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 photographical 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 ± 2.00mm to 3.10 ± 1.62 mm. Hyperpigmentation reduced from 3.50 ± 0.80 mm to 2.10 ± 1.05 mm. Hydration improved from 28 ± 10 to 55 ± 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 photographical 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.

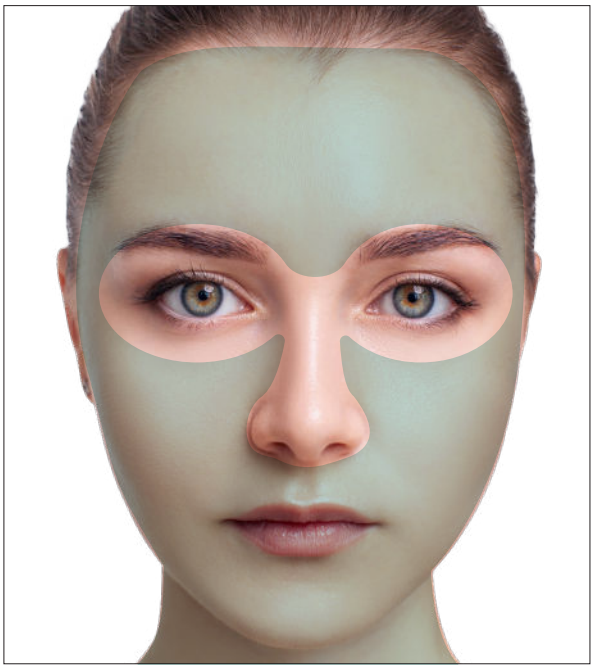


Figure 1. HIFU treatment areas marked in green in group A

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 comlpetely 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

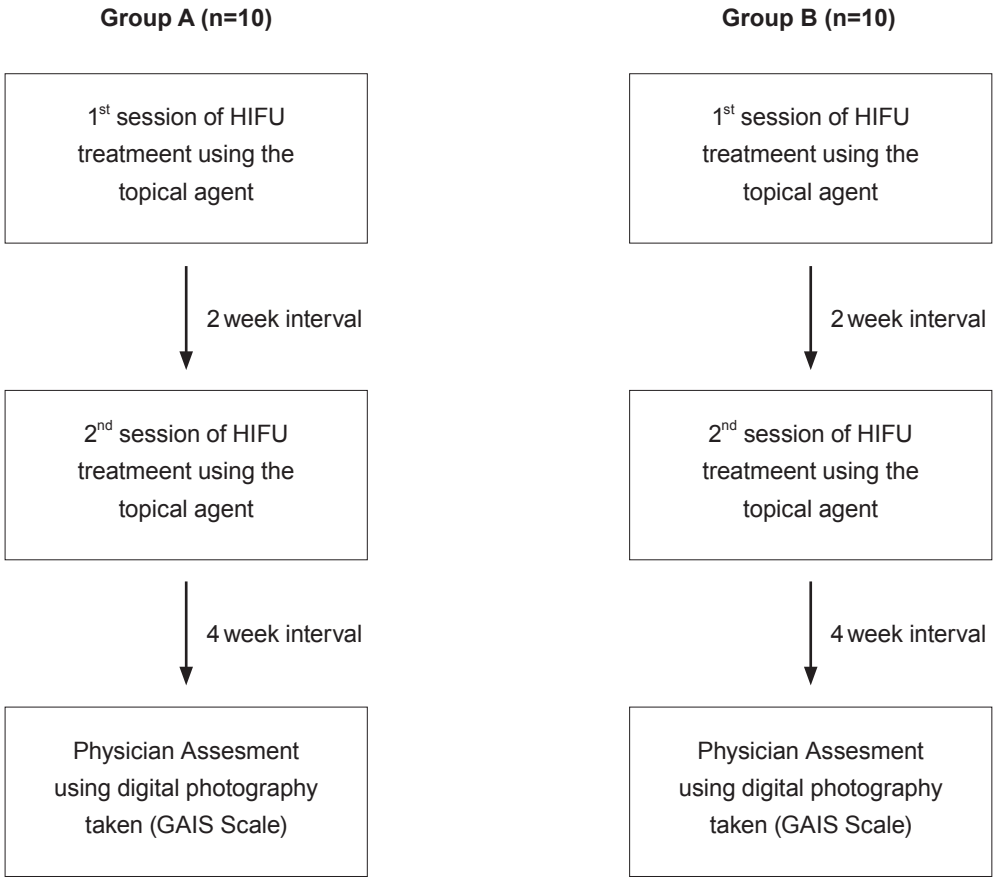
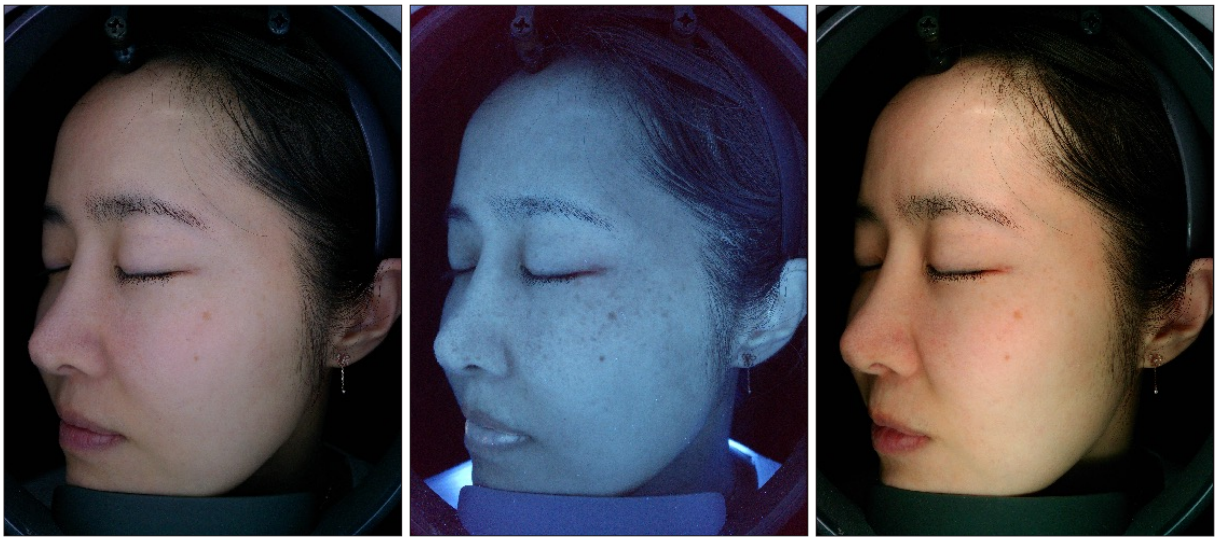


Figure 3. Study plan in Group A and B



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 ± standard deviation. P values less than 0.05 were considered statically significant.

RESULTS

	Before Treatment	After Treatment	P-value
Fine Wrinkles	6.25 ± 2.00	3.10 ± 1.62	0.0047
Hyperpigmentation	3.50 ± 0.80	2.10 ± 1.05	0.01
Hydration	28 ±10	55 ± 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±1.80	6.80 ±1.60	0.8191
Hyperpigmentation	2.82±0.86	2.82 ± 0.86	1
Hydration	25 ± 12	28 ± 14	0.6208

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

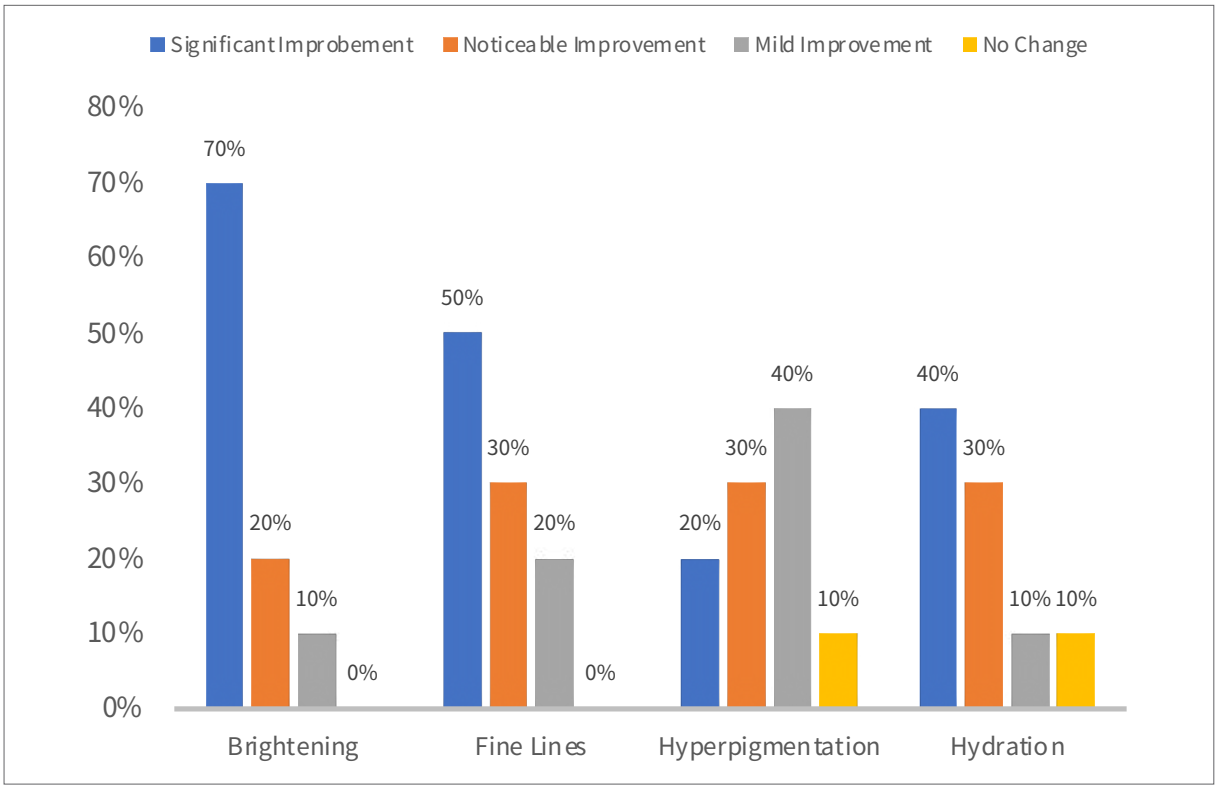


Figure 5. Group A Patient self-assessment post ULTRAFORMER MPT treatment using the topical agents

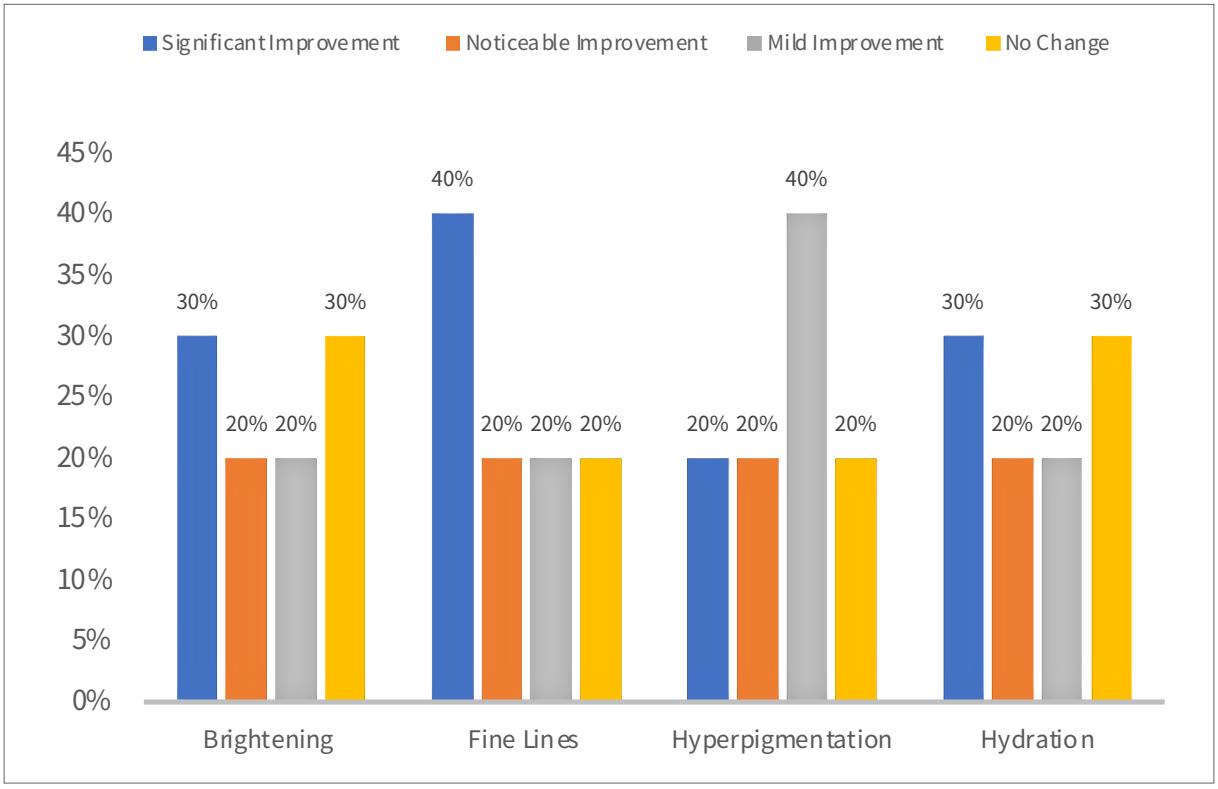


Figure 6. Group B Patient self-assessment post treatment using the topical agents

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 ± 2.00 to 3.10 ± 1.62 post two sessions of treatment. Hyperpigmentation was improved from 3.5 ± 0.80 to 2.10 ± 1.05. Hydration showed noticeable improvement from 28 ±10 to 55 ±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-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.

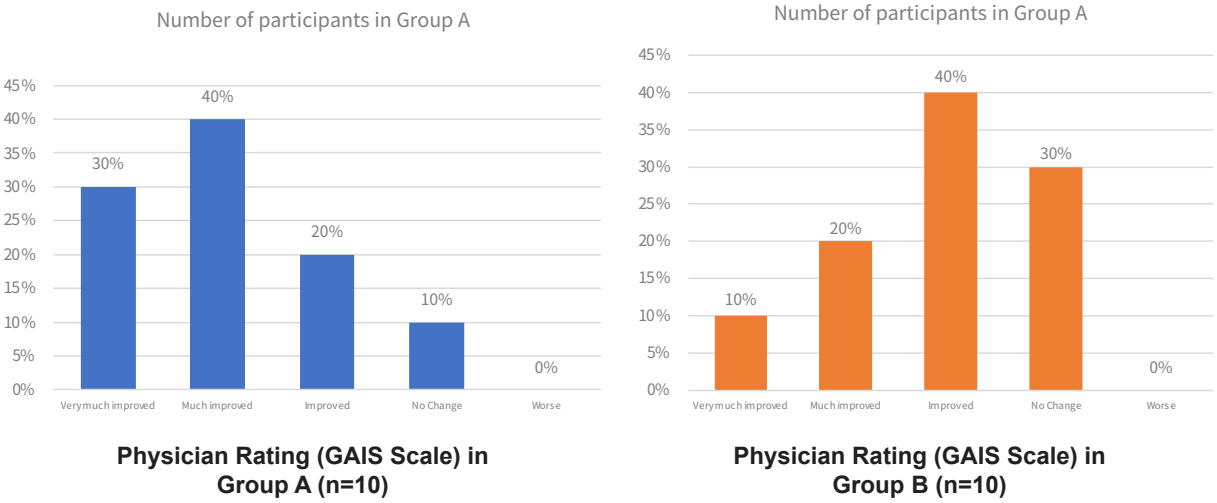


Figure 7. GAIS Scale of skin brightening effect by the physician in both gro

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. 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.

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. 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

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Efficacy and safety of high-intensity focused ultrasound (HIFU) on reduction of unwanted submental fat

Author's name:
Name of published journals

BACKGROUND A "double chin" medically submental fat has become the enemy in today's beauty standards. This condition gives the appearance of aging and obesity.The high-intensity focused ultrasound (HIFU) is considered a very safe way to reduce the submental volume.

OBJECTIVE This study aimed to evaluate the efficacy of HIFU for fat reduction in the submental area with a safe profile.

METHOD 30 patients, aged 25-60 years (20 females, 10 males) participated in 4-week follow-up(n=30). High-intensity focused ultrasound treatment was performed on submental fat by using two different cartridges with 4.5mm, and 6.0mm with MP mode. We evaluated treatment effects using Vectra (increase in volume measurement), CR-SMFRS, (Clinician Report-Submental fat rating scale) based on point 4 (0~4), SSRS (Subject Self-Rating Scale) based on point 3 (0~3), weight, and photography. The adverse event was done by using questionnaires.

RESULT A total of 30 patients were enrolled in this evaluation at the follow-up visit (4 weeks). The proportion of treatment patients satisfied with appearances and the submental fat was reduced significantly, CR-SMFRS was 10 mild patients,10 moderate patients, 8 severe patients,2 extreme patients and 16 mild patients,8 moderate patients,5 severe patients, 1 extreme patient after one session of treatment. Significant improvement was noted, $p<0.000005$. SSRS was 82% (Improvement Level) and also immediate improvement is seen for most of the patients. No significant side effects or adverse effects were reported. Anticipated common side effects were recorded which were resolved within 2 weeks.

CONCLUSION The HIFU was safe and effective in reducing the submental fat based on the results.

INTRODUCTION

Accumulation of subcutaneous fat in the submental area can lead to the loss of lower facial contour and mandibular definition. This condition gives the appearance of obesity and aging regardless of age and sex, and it has been shown to contribute to negative aesthetic and psychological effects (Kwon et al.,2021) .Liposuction is to improve the cosmetic effect but it requires anesthesia and an operating room setting and is quite expensive. Fearful of surgery, downtimes, and its complications, patients seek less invasive methods (Kamer & Minoli, 1993). As a nonsurgical technique, HIFU calls for less recovery time than a surgical facelift. Recently, several modalities have been used for non-invasive fat reduction. Due to its safe and non-invasive nature, HIFU treatment for cosmetic purposes including the reduction of submental fat has gained widespread popularity around the world. The principle of HIFU is to induce cellular damage and volume reduction of the target area selectively using coagulation by generating instant microthermal lesions at the targeted area. Various penetration depths by utilizing different cartridges 4.5mm,6.0mm focal depth contribute to the reduction of submental fat and tightening of tissues (Park et al., 2015). Also 6.0mm cartridge demonstrates the fat reduction in a certain part of the body (Choi et al., 2016, Oni et al., 2014). In this study, we evaluated clinical improvement and adverse effects.

SUBJECTS AND METHODS

30 Koreans participated in this study (Table 1). Subjects were eligible to participate by using a scale CR-SMFRS absent to extreme (point 0 to 4) and describing the overall changes and satisfaction level by using their submental fat SSRS (subject self-rating scale score 0 to 3). Key exclusion included the history of a keloid scar, pregnancy, open wounds, or lesions on the treatment area, skin infections, hemorrhagic disorder, and patients with a body BMI >35kg/m2. also, those undergoing

weight reduction programs or considering a diet were excluded. The consent form was taken from all patients, they were informed of the expected outcomes, possible side effects, and adverse effects. The protocol of this study conformed to the guidelines of the Declaration of Helsinki (1975). Evaluation and photos including the immediate post-treatment were taken by questionnaire after one month of follow-up.

Scale	0	1	2	3	4
Submental convexity	Absent	Mild	Moderate	Severe	Extreme
Description	No localised submental fat evident	Minimal localised submental fat	Prominent, localised submental fat	Marked, localised submental fat	Extreme submental convexity
Photograph of each score					

Adapted from McDiarmird *et al.* (2014). Results from a Pooled Analysis of Two European, Randomized, Placebo-Controlled, Phase 3 Studies of ATX-101 for the Pharmacologic Reduction of Excess Submental Fat. *Aesthetic Plastic Surgery*, 38(5), 849-860.

Figure 1. CR- SMFRS: Submental Fat Rating Scale scale

Baseline Characteristics of the parients	
	Subjects, n = 30
Age, mean	42
Female, n	20
Race	AII Korean patients
BMI, mean kg/m^2	26

Figure 2. Table 1 Baseline Characteristics of the patients

TREATMENT PROTOCOL

A single device HIFU device (Ultraformer MPT: Classys, Inc., Seoul, Korea) with MP mode was used in this study. The clinician used 2 different types of cartridges 4.5mm,6.0mm with 100 shots, and 120 shots (00.5J/ 0.7J) on submental fat. All the patients received a single treatment by applying topical anesthetic cream for 30~40mins. 1.0cm along the mandibular nerve was spared from the treatment area to avoid the marginal mandibular nerve (Figure 1). Additionally, a 4.5mm 30 shots (0.7J) cartridge with normal mode was used in the jawline for the synergy effect and tightening (Figure 2). Total 250 shots were delivered on average.

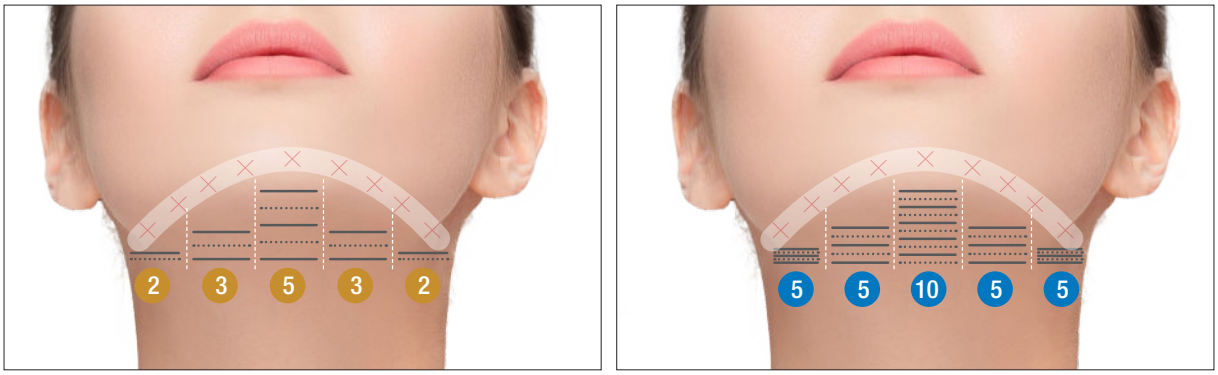


Figure 1. yellow: 6.5mm and blue: 4.5mm cartridges with MP mode were used based on the diagram.

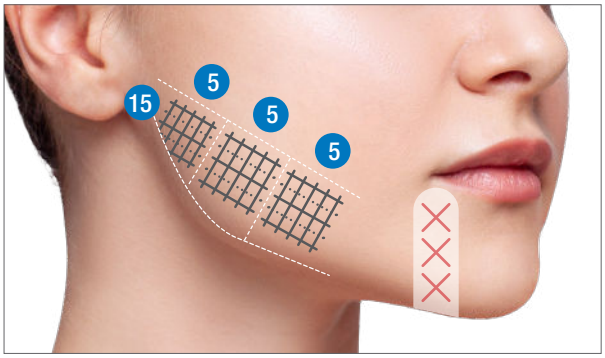


Figure 2. blue: 4.5mm cartridge with normal mode was used based on the diagram.

RESULTS AND CLINICAL EFFICACY

After one month of follow-up, the majority of the patients were satisfied with the result. The objective evaluation SSRS was 82% (74/90) of all treated patients. With 15 patients responded marked improvement (point 3), 14 patients responded mild improvement (point 2) and 1 patient (point 1) responded unchanged. CR-SMFRS is evaluated below Table 2. Signifcant improvement was noted , $p<0.000005$. Furthermore immediate improvement is seen right after the treatment.

	Before Treatment	After Treatment
Means	2.366666667	1.366666667
Variance	0.86091954	0.654022989
Pearson Correlation Coefficient(PCC)	0.871595992	
t-statistics	12.04159458	
P(T<=t) two-tailed	0.0000000000008329794	

Table 2. CR-SMFRS (Clinician Report-Submental Fat Rate Scale)

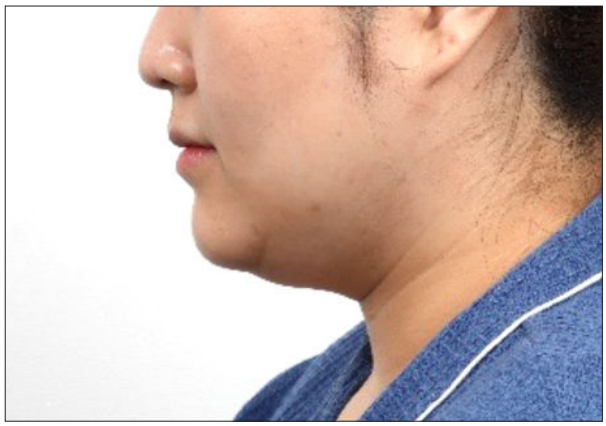



	weight	CR-SMFRS	SSRS
Baseline	55	1	-
Week 4	56kg	0	3


	weight	CR-SMFRS	SSRS
Baseline	50kg	1	-
Week 4	50kg	0	3

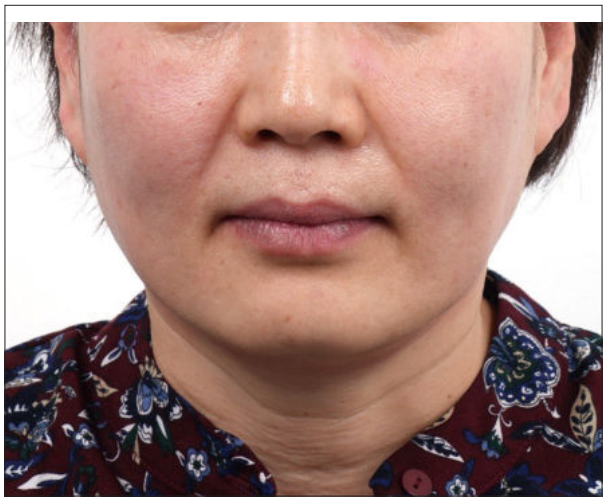

	weight	CR-SMFRS	SSRS
Baseline	90.5kg	3	-
Week 4	90.7kg	2	3


	weight	CR-SMFRS	SSRS
Baseline	68.2kg	3	-
Week 4	68.4kg	2	3




	weight	CR-SMFRS	SSRS
Baseline	79kg	4	-
Week 4	79kg	3	3


Right after the treatment

Right after the treatment


Right after the treatment

VECTRA MEASUREMENT

Three-dimensional image Vectra measurement (Canfield Scientific, Inc) analysis before and after a high-intensity focused ultrasound (HIFU) treatment session. In the side image views, topographical changes in the baseline picture compared with that of the follow-up visit. As it is shown in the diagram it indicates a decrease in submental fat.

1 Month After

SAFETY PROFILE

During the treatments, patients felt only minimal pain. No patient requested additional analgesic medication or sedation during the treatment. 18,15 and 10 patients had anticipated mild pain, erythema, and edema which resolved within 3 days. There were no adverse effects such as persistent numbness, nerve damage, and scarring after the treatment. Detailed information on the safety profile is shown in Diagram 1. All the patients were able to return to their daily activity right after the treatment.

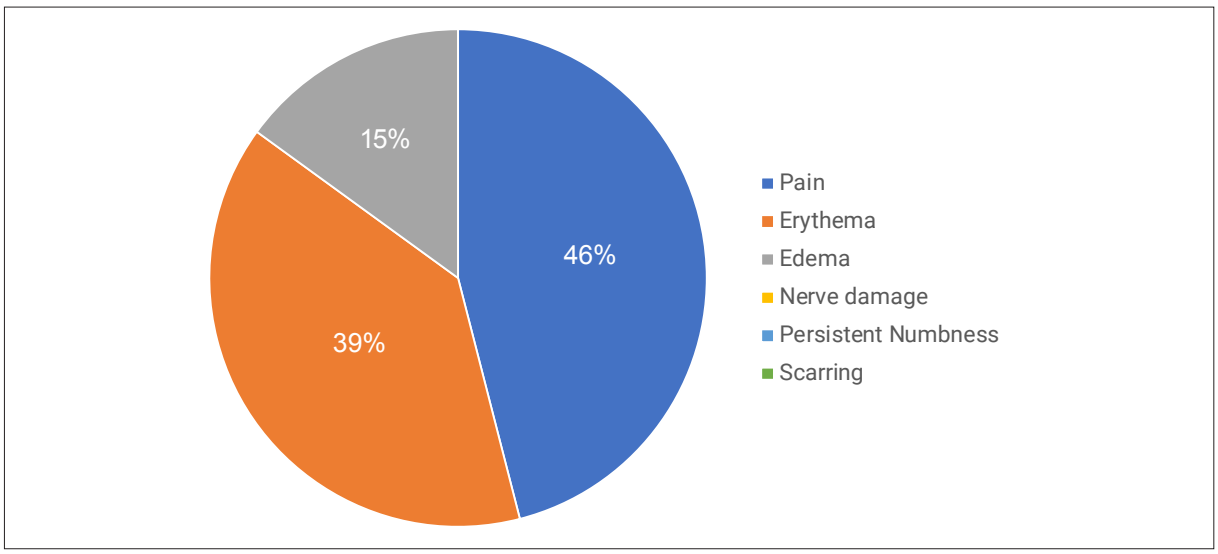


Diagram 1. Based on the questionnaires "what adverse effect have you experienced?"

CONCLUSION

The number of non-invasive with less time procedures is constantly growing in cosmetic dermatology (Kwon et al.,2021). HIFU energy destroys target adipocytes without affecting the surrounding tissues. Due to the large convergence of the ultrasounds at high frequencies, tissue destruction is limited to a small focal point. Ultrasound energy causes molecular vibrations in the area, it increases the temperature in the target

tissue above and causes the necrosis of fat cells by coagulation (Nelson et al., 2009, Laubach et., al). The results of this study demonstrated satisfactory efficacy of this triple-layer regimen for SMF. More than 80% of the treated patients subjected to only a single session showed improvements and satisfaction from the perspectives of clinician-reported and patient-reported evaluations, which was consistent with the results of the 3D Vectra result.The safety profile demonstrated only slight and transient post-treatment side effects and mild pain for most patients, which is anticipated and commonly known as the advantages of HIFU compared with other treatment approaches (Humphery et al., 2016, Scher et al., 2014). There was no serious complication such as scarring, persistent numbness and tingling sensation, nerve damage by HIFU. In addition to the tightening effects of conventional regimens, the novel 6.0-mm cartridge with MP based on the protocol showed marked improvement based on the evaluation and the follow-up. HIFU provides precise and safe means for the removal of fatty tissues. The heat from the absorbed ultrasound energy triggers liquefaction and disruption of the membrane of adipocytes (Ets & Smoller 2011). The mechanical and thermal effects can occur together, and the mechanical activity enhances local heat deposition. There has been a great deal of research into nonsurgical devices that might replicate its benefits (Gadsden et al., 2011). This parallels the general trend toward more noninvasive procedures. Despite its potential benefits, many patients inherently do not want surgery. They would prefer a noninvasive method for fat reduction and body contouring that is effective, yet comfortable and safe, with minimal downtime (Coleman et al., 2009). HIFU can is a safe, effective, and non-invasive option for fat reduction and facial lifting. Further studies should be considered with more patients conducted at multiple institutions. Additionally, there is a need for further studies using different patients and different methods such as different shots and modes.

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