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RESEARCH ARTICLE

EFFECTS OF THE INTRADERMOTHERAPY WITH PRESSURIZED INJECTION SYSTEM IN THE TREATMENT OF LOCALIZED ABDOMINAL FAT

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Abstract

Introduction: The pressurized intradermotherapy is a needle-free technology whose function is the release of medicated or cosmetological actives in the skin and the subcutaneous tissue using mechanical force, gaspressure, and shockwaves, allowing the treatment of different aesthetic changes.

Objective: To investigate the effects of intradermotherapy with a pressurized injection system in the treatment of localised abdominal fat in women.

Method: The sample consisted of 30 women with localized adiposity in the abdominal region, evaluated before and after treatment through evaluation protocols and ultrasound examinations. The volunteers were randomly distributed in to two subgroups: Pressurized intradermotherapy group (G01), to which were an adipolytic substance, a combination of different drugs, was applied, and the control group (CG), which received an injectable saline solution only. Both groups underwent four biweekly treatment sessions.

Results: The fat layer analysis 60 days after the initial application showed a significant reduction of the measurements in the comparison between groups G01 and GC; the plicometry showed a significant difference on the right side ($p = 0.04$) and the left side ($p = 0.04$); in the supraumbilical ($p = 0.001$) and infra umbilical ($p = 0.03$) perimetries. Two months after the beginning of treatment, the ultrasound examination two showed a significant reduction on the sides: right ($p = 0.03$) and left ($p = 0.03$); however, no differences in weight were found ($p > 0.05$).

Conclusion: The treated group presented a significant fat layer reduction after the treatment with the pressurised intradermotherapy protocol, with better results after the fourth application.

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Introduction:-

The localized adiposity is an alteration of fat cells, and it can be characterised as a disturbance in fat metabolism or abnormal fat growth, being one of the main complaints of aesthetic dissatisfaction among women and men. As a result, various high-tech, minimally invasive, personalised, and multi-asset-based therapeutic approaches have emerged, enabling an effective and comfortable reduction of localised adiposity to patients. (Fonseca-Alaniz et al., 2007; Gomes and Damazio, 2009)

Thus, the pressurised intradermotherapy, a needle-free technology that aims to release drugs into the skin using mechanical force, gas pressure, and shock waves, without the need to inject them with needles, allowed treatment of different aesthetic aspects, such as localised fat, sagging, and cellulite, promoting greater comfort to the patient during application (Al-Kaf and Othman, 2017; Sahoo et al., 2017).

This needleless delivery system was first described in 1936 by Marshall Lockhart, and in 1940, Higson and other researchers developed high-pressure devices that used thin jets of fluid to penetrate the skin and deposit the drug in the underlying tissue. This allowed highly viscous medicine administration, which traditional needles often failed to manage, making the application less painful. (Al-Kaf and Othman, 2017; Ravi et al., 2015)

The use of the intradermotherapy for the treatment of localised fat involves the use of drugs, reagents, and plant extracts in the fat and connective tissue layers of the skin. These consist of a wide range of agents used to open blood vessels, such as enzymes, nutrients, antibiotics, and hormones, and this treatment is indicated for small areas with excess fat or localised fat deposits, or the correction of irregularities or asymmetry of the body contour after any surgical procedure (Brown, 2006; Mohamed et al., 2015).

Mohamed et al. (2015) used intradermotherapy applications in six weekly sessions combined with diet. Phosphatidylcholine and deoxycholate were used during the applications, and the effective reduction of abdominal fat volume and thickness was verified; however, it was not possible to identify the increase of the circulating markers of inflammation or changes in glucose and lipid metabolism.

Although there are still some gaps in the intradermotherapymechanisms of action, some studies have shown promising results for the treatment of localised adiposity without major adverse effects (Mohamed et al., 2015; Rotunda et al., 2004). Thus, the present study aimed to verify the effects of the intradermotherapy with a pressurised injection system in the treatment of abdominal localised fat in women, analysing its effects through evaluation protocols and ultrasound exams.

Materials And Methods:-

This is a prospective, randomised, experimental, clinical trial. This research was approved by the Potiguar University Ethics Committee (#3.199.475) and was carried out according to the recommendations of the Consolidated Standards of Reporting Trials - CONSORT (CONSORT TRANSPARENT REPORTING OF TRIALS, 2010). All volunteers granted the researchers with their consent in writing through an informed consent form before treatment.

This study was divided into two stages. Initially, a pilot test was carried out with two volunteers to analyse the effects, and for parameters, settings. From the collected data and parameters, the research continued with a larger group of volunteers.

The simple randomisation consisted of a draw using envelopes that contained a response card, which indicated the group to which the participant would be allocated. The group allocation sequence was followed according to a computer-generated list. The intervention was tested by comparing the control group and the treated group, using independent group analysis for study control.

Participants:

This clinical study evaluated 30 women aged between 25 and 45, of body weight varying from 44.3 and 87 kg, and who had subcutaneous adiposity located in the supraumbilical region. The inclusion criteria encompassed the following: female, Body Mass Index (BMI) between 18.5 and 29.99 (normal to overweight), could not be taking

anti-inflammatory drugs until one week before treatment, could not be regular practitioners of physical activities, and could not be allergic to the substances used in the study.

Among the exclusion criteria, the volunteers adipose layer thickness should be between 1 and 4 cm, the volunteer could not be under dietary restriction (diets, dietary -education-education, or the like), and would be discontinued from the research if disagreements concerning the procedures or treatment schedule and techniques.

There was a sample loss of six participants from the control group and five from the treated group during the study due to incompatible schedules and withdrawals due to personal reasons. The volunteers were randomly distributed into two subgroups: control (CG), with nine participants (mean age of 34.3 years and mean body weight 67.27 kg); and the pressurised intradermotherapy group (G01), with ten participants (mean age of 23.4 years and mean body weight of 60.68 kg).

Evaluation Procedures:

All participants underwent assessment of anthropometric and ultrasound measurements, which were performed before the treatment, 45 and 90 days after the beginning of the applications, i.e. 15 days after the second session (1st reassessment) and 15 days after the fourth session (2nd reevaluation). For evaluation and treatment, this research used an ultrasound device (ECO PALM WIFI, 10MHZ, China); a semi-professional camera (CANON, SX530 HS, Japan); a tape measure (FIBER GLASS TAPE, China); an adipometer (SANNY, São Paulo, Brazil); a bodyweight scale (ACCUMED-GLICOMED, Rio de Janeiro, Brazil); a pressurised injection equipment (CONFORT IN™, Goiás, Brazil); and an adipolytic substance (MEZZO DERMOCOSMÉTICOS™, São Paulo, Brazil), made of caffeine, a carnivorous plant (Sundew or Drosera Ramentacea), ACTIGYM™, and LIPOXYN™.

As instruments for data collection in this research, the Localized Adiposity Physical Therapy Evaluation Protocol (PAFAL), validated by Meyer et al. (2008) was used to obtain information such as identification, history, lifestyle, physical examination, measurements, and data involving the measurement of the volunteers' weight, height, BMI, skin folds and waist circumference. Skin folds of the left and right lateral regions and 4 cm below the umbilical scar were measured three times, and the final result was based on mean value of the obtained measurements. The abdominal circumference was measured at the level of the supra and infra umbilical regions by positioning point of the tape measure 4cm above and below the umbilical scar.

The photographs were taken in orthostatism with anterior and lateral view (right and left), and the volunteer was asked to perform a 90° shoulder flexion during the photo; A tripod and a neutral coloured background were used to standardise the images.

Subsequently, the volunteers underwent ultrasound examination performed in the infra and supraumbilical region, in 6 different points of analysis: 3 areas located 4 cm above the umbilical scar and 3 areas located 4cm below it. The distance between the areas was approximately 5cm, with the volunteer in the supine position. This method allowed to evaluate the thickness of the fat layer of the abdominal region in centimetres before and after the proposed treatment.

Two days before the beginning of treatment, the volunteers underwent the predictive allergy test regarding the active substance used in the study. They received a 0.3-ml intradermal injection of the adipolytic substance to identify possible episodes of allergic reaction/irritation to the active substance, the product, or any hyperaemia, itching, and oedema. However, no volunteer presented the mentioned reactions, except for reported post-testing pain in the treated region.

Treatment Protocol:

The procedures were performed with a CONFORT IN™ pressurised injection equipment. The pressurised intradermotherapy group (G01) was treated with the adipolytic substance manufactured by MEZZO DERMOCOSMÉTICOS™, which acts by combining different elements, such as caffeine, a carnivorous plant (Sundew or Drosera Ramentacea), ACTIGYM™ and LIPOXYN™, which degrade the adipose tissue; and the control group (CG) received an injectable saline solution only.

The pilot test (first phase) considered two volunteers for effects analysis and parameter characterisation, with the first volunteer receiving the adipolytic substance, while the second volunteer was given only the saline solution,

both receiving treatment in 4 sessions with an interval of 7 days between them. However, due to the persistence of bruises in between sessions, the interval set to 15 days was discontinued.

Therefore, in the second phase, the volunteers received 4 treatment sessions in biweekly applications. During treatment, all volunteers were in the supine position and were with 0.3 ml of therapeutic or saline substance in the delimited spots of the supra and infra umbilical region, totalling 25 delimited spots.

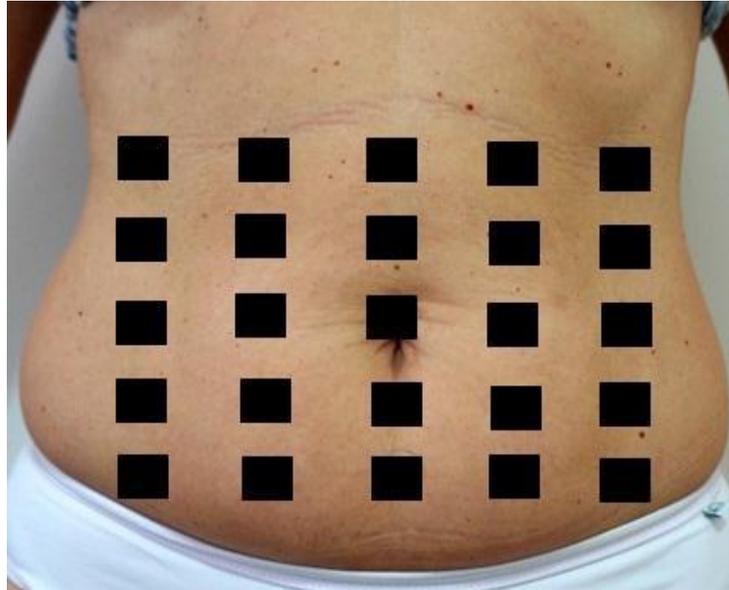


Fig 1:- Area of adipolytic and saline substance application.

In both groups, the abdominal region received an antiseptic cleansing with 70% alcohol-soaked gauze before the start of the proceedings, then demarcation was performed and immediately after injection of the adipolytic substance or saline, according to the group of research.

The reevaluation was performed 45 and 90 days after the beginning of the applications, being 15 days after the second session (1st reevaluation) and similarly, 15 days after the fourth session (2nd reevaluation), repeating all procedures performed before treatment, followed by the application of the adapted questionnaires of patient satisfaction analysis, Segot-chicq et al. (2007) and the Global Aesthetic Improvement Scale - GAIS by Narins et al. (2003).

Statistical analysis:

Statistical data analyses were performed using the Package for the Social Sciences (SPSS) (version 22.0, for Windows, SPSS, EUA). Ultrasound images and anthropometric measurements were analysed in the calculation of the fat layer reduction, comparing the means obtained before and after treatment using the t-test. Throughout the statistical analysis, a significance level of 95% was assigned, with $p < 0.05$.

Results:-

Pre-test:

The pre-test data indicated slight weight reduction (less than 1 kg) and significant perimeter measurement reduction in both volunteers. Also, plicometry values decreased with only one application of pressurised intradermotherapy, with greater loss identified in volunteer 1, who received the adipolytic substance.

Table 1:- Anthropometric data of the pilot test with volunteers.

	Volunteer 1 (Adipolytic asset)	Volunteer 2 (Saline)
Initial Weight	59.9 kg	69.0 kg
Final Weight	59.5 kg	68.3 kg

Initial Plicometry (S)	2.6 cm	3.1 cm
Final Plicometry (S)	2.3 cm	2.9 cm
Initial Plicometry (I)	2.7cm	3.6 cm
Final Plicometry (I)	2.1 cm	3.3 cm
Initial Perimeter (S)	76.5 cm	90.0 cm
Final Perimeter (S)	75.0 cm	84.0 cm
Initial Perimeter (I)	86.0 cm	93.5 cm
Final Perimeter (I)	83.0 cm	90.0 cm
Initial US (S)	2.38 cm	1.89 cm
Final US (S)	1.81cm	2.04 cm
Initial US (F)	2.54 cm	2.41 cm
Final US (F)	2.43 cm	2.33 cm

Subtitles: S: Superior; I: Inferior; US: Ultrasound.

Regarding the values presented in the ultrasound, volunteer 1 showed a reduction of 0.57 cm in the supraumbilical region and a reduction of 0.11 cm in the infra umbilical region, whereas volunteer 2 received only the saline solution and showed an increase of 0.15 cm in the supraumbilical region and a reduction of 0.08 cm in the infra umbilical region. These values are the result of the comparison between the initial and final evaluations. Skin changes, such as pain, and maintenance of bruising for more than seven days have been reported. As a result, an increase from 7 to 15 days in the interval between applications was suggested and the weekly application protocol was discontinued.

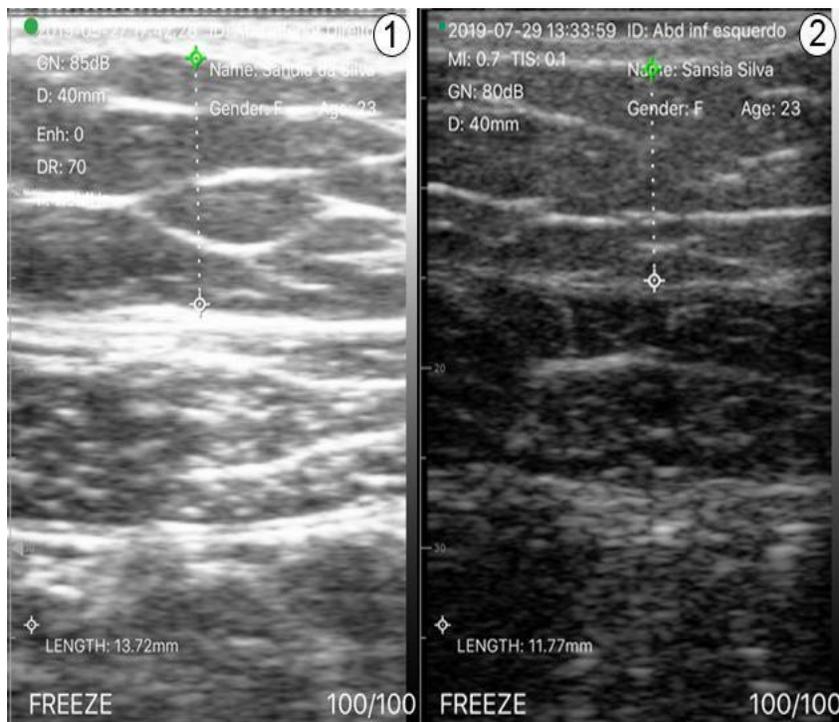


Fig 2:- Ultrasound results of the fat layer (volunteer 1).

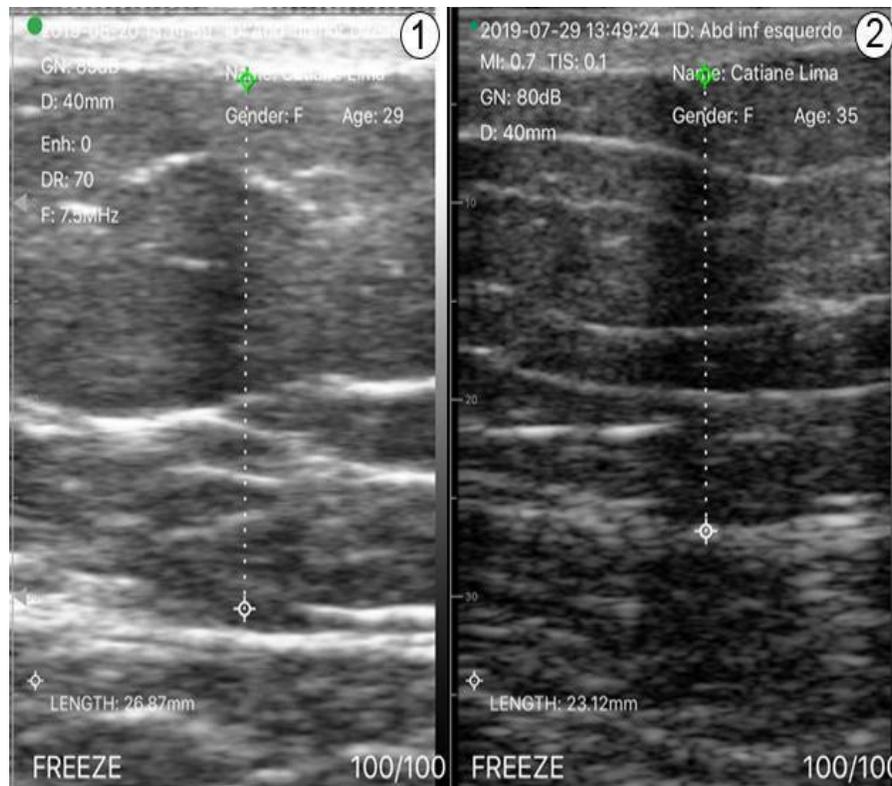


Fig 3:- Ultrasound results of the fat layer (volunteer 2).

Group Results:

The results presented by the groups with the biweekly sessions showed no statistically significant differences in weight ($p > 0.05$) in any of the evaluated moments. Analysis of right-side plicometry data showed a significant difference in results between groups G01 and GC ($p = 0.04$) in the evaluation after 90 days, similarly with left-side plicometry ($p = 0.04$). In the perimetry data, a significant difference was found in the comparison between groups also in the 90-day evaluation, both for the supra umbilical ($p = 0.001$) and the infra umbilical region ($p = 0.03$).

Table 2:- Anthropometric data of the volunteers at different times.

	GC			G01		
	Initial	45 Days	90 Days	Initial	45 Days	90 Days
	Average±DP	Average±DP	Average±DP	Average±DP	Average±DP	Average±DP
Weight	60.6±11.3	62.3±10.5	61.7±10.9	61.2±10.9	64.6±9.6	62.6±10.8
Supra Perimeter	88.8±7.4	87.1±10	87.4±9.8	92.2±12.1	81.4±10	75.5±10.6
Infra Perimeter	86.2±9.7	87.1±8.5	87.3±8.8	94.2±10.1	87.3±8,8	82.5±9.2
Right Plicometry	2.93±0.61	2.92±0.51	2.97±0.66	3.16±0.69	3.16±0,55	2.6±0.99
Left Plicometry	2.94±0.62	2.95±0.55	2.99±0.61	3.15±0.55	3.25±0,55	2.59±0.95

The fat layer thickness was evaluated via ultrasound in the pre-treatment, post-treatment 90-day periods. The treated group presented an average reduction of 0.42 cm on the left side, and 0.28 cm on the right side. The control group presented an average reduction of 0.07 cm on the left side, while the right side presented a reduction of 0.03 cm, which demonstrates the superiority in the fat layer reduction in the group that received the adipolytic substance.

Table 3:- Analysis of ultrasound examination data.

	GC		G01	
	Initial	90 Days	Initial	90 Days
	Average±DP	Average±DP	Average±DP	Average±DP
Left Side Ultrasound	2.11±0.84	2.04±0.84	2.17±0.87	1.75±0.79
Right Side Ultrasound	2.07±0.92	2.04±0.77	2.14±0.71	1.86±0.72

Statistical ultrasound results of the G01 group compared to the control group after 90 days showed a significant reduction both on the left ($p = 0.03$) and the right side ($p = 0.03$). However, in the intragroup analysis the values did not show significant reduction in both groups ($p > 0.05$).

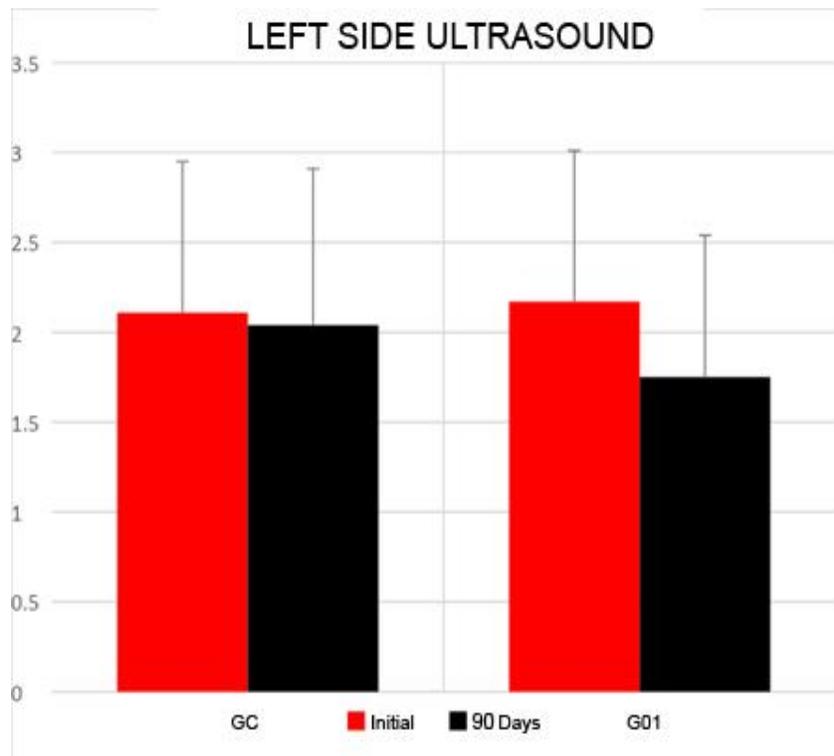


Fig 4:- Initial ultrasound results in comparison to the post 90-day ultrasound results (left side, control and treated groups).

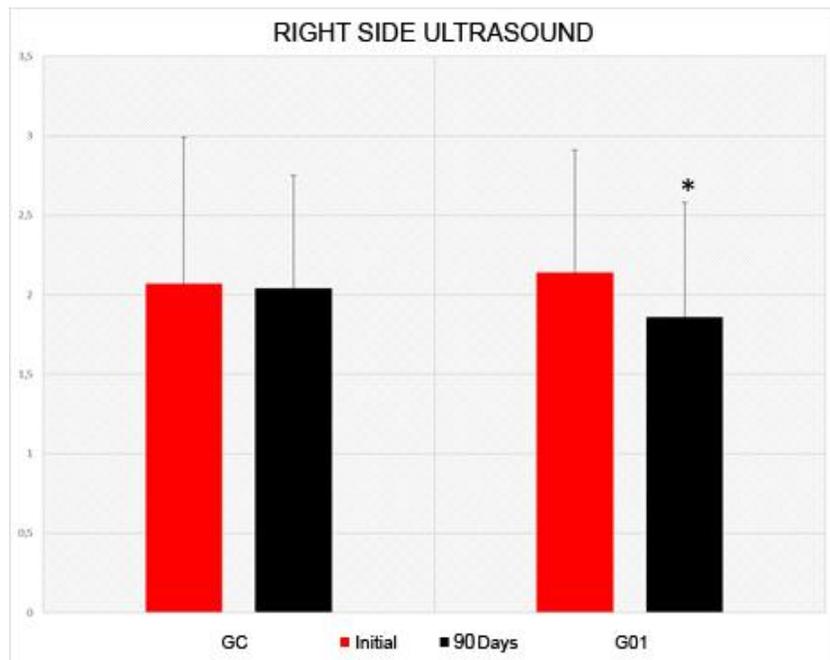


Fig 5:- Initial ultrasound results in comparison to the post 90-day ultrasound results (left side, control and treated groups).

In the applied questionnaires’ response analysis, for the topic “hyperaemia”, group G01, 60% of the volunteers reported having observed redness in all sessions, 30% until the 5th session, and 10% in the first two sessions. Within the control group, 60% have observed no hyperaemia, 10% saw it only after the first session, and 30% in the first two sessions.

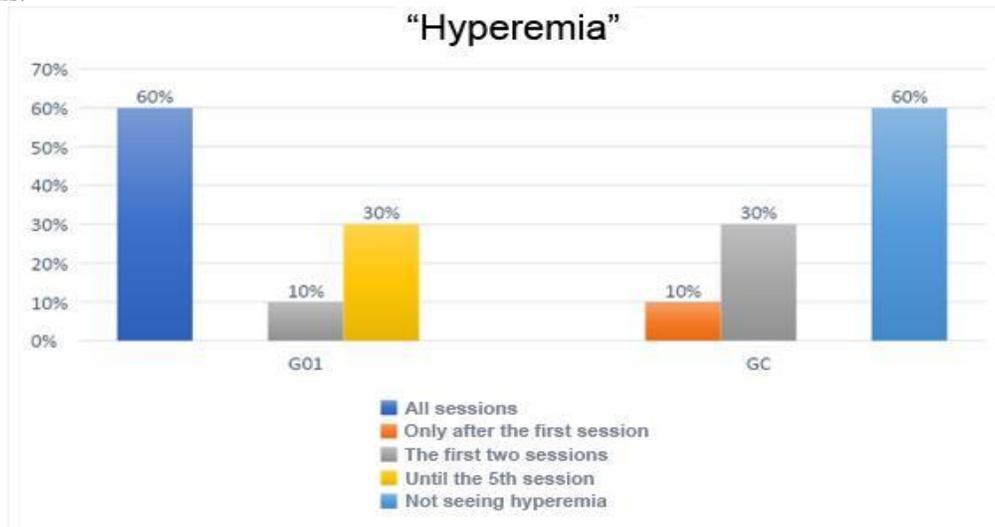


Fig 6:- Analysis on the topic “Hyperaemia” in absolute values (%).

The duration of hyperaemia in the control group manifested immediately and lingered in only two volunteers for about two or three hours. In the treated group (G01), most volunteers reported that the hyperaemia lingered for 2 to 3 hours or more.

Regarding “Marks after application”, the G01 group reported 80% of no marks, and 20% reported marks were present in all sessions, whereas in the control group, 100% of the volunteers indicated the presence of marks in all sessions. The marks lingered for a maximum 15-day period. For the topic “Improvement of oedema”, 100% of group G01 noticed improvement after 15 days, while in group GC 50% reported no improvement after 15 days, and 50% showed improvement of oedema within 15 days.

Regarding the time they noticed “Looser Clothes”, in group G01, 50% noticed it on the eighth week, 40% did not see any difference, and 10% noticed it on the second week. Within the control group, 80% did not notice it, and only 20% noticed the clothes were looser on week eight.

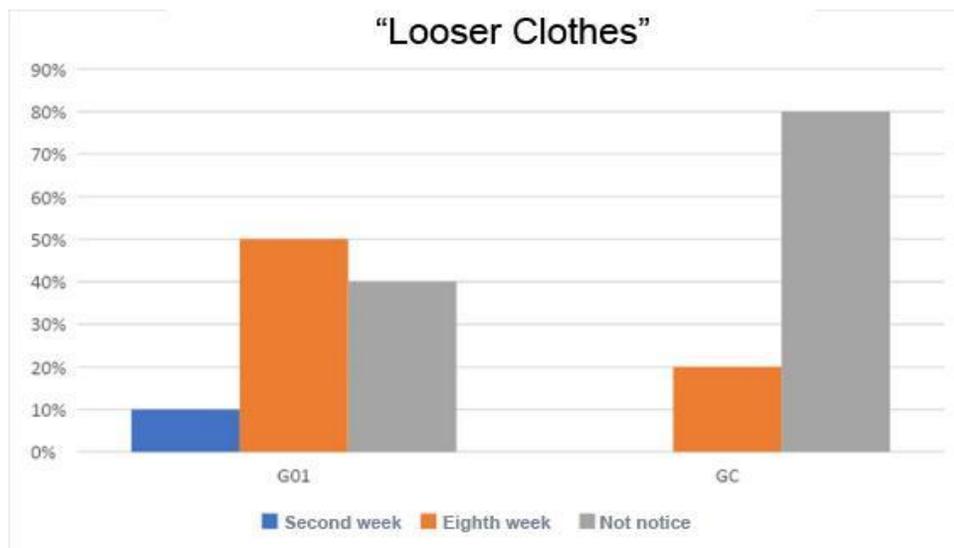


Fig 7:- Analysis on topic “Looser clothes” in absolute values (%).

Regarding the topic “Improving overall aesthetics”, the results were distributed as Unchanged, Good, Better, Much Better, and Excellent. that the responses showed that 40% of G01 volunteers reported overall aesthetics being “Better”, 30% said “Much Better”, 20% said “Excellent”, and only 10% marked “Unchanged” overall improvement. Within the control group, 40% of their volunteers reported “Unchanged” results; and for the rest of the group, the results were distributed in 20% "Much better", 20% "Better", and 20% in "Good".

Table 4:- Questionnaire analysis – topic Improved overall aesthetics.

	GC	G01
Unchanged	40%	10%
Good	20%	0%
Better	20%	40%
Much Better	20%	30%
Excellent	0%	20%

Regarding satisfaction, within the volunteers from the group treated with pressurised intradermotherapy, 90% of the volunteers reported being satisfied with the results, and only 10% were not. Within the control group, 50% reported satisfaction with the result, and 50% were not satisfied. When asked about treatment, 60% of group G01 rated it as "Excellent" and 40% as "Good". Within the CG group, 90% reported being a “good treatment”, and only 10% rated it as “excellent”.

Discussion:-

The drugs used in intradermotherapy are classified into lipolytic, thermogenic, and vasodilators, which act and assist in the treatment of aesthetic dysfunctions (Nagore et al., 2001). The combination of these active ingredients promotes potent and effective lipolysis, leading to the reduction of fat layer thickness in the area they are applied (Severo and Viera, 2018). In this study, it was found that the analysis of data 90 days after the initial application showed significant plicometry, perimetry, and ultrasound measurement reduction in the treated group compared to the control group, showing greater fat layer reduction after four pressurised intradermotherapy applications with the adipolytic substance.

The study by Rotunda et al. (2004) used porcine fat tissue and injections of the pharmacological substance sodium deoxycholate and concluded that the use of its active fraction acts as an “ionic detergent”, causing nonspecific lysis in the adipose cell wall. This study also showed that fat reduction usually requires 2 to 4 applications, with intervals of 2 to 4 weeks, however, depending on the treated area, the number of procedures may increase, corroborating with the protocol used in this study.

The adipolytic substance used in this study consists of caffeine, considered a thermogenic active, which promotes the generation of local energy, increasing cellular metabolism, which allows adiposity reduction, oedema drainage, and fluid retention in the subcutaneous tissues of faster way (Ramalho and Curvelo, 2006). Its lipolytic action is related to the mobilisation of free fatty acids from tissues, acting as a competitor for adenosine receptors, as they act by inhibiting lipolysis. There is an increase in cAMP levels, which activates sensitive hormone lipases, promoting the lipolysis (Mello et al., 2007).

In addition, there is also the presence of an active derivative of Sundew or Drosera Ramentacea, marketed under the name ADIPO-TRAP™. The genus Drosera, considered a carnivorous plant, produces naphthoquinones, a group of secondary metabolites that are widespread in nature, the main one being plumbago. This plant has antimicrobial, antiparasitic and cytotoxic properties due to its ability to act as potent inhibitors of electron transport, as decouplers of oxidative phosphorylation, and it may intercalate the double helix of the DNA, acting as biomolecule bio reductive alkylating agents, and reactive oxygen radicals (Babula et al., 2009).

Lipolysis was also favoured by ACTIGYM™, considered a marine active (Plankton extract) obtained from Bacillus sphaeroides through biotechnology. Marine Bacillus isolates produce different secondary metabolite classes, such as lipopeptides, polypeptides, macrolactones, fatty acids, polyketides, lipoamides, and isocoumarins. These compounds with versatile structures exhibit a wide range of biological activities such as antimicrobial, anti-inflammatory, anticoagulant, antiviral, antioxidant, and anticancer (Mondol et al., 2013; Mayer and Hamann, 2005).

Another compound used in the formulation of the adipolytic substance was tripeptide 41 (LIPOXYN™), considered a bioactive peptide derived from transforming growth factor β (TGF- β), which enables the conversion of triacylglycerol into glycerol and fatty acids. The action of tripeptide 41 is related to activation of NF- κ B (nuclear factor kappa B), a nuclear transcription factor that promotes the synthesis of tumour necrosis factor α (TNF α), considered a cytokine capable of initiating the lipolysis process. The peptide also reduces the expression of C/EBP (CCAAT/enhancerbinding proteins), an essential transcription factor for adipocyte differentiation, which when bound to PPAR γ (Gamma Peroxisome Proliferator-Activated Receptor) contributes to hyperplasia of the adipocyte adipose tissue. Another relevant fact of the peptide action is the increase of cAMP concentration, an important intracellular signalling factor that causes lipolysis, promoting lipid hydrolysis in triglycerides (Lima and Moraes, 2018).

In this study, the bodyweight of the volunteers did not decrease significantly; thus, the thickness of the fat layer decreased due to local treatment. This reinforces the research by Song et al. (2012), in which 25 patients with localised fat in the thigh region were divided into two groups. The treated group with 13 volunteers received a 0.08 g dose of a herbal extract diluted with 10 ml distilled water; and the control group with 12 volunteers received a saline solution for nine weeks, with one interval. There was no significant change in weight and BMI throughout the study, and the thigh circumference of the treated group was significantly lower compared to that of the placebo group in response to the proposed treatment.

Regarding the satisfaction with the treatment outcome, the volunteers in the adipolytic substance group, in a higher percentage, with which the effects were positive, as well as the results most frequently cited by them were “excellent treatment” and “very good treatment”. However, a small portion of this group was not satisfied with the results. In addition, the treated group indicated greater perception of changes in clothing measurements, oedema improvement, and overall aesthetic improvement. Thus, studies on intradermotherapy demonstrates its efficacy as a non-invasive therapeutic procedure for localised fat reduction with good receptivity, as verified by the study by Hasengschwandtner (2006), in which 15.2% of patients were satisfied after one session, and 72.4% after two sessions of this therapy.

Regarding adverse effects, such as hyperaemia, all volunteers in the treated group observed some of this reaction during therapy, whereas in the control group most reported no redness during the procedures, but this reaction is expected after adipolytic substances. According to Vega-López et al. (2016), complications may appear exceptionally and under ideal conditions of application, as they will be related to the particular characteristics or hypersensitivity of each patient. This emphasises the importance of assessing the risk/benefit of intradermotherapy interventions in the context, thus preventing the appearance of unwanted reactions.

As of the marks after application, the report of this reaction in its entirety is noteworthy of the control group, while the majority of the volunteers from the treated group did not present marks after undergoing the procedures; however, it is noteworthy that a favourable point of the pressurised intradermotherapy is the injector, also called mesogun or mesopistol. It allows doses to be delivered in a standardised and reproductive fashion, thus avoiding undesirable effects caused by the manual technique. Another reported advantage is that applications are less painful due to a stable skin tension. Also, these devices are capable of injecting even diluted and undiluted drugs, especially in lipolysis (Knoll, 2012).

The data presented by the control group showed that there was no significant reduction in the analysed variables. Also, in response to the applied questionnaires, most of the group reported that the treatment presented “unchanged” results and that they did not feel their clothes looser during the eight weeks of treatment. However, a considerable portion of the group was satisfied with the results, and classified the procedure as a “good treatment”, indicating the receptivity of the volunteers by the technique. Although there were not entirely positive results in the questionnaires evaluated, the influence of the placebo effect on some volunteers was noticeable. This was due to the simulation of the technique, the expectation created towards treatment and care and the attention given to the participants, as reported in some studies, where the placebo effect positively influenced the answers of the final control group questionnaires, even without identifying significantly different values in the variables studied (Teixeira, 2009; Palmieri et al., 2009; Mlosek et al., 2012)

The pressurized intradermotherapy may also be associated with other procedures, such as exercises combined with moderate restriction of caloric food consumption. These are mechanisms related to this therapy to reduce body fat

and overweight, and may also be performed in conjunction with other technologies such as ultrasound, lymphatic drainage, and drug combination (Agne, 2009; Fernandez et al., 2004 Monteiro et al., 2004)

Conclusion:-

The Pressurized Intradermotherapy showed favourable results in the reduction of localised adiposity, causing a reduction in the fat layer, which was analysed by perimetry, plicometry, and ultrasonography compared to the group that was treated with the saline solution alone. However, the study has limitations due to sample loss during the procedures, which prevented the equitable distribution of volunteers into the proposed groups.

Additional studies are suggested to clarify and explain their mechanisms of action, varying therapeutic substances, parameters and new treatment associations.

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