Prospective and Randomized Determination of the Efficacy of Topical Lipolytic Agents

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Numerous manufacturers are marketing topical creams, claiming that they improve or eliminate unwanted fat or cellulite in a short period of time. The active ingredient in most of these creams is theophylline, and claims have been made that it initiates lipolysis by binding to adipocyte β-adrenergic receptors. The creams are applied with vigorous massage to facilitate absorption and apply mechanical stress to the fat cells. The efficacy of these creams is largely untested. This prospective randomized study was conducted to determine whether there is scientific evidence that application of these creams alone can eliminate unwanted fat or cellulite.

Eleven women with normal body weight as defined by insurance tables applied either Skinny Dip™ or a placebo to one thigh and one half of the abdomen for 8 weeks. Each subject was examined, photographed, weighed, and measured by a study monitor on a weekly basis. There were no statistically significant differences in appearance, abdominal circumference, thigh circumference, or skin fold measurements among subjects using the active agent (Skinny Dip™) or the placebo.

This study failed to support the efficacy of topically applied lipolytic creams in eliminating unwanted fat manifesting as a localized bulge or cellulite presenting as a dimpling of the skin.

Introduction

The presentation of preliminary reports affirming the success of topically applied lipolytic agent creams incited a thigh cream craze. More than a dozen manufacturers responded to an overweight nation’s desire for firm, thinner thighs with a barrage of miracle creams. Manufacturers marketed topical lipolytic creams, which they claimed were able to break down fat. Consumers jumped at the chance to have the thighs of swimsuit models. Millions of dollars were spent on these creams whose effects were clinically undocumented.

The active ingredient in many of the lipolytic agent creams is aminophylline. Manufacturers of aminophylline creams claim they inactivate the α-adrenergic receptors of adipocytes. Normally lipolysis is triggered by the binding of epinephrine to the β-
adrenergic receptors. The binding of epinephrine to the β-adrenergic receptor triggers the synthesis of cyclic 3,5 adenosine monophosphate (cAMP). The synthesis and activation of cAMP sets off a cascade in which fatty acid production is turned off and triglyceride degradation is turned on. Binding of the α-adrenergic receptors of adipocytes by epinephrine signals the storage of triglycerides rather than their breakdown and subsequent release of free fatty acids and glycerol. This binding of epinephrine to the α-adrenergic receptors stimulates the production of phosphodiesterase, which decreases the level of cAMP. Aminophylline contains theophylline, a known promoter of lipolysis. Theophylline works by inactivating the α-receptors of adipocytes.1

It is believed that the α-adrenergic receptors located in the thigh are more responsive than the β-receptors to epinephrine and its analogues.2 Additionally, women have been found to have a greater number of fat cells than men in the gluteal, epigastric, hypogastric, and femoral regions and larger adipocytes than men in the gluteal region.3 Consequently, women are prone to unsightly adipocytes in the thighs and buttocks will increase the level of men in the gluteal, epigastric, hypogastric, and femoral known promoter of lipolysis. Theophylline works by inactivating the α-receptors of adipocytes.1

Properly controlled studies documenting the validity of this type of product are lacking. The purpose of this study was to determine the efficacy of an allegedly topical lipolytic agent (Skinny Dip™) in a prospective randomized trial with female volunteers with normal body weight.

Material and Methods

Seventeen healthy women with normal body weight and an average age of 35.9 years were recruited as study subjects. The women were randomly assigned to two groups on the basis of the last digit of their social security numbers: those with odd numbers received the experimental (Skinny Dip™) product, whereas those with even numbers received a placebo cream packaged in a Skinny Dip™ container. Subjects were instructed to make no changes in their daily activities and were specifically told not to modify their diet or exercise habits. Proper application technique was also explained. The products in the Skinny Dip™ containers (both the experimental and placebo creams) were applied twice daily to the right thigh and left side of the abdomen and then massaged into the skin for 5 minutes. The untreated left thigh and right side of the abdomen, which served as controls, were also massaged for 5 minutes.

Before the experiment began and for the subsequent 8-week study period, each subject was weighed, photographed, visually examined, and measured weekly by the same study monitor. The circumferences of the treated and untreated thighs were measured with a tape measure at fixed points determined by initial measurements determined for each subject by measuring the distance from the top of the iliac crest to the fattest point on the outer thigh. The circumference of the abdomen was also measured at fixed points determined for each subject by measuring the distance from the center of the umbilicus down to the largest protrusion of fat.

A caliper was used to measure the skin fold thickness at fixed points on the inner and outer portions of both thighs and both sides of the abdomen. The same points were used for the outer thigh caliper and the thigh circumference measurements and for the abdominal caliper and the abdominal circumference measurements. The fixed point for the inner thigh caliper readings was determined by initial measurements from the groin crease to the fattest point on the inner thigh for each subject. The subject’s menstrual cycle status was also noted in terms of before or after menstruation or currently menstruating.

Results

Eleven women completed the entire 8-week study and were judged to have been compliant with the protocol by the study monitor. Six women dropped out of the study: one became pregnant, another began a diet and was disqualified, and four lost their motivation when they observed no improvement after applying the product for 4 weeks.

Each subject’s weight remained essentially unchanged during the study period. The average weight of the 11 women was 138.6 lbs at the beginning of the study and 138.2 lbs at the end. No complications including skin rashes were reported in either the treatment or the placebo group. Subjective assessment of the results was solicited from participants, but only one Skinny Dip™ user reported improvement worthy of continued product use.
Table 1.
Difference between derived outcome of first and last visits

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Mean and standard deviation</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inner thigh caliper</td>
<td>-0.25 ± 0.73</td>
<td>0.72</td>
</tr>
<tr>
<td>Outer thigh caliper</td>
<td>-0.36 ± 0.72</td>
<td>0.35</td>
</tr>
<tr>
<td>Abdomen caliper</td>
<td>0.34 ± 0.34</td>
<td>0.94</td>
</tr>
<tr>
<td>Thigh circumference</td>
<td>-0.61 ± 0.61</td>
<td>0.03*</td>
</tr>
<tr>
<td>Weight</td>
<td>-0.50 ± 3.59</td>
<td>0.67</td>
</tr>
<tr>
<td>Abdomen circumference</td>
<td>0.00 ± 1.83</td>
<td>0.94</td>
</tr>
</tbody>
</table>

* Statistically significant result with a 97% confidence interval.

Table 2.
Probability that areas treated with Skinny Dip™ were different from controls

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Mean and standard deviation</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inner thigh caliper</td>
<td>-0.02 ± 0.13</td>
<td>0.86</td>
</tr>
<tr>
<td>Outer thigh caliper</td>
<td>0.26 ± 0.13</td>
<td>0.05*</td>
</tr>
<tr>
<td>Abdomen caliper</td>
<td>0.14 ± 0.10</td>
<td>0.15</td>
</tr>
<tr>
<td>Thigh circumference</td>
<td>0.02 ± 0.63</td>
<td>0.97</td>
</tr>
<tr>
<td>Weight</td>
<td>-0.50 ± 3.59</td>
<td>0.96</td>
</tr>
<tr>
<td>Abdomen circumference</td>
<td>0.00 ± 1.83</td>
<td>0.53</td>
</tr>
</tbody>
</table>

* Statistically significant result with a 95% confidence interval.

On the basis of the weekly visual inspections, the study monitor also did not see a noticeable difference between the treated and untreated areas. Comparison by the authors of the standardized prestudy and poststudy photographs revealed no differences between the control and treated areas in subjects using the real product. Also no differences were visible among patients receiving the experimental and placebo products.

Two different statistical approaches were used. In the first approach the probability that each of the five measurements from experimentally (i.e., Skinny Dip™) treated regions was significantly different from the placebo-treated regions was calculated by use of the Wilcoxon rank sum test. Rather than examining the outcomes directly, the difference between the treatment and control sides (control minus treatment) was noted for both the experimental and placebo groups; then the difference between the derived outcome of the first visit and the derived outcome of the last visit was calculated (last minus first) for both the experimental and treatment groups. Hence, a positive value indicates that the treated side decreased compared with the control side over the course of the study. From these derived outcome values, the mean values and associated standard deviations were calculated (Table 1). The Wilcoxon rank sum test was performed by use of the derived outcomes. Accordingly, the only significant difference (>95% probability that the experimental and placebo groups are statistically different) occurred in the thigh circumference measurements. The mean values of the thigh circumference for the experimental (-0.61 ± 0.61 cm) and the placebo (0.42 ± 0.74 cm) groups indicate that the placebo treatment was more effective than the Skinny Dip™ treatment.

Statistical analysis compared the five measurements: thigh circumference (treated and untreated), abdomen circumferences (treated and untreated), inner thigh caliper (treated and untreated), outer thigh caliper (treated and untreated), and abdomen caliper (treated and untreated). With a random effects model by Laird and Ware with SAS’s Proc Mixed data, unique regression lines were fitted to each subject (the slopes and intercepts of these lines were assumed to be normally distributed). The same (derived) outcomes were used as in the previous analysis; visit date, treatment group, and premenstrual timing of the visit were used to predict each outcome (it was found that being premenstrual did not affect the study). Treatment effect size (i.e., the effect of applying either Skinny Dip™ or the placebo on the size of all of the measured areas) and its standard deviation were calculated, as well as the probability that treated area measurements (Skinny Dip™ and placebo) differed significantly from the control measurements (Table 2).

In this case a positive treatment effect size indicated that the treatment (Skinny Dip™ and placebo) size increased. Again there was one statistically significant result—this time for the outer thigh caliper measurements. The mean value of the outer thigh caliper measurements (0.26 ± 0.13 cm) indicates that treated thighs (Skinny Dip™ and placebo) decreased in relation to the control thigh.
Statistically the two significant findings probably result from chance. Taken as a whole, the data analyses revealed no differences in either the circumference or skin fold thickness when Skinny Dip™-treated areas, placebo-treated areas, and untreated control areas were compared. Additionally, no consistent decreases in the mean treated values were observed.

Discussion

The premise behind topically-applied lipolytic agent creams seems plausible to the consumer looking for an easy way to attain smooth thighs and buttocks. If the aminophylline, which contains theophylline, an inhibitor of adipocyte storage, is applied directly to adipocytes, one would expect a decrease in the size of the adipocytes. Hence, if aminophylline were applied directly to the adipocytes in the thighs and abdomens of women, one would expect a decrease in the amount of cellulite. Hydrocrin which contains theophylline and ethylenediamine has been implicated in 13% of all cases of contact dermatitis. In Steelman’s study, of the 60 women in the treatment group, 23 dropped out because of the development of rashes. In the placebo group containing 28 women, no rashes were reported.

From our study it seems unlikely that there is any truth to the claims associated with lipolytic thigh creams that use aminophylline. However, the motivations that prompt women to resort to the use of such products are serious issues that warrant considerable attention. Not only is extra weight generally viewed as physically unattractive by society, it leads to many health problems. Irrespective of the testimonials of highly touted and heavily marketed miracles creams, at this point it seems that weight loss and exercise are still the most effective ways to improve cosmetic appearance and overall health. When it’s too good to be true, it usually isn’t true!

References