

Efficacy of supramolecular salicylic acid in combination with doxycycline in the treatment of acne

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Abstract: To determine the efficacy of supramolecular salicylic acid combined with doxycycline on acne, totally 70 patients with acne treated in our dermatology department from May 2020 to May 2021 were enrolled, and randomized (1:1) into control or experimental groups using the random number table method. The control group was given doxycycline for oral administration while the experimental group was given oral doxycycline combined with supramolecular salicylic acid for topical administration. The overall effective rate of treatment was significantly higher in the experimental group versus control group (97.14% vs. 82.86%, $P<0.05$). Patients in the control group had significantly longer mean acne regression time after treatment versus experimental group ($P<0.05$). After treatment, patients in the experimental group had significantly lower self-rating depression scale (SDS) scores and self-perceived burden (SPB) scores than the control group, while Short Form 36-item health survey (SF-36) scores were significantly higher than the control group ($P<0.05$). The overall incidence of adverse reactions was significantly lower in the experimental group versus control group (5.71% vs. 17.14%, $P<0.05$). Supramolecular salicylic acid in combination with doxycycline in the treatment of patients with acne is an optimal option, as it could better promote acne regression, reduce the level of depression and reduce the patient's self-perceived burden.

Keywords: Acne, supramolecular salicylic acid, doxycycline.

INTRODUCTION

Acne has a long course and a tendency to recur, causing prolonged physical discomfort and compromising the quality of life (QoL) of patients. Furthermore, acne affects the appearance of patients with negative effects on their daily work and interpersonal interactions, leading to a certain degree of psychological stress (Yu *et al.*, 2020). The psychological impact of acne is still significant, especially if acne does not recover over a long period of time, then for this person with acne, it will lose confidence in treating acne, and this acne will affect the aesthetics, which will create a certain amount of stress for the psyche (Yang *et al.*, 2020). For many people with acne, especially those in their teenage years, they do not pay much attention to acne in the pre-acne period, resulting in the condition developing and forming a disfiguring scarred face, leading to excessive psychological stress, triggering feelings of low self-esteem and even depression, which seriously affects mental health (Al and Al-Yousef, 2018). Therefore, effective measures in a timely manner are required to alleviate the symptoms, relieve the physical and psychological stress, and improve the quality of life of patients.

In conventional treatment, patients are mostly given some oral medication along with daily-life instructions. Doxycycline is a broad-spectrum antibacterial agent that is effective against Gram-positive cocci and negative rods, not only for infections caused by bacteria, rickettsia,

mycoplasma and chlamydia, but also for the prevention of falciparum malaria and leptospirosis infections (Aniagor *et al.*, 2021). Currently, doxycycline is commonly used as an adjunctive treatment for moderate to severe acne, but its clinical application has revealed its lack of efficacy and the presence of some side effects (MARson and Baldwin, 2018). Accordingly, alternative drugs could be considered in combination with doxycycline to enhance the efficacy. Salicylic acid is an aspirin metabolite with a positive anti-inflammatory effect, which has been extensively used for various skin diseases (Wenjia *et al.*, 2020; Yaqing *et al.*, 2020), but there are few clinical cases of combining it with doxycycline in English with acne. Based on this, the aim of this study was to investigate the clinical efficacy of supramolecular salicylic acid in combination with doxycycline in the treatment of patients with acne.

MATERIALS AND METHODS

General data

Seventy patients with acne treated in the dermatology department of our hospital from May 2020 to May 2021 were enrolled as the study population for prospective analysis, and randomly divided into control or experimental groups using the random number table method, with 35 cases in each group. There were 36 males and 34 females, between 18 years and 45 years old, with mean age of (26.37±1.25) years, with a duration of the disease of 1 month to 36 months, mean 6.45±1.25 months. The control group was given doxycycline for oral administration while the experimental group was given oral doxycycline combined with supramolecular salicylic

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acid for topical administration.

Inclusion criteria and exclusion criteria

Inclusion criteria

- (1) Patients whose clinical examination met the diagnostic criteria for acne by clinical examination (Wang *et al.*, 2019).
- (2) Patients who have been informed of the study and have voluntarily signed the informed consent form.
- (3) Patients who are allergic to the drugs used in the study.
- (4) Patients with normal mental status, consciousness, good compliance and able to cooperate with the completion of the study.

Exclusion criteria

- (1) Patients with combined renal, hepatic, cardiac or other systemic diseases.
- (2) Patients who are in preparation for pregnancy or during pregnancy.
- (3) Patients who were breastfeeding.
- (4) Patients with missing or incomplete clinical data.

Treatment method

Patients in the control group were given oral treatment with doxycycline hydrochloride capsules (Manufacturer: Guangzhou Bersero Pharmaceutical Co., Ltd., Approval number: Nation Drug Administration No. H20013375) at a dose of 100 mg per dose, twice daily for a total of 4 weeks (Xiao, 2021).

In the experimental group, the patients in the experimental group were additionally treated with topical application of supramolecular salicylic acid in addition to the oral treatment in the control group. Before application, the patients' local skin was cleaned and an appropriate amount of supramolecular salicylic acid gel (Manufacturer: produced by Borinda Biochemical Technology Co., Ltd., specification 7g*6 sticks/box) was applied by dotting on the inflammatory papules and acne, and gently and uniformly massaged the gel in. The medication was administered twice daily for a total of 4 weeks (Li *et al.*, 2021).

During the treatment period, in addition to abstaining from smoking and alcohol in both groups, patients also needed to protect themselves from the sun, maintain a regular routine, eat a light diet and drink plenty of water.

Observational indicators

- (1) Treatment efficacy. Based on the improvement of clinical symptoms and other conditions of patients before and after treatment, the number of significantly effective, effective, and ineffective cases was recorded to obtain the total efficacy (Min *et al.*, 2021). Total effective rate = (number of significantly effective + number of effective) / total number of patients × 100%

- (2) Acne regression time. Patients were observed for the regression of acne after treatment and the time taken for acne to subside was recorded.

- (3) Depression. Depression was assessed in both groups before and after therapy using the Self-rating Depression Scale (SDS) (Jokelainen *et al.*, 2019). Higher scores indicated more severe depression.

- (4) Self-perceived burden (SPB). The SPB scale was used to assess the self-perceived burden of the two groups before and after therapy (Liu *et al.*, 2022). A higher score indicated heavier psychological burden.

- (5) Quality of life (QoL). The QoL before and after treatment in both groups was evaluated through the Short Form 36-item Health Survey (SF-36), with the final score being proportional to the QoL of the patients (Lambert *et al.*, 2021).

- (6) Adverse reactions. Patients were observed for adverse reactions during treatment including redness, swelling and bleeding, and the corresponding number of cases was recorded for incidence calculation. Incidence of adverse reactions = number of patients with adverse reactions/total number of patients×100%

Ethical approval

This study was ratified and approved by the medical ethics department before implementation (Approval No.HB2032577XO), and all patients and their families signed consent forms.

STATISTICAL ANALYSIS

The data obtained were processed and analyzed using SPSS 20.0 statistical software. The measurement data were expressed as the mean ± standard deviation ($\bar{x}\pm s$), and the t-test for independent samples was performed for the comparison between two groups. The count data were expressed as %, and χ^2 test was performed for comparison between two groups. $P<0.05$ indicates that the difference is statistically significant.

RESULTS

Comparison of general data

The control group was comprised of 19 males and 16 females, between 18 years and 44 years old (mean age of 25.99 ± 1.11 years), and with the duration of the disease from 1 month to 36 months (mean of 6.29 ± 1.19 months). The experimental group was comprised of 17 males and 18 females, between 18 years and 45 years old (mean age of 26.45 ± 1.04 years), and with duration of the disease from 2 months to 36 months (mean of 6.50 ± 1.21 months). The two groups were not notably different in terms of baseline data ($P>0.05$).

Table 1: Comparison of the therapeutic efficacy between the two groups of patients

| Groups | N | Significantly effective (n) | effective (n) | Ineffective (n) | Total efficacy (%) |
|--------------------|----|-----------------------------|---------------|-----------------|--------------------|
| Experimental group | 35 | 16 | 18 | 1 | 97.14 |
| Control group | 35 | 10 | 19 | 6 | 82.86 |
| χ^2 | - | - | - | - | 11.320 |
| P | - | - | - | - | 0.001 |

Table 2: Comparison of mean acne remission time between the two groups ($\bar{X}\pm S$)

| Groups | N | Mean acne remission time (day) |
|--------------------|----|--------------------------------|
| Experimental group | 35 | 25.37±1.25 |
| Control group | 35 | 34.15±1.31 |
| t | - | 28.6869 |
| P | - | 0.0000 |

Table 3: Comparison of depression degree between the two groups before and after treatment ($\bar{X}\pm S$, points)

| Groups | N | Before treatment | After treatment |
|--------------------|----|------------------|-----------------|
| Experimental group | 35 | 68.23±1.17 | 42.36±1.19 |
| Control group | 35 | 68.41±1.21 | 55.31±1.05 |
| t | - | 0.6327 | 48.2752 |
| P | - | 0.5291 | 0.0000 |

Table 4: Comparison of SPB scores between the two groups of patients before and after treatment ($\bar{X}\pm S$, points)

| Groups | N | Before treatment | After treatment |
|--------------------|----|------------------|-----------------|
| Experimental group | 35 | 45.52±2.03 | 31.15±0.35 |
| Control group | 35 | 46.33±1.89 | 35.33±0.41 |
| t | - | 1.7277 | 45.8736 |
| P | - | 0.0886 | 0.0000 |

Table 5: Comparison of SF-36 scores between the two groups of patients before and after treatment ($\bar{X}\pm S$, points)

| Groups | N | Before treatment | After treatment |
|--------------------|----|------------------|-----------------|
| Experimental group | 35 | 60.35±1.03 | 80.12±0.35 |
| Control group | 35 | 60.33±1.01 | 74.03±0.43 |
| t | - | 0.0820 | 64.9829 |
| P | - | 0.9349 | 0.0000 |

Comparison of therapeutic efficacy

In terms of treatment effect, 16 cases were significantly effective and 18 cases were effective in the experimental group; 10 cases were significantly effective and 19 cases were effective in the control group. The experimental group obtained a notably higher treatment efficacy than the control group ($P<0.05$, table 1).

Comparison of mean acne regression time

The mean acne regression time for the control group was 34.15±1.31d, while the mean acne regression time for patients in the experimental group was 25.37±1.25d. The the control group experienced notably longer mean acne regression time than the experimental group ($P<0.05$, table 2).

Comparison of depression degree

The two groups were similar in terms of SDS scores before therapy ($P>0.05$). After therapy, the experimental group got a notably lower SDS score than the control group ($P<0.05$, table. 3).

Comparison of self-perceived burden levels

The two groups were similar in SPB scores before therapy ($P>0.05$). After therapy, the experimental group got notably lower SPB scores than the control group ($P<0.05$, table 4).

Comparison of QoL level

The two groups showed no notable difference in SF-36 scores before therapy ($P>0.05$). After therapy, the experimental group got higher SF-36 scores than the control group ($P<0.05$, table 5).

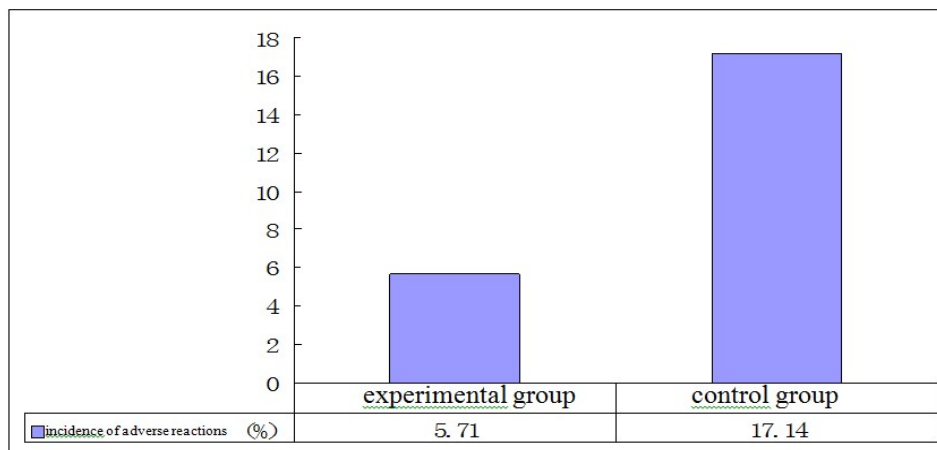


Fig. 1: Comparison of the incidence of adverse reactions between the two groups

Comparison of the incidence of adverse reactions

The experimental group had 1 case of pain and 1 case of erythema, while the control group had 2 cases of pain, 2 cases of erythema, 1 case of scarring and 1 case of bleeding. The control group showed a notably higher incidence of adverse reactions than the experimental group ($\chi^2=6.455, P=0.011$, fig. 1).

DISCUSSION

Acne is a clinically common highly prevalent skin condition that is associated with a chronic inflammatory response of the body's sebaceous glands and hair follicles, and whose causative factors involve different aspects such as daily diet, work and rest, mental stress and genetics (Jingfang *et al.*, 2021). After the onset of the disease, patients develop papules and pimples of different numbers and sizes on the skin, which compromises the patient's physical and mental health and quality of life (Alghofaili *et al.*, 2021). Especially for adolescents, during a period of dramatic physical and psychological change, adolescents are gradually developing and maturing physically and growing psychologically, while also being susceptible to interference from the outside environment (Strahan *et al.*, 2022). Most adolescents will suffer from acne during puberty along with their physical development, and the cosmetic aspects of acne will also have a great impact on adolescents psychologically (Layton *et al.*, 2021). On the one hand, mental tension and depression could aggravate acne; on the other hand, acne sufferers could develop psychosocial problems as a result of their skin lesions. Therefore, entails the exploration of safe and reliable treatment protocols.

Currently, doxycycline oral therapy is one of the common treatments for acne. The development of acne is closely associated with bacterial infection, excessive sebum secretion and inflammatory reactions, in which the patient has abnormal sebum drainage due to blocked ducts in the hair follicles (Kameswararao *et al.*, 2019). Additionally,

among the large number of microorganisms in the hair follicles, *Propionibacterium acne* triggers lipolytic decomposition that generates a substantial amount of free fatty acids with chemotactic inflammatory cells, exacerbating the condition (Huijuan and Yuan, 2020). Upon entry into the body, doxycycline remarkably inhibits the production of *Propionibacterium acnes*, inhibits the release of mediators, and relieves the inflammatory state of the skin, thereby alleviating clinical symptoms (Rajaiah *et al.*, 2022). Nevertheless, the efficacy of oral treatment with doxycycline alone is considered mediocre. The side effects of doxycycline for acne are gastrointestinal reactions, photosensitivity reactions and liver and kidney damage. The most common adverse reactions are gastrointestinal reactions such as nausea, vomiting, abdominal pain and diarrhoea (Kumar *et al.*, 2019). In addition, while taking doxycycline, some patients who are exposed to prolonged sunlight or outdoors may develop symptoms such as pemphigus, exfoliative dermatitis, photosensitivity dermatitis, skin erythema and pruritus. In this regard, it has been used clinically in combination with other pharmaceuticals in an attempt to achieve better acne treatment outcomes in recent year (Xiaojun *et al.*, 2020). Salicylic acid has powerful exfoliation, pore reduction, acne removal, pigmentation spot fading and pore cleansing effects, which has been extensively adopted in the treatment of a variety of dermatological diseases. In this study, it was used in combination with doxycycline in the treatment of acne.

The results of the present study revealed that the overall efficiency of the experimental group was significantly higher than that of the control group (94.29% vs 82.86%), and the mean time to acne regression was notably shorter in the experimental group than that in the control group, indicating better clinical efficacy after the combination therapy. The occurrence of acne results in physical discomfort, psychological burden, depression and low mood in patients, thus reducing their quality of life. In this study, the differences in SDS scores and SPB scores and

SF-36 scores between the two groups before treatment were not greatly different, while the experimental group had significantly lower SDS scores and SPB scores and higher SF-36 scores than the control group, suggesting that the combined treatment regimen better alleviates the patients' depressive state, reduces their psychological burden, and promotes a notable improvement in their quality of life. In addition, the overall incidence of adverse reactions in the experimental group was significantly lower than that in the control group (5.71% vs. 17.14%), thereby further confirming the promising clinical efficacy of the combination of supramolecular salicylic acid and doxycycline treatment for acne patients with a safety profile.

One of the most common side effects for patients taking antibiotics is gastrointestinal problems such as nausea, vomiting and diarrhoea, a condition known as antibiotic-associated diarrhoea (Kumar *et al.*, 2019). Antibiotics also cause an overgrowth of bacteria in the small intestine, which could lead to bloating and cramping that could persist even after you stop taking them. This type of infection usually requires more but different antibiotics to bring the balance of bacteria in the gut back to normal (Dănau *et al.*, 2021). As mentioned above, acne could have an impact on a person's psychological problems and antibiotics could alter the composition of the body's microbiome, which could affect neural pathways, metabolism and immunity, all of which could have an impact on a person's mental health, creating a vicious cycle. Supramolecular salicylic acid is highly effective in the treatment of acne. While removing acne, it has an excellent effect on the complexion, removes hyperpigmentation in the skin, could effectively exfoliate the aging stratum corneum and relieves rough skin (Zhang *et al.*, 2022). The supramolecular salicylic acid utilised in the treatment yields has excellent broad-spectrum antibacterial and anti-inflammatory effects, inhibiting a wide range of pathogenic bacteria in the patient's skin and relieving the local inflammatory state. Moreover, it has a bi-directional keratin conditioning effect that removes dead skin cells, penetrates deep into the pores to dissolve acne and provides anti-itching relief (Yu and Wei, 2020), thus ameliorating the patients' skin symptoms, clinical comfort, appearance and effective relief of physical and mental stress of patients. Furthermore, supramolecular salicylic acid is a new type of nano-liposomal preparation with high absorption efficiency and bioavailability, which is more conducive to the absorption of human skin and allows for rapid drug efficacy to promote rapid clinical recovery of patients. Therefore, the application of supramolecular salicylic acid in the treatment of acne is effective in dissolving acne and exfoliating the skin of patients, which is also highly effective as an anti-inflammatory agent in relieving inflammatory skin conditions. In addition, supramolecular salicylic acid, due to its favourable safety profile, excellent local tolerance

and a lower risk of significant adverse reactions post-dosing adverse reactions, when combined with doxycycline in the treatment of acne patients, their synergistic effect facilitates better relief of clinical symptoms and reduce the psychological stress of patients, achieving a favourable prognosis.

CONCLUSION

To sum up, the application of supramolecular salicylic acid combined with doxycycline in the therapy of patients with acne could better promote the regression of acne, reduce the level of depression in patients and mitigate the patient's self-perceived burden, which is considered an favourable treatment protocol in clinical practice.

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