mean ± SD)	27.36 ± 5.036 (mean ± SD)	0.53
Sex			
Male	11 (20.8%)	19 (40.4%)	0.032
Female	42 (79.2%)	28 (59.6%)	

Table 2 Baseline disease characteristics of patients enrolled in the study

Characteristics	TTO NE + ADA gel ($n = 53$) (mean ± SD)	ADA Marketed Gel ($n = 47$) (Mean ± SD)	p value (significance)
No. of lesions			
Inflammatory	7.55 ± 3.59	7.34 ± 4.56	0.645
Non-inflammatory	19.11 ± 9.70	15.57 ± 6.10	0.997
Total	26.66 ± 12.46	24.89 ± 9.20	0.961
Acne severity	15.40 ± 6.97	15.02 ± 7.56	0.879

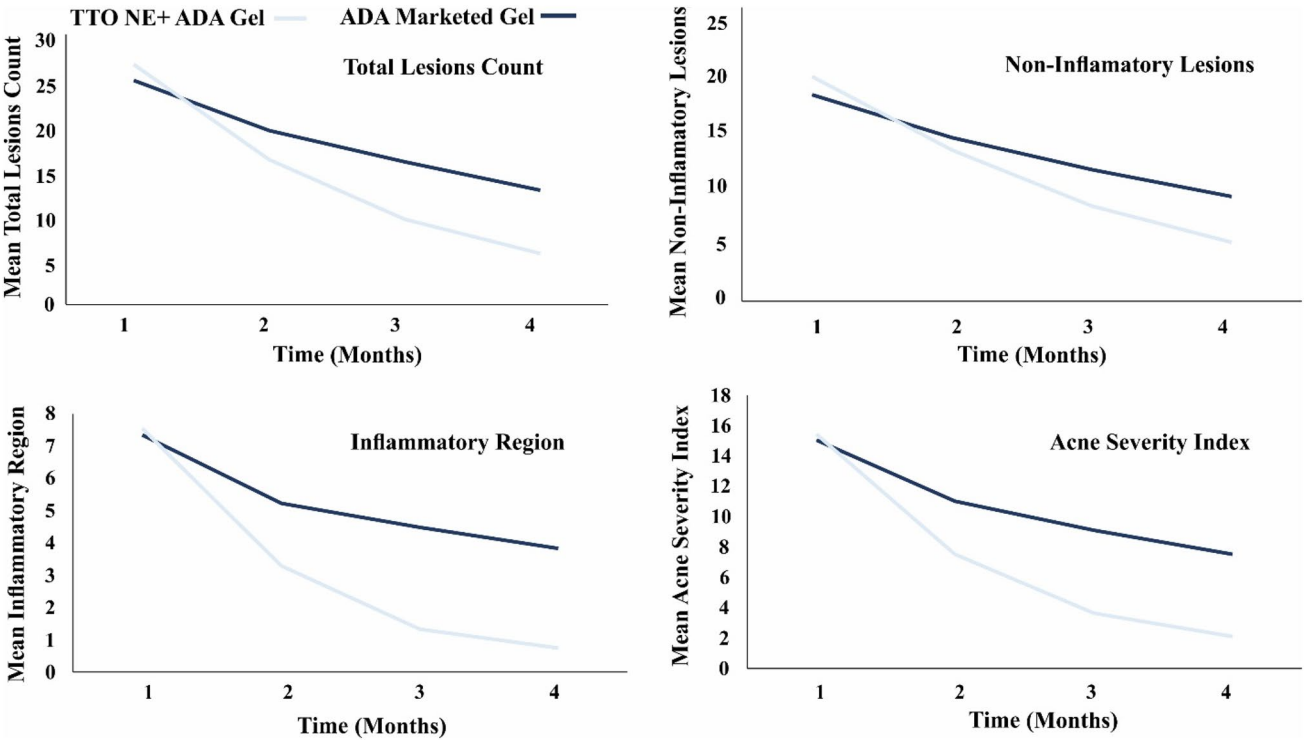

Fig. 1 Lesion reductions in clinical trials of tea tree oil nanoemulsion containing 0.1% adapalene gel (TTO NE + ADA Gel) ($n = 53$) versus adapalene marketed gel (ADA Marketed Gel) ($n = 47$)

Table 3 Reduction in lesions count of patients in TTO NE + ADA Gel versus ADA Marketed Gel during the study

Time point	B^a TLC	β^a IL	β^a NIL	β^a ASI
4 weeks	− 4.973 ± 0.7865	− 2.158 ± 0.3512	− 2.626 ± 0.5467	− 3.881 ± 0.6355
8 weeks	− 8.165 ± 1.282	− 3.356 ± 9.5057	− 4.657 ± 0.9422	− 5.877 ± 0.900
12 weeks	− 8.832 ± 1.5189	− 3.282 ± 0.5989	− 5.473 ± 1.1429	− 5.79 ± 1.020

TLC total lesions count, *IL* inflammatory lesions count, *NIL* non-inflammatory lesions count, *ASI* acne severity index

[a]Estimated parameters of GEE model

12 in comparison to other adverse events at the same measurement. Erythema was reported by patients in both groups and percent of reporting was 32.1% in TTO NE + ADA Gel and 19.1% for ADA Marketed Gel at week 4, similar to other adverse events, it was decreased in both groups over time. Burning sensation was the adverse event barely reported by patients in both groups (11.3 vs 2.1%, 5. vs 2.1% and 3.8 vs 2.1% for TTO NE + ADA GEL compared to ADA Marketed Gel at week 4, 8 and 12 respectively), and there was no significant difference for burning sensation between the two groups during the clinical trial.

Discussion

Topical adapalene a third generation retinoid with anti-inflammatory, keratolytic and anti-seborrhoeic activities, has been found to be highly effective as monotherapy or in combination with other anti-acne drugs [24]. Adapalene, in comparison with first generation retinoids, is known to have higher patient compliance and effectiveness. In current study, a new nano-based formulation of adapalene in combination with tea tree oil was developed by our group to further improve its efficacy. Tea tree oil has a broad-spectrum antimicrobial activity which is used for superficial diseases such as oral candidiasis, onychomycosis and acne [25]. The present randomized study assessed this novel preparation in patients with acne vulgaris. Evaluation of

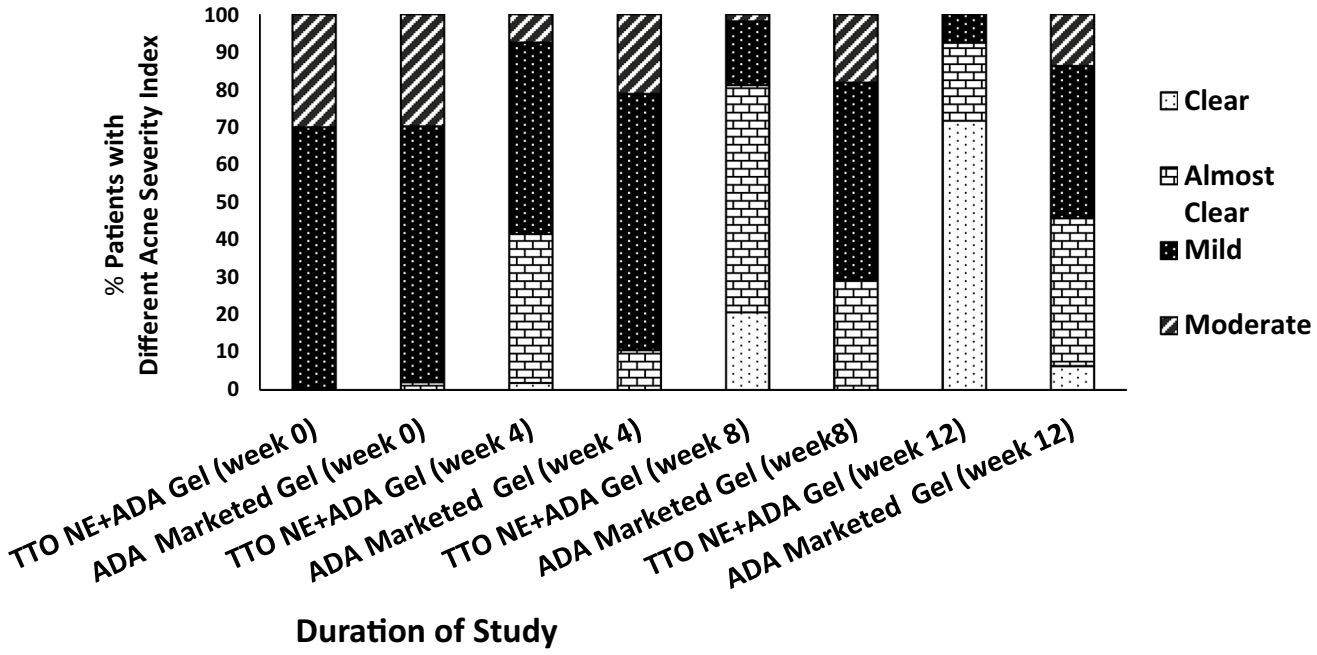

Fig. 2 Percentage of patients with different acne severity grades during the study. TTO NE + ADA Gel = tea tree oil nanoemulsion loaded adapalene gel, ADA Marketed Gel = adapalene marketed gel

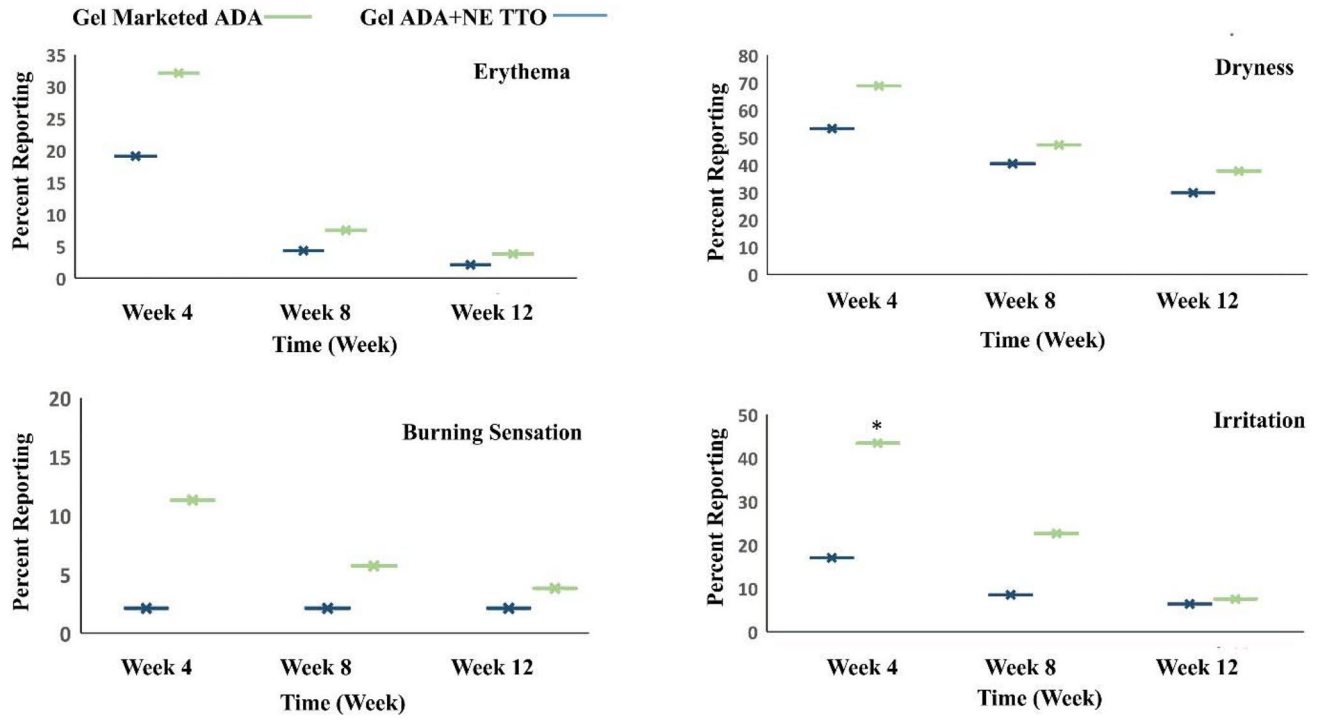

Fig. 3 Reported rates of adverse events during the clinical trials in each measurment (TTO NE + ADA Gel = tea tree Oil nanoemulsion loaded adapalene, ADA Marketed Gel = adapalene marketed gel)

mean percent change in lesion count in this clinical study revealed that the nano formulation of adapalene is significantly better than the commercial preparation in reducing total, inflammatory lesions and non-inflammatory lesions count. The result also showed a trend towards better efficacy in reducing grade of acne severity with the nanoemulsion

as compared to the commercial gel. For instance, at the end of study, 71.69% patients in nanoemulsion group had no sign of lesions, compared to 6.38% patients in commercial gel. It can be explained that the nanosized carrier improved therapeutic effect through improving delivery of active agent to the pilosebaceous units [22]. Apart from size of carrier, components which were used in nanoemulsion preparation (like surfactant, co-surfactant and oil) are known to act as permeation enhancer through skin and improve hydration of skin which play a role in improved topical delivery [2]. As a result, increased drug solubility and permeation through skin barriers can explain better efficacy of the nanoemulsion compared to the marketed formulation. A further explanation could be the presence of tea tree oil as an antibacterial agent in nano scale in this novel formulation. It has also been shown that antibacterial activity of oils increases in nanoemulsions as a result of better fusion of oil droplets with bacteria and destabilization and disruption of organism wall [26].

The results with the commercial gel in our study are comparable to the other studies with adapalene marketed gel. Results from a study evaluating effects of different concentration of adapalene in treatment of acne vulgaris have shown a 48, 57 and 43% reduction in number of total, inflammatory and non-inflammatory lesions respectively, with 0.1% adapalene gel [27]. These values were 49, 47.9 and 49.3%, respectively in our study. Another study has shown a reduction of around 48, 37 and 55% in the total, inflammatory and non-inflammatory lesion counts [28].

Earlier Parsad et al. have studied topical combination therapy with nano gel of adapalene 0.1% gel and clindamycin 1%. The results showed 79% reduction in total lesion count, 88.7% in inflammatory lesion count and 78% in non-inflammatory lesion count [29].

The result of tolerability assessment showed that irritation and dryness were the most common adverse events in both groups and were mostly mild in severity. The incidence and severity of these adverse effects was not significantly different in patients receiving TTO NE + ADA Gel group in comparison with ADA Marketed Gel except irritation that was significantly high during first weeks, which decreased over time. The profile of adverse events was similar to other studies as erythema and dryness were the most common adverse effects reported by patients [27, 28]. In one study in India, incidence and severity of adverse effect by nanoemulsion gel loaded with adapalene and clindamycin were lower than our study. This may be explained by differences in ethnicity of participants in the two studies which affect the prevalence and severity of the disease [30] as well as differences in the formulations [29]. On the tolerability aspect of tea tree oil, Enshaieh reported that ~10% patients reported minimal pruritus ~3% little burning and ~3% minimal scaling after 6 weeks treatment of patients with tea tree oil gel [23]. As far as we know, clinical trials by tea tree oil naoemulsion have not been published in the literature.

Conclusion

The result of current study suggested that tea tree oil nanoemulsion containing adapalene is more effective than adapalene marketed gel. Future studies with three arms for assessing therapeutic effect of tea tree oil nanoemulsion gel along with tea tree oil nanoemulsion loaded adapalene and adapalene marketed gel can distinguish the role of tea tree oil nanoemuslion in this novel formulation in management of acne vulgaris.

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