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A Split-Face Comparison of Novel Microneedle Patch versus Botulinum Toxin-A and Microneedle Patch for Improvement in Undereye Skin Texture

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Abstract: (1) Background: The emergence of microneedle patch technology and its development as a transdermal drug delivery platform have shown proven results in improving skin texture and appearance. This study was conducted to determine the efficacy of the microneedle patch (MNP)-only cosmesis of undereye skin texture and wrinkles against patch cosmesis with diluted botulinum toxin-A. (2) Methods: A total of 23 Thai females volunteered for this prospective clinical trial. Each participant was treated according to a split-face design, with the application of diluted botulinum toxin-A through MNP technology to the right undereye and a normal saline MNP application to the left undereye. Test areas were recorded at baseline and 2, 4, 8, 12, and 16 weeks after the initial treatment. (3) Results: Botulinum toxin-A was successfully delivered to the skin by MNP technology. After the initial treatment, these novel transdermal drug delivery patches significantly improved infraorbital hollowness at week 8 and wrinkles at week 16. In addition, the skin surface was markedly enhanced, with no adverse effects observed during the trial. (4) Conclusions: Novel MNPs are an effective and safe technology for use in the management of undereye skin aging. Combination treatment with botulinum toxin-A-impregnated devices gave a higher patient satisfaction than MNPs alone.

Keywords: microneedle patch; transdermal drug delivery; wrinkle; botulinum toxin

1. Introduction

The stratum corneum of human skin serves as its predominant barrier, an outer skin layer permitting only low penetration of topical drugs. Little more than 10–20% of active drugs delivered topically in cream permeates this external barrier [1,2]. Innovative microneedle patch (MNP) technology has recently been introduced as an attractive mechanism for transdermal drug delivery through its creation of microscopic punctures to the skin. In this respect, the efficacy of MNPs reflects this increased potential for delivering active drug molecules directly to the epidermis or dermis with minimal injury to the skin, a distinct advantage in the field of medicine and particularly for needle-phobic patients [3].

The mechanism action of the MNP to trigger the collagen deposition has two main actions: wound healing and demarcation current. In the wound healing process, the tiny, traumatized needle prick sites induce the release of growth factors, including vascular endothelial growth factor, transforming growth factor-alpha (TGF-a), TGF-beta (TGF-b), and platelet-derived growth factor (PDGF), which resulted in the production of intercellular matrix proteins. Then, under the influences of growth factors and immune skin cells,

such as monocytes, keratinocytes, and fibroblasts, which migrated and proliferated, the fibronectin matrix was formed, stimulating more collagen production. Lastly, new type III collagen is replaced by elastic collagen I from the depth of where the needle punctures upwards to the basal membrane. Additionally, microneedling imparts a demarcation current of transepithelial potential (PET), which is generally between 10 and 60 mV/mm. The electrical current varies from each part of the body, so when the microneedle induces an injury through the stratum corneum, the asymmetrical distribution of potassium sodium pumps in the lower and upper section of the epidermis, creating the electric current range of 100–200 mV/mm towards the wound. This electromagnetic current aids in facilitating the wound-healing process and stimulating, at the DNA level, the expression of protein for wound healing [3–5].

Botulinum toxin-A (BTX-A) is an extensive therapeutic used in medical and cosmetic treatment. BTX-A works by inhibiting the release of acetylcholine, a neurotransmitter. Regarding transdermal drug delivery, the fabricated MN with BTX-A has demonstrated that BTX-A has successfully penetrated the thick layer of the skin and delivered the components after thirty minutes of insertion for the treatment of palmer hyperhidrosis [6,7]. Potentially representing a novel therapeutic approach, there was no study conducted on combining BTX-A with MNPs.

For this present study, we prepared MNPs made of the polymer component poly-methyl methacrylate (PPMA). Studies suggested that microneedle arrays of PPMA polymer are the safest, most durable, and biodegradable [8]. PMMA is a synthetic polymer that has high strength and low toxicity, making it biocompatible with human skin [8].

A randomized controlled study incorporating a split-face design method was used to evaluate the effectiveness of the microneedle needle patch (MNP) alone compared with that of the botulinum toxin-A (BTX-A)-impregnated MNP to improve undereye skin texture.

2. Materials and Methods

2.1. Subjects

Twenty-five healthy women aged ≥ 40 years were recruited, and this study was conducted at Benjakitti Park Hospital, Bangkok, Thailand. The Institutional Review Board of the Human Research Ethics Committee of Thammasat University approved all study protocols (COA: 181/2022, approval date: 29 August 2022). All volunteers provided written informed consent after a full explanation of the risks and benefits of their involvement in our study. Patients' consent was also obtained prior to the use of the images for medical purposes. Based on the Scientific Assessment Scale of Skin Quality (SASSQ) [9] and Merz infraorbital hollow rating scale [10], all participants presented moderate to severe skin texture. Volunteers were excluded from participation in this study based on the following: a history of filler use within 1 year of study enrollment; the use of botulinum toxin injection in the previous 6 months; the use of laser therapy in the previous 6 months; a history of light or radiofrequency use to the face; or the use of chemical peel within 3 months of study recruitment. Volunteers with existing infectious skin disease or eczematous dermatitis, those taking immunosuppressive therapy, women with hypersensitivity or allergy to cosmetics, those using a topical anti-wrinkle regimen for at least 3 months prior to recruitment, and pregnant or lactating women were also excluded from participating in this study.

2.2. Study Design

This study was designed as a randomized controlled trial, incorporating a split-face method for comparison.

For the conduct of primary irritation testing, an inquiry into individual participants' history of allergy to PMMA was made before the application of the MNPs.

Participants were asked to clean and dry their faces entirely before applying the MNPs to both undereye regions for five minutes. Through the MNP, normal saline will be pushed directly into the MNP on the left side to act as the control and the diluted BTX-A on the

right side as the treatment side. During the applications, participants were required to massage over the patches. All participants received a single application and were followed up at 2, 4, 8, 12, and 16 weeks.

2.3. Intervention

BTX-A was purchased from Allergan (Irvine, CA, USA). The MNP combined with botulinum toxin was applied to the right undereye skin surface, while the MNP with normal saline was applied to the left undereye surface. For the treatment side, 4 units of BTX-A were diluted in 0.5 ccs of normal saline.

The MNP for this study was fabricated by the Nanoneedle Research Team, Responsive Material and Nanosensor Research Group, National Nanotechnology Center (NAN-OTEC), Thailand. MNP construction conformed to the European Committee specifications. These MNPs were manufactured at the NANOTEC cleanroom under invention patent No. TH2001004302 under ISO 13485 [11] medical equipment quality control systems. The needles were manufactured from synthetic polymer, which is polymethylmethacrylate (PMMA), and the monomer plastic used in patch production was acquired pursuant to standards of the European Medical Equipment Annex IX, Rule 5 (FDA Class I, IIA, IIB). Such standards ensure that the production process is free of contamination and that the part of the microneedle that penetrates through the skin remains sterile.

Each microneedle array was fabricated upon the fabric substrate by a photopolymerization technique. The fabric substrate with supporting plastic film at the back was placed in a resin bath with the front side down to contact the resin. The array of four-pointed star-shaped windows was engraved on a metal-coated glass mask to be used as a photomask, which was placed and aligned on the back side of the substrate. The UV light has thus been exposed through the patterned window to cure the resin and form a microneedle array on the fabric substrate. The microneedle with the substrate was taken out of the resin bath, and the plastic film was then peeled away from the fabric substrate. The microneedle array on fabric was cleaned by alcohol and DI water. Each microneedle was designed in a four-pointed star shape, as shown in Figure 1a. The four-pointed star structure of each microneedle, shown in Figure 1b, has a fin along each side of the microneedle shaft corresponding to the pattern of each window on the photomask. After the drying process, it was cut into the shape of a microneedle patch to be used in the assembly step with the other components as schematically shown in Figure 1c.

The average microneedle height (h) and base diameter (w) were 750 μm and 280 μm , respectively. Microneedle tips were situated at a distance (d) of 905 μm apart. The Microneedle array density used was 265 needles/ cm^2 . The physical properties of microneedles were characterized to evaluate the performance of the microneedle patch. The surface area of the microneedle patch in the area of 1 cm^2 is simplified and calculated from the dimension obtained by the microscopy technique and is, therefore, approximately 74,890 μm^2 . The microneedle patch evaluated the penetration performance using the polymeric film test [12]. The microneedle patch was set upside down on the top of the stack of polyurethane film used as a skin simulant. A force of 30 N was applied on the back of the microneedle patch for 60 s to insert the microneedles into the polymeric films. The number of films was checked for holes or traces from the insertion. More than 95% of the number of microneedles on the testing patch can be inserted into the 4th layer from the top of a stack of polymeric films, as shown in Figure 1d. The overall thickness of four layers of polymeric films that were obtained from the microneedle insertion is about 520 μm . Therefore, it could be evaluated that the penetration depth of a microneedle is approximately 70% of its height.

The shape of the MNP was designed to cover the undereye area, and the total area of the microneedle array patch was 5.4 cm^2 . The mechanism for delivery of active ingredients from the microneedle array patch to skin is shown in Figure 2a. When the four-point star-shaped microneedle was punctured into the skin, each fin of the microneedles could form a microchannel between the microneedle grooves and surrounding tissue because of

the skin deformation. These formed microchannels or gaps play a role as the temporary follicle channels, which are the increased delivery paths for active ingredients. Due to the skin elasticity, these channels disappeared after the MNP was taken out of the skin surface for a short while. The MNP was applied to the undereye area of each side of the face, as shown in Figure 2b. A reservoir attached to the patch could be connected to a syringe, as per the schematic structure in Figure 2c, to inject solution into the fabric. The drug solution became absorbed and flowed through the substrate and along the microchannel formed between the microneedle and surrounding tissue, before draining under the external layer of the skin.

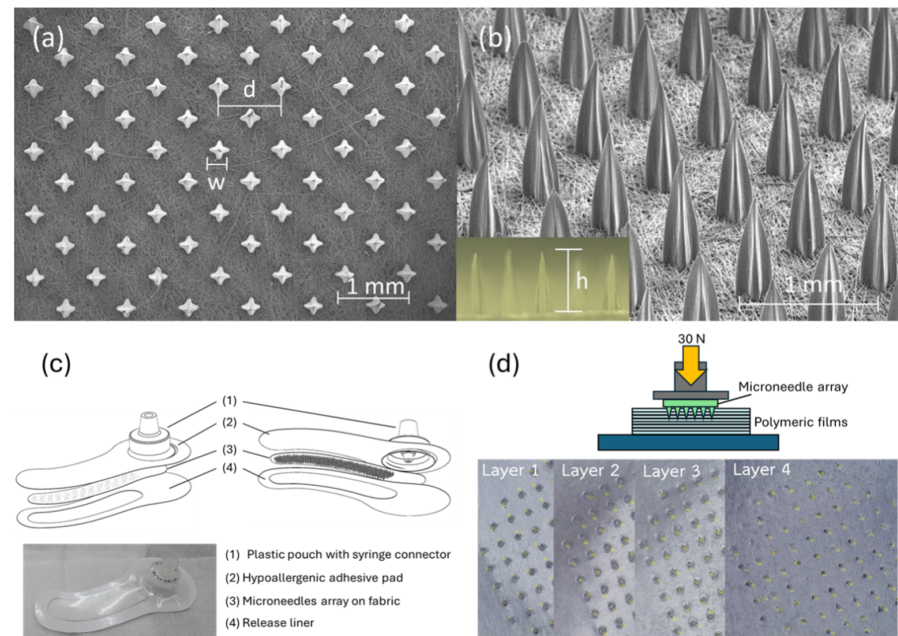


Figure 1. (a) Top view and (b) side view of the scanning electron microscope images of the four-point star-shaped microneedle array situated on the fabric substrate. (Inset) An optical image showing the height of the microneedle array. (c) Schematic structure and components of the microneedle array patch. (d) The setup for microneedle penetration depth evaluation with polymeric films and the optical images of a polymeric film in each layer after microneedle array insertion.

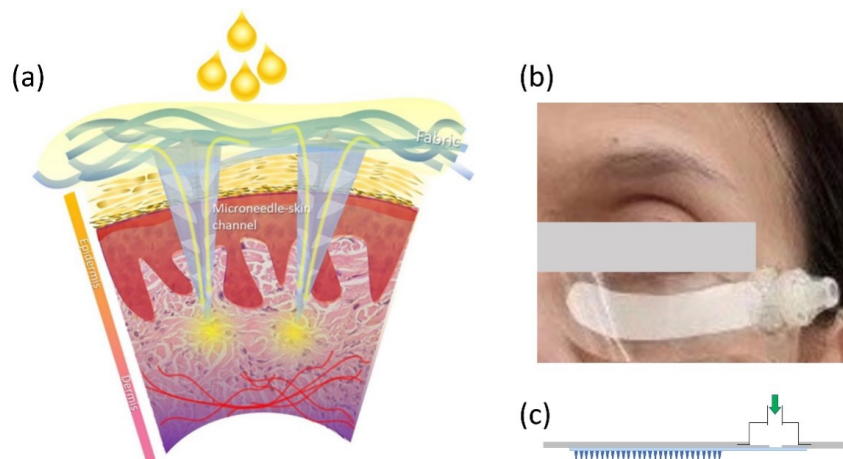


Figure 2. (a) The active ingredient or solution delivery mechanism of the four-point star-shaped microneedle array fabricated on the fabric substrate. (b) The microneedle patch was applied to each undereye area. (c) The solution was pushed through the syringe connected with the reservoir of the microneedle patch identified by the arrow in the schematic structure of the microneedle patch that was used in this clinical study.

Biocompatibility studies of microneedle material have been performed on three main topics of cytotoxicity, skin irritation, and skin sensitization, according to ISO 10993-5:2009 [13], ISO 10993-23:2021 [14], and OECD Test No. 442E, respectively. These studies have been performed by the Toxicology and Bio Evaluation Service Center (TBES), National Science and Technology Development Agency (NSTDA), Thailand. The extraction of the microneedle patch sample was found to be non-cytotoxic since the highest concentration of the extraction resulted in cell viability over 70%. The in vitro skin irritation test is classified as non-irritant, and the in vitro skin sensitization test of the extraction of the microneedle sample was negative, according to the relevant standard and criteria. The results have been approved in all topics of biocompatibility studies.

2.4. Efficacy and Safety Evaluation

Treatment efficacy was evaluated at baseline and 2, 4, 8, 12, and 16 weeks after the initial applications. Digital photographic images were obtained of all participants' undereye skin regions at 0° a degree angle in the front view. Two dermatologists blinded to the treatment side evaluated the "before" and "after" photographs through the SASSQ skin quality rating scale [9] and Merz infraorbital hollow scale [10]. A grade was reported on an average scale of the two dermatologists.

Patient satisfaction with overall skin improvement was graded 1 week after initial treatment on a scale of 0 to 4, with a score of 0 for very bad; 1 for no improvement; 2 for an improvement of 25–50%; 3 for a 50–75% improvement; and 4 for an improvement of 75–100%.

2.5. Adverse Effects

All adverse events, including skin irritation, redness, swelling, and pain, occurring during the trial period were recorded and evaluated by the same dermatologist for appropriate treatment.

2.6. Statistical Analysis

SPSS version 19.0 (SPSS, Inc., Chicago, IL, USA) was performed for statistical analyses. The data-point significance level was set at a p -value of <0.05 . A generalized linear model and sample t -test were used to compare patient satisfaction scores and clinician evaluation between the right and left undereye regions.

3. Results

3.1. Patients' Enrollment

Among the twenty-five initial participants, two women could not participate in this study because of social restrictions pertaining to the coronavirus disease 2019 pandemic. The average age of the study group of 23 participants was 51.5 years. A total of nine people (39.13%) were in their 40s, twelve people (52.17%) were in their 50s, and two people (8.69%) were in their 60s.

3.2. Efficacy End Points

BTX-A-impregnated MNPs achieved a better outcome than patches alone with respect to the Merz infraorbital hollow resting score, with a statistically significant difference from week 0 observed for each follow-up period (weeks 2, 4, 8, 12, 16; $p < 0.05$). Additionally, MNPs with BTX-A-treated undereye showed gradual improvement at each follow-up week. For the MNP with normal saline, only week 12 and week 16 showed statistical significance. Week 8 showed a significant difference between patches with BTX-A and normal saline (Figure 3).

The SASSQ was only significant with respect to wrinkles. Skin surface roughness slightly improved over the study period, without achieving statistical significance. A higher SASSQ indicated the high severity of each parameter. The wrinkle and skin surface

roughness of the undereye skin significantly decreased on the treatment side in all follow-up weeks (Tables 1 and 2).

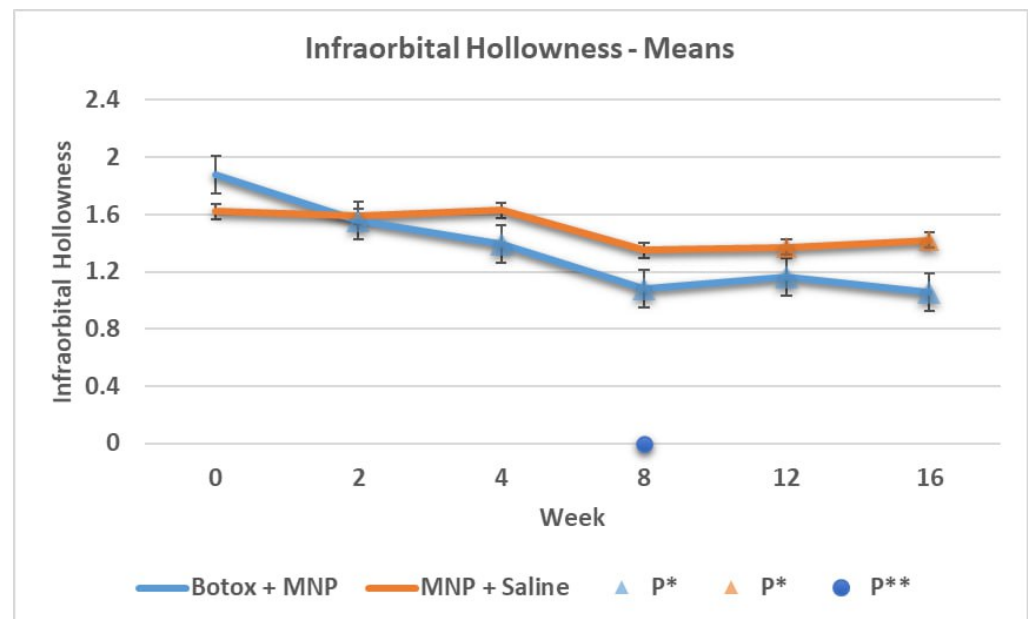


Figure 3. Merz infraorbital hollow resting scale assessed by a dermatologist; P* significant result in the within-subject group (botulinum toxin-A+ MNP, MNP+ saline); P** significant result in the between-subject group.

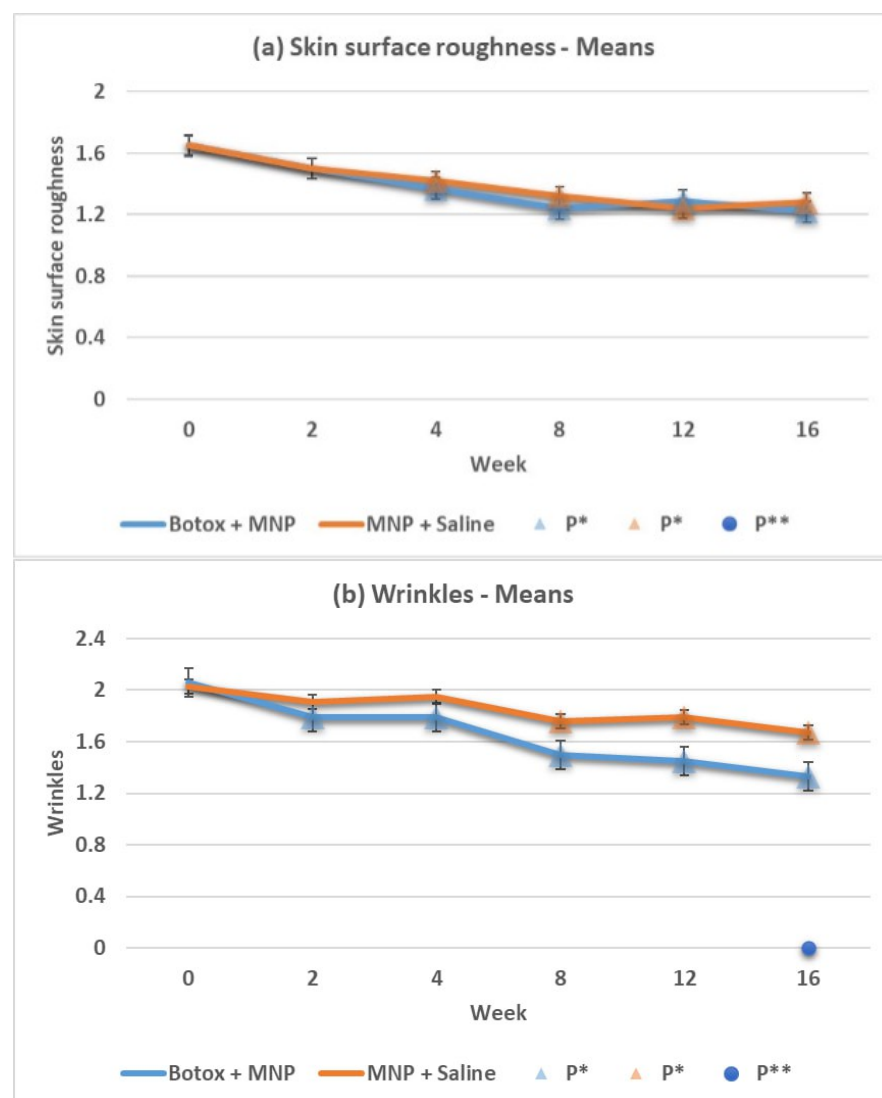
Table 1. Scientific Assessment Scale of Skin Quality (SASSQ) on skin roughness by blinded dermatologists.

Skin Surface Roughness	Indication	Mean SD	p-Value
Week 0 (n = 17)	MNP + BTX-A MNP	1.65 ± 0.058 1.65 ± 0.58	-
Week 2 (n = 19)	MNP + BTX-A MNP	1.5 ± 0.56 1.5 ± 0.56	-
Week 4 (n = 19)	MNP + BTX-A MNP	1.37 ± 0.6 1.42 ± 0.51	-
Week 8 (n = 19)	MNP + BTX-A MNP	1.24 ± 0.59 1.32 ± 0.58	0.331
Week 12 (n = 19)	MNP + BTX-A MNP	1.29 ± 0.48 1.24 ± 0.54	0.331
Week 16 (n = 18)	MNP + BTX-A MNP	1.22 ± 0.43 1.28 ± 0.46	0.163

Upon further evaluation, skin roughness started to decrease gradually from week 4 to week 16 (1.37 ± 0.6 until 1.22 ± 0.43) for the treatment side, while that for the control side with the MNP slightly improved over time. Appreciable data were observed for wrinkle improvement in the treatment from week 4 (1.79 ± 0.9), week 8 (1.5 ± 0.75), week 12 (1.45 ± 0.74), and week 16 (1.33 ± 0.79), respectively. For wrinkle evaluation, only week 16 showed statistical significance between the right and left undereye regions (p -value = 0.008), as shown in Figure 4. The correlation coefficient could not be computed because the standard error of difference was 0.

Table 2. Scientific Assessment Scale of Skin Quality (SASSQ) on wrinkles by blinded dermatologists.

Wrinkles	Indication	Mean SD	<i>p</i> -Value
Week 0 (<i>n</i> = 17)	MNP + BTX-A MNP	2.06 ± 0.81 2.06 ± 0.81	-
Week 2 (<i>n</i> = 19)	MNP + BTX-A MNP	1.79 ± 0.81 1.91 ± 0.78	0.328
Week 4 (<i>n</i> = 19)	MNP + BTX-A MNP	1.79 ± 0.9 1.95 ± 0.93	0.104
Week 8 (<i>n</i> = 19)	MNP + BTX-A MNP	1.5 ± 0.75 1.76 ± 0.86	0.137
Week 12 (<i>n</i> = 19)	MNP + BTX-A MNP	1.45 ± 0.74 1.79 ± 0.84	0.076
Week 16 (<i>n</i> = 18)	MNP + BTX-A MNP	1.33 ± 0.79 1.67 ± 0.92	0.08

**Figure 4.** Scientific Assessment Scale of Skin Quality: (a) skin surface roughness; (b) wrinkles; P* significant result in the within-subject group (botulinum toxin-A+ MNP, MNP+ Saline); P** significant result in the between-subject group.

The patient satisfaction score was higher for the treatment side. Data points showed a statistically significant difference between the treatment and control groups for all follow-up weeks, which means that more visits might lead to higher scores (Figure 5).

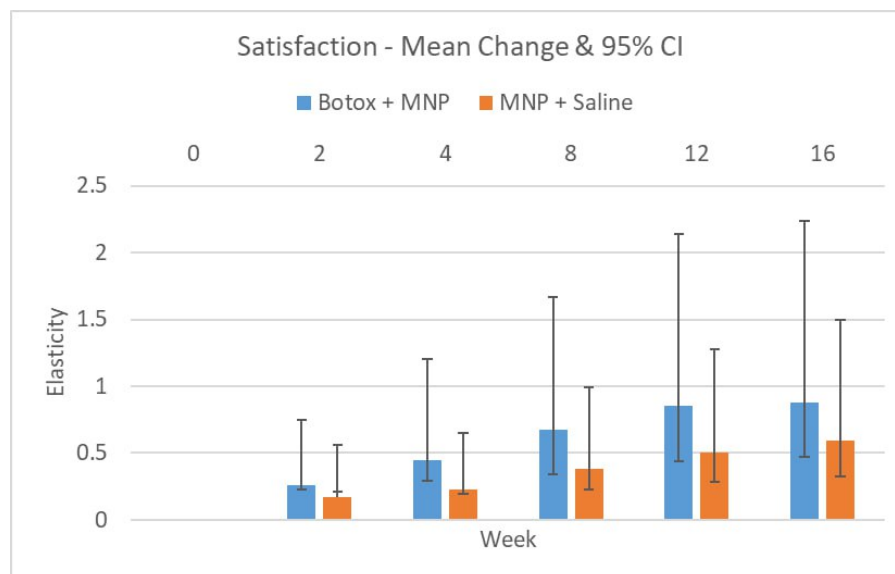


Figure 5. Patients' satisfaction score by mean change.

3.3. Safety End Points

No adverse effects were reported by participants for the control side during this study. A dermatologist's skin examination also revealed no skin abnormalities on the control side after the treatment.

4. Discussion

Research on transdermal drug delivery systems (TTDSs) has recently intensified and continues to develop rapidly with improvements in manufacturing materials. Emerging from microneedling mechanism technology, the MNP is a recent invention that is likely to offer superior performance and a better platform for microinjections. The advantages of MNPs have been demonstrated in various safety and efficacy studies of micron-size needles. A review article in 2020 concluded that the polymer-based MN represented a powerful transdermal drug delivery device for small chemical components [15]. An evidence-based clinical trial study in 2013 by Hiraishi et al. on therapeutic research confirmed using all-trans retinoic acid loaded in polymer MNPs in mice for seborrheic keratosis had a higher delivery rate and induced epidermal hyperplasia in epidermal thickness and keratocyte numbers [16,17]. Other approaches in cosmetic dermatology have been attempted for anti-wrinkle treatment. A 2014 study by Kim et al. concluded that MNP-loaded compounds could be successfully released into the skin and could safely reduce skin wrinkling using acid-loaded retinoic, and ascorbic acid-loaded MNPs demonstrated a greater penetration rate and had a concentration of retinyl retinoate and ascorbic acid of 32 and 33% *w/w*, and the proper concentration ranges were <35% *w/w* and 0–60% *w/w*, respectively [18]. Research by Choi et al. on hyaluronic acid microneedle patching to reduce crow's feet showed that MNP delivery offers excellent permeability compared to the formula itself. A reduction in wrinkle and skin elasticity improved, and no adverse effects were found [19]. In 2019, Hong et al. reported how the use of active ingredient application for microneedle patching could reduce wrinkles and improve skin rejuvenation [20]. Research has been conducted on MNPs in combination with varied drugs (retinoic acid, fillers, vitamin C) to improve skin texture and wrinkling; however, to date, there have been no clinical studies on the use of MNPs and BTX-A for undereye skin treatment.

The current study showed the impact of microneedle patching on the SASSQ infraorbital hollow resting score at weeks 12 and 16 after treatment. The improvement of skin surface roughness and wrinkling was noticeably better between weeks 8 and 16. The difference can be explained by the mechanism of action of microneedle patching. The dramatic result from microneedling was clearly visible over the ensuing 3 to 4 weeks. A skin response lasting 3 to 5 months begins with skin micro-wound healing that remains visible until four to 6 weeks, with cellular turnover and skin rejuvenation starting to improve gradually.

The combination of MNPs with four units of diluted BTX-A markedly progressed. In this study, double dilution was performed to reconstitute botulinum toxin [21], and patches were targeted intradermally into the infraorbital skin. The dermal lifting effect of BTX might increase collagen and fibroblast stimulation. We effectively achieved a significant result within a shorter period of time for the treatment side compared to that for the control group. Treatment enhanced a greater improvement of the wrinkles in the Merz infraorbital hollow at rest score and SASSQ. These results prove that the MNP has the potential for transdermal drug delivery. Promising results for BTX-A were maximally effective at between 2 and 4 weeks, continuing for about 2 to 3 months.

Microneedle patching for undereye skin treatment alone provides a good cosmetic outcome for skin texture, albeit with a less satisfactory score. Nevertheless, the application of BTX-A and MNPs significantly improved undereye skin condition compared to microneedle patching alone at the 2-month follow-up. Meanwhile, participant satisfaction ratings were higher for the treatment group. Both face sides differed significantly at week 8 for infraorbital hollowness. An observable difference in skin wrinkling was noted at week 16, but no difference in skin surface roughness was observed between the MNP with BTX-A and the MNP. Evidently, the maximal effect of microneedle patching could be obscured between weeks 8 and 16.

For both the treatment and control sides, microneedle patching worked better in the skin of mild to moderate texture and levels 1 and 2 for the Merz infraorbital hollow resting scale (Figures 6 and 7). Contrary to the severe cases, the improvements in skin texture, wrinkle, or hollowness were barely noticeable because microneedle puncturing through the epidermis avoids the orbicularis oculi muscle. As mentioned, we noticed a slight change in the Merz infraorbital hollow at the rest score. To explain this, the authors suggested the idea of boosting collagen production by the microchannels from the needles. The appearance of skin plumpness might result from the mimicking skin injury, causing an increase in interstitial fluids; however, there was no documented evidence for microneedling to enhance skin volume.

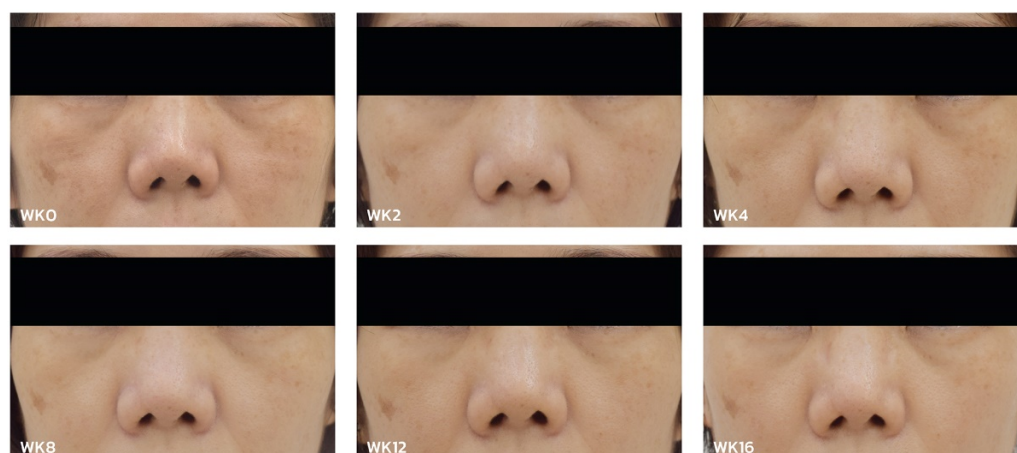


Figure 6. Photograph of subjects' undereye skin (right: MNP + botulinum toxin-A; left: MNP + normal saline).

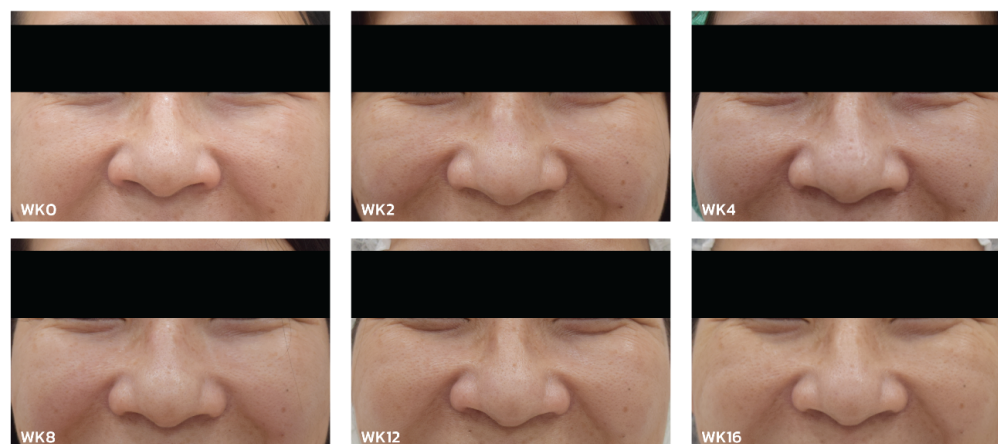


Figure 7. Photograph of subjects' under-eye skin (right: MNP + botulinum Toxin-A; left: MNP + normal saline).

5. Conclusions

This study demonstrates that microneedle patching is an effective novel transcutaneous delivery device offering many advantages to under-eye epidermis with slight ultraviolet damage. It is beneficial for needle-phobic patients, reducing anxiety and increasing comfort. Furthermore, microneedle patching presents as a sterile, single-use product, with fewer risks for clinician self-injury. The MNP is also more convenient because it is cost-efficient and saves time. Microneedle patching offers the potential for the future development of products catering to cosmetic practice. Moreover, since our unique MNP is formed with a photo fabrication technique and a fully cured microneedle is clear and transparent, each microneedle on the MNP can be used as a light guide. The light can propagate along a microneedle from the base to the tip. This behavior can open more delivery opportunities, not only for active ingredients but also for light. This property of our microneedle can synergize to develop a novel treatment. Successful production of MNPs requires further investigation in studies with a larger sample size, as well as trials incorporating longer follow-up periods. Moreover, studies to evaluate the efficiency of epidermal drug delivery and penetration should be conducted.

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Institutional Review Board Statement: Ethical approval was obtained from the Human Research Ethics Committee of Thammasat University (COA 181/2022, approval date: 29 August 2022). Written informed consent was obtained from the participants for their anonymized information to be published.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. The participants were informed and consented to the participants' photographs being published in this article.

Data Availability Statement: The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

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