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Research Article

Clinical Benefit and Safety of Microneedle Patches Composed of Magnesium: A Pilot Study in Acne Patients

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Magnesium (Mg) is a newly investigated biomaterial that corrodes physiologically in water, resulting in evolved hydrogen with beneficial effects of anti-inflammation and acceleration of the wound healing process. In addition, Mg itself has antimicrobial activity against *Cutibacterium acnes*, which play a pathogenic role in developing inflammatory acne. This study aimed to evaluate efficacy and safety of a newly developed magnesium microneedle (Mg MN) patch, with a needle length of 0.25 mm, on acne and widened pores. A total of 19 patients with mild to moderate acne and receiving no topical or oral treatment was enrolled in the study. Mg MN patches were applied to inflammatory acne lesions and widened pores on both cheeks and nose. Researchers evaluated efficacy by counting acne lesions and measuring pore sizes, porphyrin level, and sebum secretion. Any objective or subjective adverse events were recorded during the study. The number of acne lesions and scores improved significantly within seven days ($p < 0.01$). The porphyrin level tended to decrease over 12 weeks, although pore size and sebum secretion showed unsatisfactory results. No adverse reactions were noted during the study period. Mg MN patches can be useful in treating inflammatory acne lesions, and they are safe to use. For the improvement of widened pores, modification of needle length or a combination of topical agents may be required.

1. Introduction

In the biomedical realm, metallic materials such as stainless steel, cobalt, and titanium have traditionally been used as implants. In addition, biodegradable metal implants are in development. Magnesium (Mg), iron, and zinc are the new generation of biodegradable materials and have been actively evaluated [1]. Mg and Mg-based alloys are widely used materials in the medical field especially in orthopedic and cardiovascular departments [2, 3]. Using Mg as a biomaterial has several advantages. First, Mg naturally corrodes in the physiological environment. Second, intermediate corrosion products in the Mg corrosion process, such as Mg^{2+} ions, H_2 gas, and OH^-, are absorbable or physiologically present in the human body. Therefore, no toxicity has been reported.

As Mg is a highly reactive metal, it dissolves in water with the following reaction:

$$\begin{aligned} &Mg \longrightarrow Mg^{2+} + 2e^-, \\ &2H_2O + 2e^- \longrightarrow H_2 + 2OH^-, \\ &Mg^{2+} + 2OH^- \longrightarrow Mg(OH)_2, \\ &Mg + 2H_2O \longrightarrow Mg(OH)_2 + H_2. \end{aligned} \tag{1}$$

During this corrosion process, Mg generates hydrogen [4, 5]. Molecular hydrogen has been known to function as an antioxidant and anti-inflammatory agent. Previous studies delivering hydrogen by inhalation, intravenous injection, or water supplement have reported a therapeutic effect of hydrogen in the wound healing process [6]. A study on

a hydrogen-generating patch made of aluminum and calcium hydroxide demonstrated that hydrogen improved the viability of skin cells, promoted cellular migration, and enhanced collagen expression level [7].

Moreover, Mg is thought to have an antibacterial property. Robinson et al. [8] demonstrated in an in vitro study that Mg metal inhibited the growth of *E. coli*, *P. aeruginosa*, and *S. aureus*. In 2018, a halo test of a magnesium microcarrier against *Cutibacterium acnes* (*C. acnes*) was performed by the Korea Testing and Research Institute, and the results revealed that the magnesium microcarrier also has an antibacterial effect against *C. acnes*, which plays an important role in inflammatory acne lesions [8, 9].

Acne vulgaris is a common concern in patients in their 20 s and 30 s [9, 10]. The first-line treatment for mild to moderate acne patients includes application of topical retinoid, antibiotic, benzoyl peroxide, and azelaic acid [9]. These topical agents may cause irritation, scaling, and erythema, which can be a drawback for persistent use. Long-term application of topical antibiotics may carry another worrisome issue—that of antibiotic resistance. Therefore, other alternative treatment modalities have been studied and one of them, microneedling, has been introduced in the clinical field [9–12].

A microneedle (MN) is a minimally invasive appliance that shows effects through skin microinjuries and micropuncturing [11–14]. It has been effectively used in various skin diseases such as scars, acne, melasma, and skin rejuvenation. The effects of MN on skin may vary depending on material and needle characteristics and the active medicinal agent transmitted by transepidermal delivery. Based on the length and thickness of the needles, MNs can be used as noninvasive home skin care devices. The MN used in cosmetic procedures conducted by doctors in the clinic are between 0.5 and 3 mm in length, with a diameter between 0.1 and 0.25 mm, which can penetrate the papillary dermis down to the mid-dermis based on the average skin thickness of adults [11–13]. As a home device, an MN less than 0.5 mm in length cannot reach into the dermis; in general, it does not result in hemorrhages or severe skin injuries.

Various materials including metal, silicon, and polymer are used to create MN patches [11, 15]. Conventional MNs used in acne and acne scars are mostly composed of stainless steel as a physician-applied device. Stainless steel is not suitable for a home-based device or as a form of patch because of irritation and possible allergic reaction [16]. Other MN patches for individual uses at home are made of bioabsorbable needles that accelerate topical delivery of active agents only and cannot mimic the role of microneedling itself [10].

MN patches composed of microneedles made of Mg metal with a needle length of 0.25 mm in a hydrocolloid band were newly developed considering the biomedical effects of Mg and MN itself. They are expected to improve inflammatory acne lesions and prevent acne scarring when applied as a home-based device. Beneficial effects on widened pores, which are a common accompanying issue for acne patients, can also be expected due to their needling effect and the Mg-induced wound healing process. However, there have been no clinical studies about the efficacy and safety of Mg MN patches in patients with mild to moderate acne. Therefore, this pilot study was designed to investigate the safety and effectiveness of Mg MN patches as home use devices for inflammatory acne lesions and widened pores.

2. Materials and Methods

This clinical trial was approved by the Institutional Review Board of Samsung Medical Center, Sungkyunkwan University School of Medicine in Seoul, Korea (IRB approval no. SMC 2020-12-020). This study has been registered in Clinical Research Information Service (https://cris.nih.go.kr, KCT0007663). The study was conducted according to the protocols of the Declaration of Helsinki.

2.1. Patients. Patients with mild to moderate acne and between the ages of 20 and 40 years were recruited prospectively. Written informed consent was obtained before the study began. The severity of acne vulgaris was determined with the Korean Acne Grading System (KAGS) [17]. The exclusion criteria were as follows: patients who were taking any oral medication for acne treatment; women who were pregnant or lactating; patients who had been treated with botulinum toxin, ultrasound, or laser within six months; patients who had been treated with hyaluronic acid filler within one year; and patients who were using other drugs that might impact the effect of magnesium. Patient recruitment and allocation in the study is described in Figure 1(a).

2.2. Devices. The patch used in this study was a spot patch with Mg MNs on the hydrocolloid band for inflammatory acne lesions, and the patch was modified for the nose and pores of both cheeks; the patches are market-available and in use. The patch has multiple Mg microneedles of 0.25 mm in length (Figure 2).

2.3. Study Protocols. Patients were instructed to apply Mg MN spot patches once a day for papules, pustules, and nodules after washing in the evening. After eight hours of use, the patches were removed. The Mg MN spot patches were applied every night until the lesions improved. Patients were also advised to apply Mg MN pore patches to the nose and both cheeks every other night for two hours during the study period. Patients were followed for 12 weeks after starting the use of Mg MN patches. During the study period, patients were not allowed to change their daily cosmetics, including facial washes, or to use topical antiacne medication.

2.4. Clinical Assessments. At the baseline visit and on days three and seven, clinical photographs of patients were obtained to evaluate the effect of Mg MN patches on inflammatory acnes. Papules, pustules, and nodules were counted separately by an independent investigator. In this study, a discretionally calculated acne score was used to evaluate the changes in lesions over time. Two points each

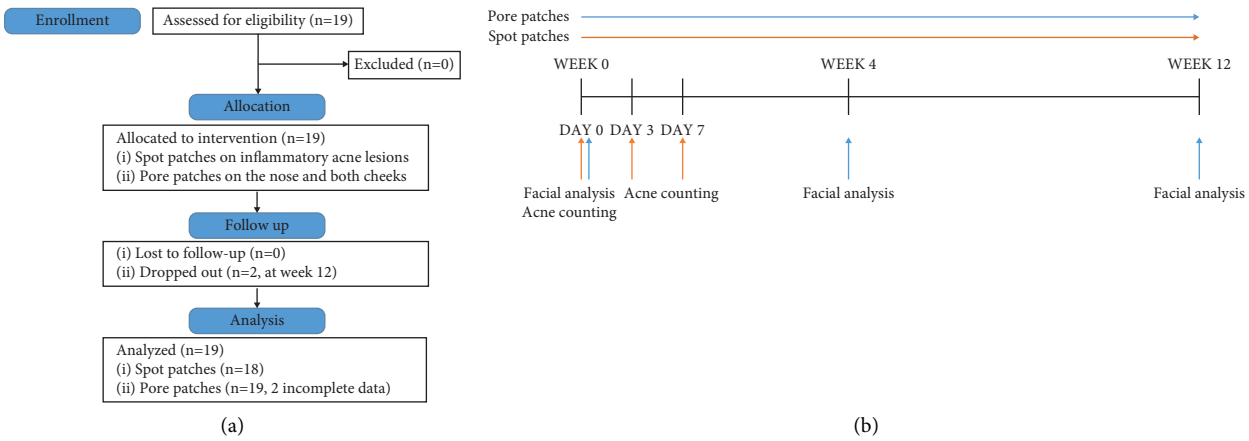


Figure 1: (a) Patient recruitment and allocation and (b) study design.

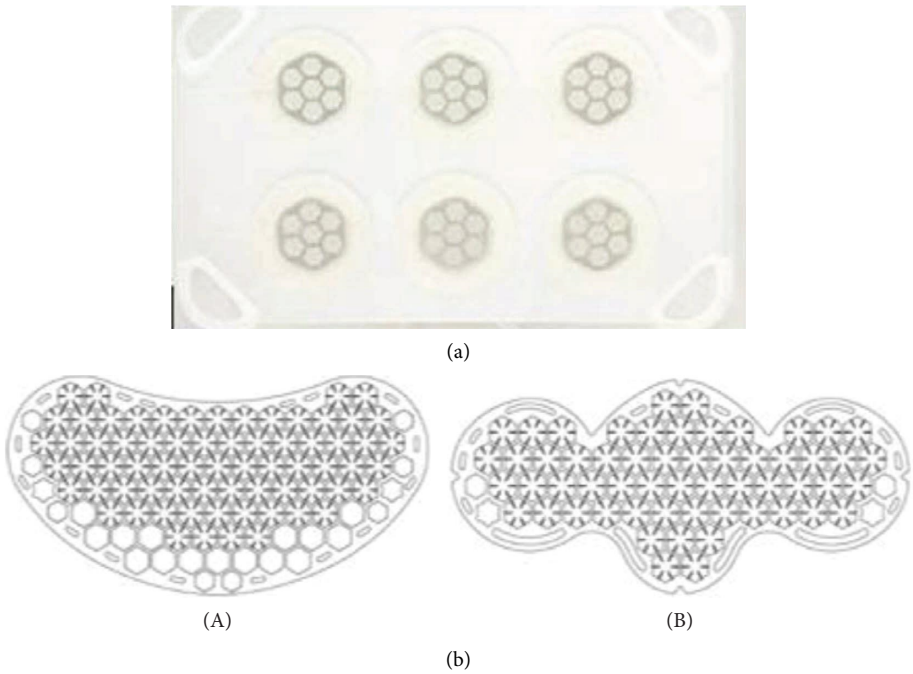


Figure 2: (a) Magnesium (Mg) MN (microneedle) patches for inflammatory acne lesions and (b) Mg MN patches for pores, (A) for cheek, and (B) for nose.

were assigned for papules, four points each for pustules, and six points each for nodules, and one point was deducted when the size of the lesion decreased or improved; for example, from pustule to papule or papule to flat erythema. New lesions occurring after the initial evaluation at baseline were excluded from the count because the evaluation focused on the clinical course of inflammatory acne when using Mg MN patches on the lesions. The pore sizes and sebum and porphyrin levels of volunteers were evaluated by using a face analyzer (Mark-Vu; PSI PLUS, Daejeon, Korea) at weeks zero, four, and twelve. Researchers checked patient compliance by individual phone calls once a week, giving an explanation of instruction and asking if they are following it well. The study design of this clinical trial is described in Figure 1(b).

To assess safety, questionnaires about subjective adverse reactions such as pruritus, burning, tingling, and pain and objective adverse reactions such as redness, edema, papules, scales, and pigmentation were obtained at each visit.

2.5. Statistical Analysis. The researchers used generalized estimating equations to determine changes over time compared to baseline. Statistical significance was defined as p value <0.05. All statistical analyses were conducted by two biostatistics specialists (SW Kim and JS Shim).

Table 1: Korean Acne Grading System (reference [17]).

Grade	Characteristics
1	Papules ≤10
2	Papules 11–30
3	Papules ≥31, nodules ≤10
4	Nodules 11–20, ±mild ongoing scars
5	Nodules 21–30, ±moderate ongoing scars
6	Nodules ≥31, ±severe ongoing scars, ±sinus tract

Table 2: Detailed scores of acne lesions of subjects. All subjects except 1 and 19 showed a decrease in acne scores. Of the 19 volunteers, 18 were analyzed because the clinical photos of one subject (subject 15) were not sufficient.

	Day 0		Day 3		Day 7		Change of state
	Lesions	Score	Lesions	Score	Lesions	Score	
A01	2	8	1	5	1	6	Stationary
A02	2	4	0	0	0	0	Improved
A03	2	8	2	4	2	4	Improved
A04	4	12	0	0	0	0	Improved
A05	2	4	1	2	0	0	Improved
A06	4	8	2	3	2	3	Improved
A07	1	4	1	2	1	1	Improved
A08	2	6	1	2	0	0	Improved
A09	4	10	1	2	0	0	Improved
A10	3	10	2	4	1	2	Improved
A11	7	20	2	6	0	0	Improved
A12	8	18	3	6	2	4	Improved
A13	2	8	0	0	0	0	Improved
A14	2	4	1	1	0	0	Improved
A16	1	2	0	0	0	0	Improved
A17	4	8	0	0	0	0	Improved
A18	3	6	1	1	0	0	Improved
A19	2	8	2	7	2	7	Stationary
Average	3.05	8.22	1.11	2.5	0.61	1.5	

3. Results

3.1. Demographics. Patients with mild to moderate acne vulgaris with a Korean Acne Grading System (KAGS) [17] score less than 3 were included in the study (Table 1). A total of 19 patients were enrolled, and the mean age of patients was 31.5 years (age range: 23–38 years). Four patients were male, and 15 patients were female.

3.2. Efficacy on Inflammatory Acne Lesions. The average number of acne lesions during the study continuously decreased from 3.06 at baseline to 1.11 after three days and 0.61 after seven days (p value <0.001). Furthermore, the average acne score calculated in this study decreased from 8.22 at baseline to 2.5 on day three and 1.5 on day seven (p value <0.001). The detailed scores of every subject decreased compared to baseline scores, except for Subject 1 and Subject 19 (Table 2). A GEE analysis was performed to observe the changes over time and showed that the number of inflammatory acne lesions and acne scores decreased over seven days (Table 3, Figures 3 and 4).

3.3. Efficacy on Pore Sizes, Sebum Secretion, and Porphyrin Counts. The mean size of pores on the nose and measured by using a facial analyzer was 43.95 at baseline, 44.79 after four weeks, and 46.47 after 12 weeks of every other night use (Table 4). This increase in size was statistically significant. The mean size of pores on cheeks was 94.79 at baseline, 94.00 after four weeks, and 93.12 after 12 weeks, which showed no significant difference (Figure 5(a)).

The mean sebum secretion of the nose, measured by using the facial analyzer, was 17.26 at baseline, 17.47 at week four, and 17.82 at week 12, with no significant difference (p value = 0.77). The mean sebum secretion of both cheeks showed a decrease after using a Mg MN patch (23.00 at baseline, 20.74 at week four, and 19.47 at week 12, but no significant difference (p value = 0.16) (Figure 5(b)).

The mean porphyrin levels of the nose and cheeks showed a tendency to decrease over time (nose: 40.47 at week zero, 36.63 at week four, and 34.41 at week 12; both cheeks 43.16 at week zero, 35.89 at week four, and 39.12 at week 12, respectively) A statistically significant decrease was noticed in both cheeks at week four compared with baseline (p value = 0.002) (Figure 5(c)).

3.4. Adverse Effects. No noticeable side effects such as redness, edema, papules, scales, and pigmentation were observed during the study period. No subjects reported any subjective adverse reactions like pruritus, burning, tingling

Table 3: Changes in the number of acne lesions and acne scores over time.

Variable	Mean ± SD	p value*	Type 3 p value
The number of acne lesions			
Day 0	3.06 ± 1.89		
Day 3	1.11 ± 0.90	<0.0001	
Day 7	0.61 ± 0.85	<0.0001	<0.0001
Acne score			
Day 0	8.22 ± 4.70		
Day 3	2.50 ± 2.33	<0.0001	
Day 7	1.50 ± 2.31	<0.0001	<0.0001

The total number of acne lesions and acne scores decreased significantly. p value is corrected by Bonferroni correction. *Compared to day 0. Abbreviation: SD, standard deviation.

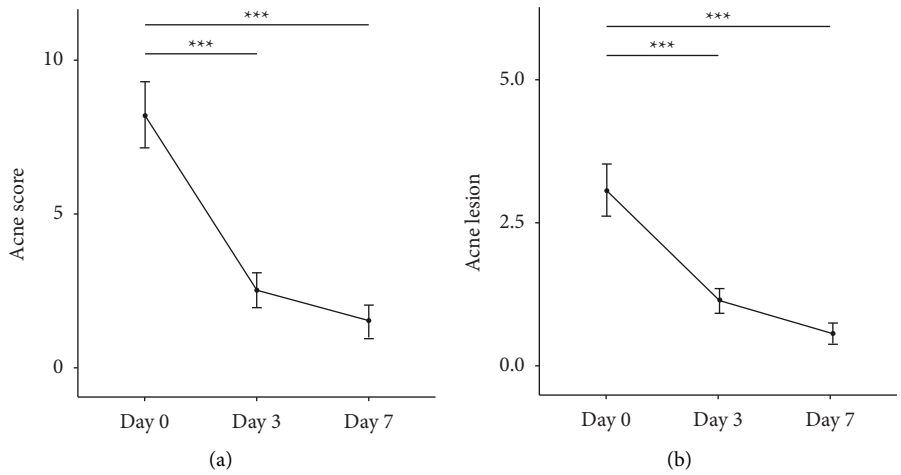
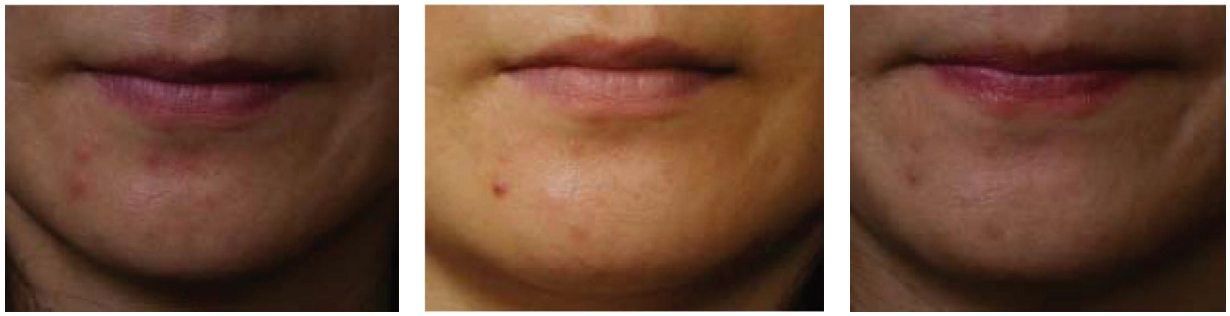
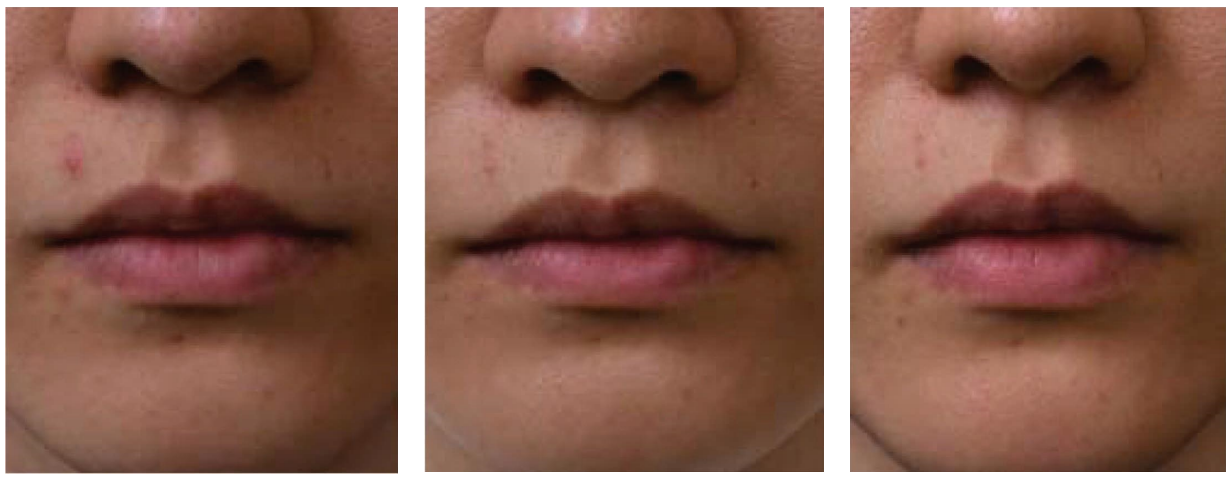


Figure 3: (a) Changes in total number of acne lesions over time and (b) changes in acne scores over time (p values less than 0.05 shown as * less than 0.01 shown as ** and less than 0.001 shown as ***); visit 1: day zero, visit 2: day three, visit 3: day seven.



(a) (b) (c)

Figure 4: Continued.



(d) (e) (f)

Figure 4: Clinical photographs: (a) patient 6 at baseline, (b) patient 6 at day three, (c) patient 6 at day seven, (d) patient 8 at baseline, (e) patient 8 at day three, and (f) patient 8 at day seven.

Table 4: Changes in pore sizes, sebum secretion, and porphyrin level of the nose and both cheeks over time.

Variable	Mean ± SD	p value*	Type 3 p value
Pore sizes of nose			
Week 0	43.95 ± 5.39		
Week 4	44.79 ± 5.33	0.1492	
Week 12	46.47 ± 6.44	0.0010	0.0019
Pore sizes of both cheeks			
Week 0	94.79 ± 9.62		
Week 4	94 ± 10.74	0.8773	
Week 12	93.12 ± 9.97	0.9004	0.6686
Sebum secretion of nose			
Week 0	17.26 ± 7.97		
Week 4	17.47 ± 8.76	1.5935	
Week 12	17.82 ± 8.46	0.9524	0.7747
Sebum secretion of both cheeks			
Week 0	23 ± 15.28		
Week 4	20.74 ± 13.54	0.1962	
Week 12	19.47 ± 13.18	0.2421	0.1650
Porphyrin level of nose			
Week 0	40.47 ± 17.35		
Week 4	36.63 ± 16.33	0.3789	
Week 12	34.41 ± 22.83	0.1685	0.1442
Porphyrin level of both cheeks			
Week 0	43.16 ± 38.89		
Week 4	35.89 ± 34.57	0.0044	
Week 12	39.12 ± 35.88	1.8416	0.0020

The mean size of pores of the nose increased significantly and the mean size of pores of both cheeks showed no difference over the course of the study. Sebum secretion did not show any difference over time, but the porphyrin level of both cheeks significantly decreased. p value is corrected by Bonferroni correction. *Compared to week 0. Abbreviation: SD, standard deviation.

sensation, and pain. Interestingly, no patients reported any acne scarring on the lesions where Mg MN patches were applied.

4. Discussion

This study found that the Mg MN patch reduced acne lesions within a few days, even when patients did not take antiacne medications or apply topical antiacne agents. This rapid improvement of inflammatory acne in days is a remarkable finding considering the clinical evidence and previous reports that showed it takes weeks for topical application of retinoid and other agents to improve inflammatory acne lesions [18]. Changes in acne scores, which reflect the time effect of Mg MN patches, implied that simple application of Mg MN patches on inflammatory acnes for eight hours

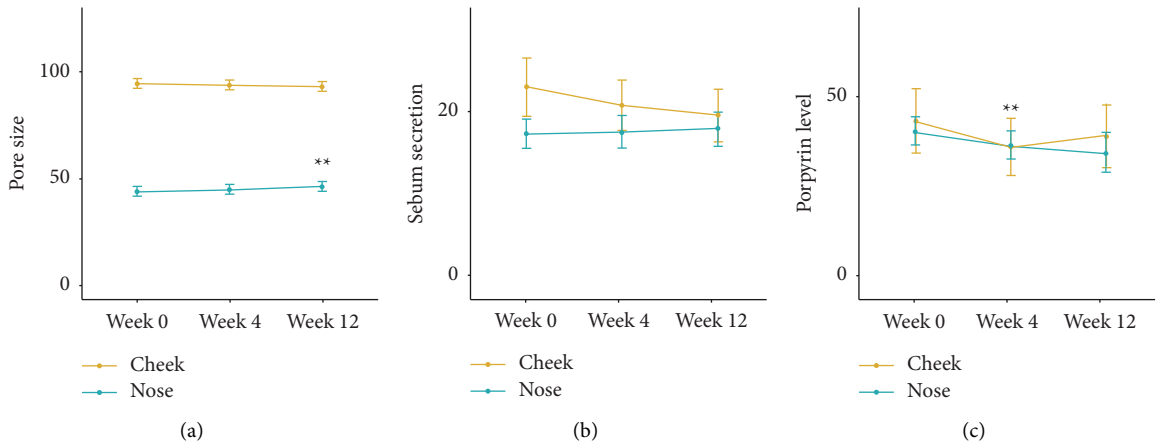


FIGURE 5: (a) Changes in pore sizes of the nose and both cheeks over time, (b) changes in sebum secretion of the nose and both cheeks over time, and (c) changes in porphyrin level of the nose and both cheeks over time (p values less than 0.05 shown as * less than 0.01 shown as ** and less than 0.001 shown as ***); visit 1: week zero, visit 4: week four, visit 5: week twelve.

during sleep has definite clinical benefits. In addition to the effect of MN needling, Mg is thought to have additional benefits of anti-inflammatory and antibacterial effects, especially against *C. acnes*.

This study has its own value through observation of courses of inflammatory acne using Mg MN patches. It is difficult to provide patient follow-up in the clinical setting as frequently as in this study. Follow-up was performed at baseline, three days, and seven days after using Mg MN patches, and the changes in inflammatory acne lesions were evaluated. As the results showed, the inflammatory lesions improved days after application of the Mg MN patch without any serious adverse events.

Acne patients often complain of widened pores and excessive sebum production. Initial uses of MN were targeted to improve skin texture, wrinkles, and atrophic scars. Therefore, the safety and efficacy of Mg MN patches on pores and sebum production were also analyzed. Unexpectedly, the pore size and sebum secretion of the nose increased at follow-up visits. On the contrary, that of both cheeks tended to decrease at weeks four and twelve compared with baseline, although they failed to show statistically significant differences. Two major causes could be considered for an unsatisfactory effect on pore size and sebum secretion. First, facial pores and sebum secretion are easily affected by exogenous factors. In some patients, the study was conducted in spring and summer, when the size of the pores might have been influenced by environmental factors [9]. To improve enlarged pores, it is essential that the dermis be sufficiently stimulated by needling to induce collagenesis [11, 15]. The length of the needles used in this study (0.25 mm) might be insufficient to show noticeable clinical effects on pore size. Adjusting the needle length, increasing use time, or using a combination of topical agents combined with MNs that can promote collagen synthesis might also be ways to increase the therapeutic effect on enlarged pores and sebum secretion.

For porphyrin level, a substantially significant reduction of both cheeks was observed. The porphyrin level of the nose also showed a tendency to decrease during the study period. This result also supported the inhibitory effect of Mg MNs against *C. acnes*, which produces porphyrin as a metabolite [19].

A limitation of this study was that there was no control group, as it was conducted as an exploratory study for evaluation of the safety and efficacy of newly developed Mg MN patches as a home care device. However, to the best of the authors' knowledge, this is the first research to explore the efficacy and safety of Mg MNs on inflammatory acne lesions and to observe changes occurring over days using Mg MN patches. Study findings showed definite improvement of inflammatory acne lesions after using Mg MN patches over days, and this study may provide a basis for further studies about dermatologic uses of Mg MNs.

5. Conclusion

In conclusion, Mg MN patches with multiple needles 0.25 mm in length can improve acne lesions within a few days and are demonstrated to be safe to use as a home care device for at least 12 weeks. To be effective in reducing pore size and sebum secretion with Mg MN patches 0.25 mm in length, changes in the formulation, method of application, or combination of topical agents for transdermal delivery could be contemplated. MNs with longer needles may provide more benefit for reduction of pores. Further randomized controlled studies with a larger number of patients and a longer follow-up period are required.

Data Availability

Datasets for this research are available on request from the corresponding author. Due to privacy and ethical concerns, details of the data are not publicly available.

Disclosure

This research has been provided as a preprint in the Research Square and Europe PMC in the following links: https://www.researchsquare.com/article/rs-1866277/v1 and https://europepmc.org/article/ppr/ppr547393.

Conflicts of Interest

The authors declare no conflicts of interest.

Acknowledgments

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