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ORIGINAL ARTICLE

Single-center, assessor-blind study to evaluate the efficacy and safety of DA-5520 topical gel in patients with acne scars: A pilot study

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Abstract

Background: Unlike various topical treatment options for acne vulgaris, options for acne scars mostly involve invasive interventions. So far, only a few clinical trials have investigated the effects of topical treatment for acne scars.

Objectives: We evaluated the safety and efficacy of DA-5520, a recently developed topical gel for the treatment of different types of acne scars.

Methods: A 12-week prospective, randomized, active-controlled, evaluator-blind, single-center study involving 36 participants with acne scars was performed. Participants were randomized into four different groups at a 1:1:1:1 ratio: laser resurfacing with DA-5520 application (test 1); laser resurfacing without DA-5520 application (control 1); comedone extraction with DA-5520 application (test 2); and comedone extraction without DA-5520 application (control 2). For 12 weeks, participants in the two test groups applied DA-5520 twice daily, while participants in the control groups applied moisturizers alone. Participants in the test 1 and control 1 groups received a single session of laser resurfacing at visit 1 (week 0). All participants were followed up at 1, 4, 8, and 12 weeks, and objective scar evaluation using the échelle d'évaluation clinique des cicatrices d'acné (ECCA) score was performed at each visit.

Results: Clinical improvement of acne scars, confirmed by the ECCA grading scale (1 for atrophic scar and 2 for hypertrophic scar), was observed after using DA-5520 when combined with laser resurfacing or individually, and no associated adverse reactions were noted.

Conclusions: Preliminary results of this study revealed that DA-5520 may be a promising new formulation for treating all type of acne scars.

KEYWORDS
acne scars, acne vulgaris, allantoin, dexpanthenol, heparin sodium

1 | INTRODUCTION

Acne scars can cause stress or depression, which greatly impairs the quality of life.[1] Approximately 43% of patients with acne develop clinically relevant scarring.[2] Despite its high prevalence and detrimental effect on the quality of life, treatment options for acne scars remain limited. Unlike various topical treatment options for acne vulgaris, options for acne scars mostly involve invasive interventions (e.g., laser resurfacing, chemical peels, or dermabrasion).[3]

Acne scars can be classified as atrophic or hypertrophic scars. Atrophic acne scars are the most common type of acne scars (80%–90%) and consist of icepick, boxcar, and rolling types. 10%–20% of acne scars are hypertrophic or keloidal scars.[4] Sometimes, various types of atrophic and hypertrophic scars can be observed in the same patient. In this study, we aimed to evaluate the efficacy and safety of DA-5520 (Dong-A Pharmaceutical Co., Ltd.), a recently developed topical scar treatment gel for the treatment of various types of acne scars.

2 | MATERIALS AND METHODS

A prospective, randomized, active-controlled, assessor-blinded, single-center study was conducted at a tertiary-referral hospital in Korea. After obtaining informed consent, men and women aged 10–55 years with at least 10 acne scars ≥2 mm in areas excluding the nose who met inclusion and exclusion criteria were included in this study (Table 1). A total of 36 participants were screened and randomized into four different groups at a 1:1:1:1 ratio (Figure 1): laser resurfacing with DA-5520 application (test 1); laser resurfacing without DA-5520 application (control 1); comedone extraction with DA-5520 application (test 2); and comedone extraction without DA-5520 application (control 2).

TABLE 1 Inclusion and exclusion criteria

Inclusion criteria
1. Men and women aged 10–55 years
2. Those with at least 10 acne scars ≥2 mm in areas excluding the nose
3. Those whose Global Acne-Grading System (GAGS) is mild (1~18 points)
4. Those with <2 acne nodules >1 cm
5. Those who voluntarily consented to study participation
Inclusion criteria
1. Active skin disease other than acne, such as infections, open wounds, scar, or inflammation in the planned treatment area
2. Intake of anti-acne medications within 4 weeks before screening
3. Known allergy or hypersensitivity to the components of the study treatment
4. Hypersensitivity to heparin (heparin-induced thrombocytopenia, HIT), bleeding tendencies, and hypothrombocytopaenia
5. Have undergone filler, laser, dermabrasion, or other medical or surgical treatment for atrophic acne scars in the past 6 months before screening, assumed to cause an effect on the research
6. Have undergone botox or filler treatment around the eyes or mouth within 12 months before screening
7. Have participated in other clinical trials within 1 month before screening
8. Have taken systemic steroids within 12 weeks before screening
9. Have used DA-5520 within 6 months before screening
10. Pregnant women, lactating women, or women planning to become pregnant
11. Have any other condition that could harm the subject or jeopardize the study objectives

All participants were provided with same hypoallergenic cleansers and moisturizers. For 12 weeks, participants in the two test groups applied DA-5520 twice daily, before using the moisturizers, while participants in the control groups applied moisturizers alone. Treatment compliance was calculated as 100% × (number of actual applications/number of scheduled applications), which was checked by self-filling application logs. Noncompliance was defined as a compliance value of <70%.

All participants were followed up at 1, 4, 8, and 12 weeks. Laser resurfacing was performed once for participants in the control 1 and test 1 groups, at the baseline visit using a 2790-nm wavelength erbium:yttrium-scandium-gallium-garnet laser (Cutera®) (2.2 J/cm,^{2} 400-μs). Comedone extraction was performed for participants in the control 2 and test 2 groups at each visit. Photographs and objective scar evaluation using the échelle d'évaluation clinique des cicatrices d'acné (ECCA) score were done at each visit for all the participants.

2.1 | Efficacy assessment

The ECCA scale is a quantitative scale developed to evaluate facial acne scar treatment in clinical practice.[5] It calculates the sum of individual types of scars and their numerical extent (Table 2). Important advantage of this scale is that it independently accounts for specific scar types in addition to the total scores; separate atrophic and hypertrophic subscores (subgrading scores) can also be calculated. Three dermatologists who were blinded to the study and trained to use the scale were the assessors. The final score was calculated as the average of three scores.

2.2 | Statistical analyses

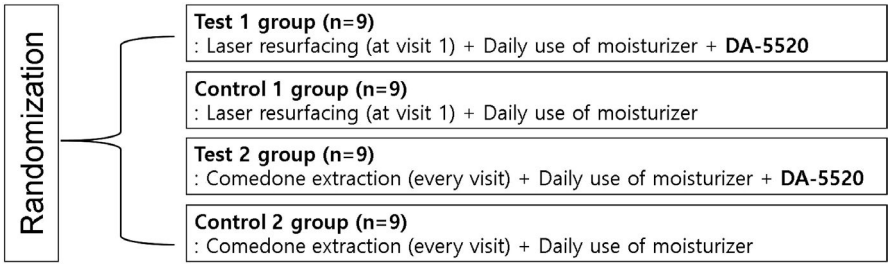
All statistical analyses were performed using SAS® version 9.4 (SAS Institute). Efficacy analysis was performed on the full analysis (FA) and per protocol (PP) sets. The safety set included all participants in the study. The efficacy outcome was analyzed using the two-sample *t* test or the Wilcoxon rank-sum test. Statistical significance was set at $p < 0.05$, and 95% two-sided confidence intervals were used.

3 | RESULTS

Thirty-six participants were included ($n = 9$ in each of the four groups) and completed the study. The FA set included all 36 participants, and the PP set included 35 participants from the FA set, with one participant excluded due to incomplete evaluation variables.

The demographic information and baseline characteristics are presented in Table 3. There were no significant differences in age, height, weight, or sex between the groups. The baseline ECCA global scores were 98.52 ± 47.49, 70.93 ± 46.52, 101.11 ± 16.15, and 99.26 ± 16.15 in the test 1, control 1, test 2, and control 2 groups, respectively. In the ECCA score, subgrading 1 score accounted for

FIGURE 1 Timeline of this study



most scores in all four groups. There were no statistically significant differences in the baseline global ECCA scores or subgrading scores between the groups.

3.1 | Efficacy outcomes

Figure 2A shows group comparisons of changes in the ECCA global scores at 1, 4, 8, and 12 weeks compared with that at baseline. There

TABLE 2 Echelle d'evaluation clinique des cicatrices d'acn´e (ECCA) grading scale

ECCA scale			
Description	Weighting factor (a)	Semi-quantitative score (b)	Grading (a × b)
V-shaped atrophic scars, diameter <2 mm, and punctiform	15	0 = no scar 1 = a few scars 2 = limited number of scars 3 = many scars	
U-shaped atrophic scars, diameter of 2–4 mm, with sheer edges	20	0 = no scar 1 = a few scars 2 = limited number of scars 3 = many scars	
M-shaped atrophic scars, diameter >4 mm, superficial and with irregular surface	25	0 = no scar 1 = a few scars 2 = limited number of scars 3 = many scars	
Superficial elastolysis	30	0 = no scar 1 = a few scars 2 = limited number of scars 3 = many scars	
Subgrading 1			
Hypertrophic inflammatory scars, scar of <2 years of age	40	0 = no scar 1 = a few scars 2 = limited number of scars 3 = many scars	
Keloid scars and hypertrophic scars that are >2 years of age	50	0 = no scar 1 = a few scars 2 = limited number of scars 3 = many scars	
Subgrading 2			
Global score (subgradings 1 + 2)			

Note: The ECCA grading scale is a tool created to standardize the diagnosis of acne scars. It comprises six items corresponding to specific types of acne scars (e.g., V-shaped, U-shaped, M-shaped atrophic scars, superficial elastolysis, hypertrophic inflammatory scars, and keloids). Subgrade 1 comprises the grading of the first type, while subgrade 2 comprises the grading of the last two types of acne scars.

was a greater decrease in the mean ECCA global score in the test 1 compared to control 1 group. Also, there was a greater decrease in the mean ECCA global score in the test 2 compared to the control 2 group. When evaluating the difference in percent reduction of the ECCA global score between the groups (Figure 2B), there was a statistically significant difference between the test 1 and control 1 groups at week 8. There were statistically significant differences between the test 2 and control 2 groups at weeks 1 and 12. At the final follow-up visit at 12 weeks, the percentage reduction was the highest in the test 2 group (24.36%).

Figure 2C shows group comparisons of the ECCA subgrading 1 scores, which evaluate atrophic scars and superficial elastolysis. There was a greater decrease in the mean ECCA global score in the test 1 compared to the control 1 group. Also, there was a greater decrease in the mean ECCA global score in the test 2 than in the control 2 group. When evaluating the difference in percent reduction of the ECCA subgrading 1 score between the groups (Figure 2D), there was a statistically significant difference between the test 1 and control 1 groups at weeks 8 and 12. There was a statistically significant difference between the test 2 and control 2 groups at weeks 4 and 12. At the final follow-up visit at 12 weeks, the percentage reduction was the highest in the test 1 group (20.11%). Representative photographs of the two participants in the test 1 group are shown in Figure 3.

Figure 2E shows group comparisons of changes in the ECCA subgrading 2 scores, which evaluate hypertrophic or keloid scars. The mean baseline ECCA subgrading 2 score was 0 in the test 1 and control 1 groups. In the test 2 group, the mean ECCA subgrading 2 score was reduced from 8.89 at baseline to 0.00 after 12 weeks, whereas in the control 2 group, the mean score was reduced from 8.89 at baseline to 7.41. When evaluating the difference in percent reduction of ECCA subgrading 2 score between the groups (Figure 2F), there was a statistically significant difference between the test 2 and control 2 groups at week 12. Representative photographs of the two participants in the test 1 group are shown in Figure 4. The analysis in the PP set also presented results similar to that of the FA set.

3.2 | Safety outcomes

No subjects developed adverse reactions in this clinical trial.

4 | DISCUSSION

DA-5520 is a topical scar treatment drug that contains 5% allantoin, 500 IU heparin sodium, and 100 mg dexpanthenol. In a preclinical animal study using a rabbit ear model of hypertrophic scarring, DA-5520 showed favorable effects in recovering skin color and reducing scar thickness.[6] These results demonstrated that DA-5520 may be a promising new formulation for scar treatment.

In this pilot study, we evaluated the efficacy of DA-5520 in two different settings: combination with laser resurfacing vs. monotherapy. In this study, we observed the clinical benefits of DA-5520 application for treating acne scars. The global ECCA score was significantly reduced in both the test groups compared with that of the control group. Interestingly, the greatest percentage reduction in the ECCA global score was observed in the test 2 group where DA-5520 alone was applied. At first glance, this result may appear questionable since the treatment effect should be better in the test 1 group where combination therapy with laser resurfacing was performed. However, this result may be because of the baseline differences. Participants with hypertrophic scars were only in the test 2 group but not in the test 1 group. Thus, when the change in the ECCA subgrading 2 score is excluded, the

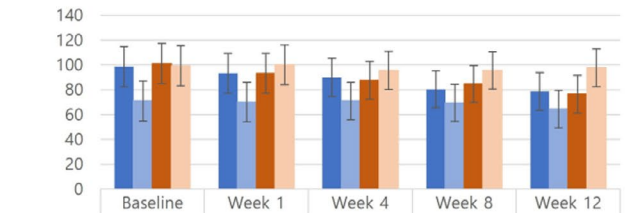
TABLE 3 Baseline demographic features and quantitative acne scar severity scores at baseline and follow-up

	Test 1 group	Control 1 group	Test 2 group	Control 2 group	*p*-Value
Age					
Mean ± SD	31.56 ± 10.48	26.44 ± 10.32	27.11 ± 10.91	26.89 ± 5.88	0.6491
Sex					
Male, *n* (%)	5 (55.56)	3 (33.33)	8 (88.89)	6 (66.67)	0.1267
Female, *n* (%)	4 (44.44)	6 (66.67)	1 (11.11)	3 (33.33)	
Height (cm)					
Mean ± SD	171.97 ± 8.37	167.34 ± 7.45	174.12 ± 4.83	171.99 ± 6.27	0.2174
Body weight (kg)					
Mean ± SD	68.78 ± 11.89	63.50 ± 14.85	75.52 ± 12.43	69.24 ± 7.64	0.3415
ECCA (Global score)					
Mean ± STD	98.52 ± 47.49	70.93 ± 46.52	101.11 ± 40.79	99.26 ± 66.92	0.5554
ECCA (Subgrading 1)					
Mean ± STD	98.52 ± 47.49	70.93 ± 46.52	92.22 ± 25.44	90.37 ± 57.95	0.6158
ECCA (Subgrading 2)					
Mean ± STD	0.00	0.00	8.89 ± 17.64	8.89 ± 17.64	0.2272

reduction in the ECCA global score is greater in the test 1 group than in the test 2 group.

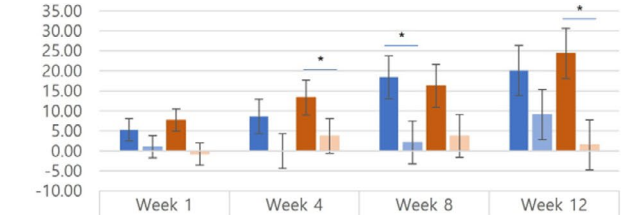
The ECCA subgrading 1 score, which evaluates atrophic scars, was significantly reduced in both the test groups compared with the control groups. Not surprisingly, in both the test 1 and control 1 groups where laser resurfacing was performed, a continuous reduction in the ECCA subgrading 1 score was observed until 12 weeks. More importantly, in the test 1 group where DA-5520 was applied adjunctively, a faster and greater improvement of atrophic scars was observed (Figure 3). In the test 1 group, the ECCA subgrading 1 score started to decrease from week 1, and a significantly greater reduction in the score compared to control 1 group was observed at 8 and 12 weeks. In general, treatment response after ablative FP is observed from approximately 3 weeks, and maximum improvement by 3–6 months, because the production of type I and type III procollagen mRNA peaks from 21 days up to 6 months after treatment.[7,8] Besides, to a lesser degree, an improvement in atrophic scars was also observed in the test 2 group where DA-5520 alone was applied without laser resurfacing. Therefore, we can assume that DA-5520 has the potential to clinically improve atrophic scars both when used adjunctively with laser treatment and when used alone.

(A) ECCA Global Score



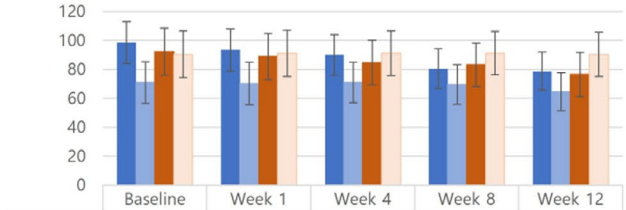
	Baseline	Week 1	Week 4	Week 8	Week 12
Test 1	98.52	93.33	90	80.37	78.7
Control 1	70.93	70.19	70.93	69.44	64.44
Test 2	101.11	93.33	87.59	84.63	76.48
Control 2	99.26	100	95.56	95.56	97.78

(B) Mean percent reduction in ECCA global score



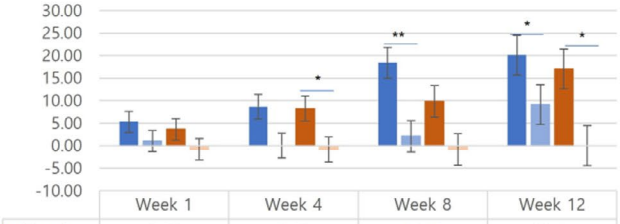
	Week 1	Week 4	Week 8	Week 12
Test 1	5.27	8.65	18.42	20.11
Control 1	1.04	0.00	2.09	9.14
Test 2	7.69	13.37	16.30	24.36
Control 2	-0.75	3.73	3.73	1.49

(C) ECCA Subgrading 1



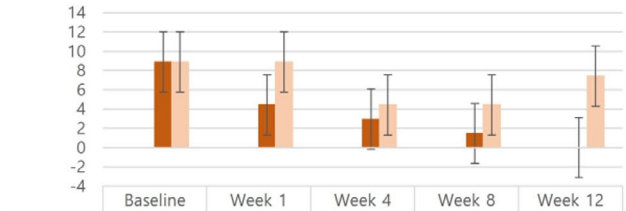
	Baseline	Week 1	Week 4	Week 8	Week 12
Test 1	98.52	93.33	90	80.37	78.7
Control 1	70.93	70.19	70.93	69.44	64.44
Test 2	92.22	88.89	84.63	83.15	76.48
Control 2	90.37	91.11	91.11	91.11	90.37

(D) Mean percent reduction in ECCA subgrading 1



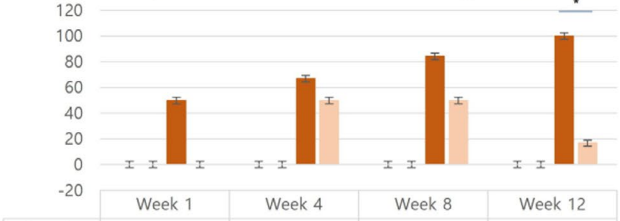
	Week 1	Week 4	Week 8	Week 12
Test 1	5.27	8.65	18.42	20.11
Control 1	1.04	0.00	2.09	9.14
Test 2	3.61	8.23	9.84	17.07
Control 2	-0.82	-0.82	-0.82	0.00

(E) ECCA Subgrading 2



	Baseline	Week 1	Week 4	Week 8	Week 12
Test 1	0	0	0	0	0
Control 1	0	0	0	0	0
Test 2	8.89	4.44	2.96	1.48	0
Control 2	8.89	8.89	4.44	4.44	7.41

(F) Mean percent reduction in ECCA subgrading 2



	Week 1	Week 4	Week 8	Week 12
Test 1	0	0	0	0
Control 1	0	0	0	0
Test 2	49.94	66.70	84.03	100.00
Control 2	0.00	49.94	49.94	16.65

FIGURE 2 Results of the efficacy assessment (A) Group comparisons of changes in the mean echelle d'evaluation clinique des cicatrices d'acn´e (ECCA) global score at 1, 4, 8, and 12 weeks versus baseline and (B) mean percent change in the ECCA global score in each group (C) Group comparisons of changes in the ECCA subgrading 1 score at 1, 4, 8, and 12 weeks versus baseline and (D) mean percent change in the ECCA subgrading 1 score in each group (E) Group comparisons of changes in the ECCA subgrading 2 score at 1, 4, 8, and 12 weeks versus baseline and (F) mean percent change in the ECCA subgrading 2 score in each group $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$

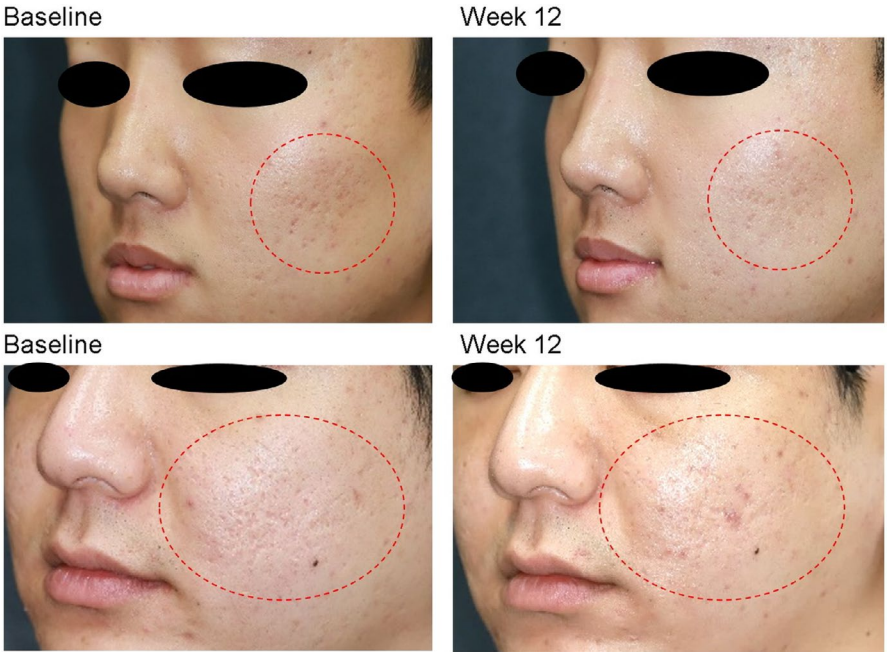


FIGURE 3 Representative photographs of two participants in the test 1 group

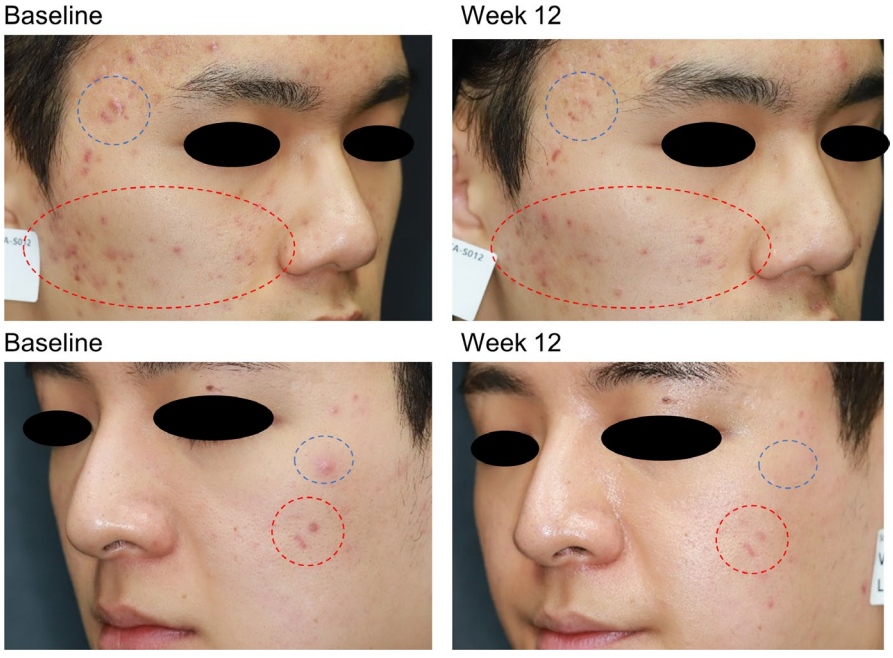


FIGURE 4 Representative photographs of two participants in the test 2 group Blue dotted circle: Hypertrophic scar; Red dotted circle: Atrophic scar

Improvement in hypertrophic scar treatment was prominent in the test 2 group (Figure 4). At 12 weeks, the percentage reduction in the ECCA subgrading 2 score was 100% in the test 2 group compared with 16.65% in the control 2 group. The efficacy of silicone-based topical scar treatment gels for the treatment of hypertrophic scars and keloids is well known.[9,10] However, the results of our study (percent reduction of 100%) may be exaggerated due to the limited sample size and a low baseline ECCA subgrading 2 score. Nonetheless, the fact that DA-5520 may be effective for both hypertrophic and atrophic scars is important because, occasionally, a patient requires treatment for both atrophic and atrophic acne scars.

The active ingredients in DA-5520 are 5% allantoin, 500 IU heparin sodium, and 100 mg dexpanthenol. Allantoin has been shown to have a wound healing, anti-irritation, hydration, recovery of necrotic tissue keratolytic, and epithelializing effect.[11] Heparin sodium has also been used topically for its anti-inflammatory, neo-angiogenic, epithelializing, and anticoagulatory properties.[12,13] When introduced transepidermally, it binds to the surface scar collagen and inhibits collagen fibrillogenesis.[14,15] Finally, DA-5520 includes dexpanthenol instead of cepae extract, which is commonly used in scar treatment gels. Although cepae extract is well known for its beneficial anti-scarring effects,[16] it may be an irritant, especially when

applied to face.[17] In contrast, the most prominent effects of formulations containing dexpanthenol include the stimulation of epithelialization, granulation and the mitigation of itching.[18–20] Dexpanthenol is known to modulate the expression of several genes crucial for wound healing.[21,22] Notably, none of the participants complained of irritation after use of DA-5520. Both the individual activities of the abovementioned active substances and synergistic effects of the combined active ingredients seem to enhance wound-healing process and to reduce scar formation.

Regarding the anti-inflammatory activity of DA-5520, it can be postulated that DA-5520 may be effective in preventing acne scars, especially when the gel is used in early phase of scar. There is growing evidence that early intervention of scars may prevent excessive scar formation.[23–25] Decreased inflammation in early wound-healing phases may modulate the formation and distribution of collagen fibers, prior to maturation. Willital et al.[25] also reported that a gel containing extracum cepae, heparin, and allantoin is effective in preventing excessive scar formation when treatment is initiated early. However, our study lacked information on the onset of scar formation, and therefore, further studies are needed to investigate the relationship between the efficacy of gel and the timing of treatment initiation.

Major limitations of this study include a small sample size, comprising Asians alone and a short follow-up period of 3 months. As collagen remodeling can last more than 1-year, a longer follow-up is needed. Furthermore, only a single session of laser resurfacing was performed in the laser resurfacing groups due to the short duration of this pilot clinical trial. Therefore, based on the positive results of this pilot study, a study with a larger sample size, various skin color, a longer follow-up period, and involving multiple sessions of laser resurfacing should be performed. Furthermore, studies should also aim to directly compare the efficacy of this product with other traditional acne scar treatment options such as microneedling or other topical formulations.

5 | CONCLUSION

Clinical improvement of acne scars, confirmed by the ECCA grading scale, was observed after DA-5520 use when used with laser resurfacing or individually, and no associated adverse reactions were noted. These results demonstrated that DA-5520 may be a promising new formulation for treating all type of acne scars.

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CONFLICT OF INTEREST

Young sung Sohn is senior research fellow at Dong-A Pharm. Co., Ltd.

AUTHOR CONTRIBUTIONS

Hye Sung Han involved in data curation, formal analysis, investigation, visualization, and writing (original draft and editing). Jae Wan Park involved in data curation, formal analysis, and visualization. Sun Hye Shin involved in data curation and validation. Kwang Ho Yoo involved in project administration and writing (review and editing). Young Sung Sohn involved in project administration, methodology, and resources. Beom Joon Kim involved in conceptualization, funding acquisition, methodology, project administration, supervision, validation, and writing (review and editing).

ETHICAL APPROVAL

This study protocol was reviewed and approved by Institutional Review Board of Chung-Ang University Hospital, approval number (IRB No.1892–006–345). The patients in this manuscript have provided written informed consent for the publication of their case details.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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