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Effect of caffeine gel and caffeine gel associated with iontophoresis in women gynoidlipodystrophy: A pilot randomized trial

Efeito do gel de cafeína e do gel de cafeína associado à iontoforese em mulheres com lipodistrofia ginóide: um ensaio piloto randomizado

Efecto del gel de cafeína y el gel de cafeína asociado con la iontoforesis en mujeres con lipodistrofia ginoide: un ensayo piloto aleatorizado

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Abstract
Caffeine has been widely used to treat gynoid lipodystrophy (GLD). Despite caffeine has been considered as a promise treatment, there is a lack of scientific evidences regarding its effect on GLD when associated with iontophoresis or others equipment. We aimed to evaluate the effects of a caffeine gel alone and associated with iontophoresis in GLD treatment. In a single-blind randomized clinical trial, women with mild/moderate GLD in the buttocks were randomized to topical caffeine gel group (CG; n=10); caffeine gel plus iontophoresis group (CIG; n=11) or iontophoresis group (IG; n=10). The groups were treated with 10 sessions, two times/week, 20 min/session. The subjects were evaluated pre and post treatment by photonumeric GLD severity scale, ultrasound image, thermography and quality of life questionnaire with a blind evaluator. There were statistical reduction in subcutaneous tissue thickness ($P \leq 0.046$) as well as in subcutaneous tissue plus dermis thickness ($P \leq 0.044$) in buttocks both in CG and CIG. GLD reduction was similar between CG and CIG, and these reductions were more pronounced than in IG ($P < 0.0001$). Furthermore, quality of life improved in all groups ($P < 0.017$). We concluded that caffeine alone and associated with iontophoresis were effective for decreasing the subcutaneous fat layer in women with GLD.
Keywords: Iontophoresis; Caffeine; Cellulite; Gynoid lipodystrophy; Thermography; Treatment.

Resumo
A cafeína tem sido amplamente utilizada para tratar a lipodistrofia ginóide (LDG). Apesar da cafeína ter sido considerada um tratamento promissor, faltam evidências científicas quanto ao seu efeito sobre o LDG quando associada à iontoforese ou outros equipamentos. Objetivamos avaliar os efeitos de um gel de cafeína sozinho e associado à iontoforese no tratamento de LDG. Em um ensaio clínico randomizado simples-cego, mulheres com LDG

leve / moderado nas nádegas foram randomizadas para o grupo de cafeína tópica em gel (GC; n=10); grupo de cafeína em gel mais iontoforese (GCI; n=11) ou grupo iontoforese (GI; n=10). Os grupos foram tratados com 10 sessões, duas vezes / semana, 20 min / sessão. Os sujeitos foram avaliados pré e pós-tratamento por escala foto numérica de gravidade de LDG, imagem de ultrassom, termografia e questionário de qualidade de vida com avaliador cego. Houve redução estatística na espessura do tecido subcutâneo (P≤0,046), bem como no tecido subcutâneo mais a espessura da derme (P≤0,044) nas nádegas tanto no GC quanto no GCI. A redução de LDG foi semelhante entre CG e GCI, e essas reduções foram mais pronunciadas do que no GI (P<0,0001). Além disso, a qualidade de vida melhorou em todos os grupos (P<0,017). Concluímos que a cafeína usada topicamente, bem como a cafeína associada à iontoforese, foi eficaz para diminuir a camada de gordura subcutânea em mulheres com LDG.
Palavras-chave: Iontoforese; Cafeína; Celulite; Lipodistrofia ginóide; Termografia; Tratamento.

Resumen
La cafeína se ha utilizado ampliamente para tratar la lipodistrofia ginoide (LDG). A pesar de que la cafeína se ha considerado un tratamiento prometedor, faltan evidencias científicas sobre su efecto sobre la LDG cuando se asocia con la iontoforesis u otros equipos. Nuestro objetivo fue evaluar los efectos de un gel de cafeína solo y asociado a la iontoforesis en el tratamiento de LDG. En un ensayo clínico aleatorizado simple ciego, las mujeres con LDG leve / moderada en los glúteos fueron aleatorizadas al grupo de gel de cafeína tópica (GC; n=10); gel de cafeína más grupo de iontoforesis (GCI; n=11) o grupo de iontoforesis (GI; n=10). Los grupos fueron tratados con 10 sesiones, dos veces / semana, 20 min / sesión. Los sujetos fueron evaluados antes y después del tratamiento mediante escala fotonumérica de gravedad de LDG, imagen de ultrasonido, termografía y cuestionario de calidad de vida con un evaluador ciego. Hubo reducción estadística en el grosor del tejido subcutáneo (P≤0.046) así como en el grosor del tejido subcutáneo más dermis (P≤0.044) en los glúteos tanto en CG como en CIG. La reducción de GLD fue similar entre CG y CIG, y estas reducciones fueron más pronunciadas que en IG (P<0,0001). Además, la calidad de vida mejoró en todos los grupos (P<0,017). Concluimos que la cafeína utilizada por vía tópica, así como la cafeína asociada con la iontoforesis, fueron efectivas para disminuir la capa de grasa subcutánea en mujeres con GLD.
Palabras clave: Iontoforesis; Cafeína; Celulitis; Lipodistrofia ginoidea; Termografía; Tratamiento.

1. Introduction

Gynoid lipodystrophy (GLD), also know as cellulite, is a localized metabolic disorder wich increases the subcutaneous tissue and affects between 80-90% of the post-pubertal women population (Janda & Tomikowska, 2014). It causes changes in the topography of the skin, characterized by ondulations and also by nodules due to herniation of subcutaneous fat within fibrous connective tissue (Emanuele, 2013).

Increased subcutaneous thickness, which is characterized by adipocytes hypertrophy, commonly cause changes in the local circulation resulting in hypoxia and tissue homeostasis alterations, leading to a local fibrotic response and arising collagen strands (Emanuele, 2013). These collagen wires connect the subcutaneous fat leading to skin traction, which results in a wavy appearance on the skin (Emanuele, 2013). Therefore, subjects may present activity limitations and quality of life impairments.

Thus, several treatments have been carried out to reduce the subcutaneous fat layer (Atamoros et al., 2018), such as the use of cosmetics containing active substances of natural origin. Methylxanthines, such as caffeine, are common examples that stimulate lipolysis and reduce the lipogenesis of adipocytes and also act in the skin microcirculation (D. Hexsel & Soirefmann, 2011).

Caffeine is the main category of active with well documented action for GLD treatment (Bertin et al., 2001). However, there is a lack of evidences regarding caffeine permeation by topical methods (Emanuele, 2013). This molecule is highly hydrophilic, and the permeation into deeper skin layers is extremely low. This inefficiency of cosmetics is related to the absence of permeation to the deeper skin layers, such as hypodermis, due to some skin barries preventing it from reaching fat cells (Iqbal et al., 2018).

In addition, cosmetics formulation present different actives, as well as a wide diversification on formulation characteristics and active concentration, making it difficult to evaluate the real effectiveness of the product (Emanuele, 2013). An interesting alternative would be its association with specific methods to promote permeation in which they can be divided

into two categories, chemicals and physicists, and the later is subdivided into invasive (*e.g.* micro needles) and non-invasive (*e.g.* iontophoresis and sonophoresis) (Iqbal et al., 2018; Kanikkannan, 2002; Luo & Lane, 2015).

Iontophoresis is an effective noninvasive method which improves substances permeation and commonly offers advantages over topical use, due to high performance in the transport of substances (Akomeah et al., 2009; Semalty et al., 2007). Despite presenting positive effects, it is known that epidermis, stratum corneum, plays the opposite role, acting as a barrier (Akomeah et al., 2009).

Teaima et al., 2018, evaluated the topical use of caffeine niosomal gel in the subcutaneous fat layer as well as its association with iontophoresis, *in vitro* in rats. They found that both methods presented good substance penetration. However, up to this moment, no study has reported the efficacy of caffeine neither alone or in association with other active compounds, as well as the use of iontophoresis associated with caffeine *in vivo* in humans. Thus, the objective of this study was to evaluate the effects of a caffeine gel in alone and associated with iontophoresis for the gynoid lipodystrophy treatment in women.

2. Methodology

2.1 Sample and study design

A longitudinal one-blind (evaluator) randomized clinical trial which was approved by institutional ethics committee (nº 2.264.773) and registred in Clinical Trials (NCT03556917) was developed.

All participants signed the informed consent term before the evaluations. Then, they were randomly allocated in three groups by the program random.org (random sequence generator). AFQ generated the random allocation sequence and OIP assigned participants to interventions.

Fifty-seven women with GLD were recruited in the city of Londrina/PR, Brazil from June 2018 to April 2019. They were recruited from the local community and among employees, students and/or their relatives of the universities involved in the study. The inclusion criteria were: mild/moderate GLD in the buttocks being evaluated by a validated photonumeric Celulite Severity Scale (*Hexsel, Dal'Forno&Hexsel Cellulite Severity Scale (CSS))* (D. M. Hexsel et al., 2009); female subjects; aged between 20 and 40 years and body mass index (BMI) lower than 30 (kg/m^2). Subjects were excluded in the presence of deregulated menstrual cycle; pregnant; breastfeeding or using antibiotic medication or steroids over 1 month of treatment of skin diseases; hypersensitivity of the skin; using cosmetics or medicines on buttocks within 1 month; history of surgical procedure (liposuction and skin treatments) on the buttocks or plan for some procedure within the study period; debilitating disease such as asthma, diabetes or hypertension and atopic dermatitis.

Sample size was calculated considering a 0.05 bilateral alpha value and a 90% power based on previous study which used ultrasound and hyaluronidase on gynoid lipodystrophy type II and found that thickness of subcutaneous tissue was 26.9±3.93 mm before treatment and 22.9±2.60 mm post-treatment (da Silva et al., 2013). Therefore, a minumum of 10 participants per group was found.

2.2 Interventions

Firstly, 10 subjects were invited to receive the treatment aiming to identify the best intensity of iontophoresis. These participants were not included in the study. Afterwards, all participants were randomly allocated into 3 treatment groups. Topical caffeine gel group 4,0% (w/w) (CG); caffeine gel positively charged plus iontophoresis group 4,0% (w/w) (CIG) and iontophoresis (distilled water) group (IG). All groups were treated with 10 sessions, two times per week with a total of 20 minutes per session. Total treated area was of $25cm^2$ in both butocks, in which for CG and CIG were applied 5 mg of product per buttock. The intensity of the current was determined according to the sensitive threshold of each patient, however we did not exceed the intensity of the device at 1 mA/cm^2 defined as being a safe intensity according to our pilot sample.

Anthropometric characteristics was collected and the BMI was calculated. All participants were assessed before and immediately after treatment by ultrasound image to analyze the thickness of subcutaneous tissue, by thermography to assess the surface temperature of the skin, by Celulite Severity Scale to access the severity of the GLD and by *CELLUQOL* to assess the quality of life in individuals with cellulite. (D. Hexsel et al., 2011)

2.3 Gel formulation

Semi-solid formulations (gel), topical, added of caffeine, commercially known as CAFEISILANE C® (Exsymol, France) and INCI as siloxanetriolalginate (and) caffeine (and) butyleneglycol. The caffeine concentration used was 4,0% (w/w). The composition used were 0,7% (w/w) of hydroxyethylcellulose, 2,0% (w/w) of glycerin, 0,5% (w/w) of cyclomethicone, 0,2% of phenoxyethanol, and sufficient amount for 100g of distilled water. The formulations were analyzed in triplicate for organoleptic characteristics, centrifugation, relative density, pH, viscosity, and cutaneous penetration *in vivo* at zero and thirty days, and were stored at room temperature (25 ± 2 °C), stove (40 ±2 °C) and refrigerator (5 ± 2 °C). The concentration of caffeine tested in the database was provided on the recommendation of the supplier (Exsymol leaflet) who found its topical use in the concentration of 3.0 to 6.0% and also based on the study conducted by Valesco et al.,2008 in which he used the same concentration of 4.0%. (Kanikkannan, 2002; Velasco et al., 2008)

2.4 Primary outcome:

Thickness of subcutaneous tissue

Ultrasound image is a method that evaluates the subcutaneous adipose layer thickness and it is considered a reliable and valid tool (Wagner, 2013). Thickness of subcutaneous tissue were assessed by classical ultrasound image (Mlosek et al., 2011) *Philips Envisor®.* The both sides (right and left) of of each participant buttocks were evaluated pre and post-treatment. The assessment was performed by a blind evaluator and each buttock was divided in 2 parts (lower and upper), the reference point used was the major trochanter of the femur and the intergluteal line. The evaluated area was of 25cm^2 from the midpoint to the dividing line. The following area were evaluated: epidermal thickness, subcutaneous tissue thickness and subcutaneous tissue plus dermis thickness.

2.5 Secondary outcomes

Thermography

Thermography is a technique that assesses the local skin temperature and is based on the detection of infrared radiation emitted by the skin. It has been considered a valid and reproducible evaluation tool for GLD (da Silva et al., 2013). The higher the temperature, the better the GLD aspect.

Thermography was assessed by *FLIR C2*, compact thermal camera. Participants remained in a upright position for 20 min of acclimation before starting the measurement. This position was chosen to achieve equilibrium in skin temperature. All measurements were performed in a controlled environment room with temperature set at 22 ± 2°C and relative humidity of 60 ± 5%. Shortly after the waiting time in the room, a picture of the buttocks was taken.

The data acquisition and analysis were performed using the software FLIR Tools+, in which the average temperature of the region of interest (ROI) was analyzed. The mean temperature of the ROI was obtained from both buttocks separately where we analyzed the maximum and the minimum temperature of each buttock by the software. Moreover, the average temperature of the left and right buttocks were obteined. The average temperatures of each buttock were used in the analysis.

CELLUQOL (Questionnaire of Quality of Life)

CELLUQOL is a quality of life questionnaire, which is valid for subjects with GLD (D. Hexsel et al., 2011). The summary questionnaire was used and the scores ranged from 8-16 points (GLD does not affect the quality of life), 16-24 points (GLD little affects the quality of life), 24-32 points (GLD affects reasonably the quality of life), 32-40 points (GLD greatly affects the quality of life).

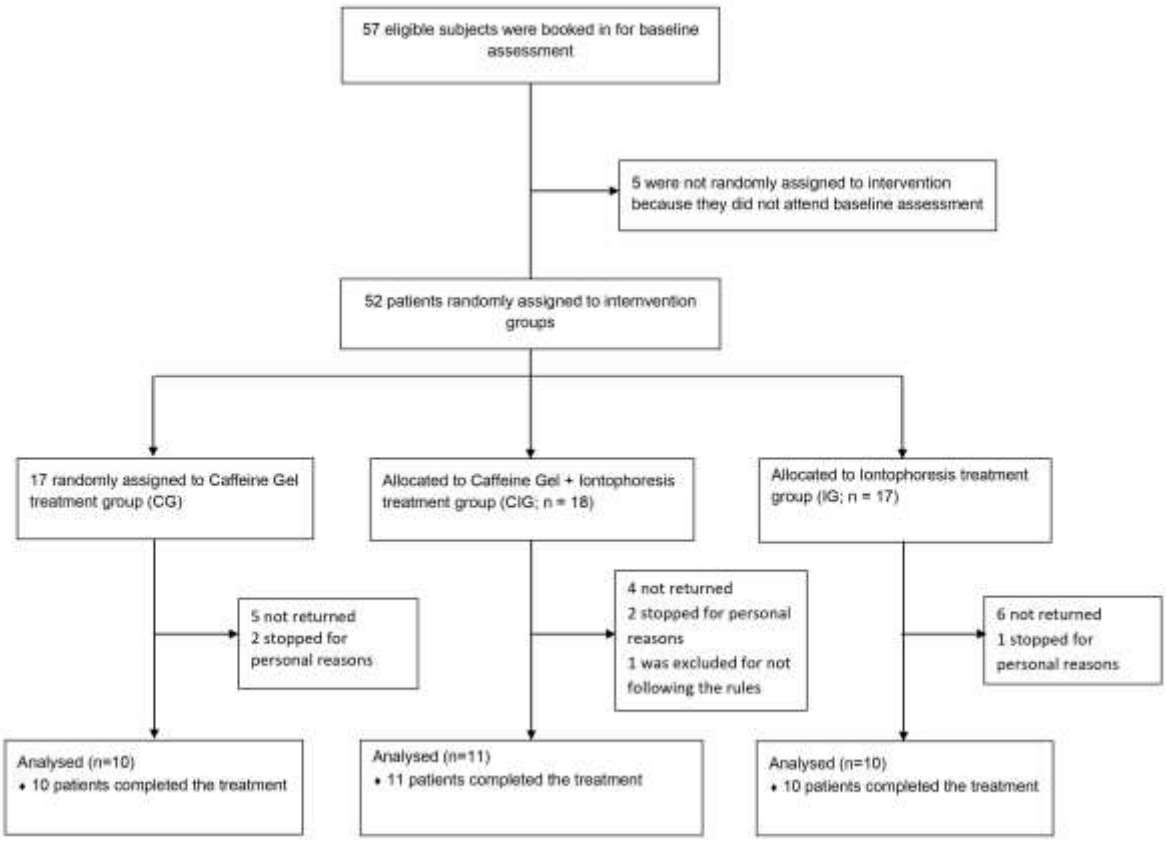
2.6 Statistics analysis

The statistical software used was the SPSS 21.0 (SPSS Inc., USA). Data distribution was analysed using the Shapiro Wilk test and the results were described as mean ± standard deviation. A two-way mixed ANOVA was used to determine whether there are differences between independent groups over time and pairwise comparisons were assessed with the Bonferroni post-hoc test. The factor 'group' was defined as between-subjects factor (inter-group) while the 'time' was defined as within-subjects factor (intra-group). Significance level was set at $P<0.05$.

3. Results

Fifty-seven participants were initially included and 31 finished the study protocol (Figure 1). The sample was composed by women with age 25 ± 5 years, BMI 25 ± 4 kg/m^2, Cellulite Severity Scale of 6 ± 2.5 points and CELLUQOL of 26 ± 6 points. Baseline data were described by groups (Table 1). The participants had no adverse effects during the study.

Figure 1. Flowchart of the study.



Source: Authors.

Table 1. Baseline characteristics.

	Caffeine Gel group (CG; n=10)	**Caffeine Gel + iontophoresis group (CIG; n=11)**	**Iontophoresis group (IG; n=10)**
Age, years	25±3	25±4	27±7
Weight, kg	63±15	62±10	74±15
Heigth, m	1.64±0.8	1.61±0.8	1,64±0,8
BMI, kg m-2	23±5	24±3	27±4
Cellulite Severity Scale (CSS), points	5±3	6±2	7±2
CELLUQOL	23.9±5.5	27.3±5.1	25,5±7,5
Ultrassound (cm)			
Epidermal thickness, left	0.28±0.51	0.29±0.31	0,30±0,33
Subcutaneous tissue + dermis thickness, left	2.34±0.96	2.67±0.50	3,37±0,89
Subcutaneous tissue thickness, left	2.07±0.93	2.38±0.50	3,06±0,89
Epidermal thickness, right	0.29±0.50	0.29±0.31	0,30±0,52
Subcutaneous Tissue + dermis thickness, rigth	2.78±1.25	3,17±0,52	3,82±0,89
Subcutaneous tissue thickness, right	2.46±1.22	2,87±0,59	3,50±0,89
Thermography (ºC)			
Thermography Left	29.9±1.4	28,6±2,1	28,6±2,0
Thermography Right	29.8±1.1	28,6±2,1	28,6±1,9

Data are described as mean ± standard deviation. BMI: Body Mass Index; CELLUQOL: a quality of life measurement for patients with GLD. Source: Authors.

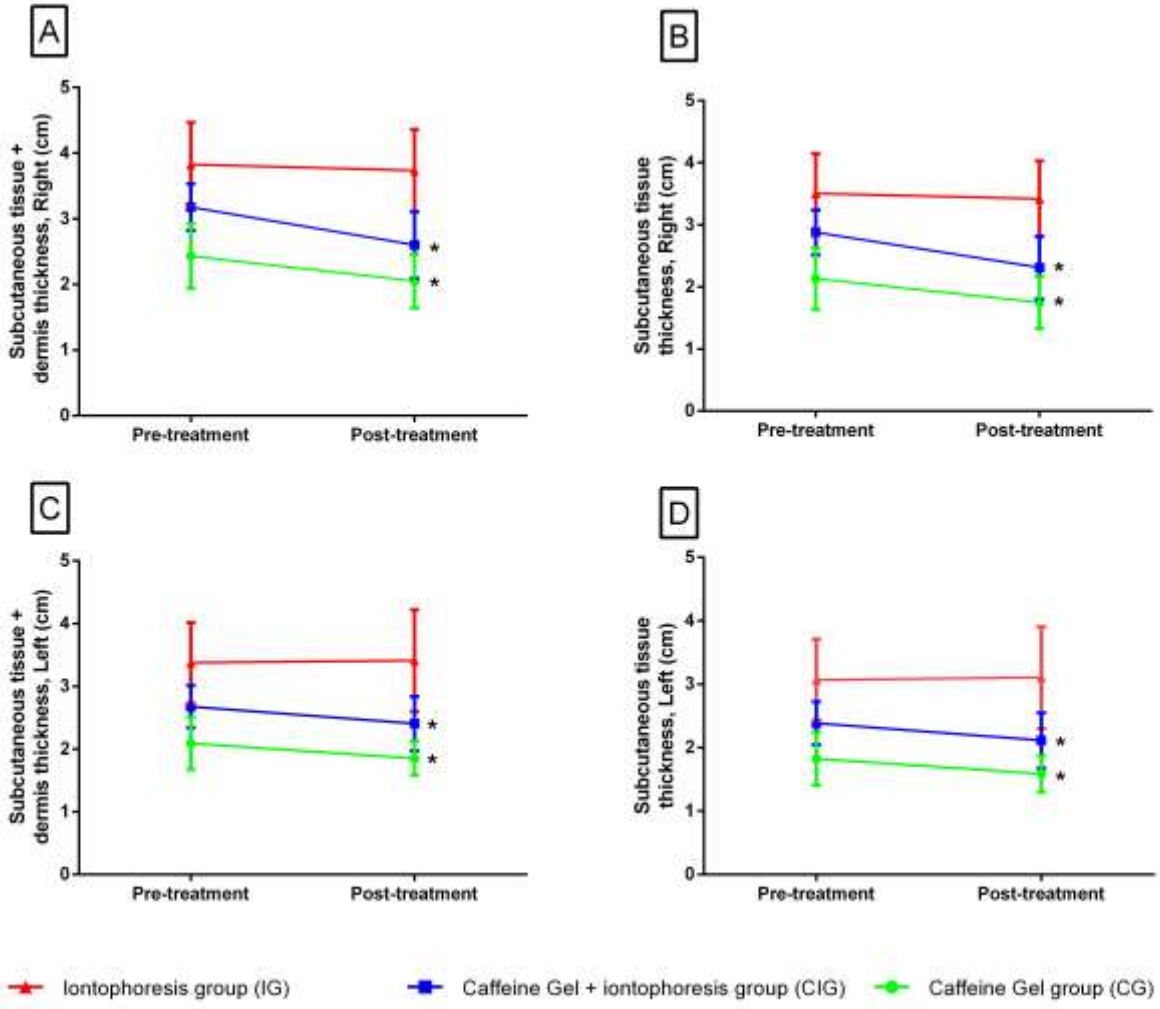
Regarding the GLD improvements after 10 sections, there were statistical differences in the subcutaneous tissue thickness after treatment ($P \leq 0.046$) and also in subcutaneous tissue plus dermis thickness in the buttocks ($P \leq 0.044$) (Table 2). Post-hoc analysis showed that the caffeine gel treatment group (CG) and the caffeine gel plus iontophoresis treatment group (CIG) were more effective than the iontophoresis treatment group (IG) on the subcutaneous tissue thickness and subcutaneous tissue plus dermis thickness in the buttocks (Table 2 and Figure 2).

Table 2. Adjusted mean difference in 10 sessions primary and secondary outcome measures in the Gel (G1), Gel plus iontophoresis (G2), and iontophoresis treatment (G3) groups.

	CG vs CIG†	CG vs IG†	CIG vs IG†	P time	P group
Ultrassound (Cm)					
Epidermal thickness, left	-0,020 (-0,059 to 0,018)	-0,031 (-0,070 to 0,009)	-0,010 (-0,049 to 0,028)	0.722	0.151
Subcutaneous tissue + dermis thickness, left	-0,570 (-1,376 to 0,236)	-1,422 (-2,245 to -0,598)*	-0,852 (-1,635 to -0,069)*	**0.044**	**0.001**
Subcutaneous tissue thickness, left	-0,545 (-1,345 to 0,255)	-1,381 (-2,199 to -0,563)*	-0,836 (-1,614 to 0,058)*	**0.046**	**0.001**
Epidermal thickness, right	0,009 (-0,036 to 0,054)	-0,009 (-0,054 to 0,037)	-0,018 (-0,063 to 0,027)	0.328	0.606
Subcutaneous Tissue + dermis thickness, rigth	-0,648 (-1,425 to 0,130)	-1,539 (-2,334 to -0,745)*	-0,891 (-1,647 to -0,136)*	**0.001**	**0.001**
Subcutaneous tissue thickness, right	-0,655(-1,431 to 0,121)	-1,522 (-2,315 to -0,729)*	-0,867 (-1,621 to -0,113)*	**0.001**	**0.001**
Thermography (ºC)					
Thermography Left	0,605 (-0,870 to 2,080)	1,185 (-0,290 to 2,600)	0,580 (-0,895 to 2,055)	0.281	0.142
Thermography Right	0,650 (-0,820 to 2,120)	1,125 (-0,345 to 2,595)	0,475 (-0,995 to 1,945)	0.220	0.165

Data are described as adjusted mean difference and 95% CI. Negative signs are due to measurement after treatment reduction (i.e. Ultrassound improvement). Two-way mixed ANOVA with Bonferroni post-hoc test. CELLUQOL: a quality of life measurement for patients with cellulite. *P<0.05; P time (difference within group); P group (difference between group). † First minus the second group.
Source: Authors.

Figure 2. Ultrassound measurements before and after interventions for (A) Subcutaneous tissue plus dermis thickness, Right; (B) Subcutaneous tissue thickness, Right; (C) Subcutaneous tissue plus dermis thickness, Left; (D) Subcutaneous tissue thickness, Left; Two-way mixed ANOVA with Bonferroni post-hoc test. *P<0.05 pre vs post-treatment.

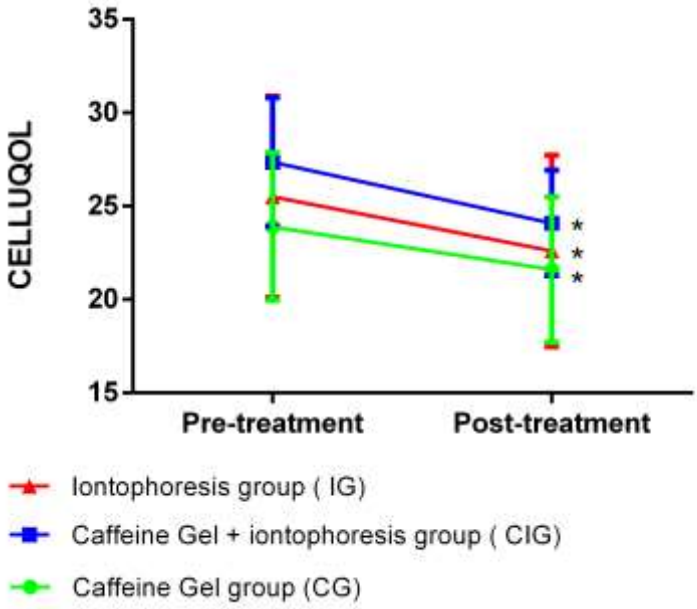


Source: Authors.

Secondary outcomes, such as thermography, did not identify significant effects of any treatment. There were no statistical differences recorded intra-group and inter-group (P>0.05 for all).

Additionally, CELLUQOL questionnaire score showed statistically intra-group differences after treatment (P<0.017) for all groups and without inter-group differences (P=0.30) (Figure 3).

Figure 3. Quality of life questionnaire (CELLUQOL) measurements across the timepoints by interventions (*P<0.017) and P=0.30 among the groups. Two-way mixed ANOVA with Bonferroni post-hoc test. *P<0.05 pre vs post-treatment.



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4. Discussion

In the present study, we observed that caffeine alone and associated with iontophoresis is effective in reducing the subcutaneous tissue thickness and the total tissue (subcutaneous tissue plus dermis thickness) after 10 sessions of treatment.

These findings confirmed the hypothesis that caffeine acts on lipolysis of the fat layer and when associated with iontophoresis it also presents good results being effective in lipolytic activity and reducing lipogenesis. Furthermore, using the association of iontophoresis with caffeine, we verified the efficacy of these two methods used together, proving by ultrasound image that these two treatments can be safely applied in the clinical practice.

Although the GLD etiology is considered as multifactorial, scientific literature have shown association between hypertrophy of adipocytes and increase of subcutaneous fat (Emanuele, 2013). Furthermore, caffeine is the most used and safest type of methylxanthine, which provides good penetration into the skin and is more rapidly absorbed, resulting in rapid action (D. Hexsel et al., 2006).

In our study, we were able to verify the real efficacy of caffeine when used in isolation, which guarantee the actual efficacy of the active compound in the subcutaneous fat layers, as well as its effectiveness when associated with iontophoresis. Therefore, the gel of caffeine may be considered as an anti-GLD product which reduces the subcutaneous fat layer, as found in other studies (da Silva et al., 2013; Hamishehkar et al., 2015; D. Hexsel et al., 2006; Wilczyński et al., 2017).

The subcutaneous fat layer was analyzed and treated on both sides (right and left) of buttocks for ethical reasons and also because we could empirically observe at the moment of the assessments of our pilot sample that the right gluteus apparently had a higher fat thickness than the other side, which was confirmed by ultrasound images (Table 1). The reason for this difference was not verified in this article. For this reason, we analyzed and divided our results on right buttock and left buttock, but both sides had a decrease in the thickness of the subcutaneous fat layer.

Semalty et al., 2007, in their review, concluded that iontophoresis is an effective technique for substance permeation and offers the advantage of topical and high-performance substance transport. The association between caffeine and

iontophoresis in our study showed to be effective and thus promoting the permeation of the active of caffeine. However, when we compared the efficacy of the use of the caffeine isolated (CG) vs the iontophoresis with the caffeine (CIG) with the post-hoc test, there were no statistically significant differences between these two groups. This result may be due to the low intensity applied in the iontophoresis current which was determined to avoid burn risks in these subjects.

When we evaluated the skin temperature by thermography, a technique that assesses the local skin temperature which is based on the detection of infrared radiation emitted by the skin was used (Nkengne et al., 2013). We could not observe statistically significant difference neither intra nor inter groups. Thermography is a type of assessment method of the GLD degree and it was shown that the thermal image camera is a repeatable and reproducible tool (Nkengne et al., 2013); however, responsiveness has not been studied yet. Thus, there are no studies from scientific literature which allow for quantitative evaluation of the temperature fields in the course of treatment of GLD (Wilczyński et al., 2017). In this study, we did not find inter-group and intra-group thermographic difference and it could be explained since any minor temperature disturbance, including even one pixel, can falsify change the results. Another hypothesis for these results is that we performed the treatment only in mild-moderate GLD degree, but perhaps we could have found significant difference in more severe degrees of GLD.

Regarding quality of life verified by the CELLUQOL questionnaire, we were able to verify an improvement in intra-group quality of life for all groups, although we did not obtain an inter-group difference. Probably all groups present improvements because of other factors that we did not evaluate or even due to placebo effect. For the next studies, we also need to analyze the power of the sample size especially for the questionnaire variable so that we can better analyze these quality of life data.

Despite the clinical relevance of this study, the high rate of drop-out and the fact that low doses intensity of iontophoresis current might underestimate the results of the iontophoresis efficacy over topical methods should be considered as limitations. However, in order to guarantee the safety and viability of treatment with iontophoresis, the current intensity was reduced based on our pilot study, where we used higher charges and defined a lower charge as the safest one. The intensity was according to the threshold of sensitivity of each patient and did not exceed 1mA / cm^2. This excessive care was to ensure that the treatment would not cause burns, allergies, discomfort or intercurrence by the current in the participants. Noteworthy, despite low intensity in the iontophoresis current, the present study showed a good efficacy of treatment in patients with GLD.

5. Conclusion

In conclusion, the use of caffeine gel alone and caffeine gel associated with iontophoresis is efficient on reduction of subcutaneous tissue thickness in woman with GLD imafter 10 sessions when assessed by ultrasound. The results demonstrated the efficacy of caffeine used alone or associated with iontophoresis on lipolysis of fat layer, being effective in lipolytic activity and reducing lipogenesis.

In our study, no intergroup difference was found in relation to the quality of life verified by the CELLUQOL questionnaire. Future studies are needed to clarify the effects in quality of life in use of caffeine gel alone and associated with iontophoresis in GLD treatment.

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