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Cryolipolysis for abdominal subcutaneous fat reduction: A prospective, multicenter, single arm, clinical study

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Abstract

Various treatment methods are used for noninvasive body contouring. To evaluate the efficacy and safety of a newly designed cryolipolysis device using a three-dimensional cooling method for abdominal fat reduction. Twenty-five participants with clinically apparent abdominal fat tissue participated in the study. The thickness of fat tissue below the umbilicus level was measured using a caliper at baseline and 12 weeks after the first treatment. The height of abdominal subcutaneous fat tissue on ultrasonography and participant satisfaction were assessed at every visit for 16 weeks. All adverse events (AEs) during the study period were recorded. p values <0.05 were considered statistically significant. Twenty-four participants completed this study; the mean BMI of participants was 29.34 ± 2.36 kg/m^2. The mean thickness of abdominal subcutaneous fat was significantly lower at 12 weeks (40.4 ± 6.8 mm, $p < 0.001$) than at baseline (49.3 ± 8.5 mm). Differences in the height of abdominal subcutaneous fat compared to that at baseline were 1.02 ± 0.41 cm (12 weeks, $p < 0.001$) and 1.13 ± 0.44 cm (16 weeks, $p < 0.001$). Rates of abdominal subcutaneous fat reduction at 12 and 16 weeks compared to that at baseline were 28.45% and 31.13%, respectively. The ratio of abdominal circumference to hip circumference at 12 and 16 weeks was significantly decreased compared to that at baseline. Most participants (95.8%) reported improvement in satisfaction scores at 16 weeks. There were no serious AEs during the entire study period. The study demonstrated the efficacy of a noninvasive cryolipolysis device using a three-dimensional cooling method for reducing abdominal subcutaneous fat.

KEYWORDS
360° surround cooling technology, body contouring, cryolipolysis, human participants, noninvasive technique

1 | INTRODUCTION

There are many body-contouring techniques, such as high-intensity focused ultrasound (HIFU), radiofrequency, low-level laser therapy, and cryolipolysis. Several newly designed modalities have recently become available to consumers, each employing a different mechanism of action to reduce the appearance of adipose tissue.[1] Cryolipolysis is a noninvasive method for removing fat by freezing involving the controlled application of cooling for localized reduction of fat deposits, with a view to reshape the contours of the body and face.

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The degree of exposure to cooling causes cell death of subcutaneous fat tissue without apparent damage to the overlying skin or other tissues.[2] This study used a new device that employs 360° surround cooling technology, unlike the conventional two-sided cooling method. It is predicted that this device can provide complete coverage of the target area and that the treatment effect will be better. In this study, we evaluated the efficacy and safety of a newly designed cryolipolysis device, CLATUU ALPHA, in abdominal fat reduction.

2 | MATERIALS AND METHODS

2.1 | Participants

This study was designed as a prospective, multicenter, single-arm clinical study and was approved by the Institutional Review Board of Chung Ang University Hospital (IRB number: 2032-004-415) and Hanyang University Hospital (IRB number: 2020-03-041). All participants voluntarily participated in this clinical study and provided informed consent.

The participants considered were between 19 and 65 years of age and had clinically apparent fat tissue on the abdomen. Clinically apparent fat tissue was defined as a thickness of fat tissue below the umbilicus level measured by caliper ≥1.5 cm. Inclusion criteria included body mass index (BMI) ≤35 kg/m^2 and a change in body weight within the last 1 month ≤5 percentiles. Additionally, all participants were required to maintain a stable weight and lifestyle, including caloric intake and exercise, during the entire clinical study period (Table S1).

The exclusion criteria included a history of abdominal liposuction, abdominoplasty, mesotherapy, HIFU therapy, cryolipolysis, dermal filler, radiofrequency, or laser treatment within the last 6 months. Participants with any cutaneous disease or scars on the abdominal skin, other cold-related systemic diseases (Raynaud's phenomenon, cold urticaria, cryoglobulinemia, and paroxysmal cold hemoglobinuria), pregnancy, or lactation were also excluded.

2.2 | Device

The cryolipolysis device used in this study was the CLATTU ALPHA (CLASSYS Inc., Seoul, Korea). This device has applicators that deliver cooling energy to the subcutaneous fat tissue. A cup-shaped applicator was applied to the target abdominal area. Abdominal tissue with accumulated subcutaneous fat was vacuum-suctioned into the applicator. The energy generated by the cooling plate in the applicator freezes a significant portion of the subcutaneous fat layer. It induces the natural process of apoptosis or death of fat cells without damaging the surrounding tissues or nerve regions. Unlike the conventional two-sided cooling devices utilized by previous methods, this newly designed CLATTU ALPHA has a cooling plate inside the applicator, which is composed of a three-dimensional cooling method (360° cooling method). Therefore, it is expected to provide complete coverage of the targeted area and effectively reduce the excessive accumulation of subcutaneous fat.

2.3 | Treatment procedure

The targeted abdominal subcutaneous was an oval shape designed using a grid such that the part of the lower abdomen with the most fat distribution visible to the naked eye was the center while the participant was standing. Subsequently, left and right straight lines were drawn on the area to be the center of the treatment area. The left and right ends and center of the line were marked on this straight line. The center of the procedure was set to intersect the left and right straight lines when a vertical line was drawn from the umbilicus. Using a grid in a straight line, we drew up and down curves to make an oval shape; however, the short radius of the oval was designed to be 4 cm or greater. The top of the designed oval shape was at least 3 cm downward from the umbilicus. Neither end of the designed oval shape reached the pelvic bones (Figure 1).

Participants lay down on the bed and the upper body was elevated by approximately 45°. The CLATTU ALPHA exclusive pad was spread and attached to the center of the designed treatment area; however, all attached surfaces were made to adhere sufficiently to the skin without air bubbles and wrinkles. The transducer was attached perpendicular to the center of the treatment area where the pad was attached. The cooling level, suction level, and procedure time applied to the participant varied depending on abdominal subcutaneous fat layer height and the participants' pain level during the procedure.

In this study, the treatment settings were cooling level 4–5 (−7 to 9°C) and suction level 3–5 (−40 to 60 kPa), and one treatment session



Cooling	4 ~ 5 level (-7 ~ -9°C)
Suction	4 ~ 5 level (-40 ~-60 kPa)
Time	50 ~ 60 minutes

FIGURE 1 Schematic map of treatment for the abdomen

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was 50 to 60 min. All participants underwent two treatment sessions at 4-week intervals. For each participant, a second treatment was performed at the same site as the first treatment.

2.4 | Efficacy assessment

The participants were followed up with at 4, 8, 12, and 16 weeks after the first treatment. The weight and BMI of the participants were recorded, and standardized digital clinical photographs were taken using consistent participant positioning, camera settings, and room lighting at every visit. At baseline and 12 weeks, the thickness of fat tissue below the umbilicus level was measured twice using a caliper, and the average of the two values measured was used as the result.

The height of the abdominal subcutaneous fat tissue was measured by abdominal ultrasonography at every visit. The ultrasound measurement area was designed to have the same shape as that of the treatment area (Figure 2). The height of abdominal subcutaneous fat tissue was measured twice, and the average of the values was used as the result. We calculated the rate of abdominal subcutaneous fat reduction using the difference in the height of subcutaneous fat tissue at each follow-up visit compared with that at the baseline.

Abdomen and hip circumferences were measured at each visit. Abdominal circumference was measured horizontally at the central point of the treatment area. Hip circumference was measured horizontally at the level of the largest portion of the hip. We then calculated the ratio of abdominal to hip circumference.

Three blinded independent evaluating investigators (EIs) assessed randomized photographs of the participants at baseline and 12 weeks. The three EIs were asked to determine which photograph (at baseline or 12 weeks) was taken at week 12 (photograph with reduction of subcutaneous fat tissue). Of the evaluation results of the three EIs, two or more judges producing the same evaluation was used as the result of the abdominal photography discrimination rate.



FIGURE 2 Area of ultrasonographic measurement on the abdomen

Participant satisfaction was assessed based on the degree of improvement in the reduction of abdominal subcutaneous fat at 4, 8, 12, and 16 weeks after the first treatment. The grading scale of the satisfaction of the participants was as follows: 4 = 75% to 100% improvement, 3 = 50% to 74% improvement, 2 = 25% to 49% improvement, 1 = 1% to 24% improvement, 0 = no improvement, and −1 = worse.

2.5 | Safety assessment

Participants were asked about any adverse events (AEs) at each visit, and AEs that occurred during the study period were recorded. The treatment investigators examined the treatment sites for treatment-related events, including bruising, swelling, erythema, and frostbite after the procedure. Laboratory tests, including complete blood test, lipid level, liver function test, kidney function test, coagulation test, and serum human chorionic gonadotropin, were performed at baseline and 16 weeks. The degree of pain was evaluated using the numeric rating scale (NRS) during and immediately after the treatment procedure. The NRS was scaled from 0 (no pain at all) to 10 (extremely intolerable pain).

2.6 | Statistical analysis

Statistical analyses were performed using SPSS version 25.0 for Windows (SPSS Inc., Chicago, IL) and R version 4.1.2 (2021-11-01). The sample size of 20 participants was calculated using a one-sided test according to the reduction rate of mean abdominal subcutaneous fat tissue measured by ultrasonography score at week 12 with power of 80% at a significance level of 2.5%.[3] The planned enrollment was 25 participants, assuming a dropout rate of 20%. A superiority margin of 10% was calculated based on previously published studies.[2,4,5] Statistical comparisons before and after treatment were performed using repeated measures ANOVA test. Data are presented as the mean ± standard deviation. For the primary efficacy endpoint, a one-sided test was performed, with a 97.5% confidence interval. For the secondary efficacy endpoint, a two-sided test was performed, and p values <0.05 were considered statistically significant.

3 | RESULTS

3.1 | Demographics and procedures

A total of 28 participants were screened, and 25 participants were enrolled in the study. During the study period, one participant was excluded because of the inclusion/exclusion criteria (BMI ≤35 kg/m^2, a change in body weight within the last 1 month ≤5 percentiles, and maintaining a stable weight and lifestyle). Therefore, 24 participants completed the entire study for up to 17 weeks.

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Among the 25 participants, 72.0% (n = 18) were Korean and 28.0% (n = 7) were foreign participants. The Fitzpatrick skin types of the participants were as follows: type I–II, 16.0% (n = 4); type III–IV, 72.0% (n = 18); and type V–VI, 12.0% (n = 3). The proportion of male participants was 20.0% (n = 5) and that of female participants was 80.0% (n = 20). The mean age of the participants was 39.1 ± 11.6 years. The mean height was 164.4 ± 7.3 cm, and the mean weight was 79.9 ± 8.3 kg (Table 1). The mean BMI of the participants was 29.56 ± 2.53 kg/m^2 and the thickness of abdomen fat tissue was 50.18 ± 9.28 mm.

TABLE 1 Demographics of the subjects

Demographics	Total (n = 25)
Ethnicity, n (%)	
Korea	18 (72.0%)
Other	7 (28.0%)
Fitzpatrick skin type, n (%)	
Type I–II	4 (16.0%)
Type III–IV	18 (72.0%)
Type V–VI	3 (12.0%)
Sex, n (%)	
Male	5 (20.0%)
Female	20 (80.0%)
Age (years)	
Mean ± SD	39.1 ± 11.6
Median	41.0
Min, max	23, 58
Height (cm)	
Mean ± SD	164.4 ± 7.3
Median	163.6
Min, max	150.3, 177.5
Weight (kg)	
Mean ± SD	79.9 ± 8.3
Median	79.3
Min, max	62.4, 94.0

The treatment (cooling level 4–5 [−7 to 9°C] and suction level 3–5 [−40 to 60 kPa]) was applied as determined in this clinical study. The treatment time was 50 min in one patient (4.0%) and 60 min in 24 patients (96.0%) in the first procedure. All 25 participants (100%) were treated for 60 min during the second procedure.

3.2 | Efficacy

The mean height of the abdominal subcutaneous fat tissue measured using abdominal ultrasonography was 3.57 ± 0.74 cm at baseline and 2.55 ± 0.62 cm at 12 weeks (Figures 3 and 4). The rate of abdominal subcutaneous fat reduction at 12 weeks compared to that at baseline was 28.45%and the lower limit of the 97.5% confidence interval was 24.428 (p = 1.9E-13). The reduction rate of abdominal subcutaneous fat at week 12 compared with that at baseline was clinically and statistically significant.

The difference in the height of the abdominal subcutaneous fat compared to that at baseline was 0.61 ± 0.31 (at 4 weeks), 0.85 ± 0.39 (at 8 weeks), 1.02 ± 0.41 (at 12 weeks), and 1.13 ± 0.44 (at 16 weeks). The decrease in the height of abdominal subcutaneous fat was statistically significant at every follow-up visit (Table 2). The mean thickness of abdominal fat tissue measured using calipers was significantly decreased at 12 weeks (40.4 ± 6.8 mm, p < 0.001) compared to that at baseline (49.3 ± 8.5 mm).

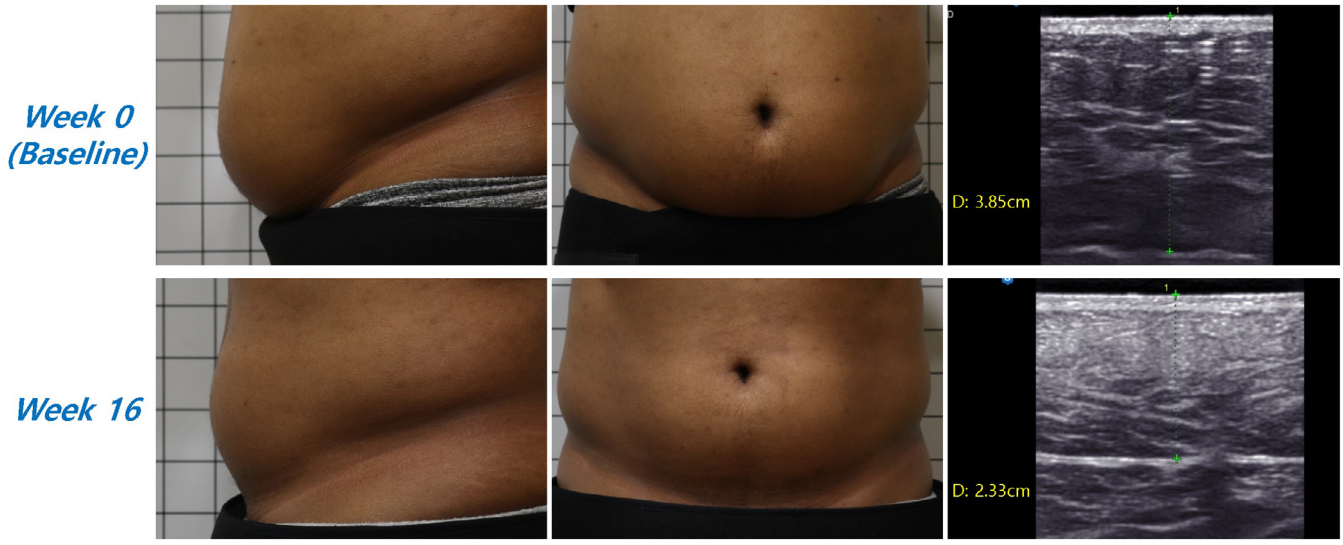


FIGURE 3 Clinical photographs and sonographic images of the representative participant (I). Height of the abdominal subcutaneous fat tissue measured using abdominal ultrasonography was 3.85 cm at baseline and 2.33 cm at 16 weeks

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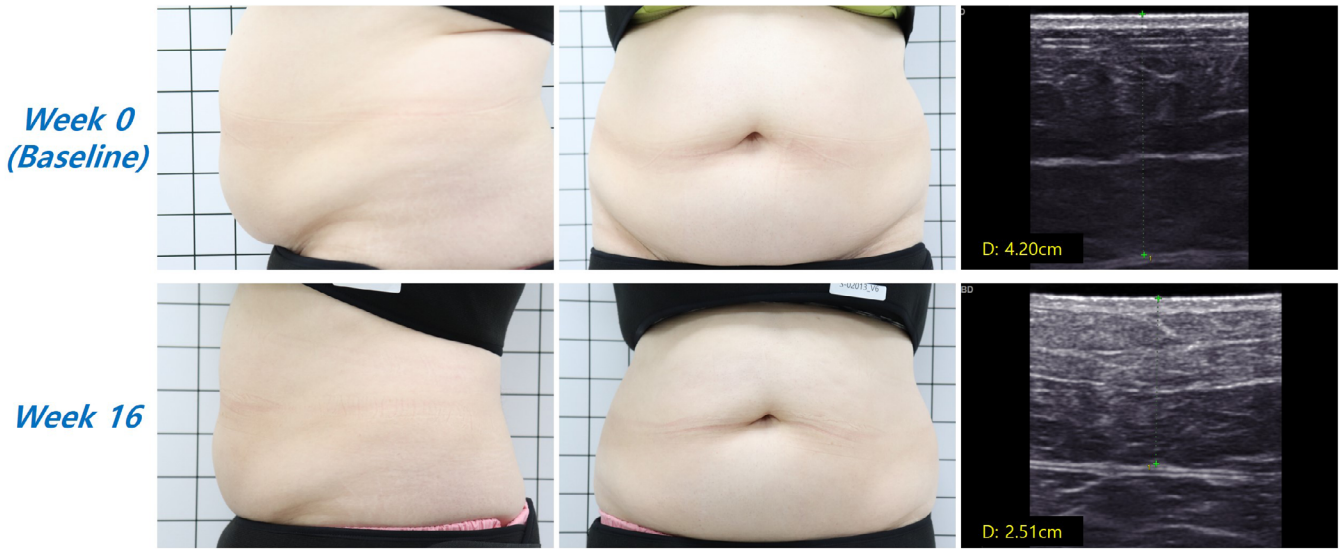


FIGURE 4 Clinical photographs and sonographic images of the representative participant (II). Height of the abdominal subcutaneous fat tissue measured using abdominal ultrasonography was 4.20 cm at baseline and 2.51 cm at 16 weeks

TABLE 2 Difference in mean height of abdominal subcutaneous fat tissue in participants measured by ultrasonography compared to baseline

Visit		Height (cm)	F	*p*-value
Week 0 (baseline)	*n*	24	78.265	<0.000
	Mean ± SD	3.57 ± 0.74		
Week 4	*n*	24		
	Mean ± SD	2.96 ± 0.74[a]		
Week 8	*n*	24		
	Mean ± SD	2.72 ± 0.68[a]		
Week 12	*n*	24		
	Mean ± SD	2.55 ± 0.62[a]		
Week 16	*n*	24		
	Mean ± SD	2.44 ± 0.49[a]		

[a]$p < 0.000$ compared with baseline (week 0) on repeated measures ANOVA test.

The mean weight and BMI of the participants at 16 weeks were 78.72 ± 8.76 kg and 29.03 ± 2.40 kg/m^2, respectively. There were no significant differences compared to the mean weight and BMI at baseline (79.54 ± 8.36 kg and 29.34 ± 2.36 kg/m^2, respectively). The ratio of the abdominal circumference to the hip circumference was 96.56 ± 5.10 (baseline), 95.98 ± 5.36 (4 weeks), 95.45 ± 5.60 (8 weeks), 94.59 ± 4.98 (12 weeks), and 94.47 ± 5.27 (16 weeks). Compared to that at baseline, the ratios of the abdominal circumference to hip circumference at 12 and 16 weeks were significantly decreased (Table 3).

EIs evaluated randomized photographs of participants at 12 weeks compared to the baseline photographs. The discrimination rate of abdominal photography was 87.5%. As a result of the satisfaction of participants at 16 weeks, 23 participants (95.8%) reported improvement, and one participant (4.2%) did not show any improvement (Table 4).

3.3 | Safety profile

The mean NRS during the first procedure was 1.56 ± 1.26, and the mean NRS immediately after the first procedure was 2.88 ± 1.30. At 4 weeks, the mean NRS during the second procedure was 1.72 ± 1.57, and the mean NRS immediately after the second procedure was 3.28 ± 1.86. There was no difference in pain between immediately after the first procedure and immediately after the second procedure ($p = 0.273$). However, no pain was reported at 8, 12, or 16 weeks.

Most reported AEs were related to treatment and restricted to the application site, and included including pain, erythema, numbness, and bruising. These AEs were mostly mild and disappeared within 2 weeks after the procedure. There were no clinically significant changes in laboratory examinations, including complete blood count, lipid level, liver function test, kidney function test, coagulation test,

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TABLE 3 Differences in mean weight, body mass index, abdominal circumference, and ratio of abdominal to hip circumference in participants compared to baseline

Visit		Weight (kg)	BMI (kg/cm^2)	Abdominal circumference (cm)	Ratio of abdominal to hip circumference
Week 0 (baseline)	*n*	24	24	24	24
	Mean ± SD	79.54 ± 8.36	29.34 ± 2.36	104.39 ± 5.78	96.56 ± 5.10
Week 4	*n*	24	24	24	24
	Mean ± SD	79.57 ± 8.71	29.34 ± 2.41	102.92 ± 5.88[a]	95.98 ± 5.36
Week 8	*n*	24	24	24	24
	Mean ± SD	79.57 ± 8.71	29.36 ± 2.50	101.91 ± 5.91[a]	95.45 ± 5.60
Week 12	*n*	24	24	24	24
	Mean ± SD	78.98 ± 8.75	29.13 ± 2.45	100.83 ± 5.68[a]	94.59 ± 4.98[a]
Week 16	*n*	24	24	24	24
	Mean ± SD	78.72 ± 8.76	29.03 ± 2.40	100.47 ± 5.85[a]	94.47 ± 5.27[a]
F	2.844		2.868	35.18	10.13
p-value	0.060		0.059	0.000	0.000

Abbreviation: BMI, body mass index.
[a]$p < 0.000$ compared with baseline (week 0) on repeated measures ANOVA test.

TABLE 4 Satisfaction of the participants at week 16

Scale	Description	*n* (%)
−1	Worse	0 (0.0)
0	No improvement	1 (4.2)
1	1%–24% improvement	6 (25.0)
2	25%–49% improvement	3 (12.5)
3	50%–74% improvement	6 (25.0)
4	75%–100% improvement	8 (33.3)

and serum human chorionic gonadotropin level, at 16 weeks compared to that at baseline. No serious AEs occurred during the study period.

4 | DISCUSSION

Cryolipolysis is a noninvasive method for reducing subcutaneous fat. It was originally developed for cooling medical devices and is known to be effective in relieving pain and muscle spasm and improving local circulation. It provides controlled cooling energy at the desired fat tissue and reduces subcutaneous fat at the application site without damaging the other tissues.[6,7] The principle of cryolipolysis was discovered by Dr. Dieter Manstein and Dr. R. Rox Anderson, who worked at the Wellman Center of Massachusetts General Hospital, an educational institution at the Harvard Medical School in Boston. Their research showed that when subcutaneous fat tissue is exposed to low temperatures, local subcutaneous panniculitis occurs and fat tissues in the panniculitis lesions decrease.[7,8] Using this principle, various studies related to subcutaneous fat reduction have been conducted, and cryolipolysis technology has been developed.

Several recent studies have confirmed the efficacy and safety of excessive subcutaneous fat reduction in various parts of the body using cryolipolysis. Kilmer et al. confirmed that there was an average reduction of 20% (2.0 mm) in subcutaneous fat under the chin viewed using ultrasonography. The treatment settings of this study were as follows: two sessions, 6-week intervals, treatment duration of 60 min, and a cooling temperature of −10°C.[9] In addition, there were other research results confirming the effectiveness of submental cryolipolysis viewed using ultrasonography or MRI.[10,11] For flank and abdominal subcutaneous fat tissue, several studies have shown that the rate of fat reduction was 20% to 25% in the efficacy assessment using ultrasonography, and the effectiveness lasted up to 6 months.[2,3,12,13] In applying cryolipolysis to the thighs, the effect of reducing subcutaneous fat by 2.6 to 3.3 mm in the ultrasonography was confirmed.[14,15] Carruthers et al. obtained a 3.2-mm reduction in the subcutaneous fat layer after applying cryolipolysis to the upper arms.[16] Park et al. revealed that as a result of applying cryolipolysis to 10 male participants with pseudogynecomastia, the post-treatment breast adipose tissue in the participants was significantly reduced compared to that before the procedure.[17]

After cryolipolysis, necrosis occurs in the targeted adipose tissue, which destroys fat tissue. The destroyed adipocytes induce a wound-healing response to activate macrophages, resulting in an inflammatory response. Macrophages reduce adipose tissue by processing lipids and cellular debris of adipocytes in the liver through the lymphatic system 14 to 30 days after the procedure. Therefore, through this process, fat cell residues, such as lipids and cellular debris, could affect the composition of blood and liver function. Klein et al. confirmed that there were no significant differences in

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blood lipid levels and liver function test results before and after cryolipolysis.[6,8,18]

In the present study, a cryolipolysis device designed to provide complete coverage of the targeted area using a three-dimensional cooling method was applied to abdominal subcutaneous fat. All participants received two treatment sessions at 4-week intervals to achieve optimal clinical effects based on the period of healing response and activated macrophage actions after the procedure. We confirmed that the reduction in abdominal subcutaneous fat was statistically significant until 16 weeks after the first procedure. The height measured by ultrasonography, thickness measured by calipers, and circumference measured by tape measure all showed significant differences. Most participants complained of mild pain during and immediately after the procedure; however, there was no persistent pain in any participant. Regarding the safety profile, there were no clinically significant changes in blood lipid levels and liver function tests 16 weeks after the first procedure. Therefore, based on the results of this study, the efficacy and safety of a newly designed cryolipolysis device for abdominal subcutaneous fat reduction were demonstrated.

The relatively small number of participants and short-term follow-up period are potential limitations of our study. Further clinical studies with a larger number of participants and longer follow-up periods are recommended to further prove the efficacy and safety of the device. In addition, requesting the maintenance of habits such as dietary intake or physical activity did not guarantee the absolute control of confounding variables. Another limitation of this study is that treatment protocols have yet to be optimized to maximize the results. Clinical studies comparing the efficacy of different treatment settings or application to other body parts will be helpful in establishing an optimal treatment protocol for various fat-accumulated areas.

In conclusion, the non-invasive cryolipolysis device using three-dimensional cooling method was effective and safe for reducing abdominal subcutaneous fat tissue.

AUTHOR CONTRIBUTIONS

Sun Young Choi: Original draft, investigation. Jae Wan Park: Original draft, investigation. Young Gue Koh: Validation, investigation. You Jin Jung: Validation, investigation. Yun Jung Huh: Validation, investigation. Eun Jung Ko: Investigation, supervision. Kwang Ho Yoo: Review and editing manuscript, investigation, supervision. Joon Seok: Review and editing manuscript, investigation, supervision. Soo Yeon Kim: Conceptualization, methodology, investigation. Mihn Sook Jue: Review and editing manuscript, investigation, supervision. Joo Yeon Ko: Conceptualization, methodology, review and editing manuscript. Beom Joon Kim: Conceptualization, methodology, review and editing manuscript.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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