Safety, Tolerance, and Patient Satisfaction With Noninvasive Cryolipolysis

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BACKGROUND Comprehensive assessment of safety, tolerance, and patient satisfaction has not been established from noninvasive body contouring techniques, such as low-level laser therapy, ultrasound, radiofrequency, and infrared light, for reduction of subcutaneous fat.

OBJECTIVE This multicenter study investigated the clinical outcomes of noninvasive cryolipolysis in European subjects.

METHODS A retrospective study was performed at clinical sites in Belgium and France. Safety was assessed according to reports of side effects. Tolerance was evaluated according to pain scores and patient perception of treatment duration. Clinical outcomes were assessed according to patient surveys, caliper measurements, and assessment of photographs.

RESULTS The investigators treated 518 patients. No significant side effects or adverse events were reported. The procedure was well-tolerated, with 89% of respondents reporting a positive perception of treatment duration and 96% reporting minimal to tolerable discomfort. Survey results demonstrated 73% patient satisfaction and that 82% of patients would recommend the cryolipolysis procedure to a friend. Caliper measurements demonstrated 23% reduction in fat layer thickness at 3 months. Abdomen, back, and flank treatment sites were most effective, with 86% of subjects showing improvement per investigator assessment.

CONCLUSIONS With proper patient selection, cryolipolysis is a safe, well-tolerated, and effective treatment method for reduction of subcutaneous fat.

The authors have indicated no significant interest with commercial supports.

Liposuction is a popular surgical procedure for body contouring, but concerns remain regarding the invasiveness of the procedure, anesthesia, and downtime for recovery. Noninvasive body reshaping techniques have been investigated, including low-level laser therapy, ultrasound, radiofrequency, and infrared light, but results have been inconsistent and there has been little scientific evidence of efficacy.[1] Cryolipolysis, a new technique for noninvasive fat removal, was investigated for safety, tolerance, and patient satisfaction.

Background

Prior studies have shown that cold exposure can induce panniculitis, which is local inflammation in subcutaneous fat. Cases have been described in adult female equestrians[2,3] and infants[4] showing clinically significant inflammation after minor cold exposure.

Preclinical studies were performed to investigate the effect of controlled cold application to the skin surface and the resulting selective damage to subcutaneous fat. Three complementary porcine preclinical studies were conducted for initial explo-

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ration, dosimetry evaluation, and safety assessment measuring lipid levels.[5] The investigators found that selective reduction in superficial fat was achieved using the cryolipolysis procedure without causing injury to the epidermis or dermis. The investigators found that 80% of the superficial fat layer was removed 3.5 months after treatment, for a total fat loss of 40%.[5] Histologic analysis from the porcine models found that controlled, selective cooling could be used to induce an inflammatory response in the subcutaneous fat approximately 24 hours after the cold treatment. Time course evaluation found that the inflammatory response intensified as histiocytes, neutrophils, lymphocytes, and other mononuclear cells surrounded adipocytes, leading to subsequent digestion of the fat cells. The inflammatory process was found to decline 90 days after treatment. The preclinical safety studies established no effect on serum lipid levels in the animal models while attaining significant reduction in subcutaneous fat without damaging the epidermis or dermis.

Clinical studies were performed to investigate the efficacy of cryolipolysis in 32 subjects, with efficacy assessed according to ultrasound measurement of the fat layer, pre- and post-treatment photograph comparison, and physician assessment. The study found an average fat reduction of 22.4% in subjects assessed 4 months after treatment.[1,6] A separate study of 10 subjects assessed efficacy and effect on nerve fibers after cryolipolysis. The investigators found an average fat layer reduction of 25.5% at 6 months after treatment. Although approximately one-third of the subjects experienced transient reduction in sensation in the treated site, all experienced restoration of sensation within 7 weeks (mean 3.6 weeks).[7]

Although numerous clinical studies have been conducted at U.S. sites, only a limited number of patients have been treated and studied at international sites. This study investigated tolerance, safety, and patient satisfaction of cryolipolysis in a multicenter European trial. A subset of the patient population was also assessed according to caliper measurements and clinical photograph review.

Materials and Methods

This article reports the results of a retrospective multicenter study from two European clinical sites, one in France and one in Belgium, where patients received cryolipolysis treatments (CoolSculpting, ZELTIQ Aesthetics, Pleasanton, CA). The study was conducted between July 2009 and February 2012.

Trained clinicians collected patient data on age, sex, medical history, and Fitzpatrick skin type. The chart review was conducted at 891 cryolipolysis treatment sites on 518 patients. Study subjects were not identified in the results, so the study was exempt from independent human research review committee approval, although principles of the 1975 Declaration of Helsinki were followed.

The primary study endpoints were assessment of cryolipolysis procedure safety and tolerance. Clinicians recorded the number of treatment cycles, area(s) treated, side effects, and adverse events. Immediate side effects and tolerability were assessed in the clinic after treatment. Short-term side effects were evaluated by telephone follow-up 1 month after treatment.

As a secondary study endpoint, treatment efficacy was evaluated according to a patient satisfaction survey, caliper measurements, and clinical assessment of photographs. Overall patient satisfaction was assessed at the Belgian study center in a follow-up office consultation 3 months after treatment and at the French study center in a telephone follow-up at times more than 3 months after treatment. Satisfaction with the procedure was assessed using a 4-point scale (extremely satisfied, satisfied, neutral, and disappointed).

A subset of the patient population (49/518) underwent caliper measurement of fat layer reduction and clinical assessment of standardized pre- and

post-treatment photographs. Caliper measurements were taken at the treatment site and a control site. The control site was selected from a region not receiving treatment (e.g., if flanks were treated, the control site was the abdomen). A plastic template was created for the treatment and control sites of each study subject with landmark features such as moles and scars noted. Landmarks were recorded to facilitate precise positioning of the calipers to ensure that the same sites would be measured before treatment and at the follow-up visit. To minimize operator error, the same properly trained clinician took caliper measurements at each visit. Care was taken to position the subject consistently during measurement with arms folded above the head, posture upright, and legs slightly spread with feet precisely positioned over footmarks on the floor.

Results

Five hundred eighteen patients were treated (73% female, 27% male; mean age 42.7 ± 22.6). The majority of subjects had Fitzpatrick skin types II (n = 200, 38%) and III (n = 207, 40%). There were no subjects with Fitzpatrick skin type I, 78 with type IV was (15%), and 33 with types V and VI (6%).

A variety of treatment areas were studied in an effort to assess safety and efficacy, as shown in Figure 1. There were 891 total areas treated, comprising the flanks (love handles) (59%), abdomen (28%), back (12%), inner thighs and knees (1%), and buttocks (1%). The majority of sites were treated once (86.5%), although some areas were treated two (13%) or three (0.5%) times.

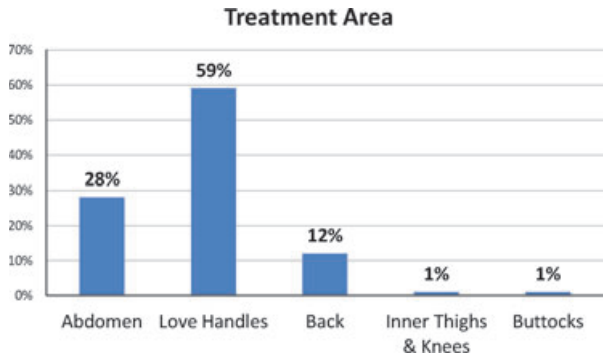

Figure 1. The majority of treatments were to the love handles (59%) and abdomen (28%).

Side Effects

Side effects from the cryolipolysis treatment were minor. Erythema was reported in 100% of cases. The skin aspect immediately after treatment was observed to be clay-like (52%), as illustrated in Figure 2, or stiff (48%), as shown in Figure 3.

Additional side effects observed immediately after treatment included rare vasovagal reaction (2.1%) after anterior abdominal area treatment and varying levels of pain. In 96% of patients, the pain was reported as minimal to tolerable. Severe pain was reported in 4% of patients, occurring only during

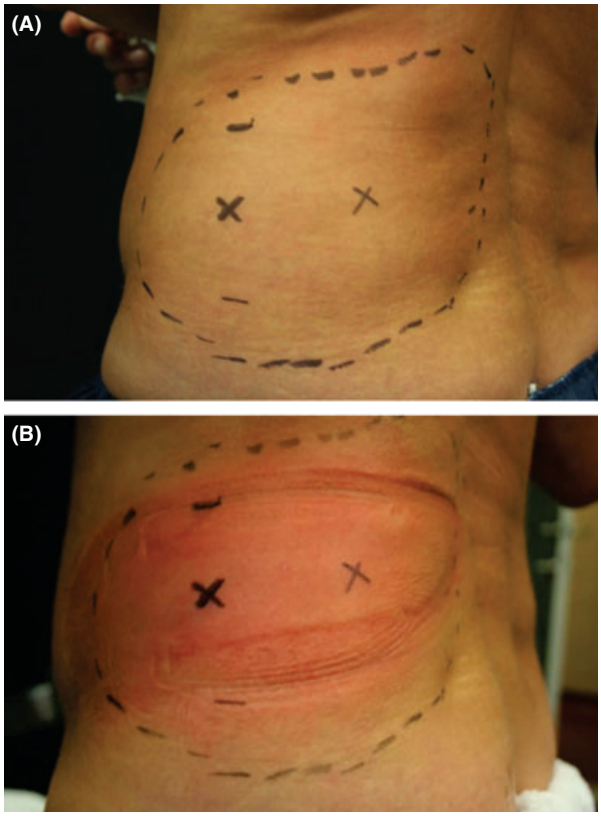

Figure 2. Pre- (A) and immediate post-treatment (B) photographs of a flank treatment demonstrate the clay-like nature of the tissue immediately after cryolipolysis.

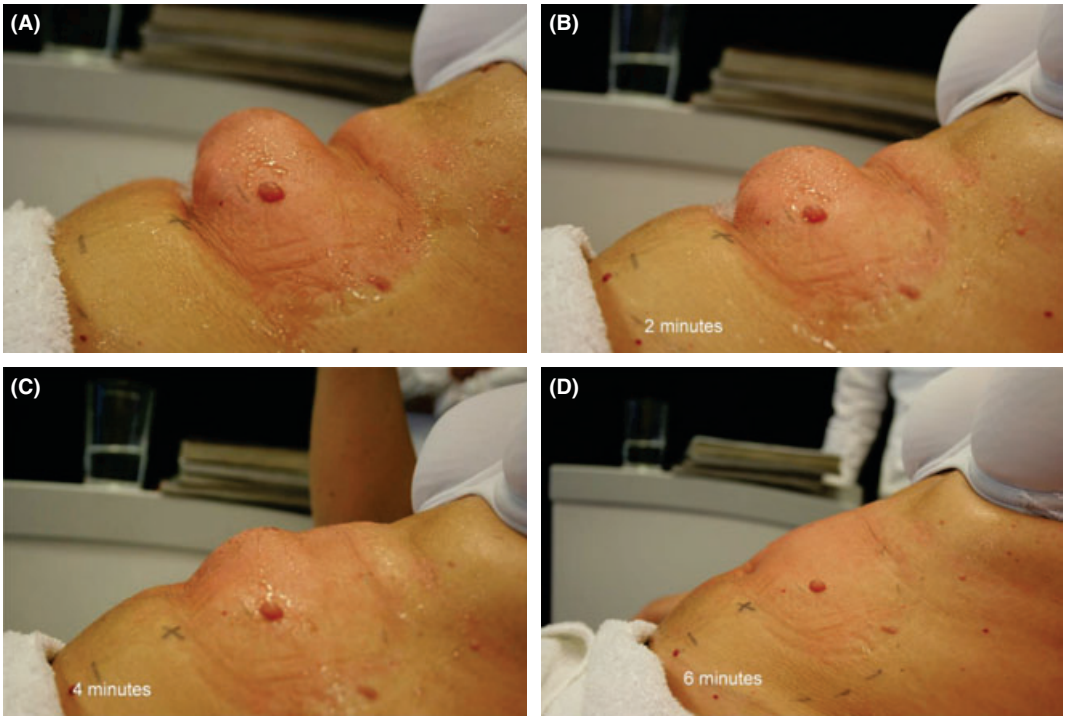

Figure 3. Post-treatment photographs of an abdomen treatment demonstrate the stiff "butter stick" nature of the tissue immediately after cryolipolysis, followed by resolution at 2, 4, and 6 minutes.

the initial 5 minutes of cryolipolysis, with no interruption of treatment required.

Tolerability of the cryolipolysis treatment was assessed by querying patients on their perception of treatment duration. Figure 4 shows that the procedure was well-tolerated, with 77% feeling the time was "about right," 11% feeling the procedure was shorter, and 1% feeling the treatment was much shorter than the actual treatment time. Only 11% of respondents felt the procedure was too long.

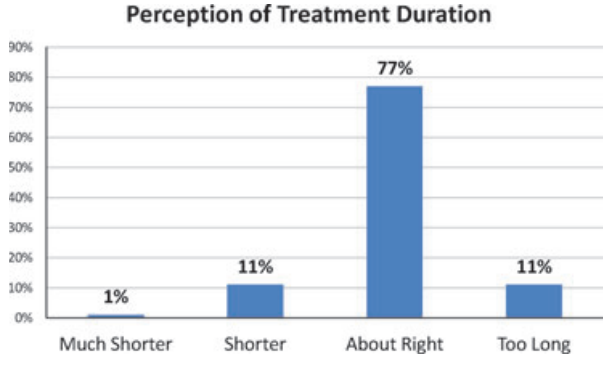

Figure 4. Procedure was well-tolerated, as shown by patient perception of treatment time (n = 49).

Of the total patient population, 92% (n = 479) were assessed for short-term side effects 1 month after treatment, but 8% (n = 39) could not be located for assessment. In those assessed, there were few short-term side effects noted; 9.8% of patients reported bruising in the treatment area, which was determined to be caused by the vacuum handpiece.

Transient changes in sensitivity were reported in a small number of patients. Decreased sensitivity in the treatment area was reported in 0.4% (n = 2) of patients, and both cases resolved spontaneously in 1 to 5 weeks. Transient increased sensitivity in the treatment area was reported in a larger percentage of patients—2.5% (n = 12) within the first few days after treatment. One case of increased sensitivity was reported after treatment of the flanks and the remaining 11 cases after treatment of the abdomen. Respondents noting increased sensitivity were not

affected enough to decrease their normal activities, except for one patient who was a fitness instructor. All cases of increased sensitivity spontaneously resolved in 3 weeks or less. Recommended treatment was ibuprofen (400 mg twice daily) until resolution.

Twelve patients (2.5%) also reported nodular or diffuse infiltration in the treatment area within a few days after treatment. Erythema and pain accompanied infiltration, which lasted 8 to 25 days. Recommended treatment was ibuprofen (400 mg twice daily) or acetaminophen (2–4 g once daily). All cases resolved spontaneously, with complete regression. Anecdotal evidence suggests that these patients experienced greater efficacy than those who did not experience infiltration. It is hypothesized that a more-pronounced inflammatory response triggered a more-pronounced response to treatment. Figure 5 demonstrates a case of nodular infiltration, with the pretreatment photograph and a 3-month follow-up photograph showing a region of red, indurated, sensitive plaque in the treatment area.

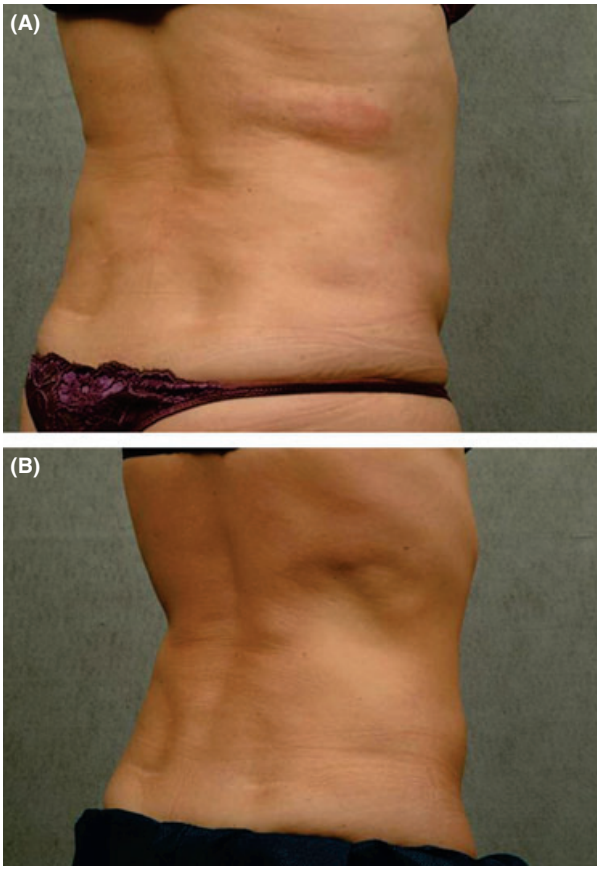

Figure 5. Post-treatment photographs at 5 days (A) and 3-month follow-up (B) demonstrate a nodular infiltration.

In summary, short-term side effects included bruising, transient changes in sensitivity, and nodular or diffuse infiltration at the treatment site. All reported short-term side effects resolved spontaneously. There were no reports of persistent erythema, blistering, or skin necrosis. There were no cases of dyschromia, including in the 32 patients with Fitzpatrick skin types V and VI.

There were no long-term side effects. No adverse events were reported.

Effectiveness

Efficacy assessment was a secondary endpoint for this study and was gauged using three metrics: patient-reported satisfaction scores, caliper measurement of fat layer reduction, and investigator assessment from standardized pre- and post-treatment photographs.

Patient Satisfaction Scores

Treatment efficacy was evaluated by consultation 3 months after the procedure at the Belgian clinical center, which treated 75 of the 518 patients in this study; 66% of these patients (n = 49) were evaluated at 3 months, and 34% (n = 26) could not be located.

The French clinical center, which treated 443 of the 518 patients in the study, also evaluated treatment efficacy in telephone follow-up; 44% of these patients (n = 194) were evaluated more than 3 months after treatment, and 56% (n = 249) could not be located. The results reported here represent the combination of patients from both sites (n = 243).

Patients were asked whether they were extremely satisfied, satisfied, neutral, or disappointed in their

Figure 6. Patient satisfaction surveys revealed that most patients were satisfied (n = 243).

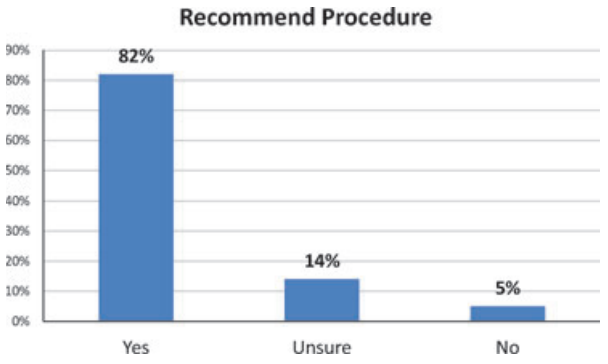

Figure 7. Eighty-two percent of patients would recommend the procedure to others.

results. Satisfaction surveys found that 73% reported being extremely satisfied or satisfied (Figure 6).

When asked whether they would recommend the cryolipolysis procedure to a friend, 82% said yes, 14% said they were unsure, and 5% said no (Figure 7). Some patients chose not to answer the recommendation question (n = 21). These patients and those who stated that they would not recommend the procedure were asked to explain the reason for their response. Patients highlighted multiple reasons for their inability to answer or lack of recommendation, including expense (n = 20), pain (n = 3), length of treatment (n = 6), and insufficient efficacy (n = 19).

Caliper Measurements

Treatment efficacy was assessed according to caliper measurements before treatment and at the 3-month follow-up consultation (n = 49). Patients were instructed not to change diet or exercise habits in order to maintain stable weight during the study. Attention was given to proper patient selection; only non-obese, fit patients with localized fat deposits were included. Weight was measured before treatment and at the follow-up visit. Mean weight was 65.9 ± 11.3 kg before treatment and 66.0 ± 11.7 kg at the follow-up visit—a statistically insignificant change.

Caliper measurements were taken at the treatment site and a control site. When comparing the treated site with the control site, 94% of subjects showed a reduction in fat thickness. On average, the subjects had a 23% reduction in fat thickness at the treated site. In contrast, the control site showed a statistically insignificant change in fat thickness, with mean caliper measurements of 3.18 ± 1.02 cm before treatment and 3.14 ± 1.02 cm at follow-up.

Investigator Assessments

Finally, the investigator performed an efficacy assessment by grading pre- and 3-month post-treatment photographs (n = 49). Based on the investigator's analysis, 73% of the subjects displayed reduction of fat thickness in the treated area. The most effective treatments seemed to occur in the abdomen and flank sites—85.5% of subjects showed improvement in these two treatment sites. In comparison, there seemed to be little to no visual indication of treatment response in the thigh, knee, and buttock areas.

Figure 8 illustrates a lower abdomen treated with two treatment cycles. Patient weight was 0.1 kg greater in the 3-month follow-up photograph, yet caliper measurement of the treatment area showed a 2.2-cm decrease in fat thickness. Figure 9 shows flanks in pre- and 2-month post-treatment follow-up photographs. The treated site shows visible and significant reduction in the flank fat layer and a more contoured appearance.

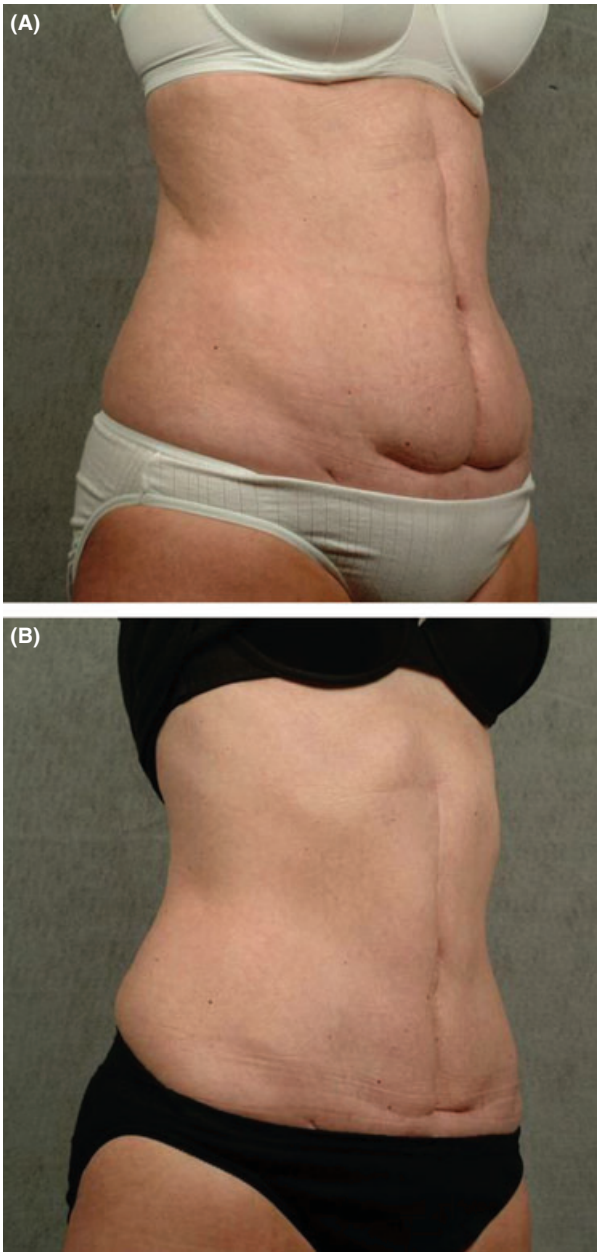

Figure 8. Lower abdominal treatment before (A) and 3 months after treatment (B) showing visible reduction in adipose tissue and 2.2-cm reduction in caliper measurement.

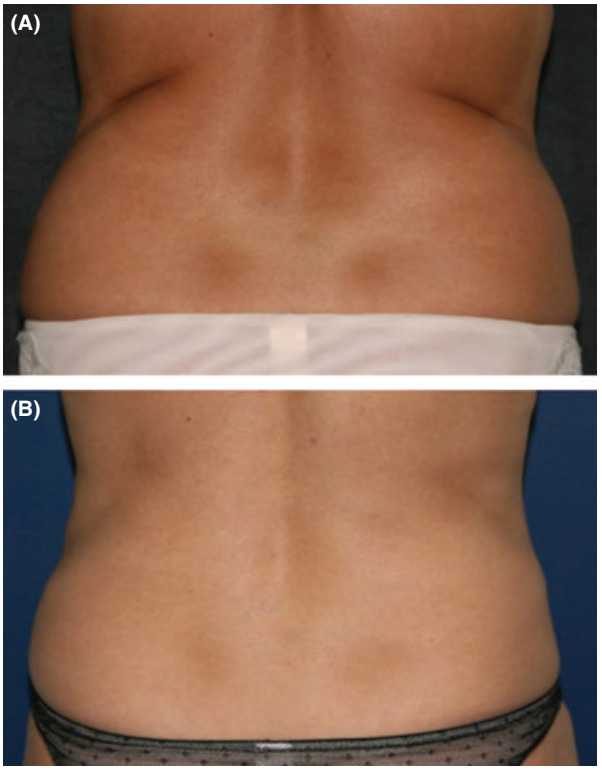

Figure 9. Flank treatment before (A) and 2 months after treatment (B) showing visible reduction in excess fat.

Discussion

Cryolipolysis appears to be safe and well-tolerated for fat layer reduction. As shown in this multicenter European study, the procedure produced only minor side effects. There were no cases of dyschromia, as is often the case in laser skin treatment of patients with Fitzpatrick skin types V and VI.[9] No patients reported persistent erythema, blistering, or skin necrosis. Although there were reports of bruising from the vacuum handpiece (9.8%), transient increased (2.5%) and decreased (0.4%) sensitivity, and nodular or diffuse infiltration at the treatment site (2.5%), all conditions resolved spontaneously. The resolution of transient sensitivity changes is consistent with findings of previous researchers.[7] No long-term side effects or adverse events were reported.

Patients also demonstrated that cryolipolysis is well-tolerated for reduction of subcutaneous fat. During the procedure, 96% of subjects reported minimal to tolerable discomfort. Only 4% reported severe pain, which occurred during the initial 5 minutes of treatment and was not severe enough to require interruption of treatment. A survey of patient perception of treatment duration further

demonstrated that the procedure is well-tolerated, with only 11% feeling that the procedure was too long.

A patient satisfaction survey conducted 3 months or more after treatment found that most patients were satisfied with the treatment. Investigators found that 35% were extremely satisfied, 38% satisfied, 23% neutral, and 4% disappointed. Most patients (82%) also stated that they would recommend the cryolipolysis procedure to a friend.

The study results demonstrate that the cryolipolysis procedure is effective in reducing fat layer thickness. Subjects attained an average 23% reduction in fat thickness at the treated site, as determined according to caliper measurements at 3-month follow-up. Investigator assessment of pre- and post-treatment photographs found that 86% of the patients achieved reduction of fat thickness in the treated flank and abdomen areas.

The investigators also found that careful patient selection, proper anatomic site selection, and adequate number of treatment cycles are critical for achieving successful patient outcome. The most-effective treatment was noted in the abdomen and flank sites. The investigators observed limited treatment response with fibrous bulges in areas such as the thighs, knees, and buttocks. Further research should be performed to optimize treatment time, number of cycles, and perhaps handpiece shapes to improve cryolipolysis efficacy in fibrous bulges, which are typically difficult to treat.

Additional fundamental research should be performed to establish the mechanism of action by which cryolipolysis damages adipocytes. It is not known why adipocytes are more sensitive to cold than other cell types and how adipocyte apoptosis occurs and leads to inflammatory infiltration at the treatment site.[8]

Conclusion

Results of this retrospective multicenter European study found that cryolipolysis is a safe and well-tolerated nonsurgical procedure to reduce fat layer thickness. With proper patient assessment, efficacy and patient satisfaction can be consistently and frequently achieved.

References

1. Avram MM, Harry RS. Cryolipolysis for subcutaneous fat layer reduction. Lasers Surg Med 2009;41:703–8.
2. Rotman H. Cold panniculitis in children. Arch Dermatol 1966;94:720–1.
3. Duncan WC, Freeman RG, Heaton CL. Cold panniculitis. Arch Dermatol 1966;94:722–4.
4. Beachman BE, Cooper PH, Buchanan CS, Weary PE. Equestrian cold panniculitis in women. Arch Dermatol 1980;116:1025–7.
5. Manstein D, Laubach H, Watanabe K, Farinelli W, et al. Selective cryolysis: a novel method of non-invasive fat removal. Lasers Surg Med 2009;40:595–604.
6. Dover J, Burns J, Coleman S, Fitzpatrick R, et al. A prospective clinical study of non-invasive cryolipolysis for subcutaneous fat layer reduction—interim report of available subject data. Lasers Surg Med 2009;S21:45.
7. Coleman SR, Sachdeva K, Egbert BM, Preciado J, et al. Clinical efficacy of non-invasive cryolipolysis and its effects on peripheral nerves. Aesthetic Plast Surg 2009;33:482–8.
8. Nelson AA, Wasserman D, Avram MM. Cryolipolysis for reduction of excess adipose tissue. Semin Cutan Med Surg 2009;28:244–9.
9. Alster TS, Tanzi EL. Complications in laser and light surgery. In: Goldberg DB, editor. Laser skin surgery. vol 2. Philadelphia: Elsevier; 2005. pp. 103–17.

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