

# Non-invasive High-Intensity Focused Ultrasound for Skin Brightening Efficacy Using a Topical Agent Containing Glutathione and Hyaluronic Acid.

Author's name:

Name of published journals

---

## ABSTRACT

**BACKGROUND** There are many studies on the effects of skin rejuvenation, lifting and tightening using high-intensity focused ultrasound (HIFU), but there are no clinical papers on the absorption and clinical effects of topical agents through the vibration of HIFU and the sensation of heat on skin (Park, Kim, Kim, Ro, & Ko, 2015). The purpose of this study is to verify whether the skin rejuvenation effect can be enhanced by performing the HIFU procedure in parallel with a topical agent containing glutathione and hyaluronic acid.

**OBJECTIVE** The purpose of this study is to identify the clinical and photographic changes observed in patients between a treatment administered in combination with and without HIFU. The treatment involves two sessions of applying a topical agent containing glutathione and hyaluronic acid. This study was designed to compare the skin brightening effects from each treatment.

**METHOD** Twenty female volunteers, aged 30–55 years, were randomly divided into two groups. Group A (n = 10) underwent a series of two non-invasive HIFU (high-intensity focused ultrasound) treatments using a topical agent containing glutathione and hyaluronic acid. In Group B (n = 10), the participants underwent the same series of two treatments using topical agents without HIFU treatment. Digital photographs (EOS Rebel SL3, Canon Inc., Japan) and patient surveys for treatment satisfaction were measured and obtained (using scale of 1 to 4.) Fine wrinkles, hyperpigmentation, and hydration were measured with A-One Smart™, a multi-functional imaging system (BOMTECH Inc., South Korea). Skin brightening effects were measured by the Global Aesthetic Improvement Scale (GAIS Scale) and assessed by a physician on a scale of 1 to 5.

**RESULT** In Group A, fine wrinkles, hydration and hyperpigmentation were significantly improved following three treatments ( $P < 0.05$ ). Fine wrinkles

reduced from  $6.25 \pm 2.00$  mm to  $3.10 \pm 1.62$  mm. Hyperpigmentation reduced from  $3.50 \pm 0.80$  mm to  $2.10 \pm 1.05$  mm. Hydration improved from  $28 \pm 10$  to  $55 \pm 11$  mm. More than half of patients reported there was significant improvement on brightening, fine lines, hyperpigmentation, and hydration following the treatment. There were no reported complications. In Group B, there was no statistically significant change in clinical skin attributes.

**CONCLUSION** HIFU procedure in parallel with a topical agent containing glutathione and hyaluronic acid effectively helps to improve skin quality with brightening effects. No adverse effect was reported. Noticeable improvements were found clinically and photographically. In contrast, without the combination of HIFU treatment, applying the topical agent manually did not lead to the same clinical results.

**KEYWORDS** non-invasive, high-intensity focused ultrasound (HIFU), glutathione, hyaluronic acid, facial rejuvenation, fine wrinkle reduction, skin brightening, topical agents, skin tightening

## INTRODUCTION

Non-invasive high-intensity focused ultrasound (HIFU) treatment has been accepted as a safe, reliable method for facial lifting and tightening (Ayatollahi et al., 2020). Clinical changes associated with HIFU have been reported in clinical articles (Sklar et al., 2014). These include a reduction in fine lines and hyperpigmentation, and improved skin elasticity, skin rejuvenation effects and lifting (Day, 2014). In an effort to boost the clinical results following HIFU treatment, clinicians began using combination treatments with other modalities such as laser and radio frequency (RF) (MCNAMARA, 2007). However, there are no clinical papers on clinical effects of the absorption of topical agents through the vibration of HIFU and the heating sensation to the skin in an effort to yield an optimal clinical outcome. This study was designed to identify the clinical and photographic changes observed following two sessions of treatment that involves applying a topical agent containing glutathione and hyaluronic acid with or without the combination treatment of HIFU to determine whether skin brightening effects could occur following the treatments in each group (Dilokthornsakul et al., 2019).

## SUBJECTS AND METHODS

**PATIENTS** Twenty Asian female volunteers, aged 30–55 years with Fitzpatrick skin types II–III, were randomly divided into two groups. To participate in the study and evaluate the effects of HIFU treatment used in combination with topical agents, the patients signed consent forms. The study conformed to the guideline of the 1975 Declaration of Helsinki. Exclusion criterion considered were patient conditions including pregnancy, breastfeeding, electrical implants, open wound, skin infection of any type, autoimmune diseases, and hemorrhagic disorders or dysfunction.

Each patient was advised to not use simultaneous skin therapy involving anti-aging agents 6 weeks before or during the study period. Digital photographs were taken prior to and 4 weeks post-treatment, and participants'

satisfaction was measured. A physician assessed the brightening effect of the photographs taken using the GAIS Scale (Rating 1: Very Much Improved, 2: Much Improved, 3: Improved, 4: No Change, 5: Worse). In Group A (n = 10), two HIFU treatments were performed with topical agent application. A single operator using a HIFU device (ULTRAFORMER MPT, CLASSYS Inc., South Korea) treated all participants. Using the topical agent containing glutathione (contents: 8%, capsulated) and hyaluronic acid, one session of the treatment protocol consisted of a 1.5mm cartridge with 500 shots (0.2~0.3 Joule) applied over the full face. The average treatment lasted approximately 7 minutes and was repeated at 14-day intervals for a total of two treatments.



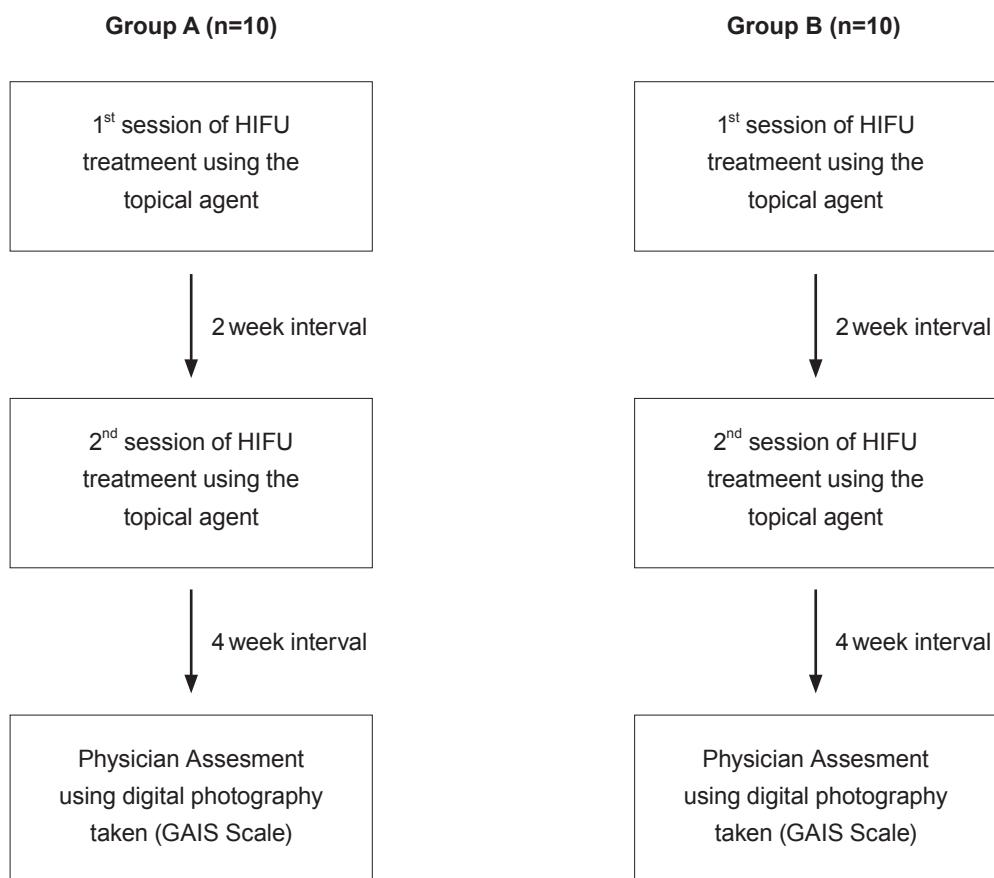
Figure 1. HIFU treatment areas marked in green in group A

Rating	Marisa Steans	Description
1	Very much improved	Optimal cosmetic result in this subject
2	Much improved	Maked improvement in appearance from the initial condition, but not completely optimal for this subject
3	Improved	Obvious improbement in appearance from initial condition, but a re-treatment is indicated
4	No change	The appearance is essentially the same as the original condition
5	Worse	The apperance is worse than the original condition

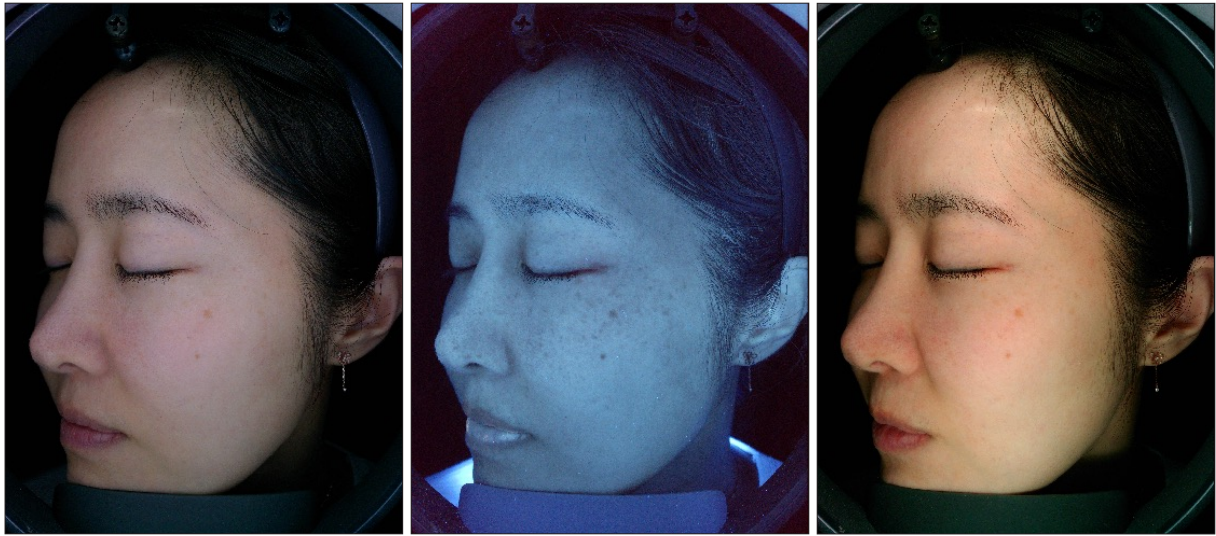
**Figure 2.** GAIS Scale assessed by the physician

In Group B (n = 10), two treatments were performed. A single operator treated all participants using the topical agent containing glutathione and hyaluronic acid by manual application. The average treatment lasted approximately 5 minutes and was repeated at 14-day intervals for a total of two treatments. Following the second treatment, digital photographs and multi-functional imaging system photographs were

taken of both groups. Participants' satisfaction was measured using a scale of 1–4 (1 = no improvement, 2 = minimal improvement, 3 = noticeable improvement, 4 = significant improvement). Patients were asked to assess changes in the following skin attributes: brightening, fine lines, hyperpigmentation, and hydration. A physician assessed the brightening effects in the photographs taken using the GAIS Scale



**Figure 3.** Study plan in Group A and B



Before the treatment\_ Group A



After the treatment\_ Group A

**Figure 4.** Fine lines, hyperpigmentation, and hydration observed prior to and following a series of HIFU treatment using the topical agent with the multi-functional imaging system.

## STATISTICAL ANALYSIS

Statistical analysis was performed using descriptive analysis. Standard deviation and mean values were analyzed by using the Excel program (version. Microsoft

Excel 2016 16.0.6741.2048). Data are presented as mean  $\pm$  standard deviation. P values less than 0.05 were considered statically significant.

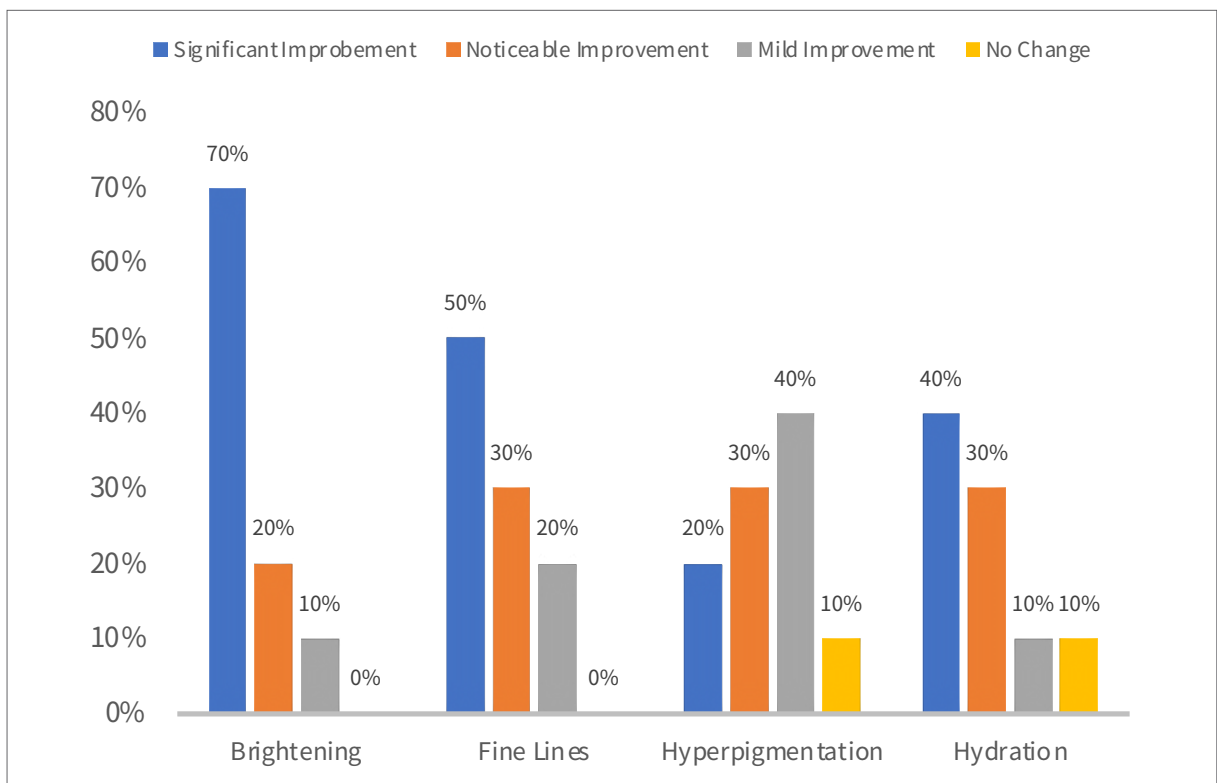
## RESULTS

	Before Treatment	After Treatment	P-value
Fine Wrinkles	6.25 $\pm$ 2.00	3.10 $\pm$ 1.62	0.0047
Hyperpigmentation	3.50 $\pm$ 0.80	2.10 $\pm$ 1.05	0.01
Hydration	28 $\pm$ 10	55 $\pm$ 11	0.0004

**Table 1.** Group A: Results from A group denoting changes following a series of HIFU treatment using the topical agent

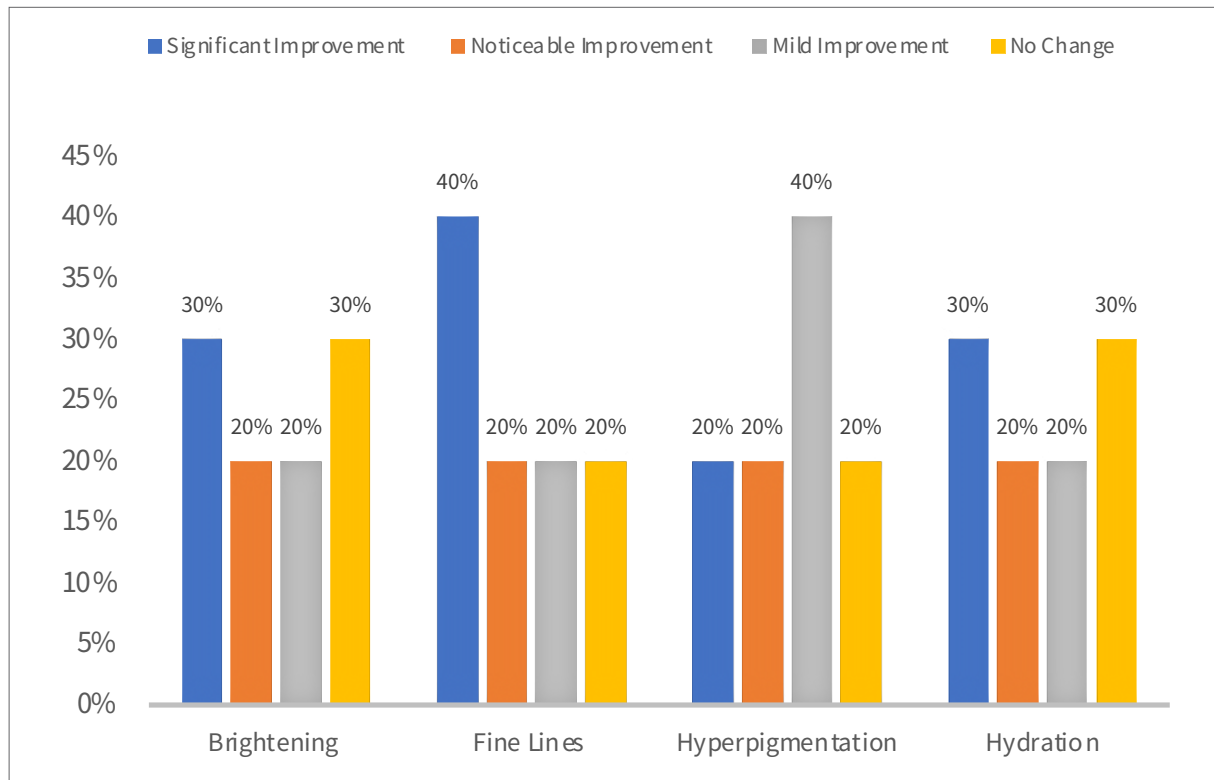
	Before Treatment	After Treatment	P-value
Fine Wrinkles	6.98 $\pm$ 1.80	6.80 $\pm$ 1.60	0.8191
Hyperpigmentation	2.82 $\pm$ 0.86	2.82 $\pm$ 0.86	1
Hydration	25 $\pm$ 12	28 $\pm$ 14	0.6208

**Table 2.** Group B: Results from B group denoting changes following a series of the topical treat



**Figure 5.** Group A Patient self-assessment post ULTRAFORMER MPT treatment using the topical agents

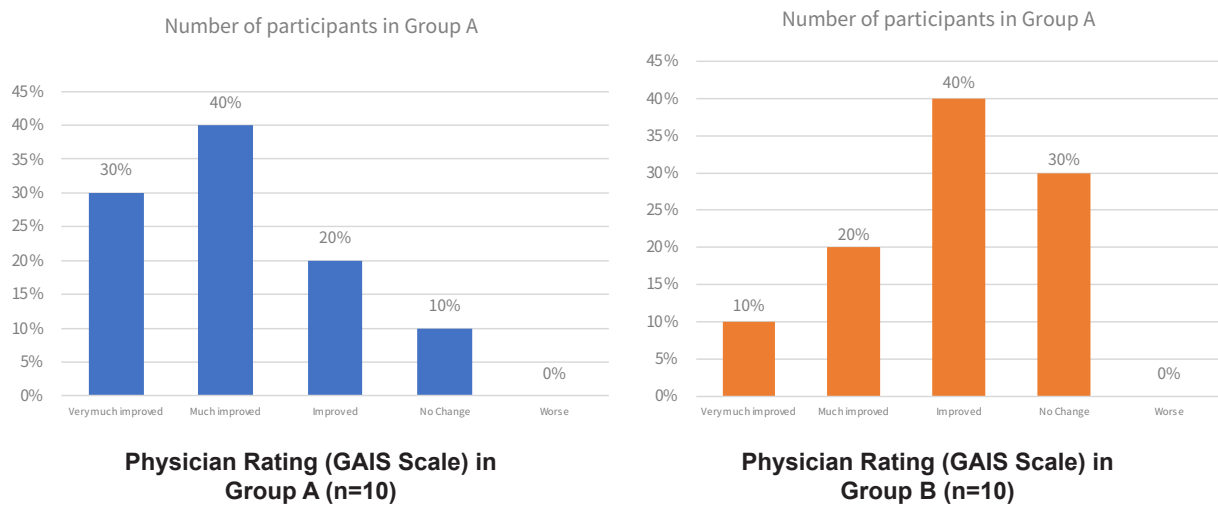




**Figure 6.** Group B Patient self-assessment post treatment using the topical agents

Obtained data from Group A and Group B were compared by t-test. In Group A ( $n = 10$ ), measured by the multi-functional imaging system, fine wrinkles decreased from  $6.25 \pm 2.00$  to  $3.10 \pm 1.62$  post two sessions of treatment. Hyperpigmentation was improved from  $3.5 \pm 0.80$  to  $2.10 \pm 1.05$ . Hydration showed noticeable improvement from  $28 \pm 10$  to  $55 \pm 11$ . More than two-thirds of patients reported significant or noticeable improvement in the surveyed skin conditions of brightening and fine lines (Figure 5). Qualitatively, improvement of fine wrinkles and hyperpigmentation were most commonly observed (Table 1). No complications or adverse effects were reported by or noted in any of the participating patients. Figures 5 and 6 illustrate the clinical improvement in group A and group B, respectively. To assess the skin brightening effect post treatment, obtained digital photographs from Group A and Group B were analyzed by a single physician using the GAIS scale (Figure 7). 70% of the participants in Group A showed very much improved or much improved ratings according to the GAIS Scale. In Group B ( $n = 10$ ), minimal change in any of the

surveyed skin conditions were noted following two sessions of the treatment. Slight improvement was noted but was not statistically significant ( $P\text{-value} > 0.05$ ) (Table 2). Also, only 30% of the participants in Group B showed very much improved or much improved ratings according to the GAIS Scale.



**Figure 7.** GAIS Scale of skin brightening effect by the physician in both gro

## DISCUSSION

Having clear, smooth and youthful skin has been seen as highly desirable by many, which stimulated the development of more advanced technologies and modalities for skin rejuvenation such as radiofrequency, laser ablation, external low-level lasers, and non-thermal ultrasound (Abraham et al., 2004, Mulholland et al., 2012).

Likewise, high-intensity focused ultrasound (HIFU), a widely used, non-invasive technique, has been demonstrated as the gold standard of skin rejuvenation and tightening in combination with other modalities (Celik, 2016). However, there are no clinical papers on the clinical effectiveness of the absorption of topical agents through the vibration of HIFU and the sensation of heat on skin. This study is to verify whether the skin brightening effect can be enhanced by performing the HIFU procedure in parallel with a topical agent containing glutathione and hyaluronic acid (Bukhari et al., 2018, Manggabarani et al., 2018).

During the treatment in Group A, HIFU energy was delivered using circular hand-piece movement in parallel with the application of a topical agent containing glutathione and hyaluronic acid, which resulted in a warming sensation with ultrasound vibration. Glutathione, one of the skin-whitening agents used in the cosmetic industry, is an antioxidant commonly found

in the human body that results in several systemic effects, defense from viral infections, and antitumor activities (Watanabe et al., 2014). Several studies and in vitro experiments expressed that glutathione showed anti-melanogenic effects; thus, it is related with melanin production (Sitohang & Ninditya, 2020). Likewise, Hyaluronic acid has a wide range of usage with its various physicochemical properties, such as biodegradability and nontoxicity. A powerful antioxidant, hyaluronic acid is perhaps best known for its ability to bond water to tissue; therefore, hyaluronan production increases in proliferating cells and hydration between the cells is enhanced (Ke et al., 2011, Sudha & Rose, 2014).

This study demonstrated that two sessions of HIFU treatments in parallel with applying a topical agent that includes glutathione and hyaluronic acid resulted in noticeable skin brightening effects and skin rejuvenation effects by the reduction of fine lines and hyperpigmentation with improved hydration. Clinical improvement was measured photographically using the GAIS Scale and the multi-functional skin assessment imaging system, and most of the patients reported significant or noticeable improvement in several skin attributes. These findings demonstrated the benefits and efficacy of the HIFU treatment in combination with applying a topical agent that includes the active

ingredients for skin rejuvenation and skin brightening effects.

This study also clearly proves that there were no unwanted and adverse effects post HIFU treatment.

## **CONCLUSION**

HIFU treatment used in parallel with the application of a topical agent containing glutathione and hyaluronic acid effectively helps to improve skin quality with brightening effects. No adverse effect was reported.

Clinically, scarring, pigment problems, or texture abnormalities following treatment have not been reported. These data indicate the HIFU procedure is safe without any adverse effects.

Noticeable improvements were found clinically and photographically. In contrast, without the combination of HIFU treatment, applying the topical agent manually did not lead to the same clinical results.



**CLINICAL PHOTO**



**Right after the treatment**



**Right after the treatment**



**Right after the treatment**



**Right after the treatment**



**Right after the treatment**



**Right after the treatment**

## References

- Ayatollahi, A., Gholami, J., Saberi, M., Hosseini, H., & Firooz, A. (2020). Systematic review and meta-analysis of safety and efficacy of high-intensity focused ultrasound (HIFU) for face and neck rejuvenation. *Lasers in Medical Science*, 35(5), 1007–1024. <https://doi.org/10.1007/s10103-020-02957-9>
- Celik, N. (2016). HIFU, Laser and Micro HIFU Research and Reports in Focused Ultrasounds for Face Remodelling. *Journal of Obesity & Weight Loss Therapy*, 6(4). <https://doi.org/10.4172/2165-7904.1000316>
- Day, D. (2014). Microfocused ultrasound for facial rejuvenation: current perspectives. *Research and Reports in Focused Ultrasound*, 13. <https://doi.org/10.2147/rrfu.s49900>
- Dilokthornsakul, W., Dhippayom, T., & Dilokthornsakul, P. (2019). The clinical effect of glutathione on skin color and other related skin conditions: A systematic review. *Journal of Cosmetic Dermatology*, 18(3), 728–737. <https://doi.org/10.1111/jocd.12910>
- MCNAMARA, D. (2007). Combined Therapy Optimizes Facial Rejuvenation. *Skin & Allergy News*, 38(9), 22. [https://doi.org/10.1016/s0037-6337\(07\)70701-5](https://doi.org/10.1016/s0037-6337(07)70701-5)
- Sklar, L. R., El Tal, A. K., & Kerwin, L. Y. (2014). Use of Transcutaneous Ultrasound for Lipolysis and Skin Tightening: A Review. *Aesthetic Plastic Surgery*, 38(2), 429–441. <https://doi.org/10.1007/s00266-014-0286-6>
- Abraham, M., Chiang, S., Keller, G., Rawnsley, J., Blackwell, K., & Elashoff, D. (2004). Clinical evaluation of non-ablative radiofrequency facial rejuvenation. *Journal of Cosmetic and Laser Therapy*, 6(3), 136–144. <https://doi.org/10.1080/14764170410023802>
- Bukhari, S. N. A., Roswandi, N. L., Waqas, M., Habib, H., Hussain, F., Khan, S., Sohail, M., Ramli, N. A., Thu, H. E., & Hussain, Z. (2018). Hyaluronic acid, a promising skin rejuvenating biomedicine: A review of recent updates and pre-clinical and clinical investigations on cosmetic and nutricosmetic effects. *International Journal of Biological Macromolecules*, 120, 1682–1695. <https://doi.org/10.1016/j.ijbiomac.2018.09.188>
- Ke, C., Sun, L., Qiao, D., Wang, D., & Zeng, X. (2011). Antioxidant activity of low molecular weight hyaluronic acid. *Food and Chemical Toxicology*, 49(10), 2670–2675. <https://doi.org/10.1016/j.fct.2011.07.020>
- Mulholland, R. S., Ahn, D. H., Kreindel, M., & Paul, M. (2012). Fractional Ablative Radio-Frequency Resurfacing in Asian and Caucasian Skin: A Novel Method for Deep Radiofrequency Fractional Skin Rejuvenation. *Journal of Cosmetics, Dermatological Sciences and Applications*, 02(03), 144–150. <https://doi.org/10.4236/jcdsa.2012.23029>
- Park, H., Kim, E., Kim, J., Ro, Y., & Ko, J. (2015). High-Intensity Focused Ultrasound for the Treatment of Wrinkles and Skin Laxity in Seven Different Facial Areas. *Annals of Dermatology*, 27(6), 688–693. <https://doi.org/10.5021/ad.2015.27.6.688>
- Sitohang, I. B. S., & Ninditya, S. (2020). Systemic Glutathione as a Skin-Whitening Agent in Adult. *Dermatology Research and Practice*, 2020, 1–6. <https://doi.org/10.1155/2020/8547960>
- Sudha, P. N., & Rose, M. H. (2014, January 1). Chapter Nine - Beneficial Effects of Hyaluronic Acid (S.-K. Kim, Ed.). ScienceDirect; Academic Press. <https://www.sciencedirect.com/science/article/abs/pii/B9780128002698000099>
- Watanabe, F., Hashizume, E., Chan, G. P., & Kamimura, A. (2014). Skin-whitening and skin-condition-improving effects of topical oxidized glutathione: a double-blind and placebo-controlled clinical trial in healthy women. *Clinical, Cosmetic and Investigational Dermatology*, 267. <https://doi.org/10.2147/ccid.s68424>