

Cryolipolysis: A Historical Perspective and Current Clinical Practice

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Dermatologists have long used cold-based therapeutic approaches for a variety of applications. Based on the differences in chemical composition, it is possible to selectively target certain tissues rich with lipid, while sparing the surrounding tissue predominantly containing water. With historical observations of cold-induced panniculitis suggesting the feasibility of this strategy, cryolipolysis has emerged as a new methodology using controlled cooling to selectively target fat. Both preclinical and clinical studies have established the safety and efficacy of cryolipolysis for noninvasive body contouring. This review will focus on the evolution of cryolipolysis from initial case reports of cold-induced panniculitis, to preclinical and clinical studies, and the current clinical practice.
Semin Cutan Med Surg 32:31-34 © 2013 Frontline Medical Communications

KEYWORDS cryolipolysis, cryotherapy, body contouring, fat, panniculitis

Cryotherapy has a storied history in dermatology. From the early use of carbon dioxide (“dry ice”) to the current benchmark, liquid nitrogen, dermatology as a specialty has long recognized the utility of cold-based therapies in the nonselective destruction of tissue. Indeed, cryotherapy is used for destruction of actinic keratoses, verrucae, and superficial skin tumors routinely in dermatology.¹ While these approaches with liquid nitrogen at a temperature of -196°C have largely relied on non-specific cryoinjury, technology tailored to selectively target fat at far warmer temperatures was recently introduced. In 2007, Manstein et al² reported a novel noninvasive method for fat reduction, termed “cryolipolysis.” This concept was built on several cues from clinical observations.

The first report of adipose tissue and its sensitivity to cold injury dates back to 1902 by Hochsinger.³ He described firm nodules under the chin in young children, what he deemed an “acute freezing reaction.” It was not until 1941 that Haxthausen⁴ published a case series of 4 young children and a teenager who had developed what he termed “adiponecrosis e frigore.” He observed that these lesions occurred in the winter after exposure

to extreme cold. Reports from 1940 to 1970 echoed these original findings, with red indurated nodules indicative of cold-induced panniculitis occurring in a variety of clinical situations, including in children and adults, after various cold insults.⁵⁻⁷ In 1970, Epstein and Oren⁸ coined the term “popsicle panniculitis” after reporting the presence of a red indurated nodule followed by transient fat necrosis in the cheek of an infant who had been sucking on a popsicle. Ice cube exposure on the buttocks of this child produced the same lesions. These observations led to the concept that lipid-rich tissues are more susceptible to cold injury than the surrounding water-rich tissue. The susceptibility is even more refined. In most of these cases, children and infants were more frequently affected than adults. These reports point to some clues that confirm the fundamental biochemistry that we observe on a daily basis in our kitchen. Saturated fats, such as butter, are solid at room temperature, whereas their less-saturated counterparts, such as olive oil, are in a liquid state at the same temperature. Indeed, babies’ and young children’s fat is a bit more like butter, with more saturated fats such as palmitic and stearic acid in their adipose tissue.⁹ This has been experimentally confirmed in animal models when young pigs fed saturated fats were more likely to have cold-induced lipoatrophy than those fed unsaturated fats.¹⁰

Preclinical Studies

With these historical observations in mind, a pilot clinical study sought to determine the feasibility of fat reduction using the external application of cold. A single Yucatan pig was exposed to a copper plate cooled to -7°C with circulating

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Disclosures: The authors have completed and submitted the ICMJE Uniform Disclosure for Potential Conflicts of Interest. Dr. Avram is a consultant for Zeltiq Aesthetics, Inc. Dr. Jalian has nothing to disclose.

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antifreeze solution. Firm pressure was used to ensure contact as well as to decrease perfusion, facilitating a more rapid rate of cooling. Three months after exposure, all 10 sites demonstrated visible indentation with a measurable decrease in superficial fat layer thickness.² A subsequent study confirmed this finding in 3 swine, with >30% reduction in the thickness of the superficial fat layer in the treatment area, as measured by ultrasonography.¹¹ In both these studies, there was limited incidence of transient hyperpigmentation that resolved within 1 week. No ulceration or hypopigmentation was noted. Moreover, no significant change in serum lipids or liver function was noted.

In vitro studies on adipocyte cell cultures suggest that cold-induced adipocyte apoptosis is partially responsible for the clinical effect.¹² An alternate mechanism is reperfusion injury of cryosensitized adipocytes, leading to inflammation, generation of reactive oxygen species, and cell death. Histology reveals a reproducible sequence of events after treatment. Immediately after treatment, there is no histologic evidence of adipocyte damage. This is in stark contrast with heat-based treatments that rely primarily on either selective or nonselective thermal damage and immediate thermal coagulation or necrosis. As early as 2 days after treatment, an inflammatory infiltrate is observed that quickly culminates into a predominantly lobular panniculitis 2-4 weeks after treatment (Fig. 1). This inflammation may last up to 3 months after treatment. Macrophages present within the infiltrate are thought to ingest and clear apoptotic adipocytes. During the 3 months after treatment, there is a gradual clearance of adipocytes and apparent widening of fibrous septae, which is concomitant with the clinical end point of reduction in the fat layer.

Clinical Studies

The current clinical device used for cryolipolysis is composed of a cup-shaped applicator that uses a vacuum to draw the target area into the applicator and position it between 2 cooling plates. The vacuum reduces blood flow to the area, facilitating cooling, while the cup-shaped applicator allows for more optimal contouring ability. A cooling intensity factor is then selected, a value that represents the rate of heat efflux out of the tissue. Treatment duration is 60 minutes. Toward the end of the treatment, a massage cycle engages to facilitate homogeneity of crystallization within the treatment site. Various hand pieces are available to tailor the treatment to a specific contour. After removal of the applicator, the immediate clinical end point is apparent as a solid block of tissue in the shape of the applicator (Fig. 2). This quickly resolves, and limited clinical studies support the use of postprocedure manual massage to increase treatment efficacy.¹³

A series of clinical studies confirmed the efficacy of cryolipolysis for improvement in localized adiposity. Clinical trials first demonstrated improvement in adiposity of the flanks, so-called "love handles," in 32 subjects.¹⁴ Subjective improvement, measured both by subject and investigator assessment, was evident. Ten subjects who underwent ultrasonography examination demonstrated a 22.4% average reduction of fat-layer thickness. A subsequent larger pro-

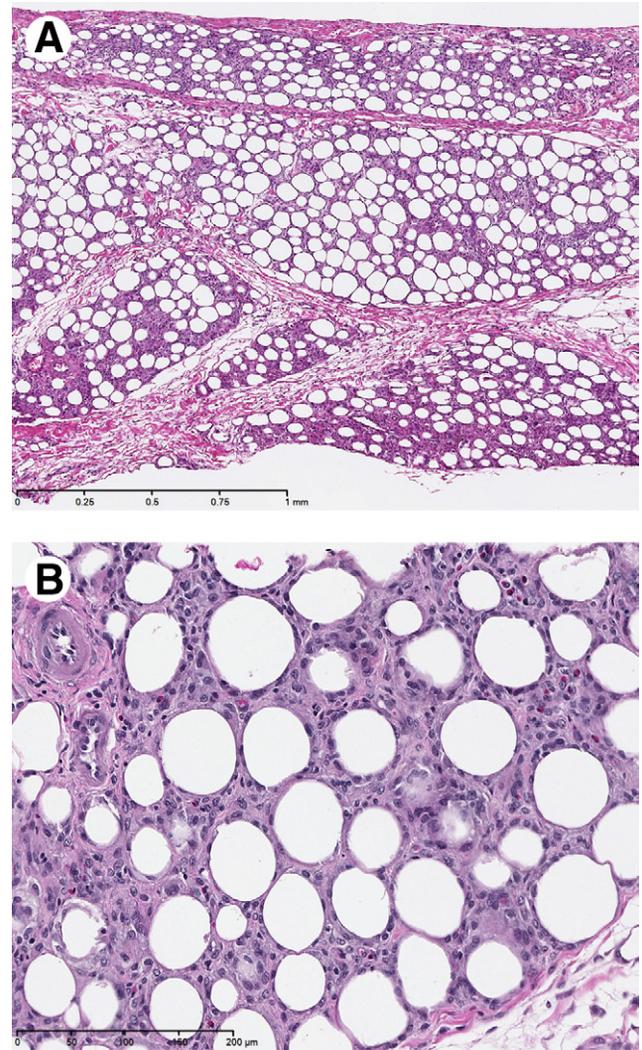


Figure 1 One week after localized cooling of porcine skin. Note the predominantly lobular panniculitis throughout the adipose tissue (A, 5×). On higher magnification (B, 20×), individual adipocytes are surrounded by a predominantly mononuclear cell infiltrate. Figure courtesy of Wellman Center for Photomedicine.

spective study of 50 subjects confirmed this subjective improvement. Three blinded physician investigators were able to differentiate between pretreatment vs posttreatment sites in 82% of the cases.¹⁵ Based on these data, the device gained Food and Drug Administration clearance for the flanks in 2007. Since its initial clearance, multiple studies have confirmed safety and efficacy of the device, including in the setting of multiple repeat treatments¹⁶ and darker skin phototypes.¹⁷ Cryolipolysis recently gained Food and Drug Administration clearance for use on the abdomen in 2012.

Many practitioners have performed cryolipolysis treatment in patients with focal adiposity in other sites. Any provider using the device in "off-label" locations should pay close attention to ensure sufficient adiposity for efficacy. Care should also be taken to avoid areas with superficial nerve bundles, such as the upper arm, as this can result in temporary dysesthesia distal to the treatment area (see discussion of side effects later in text).



Figure 2 Immediate clinical end point after removal of the applicator. Note the raised “frozen” tissue with surrounding erythema. Figure courtesy of Wellman Center for Photomedicine.

Patient Selection

As with any device-based treatment, patient selection is paramount. One should obtain a thorough medical history, including medications, rheumatologic history, and surgical history, particularly prior to abdominal surgery. Physical examination should aim at determining whether the patient is a good candidate. Areas with focal adiposity should be easily lifted from the underlying musculature. There should be a sufficient fat layer, otherwise the device may not attach correctly with the vacuum applicator. In those with previous abdominal surgeries, physical examination should focus on palpating for a hernia both in the recumbent position and also while the patient performs a Valsalva maneuver, as there is a potential for hernia incarceration with the vacuum suctioning.

Patient counseling is also an important predictor of satisfaction. Potential patients should be made aware of the moderate efficacy of the device. Patients should also be informed that the results are delayed and can take up to 3 months to notice a difference. There is usually a clear improvement, however this treatment does not approach the efficacy of liposuction. Cryolipolysis is not a substitute for diet and exercise, and treatment is largely cosmetic, offering minimal health benefits. This is not a weight-loss device, and it is not suitable for those who are looking to achieve global weight loss. Moreover, those with predominantly visceral fat are poor candidates and should not have this treatment. Figure 3 shows a representative outcome after a single application to the right flank before and 2 months after treatment.

There are some relative contraindications. The device manufacturer recommends caution when treating those with cold-sensitive disorders, including Raynaud’s phenomenon, cold urticaria, cryoglobulinemia, and paroxysmal nocturnal hemoglobinuria. Because of the temporary neurologic effects (discussed later in the text), it may be prudent to exercise caution in those with known neurologic disease (eg, multiple sclerosis).

Adverse Events

There have been roughly 450,000 cryolipolysis treatments since its introduction. In addition to efficacy, clinical experience points to the relative safety of this device. Immediately after treatment, there is expected edema and erythema that can last for up to 72 hours. Ecchymosis secondary to the vacuum applicator is not uncommon, especially in those on anticoagulation medications. In addition to these transient effects, decreased cutaneous sensation is common. Nearly all patients experience some sort of dysesthesia in the treatment



Figure 3 Representative clinical result before (left) and after (right) cryolipolysis. Patient underwent 1 treatment cycle to the right flank using standard manufacturer’s instructions. Results shown are 2 months after treatment. Figure courtesy of Wellman Center for Photomedicine.

site, which largely resolves within 1 week.¹⁸ However, there can be limited residual decrease in sensation that can last up to 2 months. No reports exist of cases of permanent sensory alteration after cryolipolysis treatment. Similar to the animal studies, no significant change in triglyceride levels or liver function tests was reported in the human studies.¹⁹

Perhaps in connection with these transient neurologic connections, rare reports of severe pain emerged after cryolipolysis treatments. With an incidence of 1 in 1500 patients, the pain is described as severe shooting and jabbing in the treatment area 1 week after treatment. The incidence appears to be higher when using the larger treatment applicator. The mechanism remains unclear but may be related to hyperalgesia associated with transient nerve damage and subsequent regeneration or perhaps a more robust panniculitis. In the initial report of 23 patients, adequate pain control was achieved with topical or oral analgesics. All cases resolved spontaneously within 1-4 weeks.²⁰

This is an intriguing new technology, but both physicians and patients should be aware that there are important limitations. Because of the size of the applicator, currently only focal collections of adiposity can be targeted. This is in contrast to other commercially available body contouring devices that can treat larger areas in 1 treatment session. Also, the current clinical benefit is modest, and multiple treatments may be required to achieve the desired clinical outcome. Finally, we are currently still unaware of the long-term side effects of this treatment. As the popularity of the device increases and we move further away from initial approval, rarer side effects may emerge.

Conclusions

The selective targeting of lipid-rich tissue with cold has ushered in a novel methodology with moderate efficacy for non-invasive fat reduction. While cryolipolysis is not a weight-loss tool, it can effectively improve focal pockets of adiposity, resulting in an improvement in body contour. The technology is still young, but current clinical experience points to a favorable safety profile with mild transient adverse events.

We have long recognized the utility of cold-based therapies for the nonselective destruction of tissue. In the past, we have relied on modalities using temperatures far exceeding the freezing point of water. Astute attention to clinical cues provided by historical observations led to the evolution of selective targeting of fat. By adapting this strategy to use far warmer temperatures, we can now preferentially target lipid-rich tissue without affecting the surrounding tissue rich with water. Treatment outcomes may be further optimized with additional studies. The knowledge that the target's susceptibility to injury is in turn dictated by its chemical composition

enables us to fine-tune the treatment for different clinical outcomes. With this paradigm in mind, other novel cold-based therapies are theoretically foreseeable. Cryolipolysis has enjoyed the most commercial success in this venue; however, other novel approaches to selectively target tissue are in the pipeline.

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