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Magnesium microneedle patches for under-eye wrinkles

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Abstract

Microneedling is a common cosmetic procedure for improvement of wrinkles, acne, scars, and other conditions. Various microneedle (MN) patches have been developed as home care therapy for wrinkles and skin texture. Most of them are made of soluble and absorbable needles. To evaluate the efficacy and safety of non-absorbable magnesium (Mg) MN patches on under-eye wrinkles. A total of 20 subjects aged 27–58 years was enrolled in the study. The subjects applied Mg MN patches on the under-eye wrinkle area for 1–2 h every other night for 12 weeks. The evaluation comprised grading by clinicians, measuring the wrinkle index with a facial analyzer, and measuring the dermal thickness of the under-eye area with ultrasonography. Any adverse events and discomfort were addressed during the study. The application of Mg MN patches on under-eye areas showed improvements in under-eye grading scale, wrinkle index, and dermal thickness after 12 weeks. The mean grading scale significantly improved after 8 weeks of application ($p < 0.01$). The wrinkle index showed significant improvement after 12 weeks on the right under-eye area ($p < 0.05$). The dermal thickness of the under-eye area tended to increase, but no statistically significant changes were observed. Non-absorbable Mg MN patches can be used for under-eye wrinkles with minimal discomfort.

KEYWORDS
efficacy, magnesium, microneedle patch, safety, under-eye wrinkles

1 | INTRODUCTION

Microneedles (MN) are extremely small, micro-sized needles placed in an array, designed to penetrate the outer layer of the skin.[1–5] Since the first presentation of MN, there have been numerous developments of structures, morphologies, geometries, sizes, and materials.[1–5] MN has been widely used in fields of dermatology including skin rejuvenation and treatment of dermatologic diseases (e.g., scars, acne vulgaris, androgenic alopecia, alopecia areata, and other pigmentary disorders).[2,4]Two possible mechanisms of action of MN have been suggested: via the wound healing cascade resulting from microinjuries created by MN and through transdermal delivery of various products bypassing the stratum corneum.[1–5]

Based on the length and thickness of needles, MN can be used as a non-invasive home skin care device. The microneedles 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,

Donghwi Jang and Joonho Shim contributed equally to this work.

considering the average skin thickness of adults.[1–5] As a home device of MN less than 0.5 mm in length cannot reach into the dermis in general, it does not result in hemorrhages or severe injuries to the skin. Interest in home care devices has been on a steep rise, especially in the era of the COVID-19 pandemic, and the usefulness and safety of these MN used for cosmetic purposes at home should be evaluated.

Most MNs are being widely used as a modality for transepidermal delivery of cosmeceutical molecules across the skin and almost MNs for subjects' self uses at home are composed of absorbable or soluble needles like hyaluronic acid.[6–10] However, it is well known that needling itself improves skin appearance.[1–5] Therefore, we tried to evaluate the clinical efficacy and safety of the non-absorbable Magnesium MN patch on textural improvement of skin. Under-eye wrinkles, which are the first sign of aging, are the most common complaints of patients, even those in their 20s and 30s. Skin in the under-eye area is thinner than other sites. Therefore, we designed the study to assess the efficacy and safety of Mg MN patches for treating under-eye wrinkles.

2 | MATERIALS AND METHODS

2.1 | Subjects

This study was a prospective study approved by the Institutional Review Board (IRB) of Samsung Medical Center (IRB approval no. SMC 2020-12-020). Informed consent was voluntarily and appropriately obtained from the subjects.

The inclusion criteria for subjects were individuals aged between 20 and 59 years with more than grade 1.5 of under-eye wrinkles as evaluated by clinicians. Subjects were excluded if they had a history of botulinum toxin injection, any kind of laser treatment, or radiofrequency and ultrasound therapy 6 months before enrollment. Also excluded were patients with a history of hyaluronic filler injection 1 year before the study period or those currently pregnant or lactating.

2.2 | Microneedle patch

The MN patch applied on the under-eye area consisted of an adhesive hydrocolloid pad and Mg needles with a needle length of 0.23 mm. The size of the patch was 55.44 × 23.58 mm with a height of 0.37 mm (Figure 1).

2.3 | Grading of under-eye wrinkles

For evaluation of under-eye wrinkles, a modified photonumeric grading scale was developed (Figure 2), as there was no established wrinkle grading scale specific to the under-eye area. Based on the numbers of fine, moderate, and deep wrinkles, the scale ranged from 0 to 4 (0: no wrinkles, 4: numerous distinct fine and moderate wrinkles with numerous deep wrinkles).

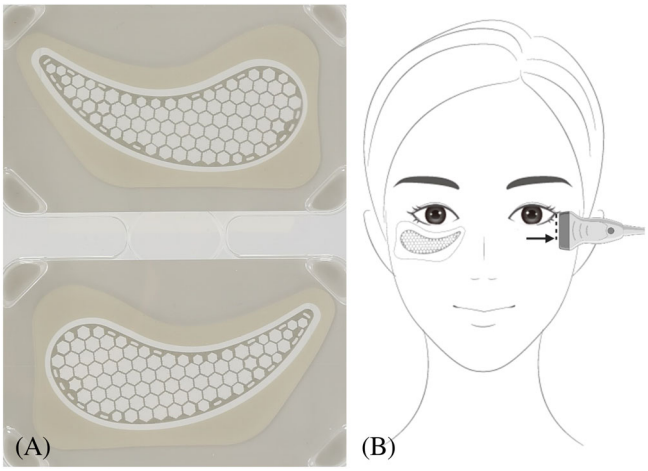

FIGURE 1 (A) An image of a microneedle patch. (B) The patch application on the under-eye area. The locations of the measurement site of the dermal thickness using ultrasonography are shown (indicated by black arrow, 2 cm below the lateral canthus of both eyes)

2.4 | Study design

The subjects were instructed to apply a Mg MN patch for 1–2 h on the under-eye area every other night for 12 weeks. Those who experienced mild discomfort or irritation were instructed to apply the patch for 1 h. The subjects visited the clinic at weeks 0 (baseline), 2, 4, 8, and 12.

At every visit, a medical photograph was collected, and the wrinkles of the under-eye area were evaluated by two independent blinded dermatologists based on the wrinkle grading scale using photographs. The wrinkle indices of the under-eye area were evaluated with a facial analyzer (Mark-Vu®; PSI PLUS, Deajeon, Korea) at weeks 0, 4, 8, and 12 of the study. The dermal thickness of the under-eye area was measured with ultrasonography (HS40®; Samsung Medison, Seoul, Korea) at weeks 0 and 12. The points measured by ultrasonography were along the line, 2 cm below the lateral canthus of the eye (Figure 1).

Subjects were advised to use their usual cosmetics and not to change any cosmetics during the study period. Any discomfort or adverse events were reported by subjects during the study period.

2.5 | Statistical analysis

The Wilcoxon signed rank test was used to compare the wrinkle grades, the wrinkle index measured by the facial analyzer, and the dermal thickness measured by ultrasonography between time points. The generalized estimating equation model was used to estimate the effects of sex and age on each measurement. Statistical significance was defined as p-value < 0.05, and all statistical analyses were carried out using SAS version 9.4 (SAS Institute, Cary, NC, USA). All statistical analyses were conducted by two biostatistics specialists (SW Kim and JS Shim).

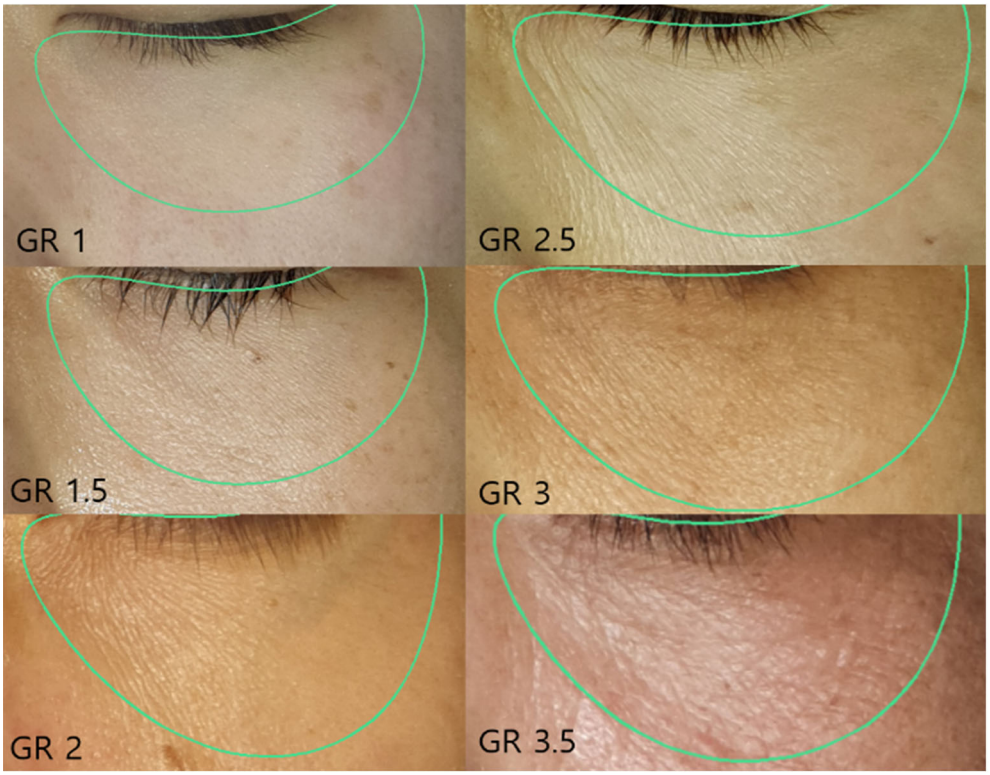

FIGURE 2 The grading scale of under-eye wrinkles was developed for the evaluation of under-eye wrinkles. Grade 1 (GR 1): a few distinct, fine wrinkles; Grade 1.5 (GR 1.5): a few distinct, fine wrinkles with one or two moderate wrinkles; Grade 2 (GR 2): numerous distinct, fine wrinkles with a deep wrinkle confined to the medial side; Grade 2.5 (GR 2.5): numerous distinct, fine wrinkles with a few moderate wrinkles; Grade 3 (GR 3): numerous distinct, fine wrinkles with a deep wrinkle on both medial and lateral sides and/or indistinct bag under eyes; Grade 3.5 (GR 3.5): numerous distinct, fine wrinkles with three or four deep wrinkles and/or distinct bags under eyes. Grade 0 (no wrinkles) and Grade 4 (numerous distinct, fine, and moderate wrinkles with numerous deep wrinkles) are not shown in the picture

3 | RESULTS

3.1 | Demographics

Twenty subjects who visited the participating center from February 2021 to March 2021 were enrolled, and 19 subjects completed the study. One subject was excluded from the study due to loss of follow-up. None of the subjects had any contraindications for application of the Mg MN patch. Nineteen subjects with a mean age of 41 years (range: 27–58 years) were included in the study; five were male and 14 were female.

3.2 | Grading of the under-eye wrinkle area

Nineteen subjects completed the follow-up period and showed favorable improvement of wrinkles in the under-eye area (Figure 3). The mean grade of the 19 subjects was 2.079 ± 0.534 at week 0, 2.000 ± 0.553 at week 2, 2.000 ± 0.471 at week 4, 1.833 ± 0.542 at week 8, and 2.026 ± 0.565 at week 12 (Table 1). The mean grade showed a gradual decrease, with statistically significant improvement at week 8 ($p = 0.008$) (Figure 4).

3.3 | The wrinkle index measured by the facial analyzer

The mean wrinkle index measured by the facial analyzer was 28.632 ± 3.303% at week 0, 27.895 ± 2.767% at week 4, 27.895 ± 2.998% at week 8, and 27.421 ± 2.546% at week 12 on the right under-eye area, which showed a gradual decrease (Figure 5 and Table 2). The mean wrinkle index on the left under-eye area also showed a gradual reduction (28.053 ± 3.793% at week 0, 27.579 ± 3.656% at week 4, 27.79 ± 3.457% at week 8, and 26.947 ± 2.99% at week 12). At week 12, the improvement of wrinkle index from baseline at week 0 was statistically significant on the right under-eye area ($p = 0.019$).

3.4 | Dermal thickness measured by ultrasonography

The mean dermal thickness measured by ultrasonography was 0.143 ± 0.028 mm at week 0 and 0.146 ± 0.026 mm at week 12 on the right under-eye area and 0.143 ± 0.027 mm at week 0 and 0.153 ± 0.028 mm at week 12 on the left under-eye area. A tendency for an increase in dermal thickness of both sides was demonstrated (Figure 6 and Figure 7), but no statistically significant changes were noted.

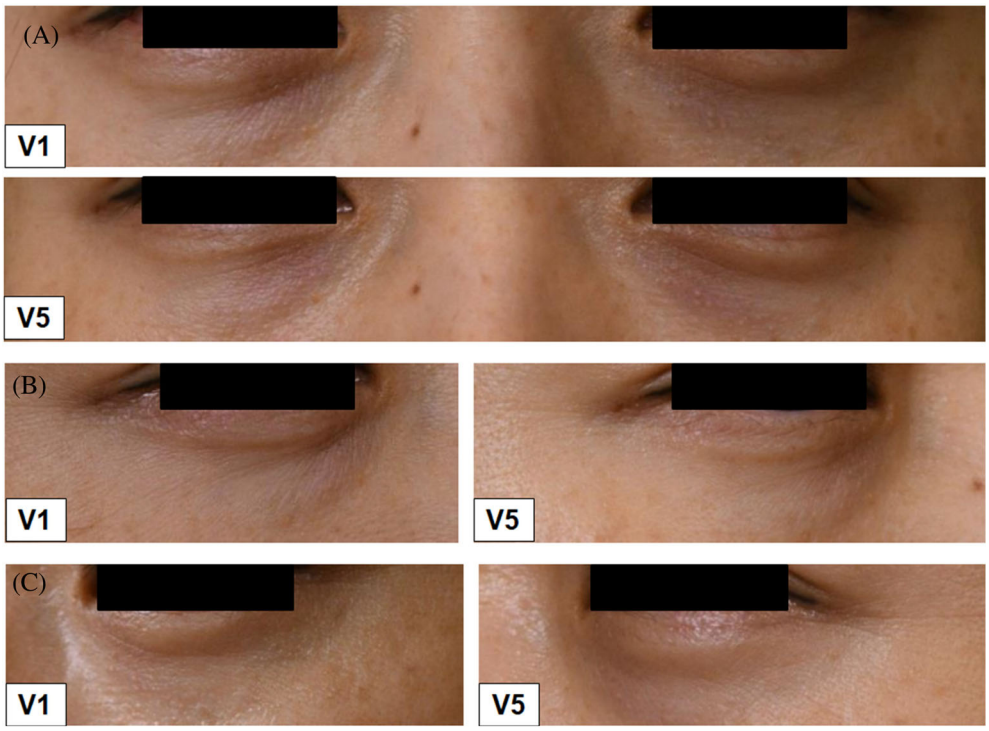

FIGURE 3 Photographs of a representative subject with under-eye wrinkles showing clinically favorable improvement. (A) Frontal view at V1 (week 0) and at week V5 (week 12), (B) right oblique view at V1 and V5, and (C) left oblique view at V1 and V5

TABLE 1 The mean grading scale of under-eye wrinkles from week 0 (V1) to week 12 (V5) after the application of MN patch

Variable		
Grading scale	**Mean ± SD**	***p****
Week 0	2.079 ± 0.534	
Week 2	2.000 ± 0.553	0.233
Week 4	2.000 ± 0.471	0.233
Week 8	1.833 ± 0.542	0.008
Week 12	2.026 ± 0.565	0.346

Wilcoxon signed-rank test was used to assess statistical significance.
Abbreviation: SD, standard deviation.
*Compared to week 0.

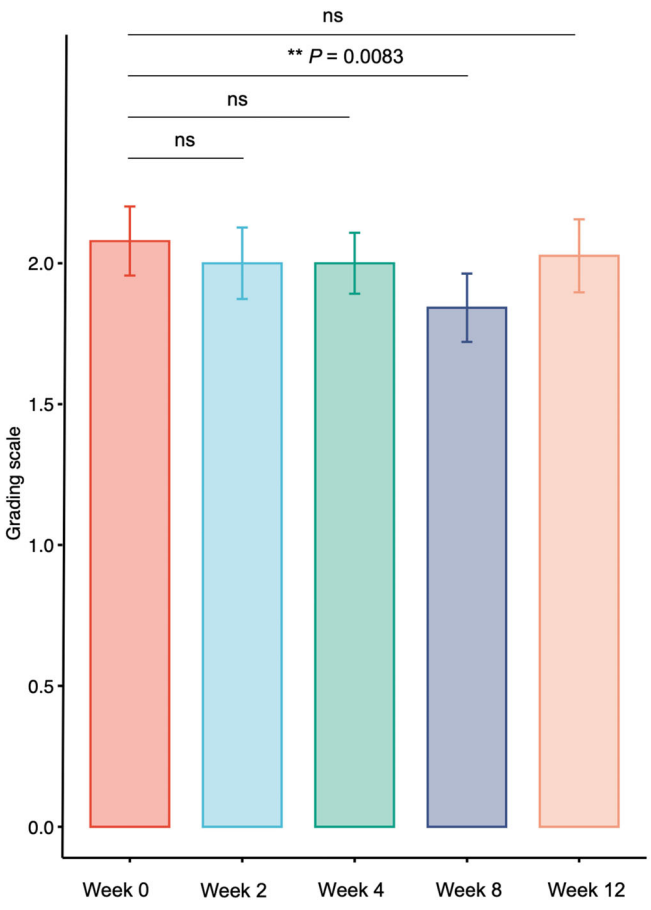

FIGURE 4 The mean grading scale of under-eye wrinkles from week 0 (V1) to week 12 (V5) after application of MN patch. **$p < 0.01$, statistically significant compared with week 0

3.5 | Adverse effects and events

No serious adverse events including edema, bleeding, or dyspigmentation on the skin were reported by or observed in any subjects throughout the study period. One subject complained of mild irritation after applying MN patches after 6 weeks. The discomfort disappeared after the subject was instructed to shorten the application time to an hour.

4 | DISCUSSION

In the present study, the efficacy and safety of Mg MN patches on under-eye wrinkles were assessed. Overall, the grading scale of under-eye wrinkles evaluated by clinicians, the wrinkle index

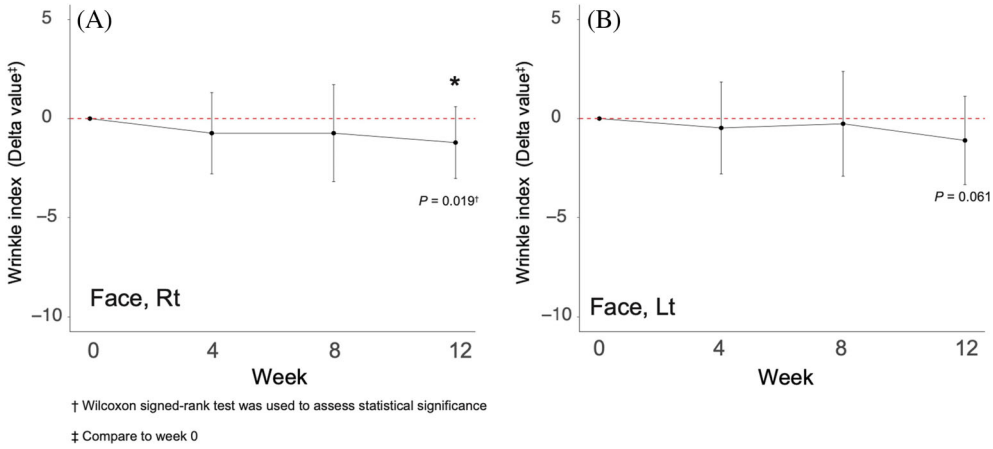

FIGURE 5 The mean change of wrinkle index by facial analyzer (Mark-Vu®) (A) right and (B) left under-eye area from week 0 (V1) to week 12 (V5). *$p < 0.05$, statistically significant compared with week 0

TABLE 2 The changes in wrinkle index by facial analyzer (Mark-Vu®)

	Rt		Lt	
Variable	Mean ± SD	p*	**Mean ± SD**	p*
Week 0	28.632 ± 3.303		28.053 ± 3.793	
Week 4	27.895 ± 2.767	0.136	27.579 ± 3.656	0.358
Week 8	27.895 ± 2.998	0.218	27.79 ± 3.457	0.544
Week 12	27.421 ± 2.546	0.019	26.947 ± 2.99	0.061

Wilcoxon signed-rank test was used to assess statistical significance.
Abbreviation: SD, standard deviation.
*p Compared to week 0.

measured by the facial analyzer, and the dermal thickness assessed by ultrasonography showed a tendency to improve. Wrinkle grading was initially conducted on each side of under-eye area, which did not show much difference. Therefore, it was used for the whole area evaluation. Based on the wrinkle grading, substantial improvement after 8 weeks of application was observed. Objective analysis of the wrinkle index using a facial analyzer demonstrated significant improvement at week 12 on the right under-eye area. Although no statistically significant improvement was found on the left under-eye area, the winkle index on the left side also showed gradual tendency for improvement. Dermal thickness failed to show a statistically significant increase based on ultrasonography measurement. However, it showed a tendency for improvement at the 12-week follow-up. Wrinkle grades cannot be as detailed as a wrinkle index, which was calculated as the area of wrinkles to the whole area of the lower eye area, considering the weighted value of wrinkle depth. Therefore, there can be a discrepancy between wrinkle grade and wrinkle index assessed by a facial analyzer. Evaluation by clinicians using a wrinkle grading system reflects general evaluation, while a wrinkle index can indicate the fine distinction of wrinkles in terms of length and depth. Therefore, objective analysis should be accompanied by clinical grading for a better evaluation. Collectively, the overall study result showed some improvement in wrinkles after using Mg MN patches every other night for 12 weeks.

There are several reports about the effect of MN patch on wrinkles. Ha et al. reported the effect of micro-spicule-containing epidermal growth factor for treatment of periocular wrinkles.[6] After applying it for 8 weeks, the subjects showed marked clinical improvement of periocular wrinkles and statistically significant increase in dermal depth and density compared to the EGF alone group. Similarly, treatment with a hyaluronic-acid-containing MN patch showed clinical improvement of crow's feet wrinkles and increased skin elasticity after 8 weeks of treatment.[7] An additional study of hyaluronic-acid-containing MN patches combined with acetyl hexapeptide-8 and epidermal growth factor showed significant improvements in periorbital and nasolabial fold wrinkles compared to the hyaluronic acid patch alone group after 1 month of treatment.[8] A case of a combination of an MN patch with topical agents has also been documented. Hong et al. reported clinical improvement after a combination treatment of wrinkle cream containing adenosine and an MN patch on crow's feet and nasolabial fold wrinkles.[9] Likewise, sequential application of an adenosine-loaded MN patch and topical adenosine-loaded cream on crow's feet wrinkles showed improvement in wrinkle depth, dermal density, elasticity, and hydration.[10] Most previous studies regarding the effect of MN patches were focused on the wrinkles especially on the crowfeet areas and the nasolabial folds with a combination of cosmeceutical molecules.[6–10] All previous study used soluble and absorbable MN mainly made of hyaluronic acid.[6–10] The present study focused on the effect of the non-absorbable Mg MN patch itself on under-eye wrinkles. To the best of our knowledge, this is the first report on the safety and efficacy of non-absorbable MN patches on wrinkles for 12-week usage as a home device.

Skin microneedling is a relatively minimally invasive procedure involving superficial and controlled puncture of the skin. As a medical device, the standard medical derma roller with multiple microneedles is composed of stainless steel, usually 0.5–3.0 mm in length and 0.1–0.25 mm in diameter.[11] The microneedle itself can reach down into the mid-dermis, and bleeding after application of MN is a common result that initiates the wound healing process. Considering the thickness of the epidermis, Mg MN patches with a needle length of 0.23 mm do not induce bleeding or serious wounds when applied at

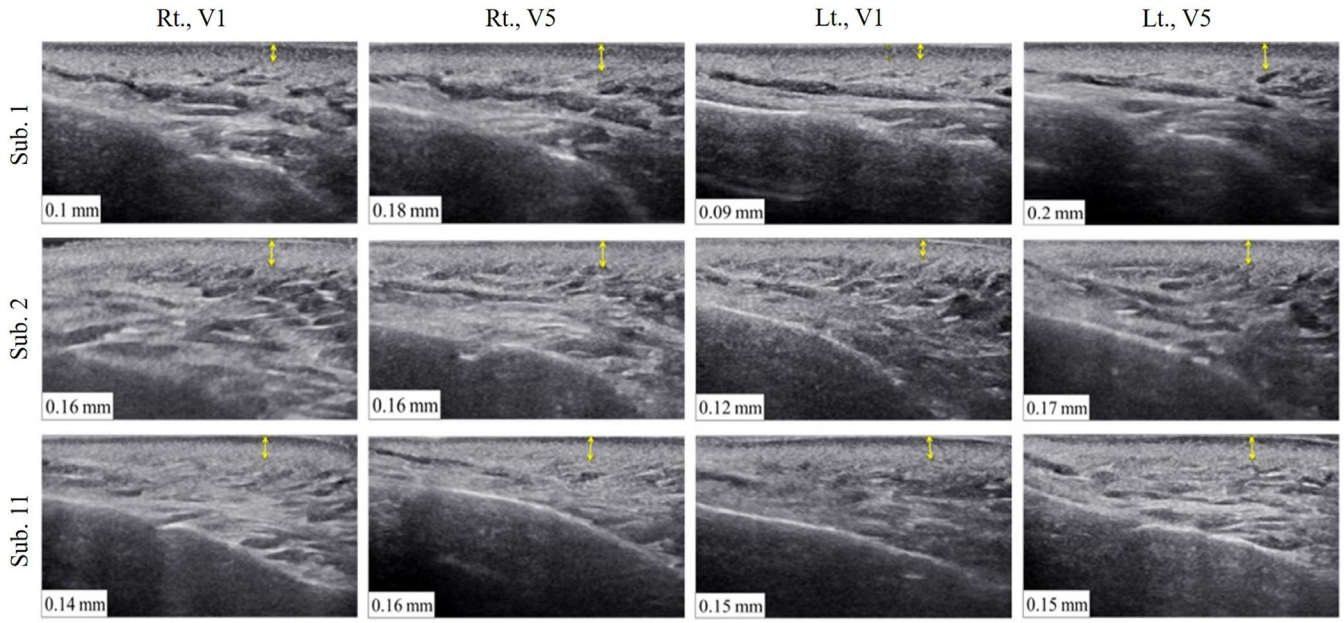

FIGURE 6 The ultrasound images of the representative subjects at V1 (week 0) and V5 (week 12)

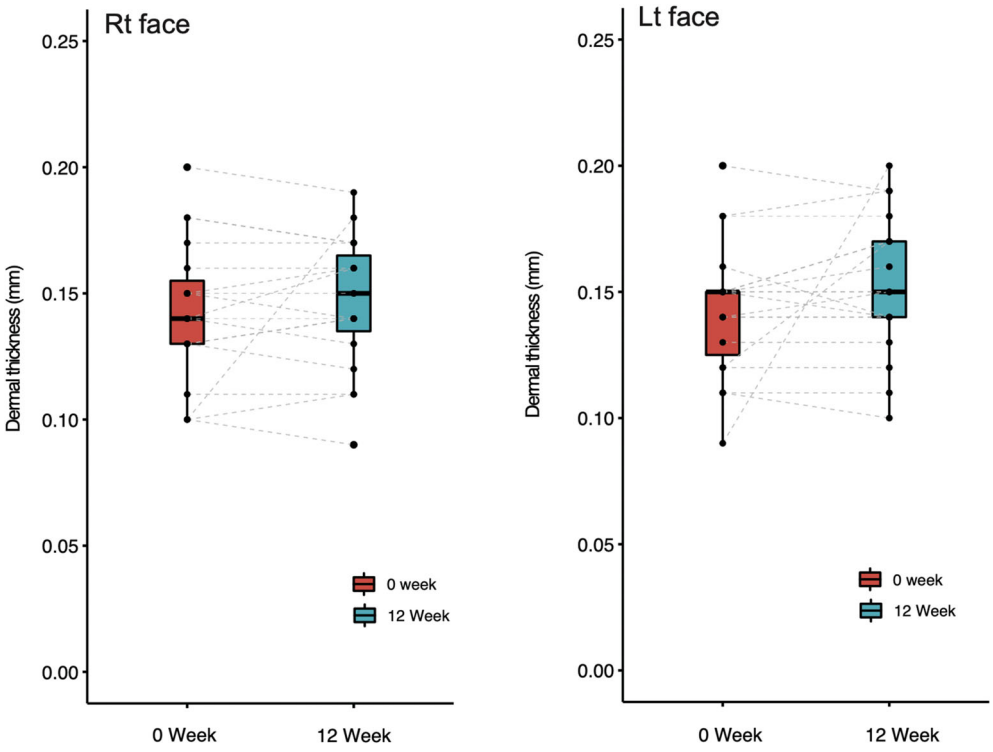

FIGURE 7 The comparison of mean dermal thickness of the right and left under-eye areas at week 0 (V1) and week 12 (V5)

home. However, the treatment can induce microinjuries in the stratum corneum and keratinocytes, which stimulate inflammatory responses from keratinocytes, resulting in stimulation of dermal fibroblasts. Previous research focused on change of the transepithelial potential produced by MN in addition to multiple injuries in the skin that stimulate the wound healing process.[12] Improvement of wrinkles can be expected after MN use in that MN induces microinjuries in the skin, which can initiate an inflammation cascade for the wound healing process, and MN might have other beneficial effects on ionic changes in the epidermis. Another report demonstrated that a medical-grade MN made of stainless-steel changed the electrolyte environment of the intercellular space when it entered the SC.[13]

Various materials including metal, silicon, and polymer are used to create MN patches.[1,3,5] In this study, the MN patch was composed of magnesium metal, which is well known to play a beneficial role in the skin.[14–16] The magnesium ion plays a role in increasing skin hydration,

barrier function, and facilitating skin proliferation and epidermal differentiation to reduce inflammatory responses. Previous studies also showed that an increase of magnesium ion in the stratum corneum and epidermis stimulated the proliferation of keratinocytes.[17,18] There also have been several reports of topical agents including magnesium ion regarding favorable effects on different types of dermatitis including diaper dermatitis, contact dermatitis, and atopic dermatitis.[15,19,20] On the basis of previous studies,[14–20] we speculated that Mg MN patch might provide additional clinical benefit over the conventional stainless-steel needling of the same length. However, the potential role of Mg in Mg MN patches in the improvement of wrinkles is needed to be defined in the following functional studies. Considering that we did not combine any active molecules with MN patches, and the needle size was not long enough to reach the dermis, beneficial effects of MN patches can be augmented when combined with topical agents.

This study had several limitations. The small number of subjects and the 12-week study period might have affected the results. The MN patches used in the study were developed as a home care device. Therefore, application for longer times in a larger number of subjects might show considerable improvement of wrinkles in thin skin areas. The needle size of the MN patches used in this study was only 0.23 mm. As one of the suggested mechanisms of MN patches is to damage the epidermis and induce microinjury to set up a wound healing cascade, other possible mechanisms of neovascularization and neocollagenesis that take place in the dermis might not be initiated with shorter needles.[4] Further studies of MN patches with various needle sizes, especially long enough to reach the dermis, might show a better effect on wrinkles.

In conclusion, Mg MN patches with needles 0.23 mm in length can be safely used for improvement of wrinkles in thin skin areas such as under-eye sites at home. Further studies including a split-face study with a greater number of subjects are required.

AUTHOR CONTRIBUTIONS

Jong Hee Lee was a principal investigator and conceived the experimental design of the study. Donghwi Jang and Joonho Shim served as the first author and participated in data analysis and drafting of the manuscript. Dong Min Shin and Hyungrye Noh analyzed and interpreted the results. Se Jin Oh and Ji-Hye Park participated in the analysis. Jong Hee Lee, Donghwi Jang and Joonho Shim wrote the final manuscript. All authors performed the research experiments and reviewed and approved the final manuscript.

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CONFLICT OF INTEREST

We have no conflict of interest except national funding by the Ministry of Trade, Industry, & Energy (MOTIE, Korea).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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