TECHNICAL-SCIENTIFIC REPORT

RESEARCH PROJECT: Effects of Transcutaneous Electrical Nerve Stimulation on Blood Pressure in Hypertensive Patients: A Randomized Clinical Trial

Ethics committee approval number: CAAE 40091020.0.0000.5335
Clinical Trials number: NCT06025643
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Sponsor: Leonhardt's Launchpads by Cal-X Stars

Introduction

Arterial hypertension (AH) is a chronic, non-communicable, and multifactorial disease, characterized by a persistent elevation of blood pressure (1). According to the 2020 Brazilian Hypertension Guidelines (1), an individual is considered hypertensive if they have a systolic blood pressure ≥ 140 mmHg and diastolic blood pressure ≥ 90 mmHg measured in a clinical setting, or a systolic blood pressure ≥ 130 mmHg and diastolic ≥ 80 mmHg diagnosed through a 24-hour ambulatory blood pressure monitoring (ABPM).

Transcutaneous electrical nerve stimulation (TENS) is widely used as a pain relief tool in rehabilitation and its safety has been validated by robust evidence (2). In recent years, complementary non-pharmacological alternatives have been sought for hypertensive patients who are difficult to manage or non-adherent to drug treatment. However, there is a lack of evidence in the literature regarding the effects of TENS on blood pressure regulation (3) and its influence on autonomic nervous system control (4).

The studies published to date include few participants and are methodologically weak (5–8), however, their results encourage further well-designed research. In addition, TENS is a low-cost, non-invasive therapy that can be applied in the home setting (3).

To the best of our knowledge, no study to date has investigated the optimal application site for reducing blood pressure levels or for modulating autonomic control in individuals with essential hypertension. Therefore, through a randomized controlled clinical trial, we aim to assess the effect of low-frequency TENS applied to different anatomical sites on blood pressure and autonomic control in patients with primary hypertension.

Métodos

Design and Ethical Aspects

This study is a randomized, single-blind clinical trial. The research project was approved by the Research Ethics Committee of the Irmandade Santa Casa de Misericórdia de Porto Alegre - ISCMPA (CAAE: 40091020.0.0000.5335; number: 6.180.526) and registered on the ClinicalTrials.gov platform (NCT06025643).

Participants

Patients with essential hypertension (systolic blood pressure ≥ 130 mmHg and diastolic blood pressure ≥ 80 mmHg) diagnosed by ABPM, aged between 20 and 75 years, of both sexes, recruited from the community between november 2023 and november 2024, were included in the study. Patients with congestive heart failure, cardiac pacemaker, previous cardiac surgeries, serum creatinine > 2.5 mg/dL, decompensated diabetes mellitus, change in antihypertensive medication therapy in the two months prior to starting the TENS protocol, and smokers were excluded.

Setting

The evaluations took place at the Cardiology Center of the São Francisco Hospital of ISCMPA and at LaSalle University. The interventions were performed at the Integrated Cardiopulmonary and Metabolic Rehabilitation Service of the Pereira Filho Pavilion of ISCMPA.

Randomization and Blinding

Randomization (allocation ratio 1:1:1:1) was performed through the website randomization.com. The list with the sequence of numbers was generated by a researcher blinded to the study and revealed only at the beginning of the intervention program to the physical therapists who performed the TENS protocols to ensure allocation concealment. Patients were allocated to one of four groups: 1) Cervicothoracic Stimulation Group (CTG); 2) Renal Stimulation Group (RG); 3) Combined Stimulation Group (ComG); or 4) Control Group (CG).

Outcomes and Measurement Instruments

Blood pressure was considered the primary outcome of this study and was assessed using ABPM. Autonomic control was considered the secondary outcome and assessed through heart rate variability analysis.

Avaliação da pressão arterial

Blood pressure was measured by ABPM over 24 hours. Each patient used a blood pressure monitor (Dyna-MAPA NG, Cardios, São Paulo, Brasil) placed on their arm, which automatically inflated the cuff every 20 minutes during the day and every half hour from midnight to 7 a.m. The following parameters were measured and evaluated over the 24h: systolic BP (SBP), diastolic BP (DBP), PP (SBP-DBP) and mean arterial pressure (MAP) (9).

Assessment of autonomic control

The assessment of autonomic control was performed by analyzing heart rate variability after recording with a heart rate monitor (Polar®, RS800CX model, Finland). The sensor belt was placed on the patient's chest, and the signal was automatically recorded during the R-R interval. Patients initially remained supine and were instructed to remain calm and not move. After a brief period of rest (10 minutes) to stabilize the heart rate, the signal was recorded for 10 minutes in this same position to assess the parasympathetic nervous system. To assess the sympathetic nervous system response, the patient was instructed to stand up after the exam, and the signal was then recorded for another 10 minutes in the upright position (10–12). Data analysis was subsequently performed in Kubios 2.0 software, using frequency domain data.

Intervention

A properly calibrated Stimulus R device (HTM, São Paulo, Brazil) was used to administer TENS. The electrical current was applied twice a week in the first and second weeks of treatment (with a one-day interval between applications) and three times a week in the third and fourth weeks (with a one-day interval between applications), totaling 10 applications over four weeks, regardless of the treatment group.

Participants were comfortably accommodated in an air-conditioned room (23ºC) and positioned in the supine position (4). After 15 minutes of rest, blood pressure, heart rate, and peripheral oxygen saturation (SpO_2) were measured. A sphygmomanometer and

stethoscope were used to measure blood pressure, and a portable oximeter (GTECH®) was used to measure heart rate and SpO_2.

Prior to TENS application, the skin was cleaned with 70% alcohol and the electrodes were positioned at the respective current application sites. TENS was applied using a low frequency (5 Hz), a pulse width of 200 μs, and an intensity sufficient to reach the sensory threshold. The intensity was adjusted every five minutes to avoid accommodation of the stimulus, as long as it did not reach the motor threshold. The session duration was 30 minutes. At the end of each application, all vital signs were rechecked.

The type, size, and application location of the electrodes are described below, depending on the allocation group.

CTG: Self-adhesive electrodes (5x5 cm) were positioned in the cervicothoracic ganglion region, located between the C7 and T4 vertebral processes, bilaterally.
RG: Self-adhesive electrodes (5x9 cm) were positioned on the abdomen (anatomical region corresponding to the kidneys) and dorsal region at the level of the 10th thoracic vertebra, bilaterally.
ComG: Self-adhesive electrodes (5x5 cm) in the cervicothoracic ganglion region, located between the C7 and T4 vertebral processes, bilaterally; rubber clip-type electrodes on the earlobe, bilaterally; self-adhesive electrodes (5x5 cm) on the wrist, bilaterally; self-adhesive electrodes (5x5 cm) on the tibial nerve path, bilaterally.

The control group did not receive any intervention; they were just assessed and reassessed at the same time points as the treated groups.
Figure 1 shows the electrode placement and TENS application site for each intervention group.

Statistical Analysis

The sample size calculation was performed using BioEstat 5.0 software and it was based on a randomized clinical trial conducted by Sartori et al. (4). A sample of 20 patients per group was estimated, predicting losses, using the mean and standard deviation values of the low-frequency TENS (84.3±10.5) and placebo (81±17.1) groups for the PAD outcome, considering an alpha error of 5% and a power of 95%. Therefore, 80 patients were estimated for the sample size of this study.

Graphpad Prism software, version 5, was used for data analysis. Normality was verified using the Shapiro-Wilk test. Data are presented as means and standard deviations, medians and P25-P75 values, or frequencies. One-way ANOVA with Bonferroni or Dunss post hoc tests and the Kruskal-Wallis test were used to compare groups at baseline, according to data normality. Categorical variables were analyzed using the chi-square test. Two-way ANOVA for repeated measures with Bonferroni post hoc tests was performed to compare the effect of group interactions with time for the outcomes blood pressure and autonomic control. The significance level was set at 5% ($p<0.05$).

Results

Forty patients were included in this study. Figure 2 details the selection process and group composition. The sample characteristics by allocation group are presented in Table 1. With the exception of age and weight, the groups did not differ at baseline.

Table 1. Sample characterization

	CTG (n=10)	RG (n=10)	CGom (n=10)	CG (n=10)
Sex (M/F)	6/4	6/4	4/6	4/6
Age (years)	54 ± 11	63 ± 8	60 ± 7	47 ± 14*#
Weight (kg)	83.8 ± 7.1	84.9 ± 18.1	74.4 ±	92.2 ± 12.3#
Height (m^2)	1.68 ± 0.1	1.67 ± 0.1	1.64 ± 0.1	1.68 ± 0.1
BMI (kg/m^2)	30.23 (26.5-32.7)	28.67 (27.1-34.7)	26.92(26-28.3)	31.12(30.3-36.7)
Diagnostic time (months)	72 (60-186)	164.5 (6246)	180 (30-312)	72 (9.75-189)
Medications				
- Antihypertensive	8	9	8	9
- Diuretic	2	5	4	3
- Statin	3	1	2	1

Legend: CTG: cervicothoracic group; RG: kidney group; ComG: combined group; CG: control group. Data are presented as mean ± SD or median and percentile (P25-P75) and frequencies* $p< 0.05$ vs RG; # $p<0.05$ vs ComG. One-way ANOVA. Bonferroni or Dunn's post hoc test. Kruskal-Wallis and Chi-square tests.

Safety

TENS proved to be safe for patients with essential hypertension, regardless of the application site. No significant changes in vital signs were observed immediately after the electrical current application between the groups. Only a reduction in heart rate was observed in the RG (time effect). Patients also reported no adverse effects after the TENS session or between sessions.

Tables 2 and 3 shows the vital sign values assessed before and immediately after the TENS sessions, as well as the average stimulation intensity used in each group, respectively.

Table 2. Vital signs before and immediately after TENS application in hypertensive patients

	CTG (n=10)		RG (n=10)		ComG (n=10)	
	Pre	Post	Pre	Post	Pre	Post
HR (bpm)	77 (69-84)	72 (66-82)	74 (68-84)	70 (62-75)*	75 (74-80)	71 (69-75)
SpO2 (%)	98 (97-98)	97 (97-98)	97 (94-98)	98 (97-98)	97 (97-98)	98 (97-98)
SBP(mmHg)	136 (131-137)	132 (124- 141)	140 (131-151)	137 (127-150)	140 (134-150)	144 (134 -151)
DBP(mmHg)	85 (82-87)	84 (77-88)	83 (78-88)	79 (77-87)	83 (76-90)	83 (77-92)

Legend: CTG: cervicothoracic group; RG: kidney group; ComG: combined group; HR: heart rate; SpO2: peripheral oxygen saturation; SBP: systolic blood pressure; DBP: diastolic blood pressure. Os valores são apresentados em mediana e percentil (P25-P75). *p<0.05 vs pre. Two-way ANOVA with Bonferroni post hoc.

Table 3. TENS stimulation intensity per hemibody

	CTG (n=10)	
	R hemibody	L hemibody
Intensity (mA)	24.93 ± 7.5	24.8 ± 7.8
	RG (n=10)	
	R hemibody	L hemibody
Intensity (mA)	24.6 ± 9.8	24.8 ± 7.8
	ComG (n=10)	
	R hemibody	L hemibody
Minimum intensity (mA)	20.6 ± 5.6	24.8 ± 7.8
Maximum intensity (mA)	39.9 ± 8.9	44.8 ± 21.8

Legend: CTG: cervicothoracic group; RG: kidney group; ComG: combined group; R: right; L: left. Values are presented as mean ± standard deviation. For the ComG group, we chose to show the minimum and maximum intensity since this group had four application sites with different stimulation intensities.

Effectiveness

There was a reduction in systolic and diastolic blood pressure for the group that received sensory stimulation in the kidney region (RG) at the end of the treatment protocol, but there was no difference when compared to the other groups. The pre- and post-treatment values for systolic and diastolic blood pressure for all groups can be seen in Table 4. Figures 1 and 2 illustrate the behavior of systolic and diastolic blood pressure

in the four groups before and after the intervention protocol with TENS or control. Figures 3 and 4 show the variation (post-pre) of the four groups for the same outcome.

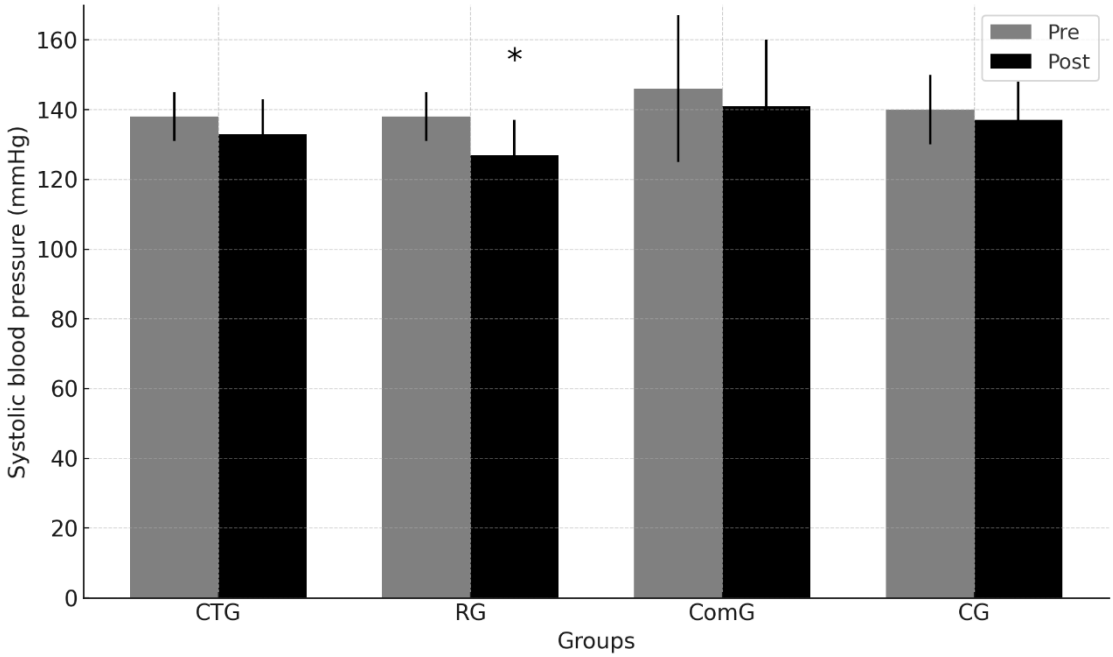


Figure 1

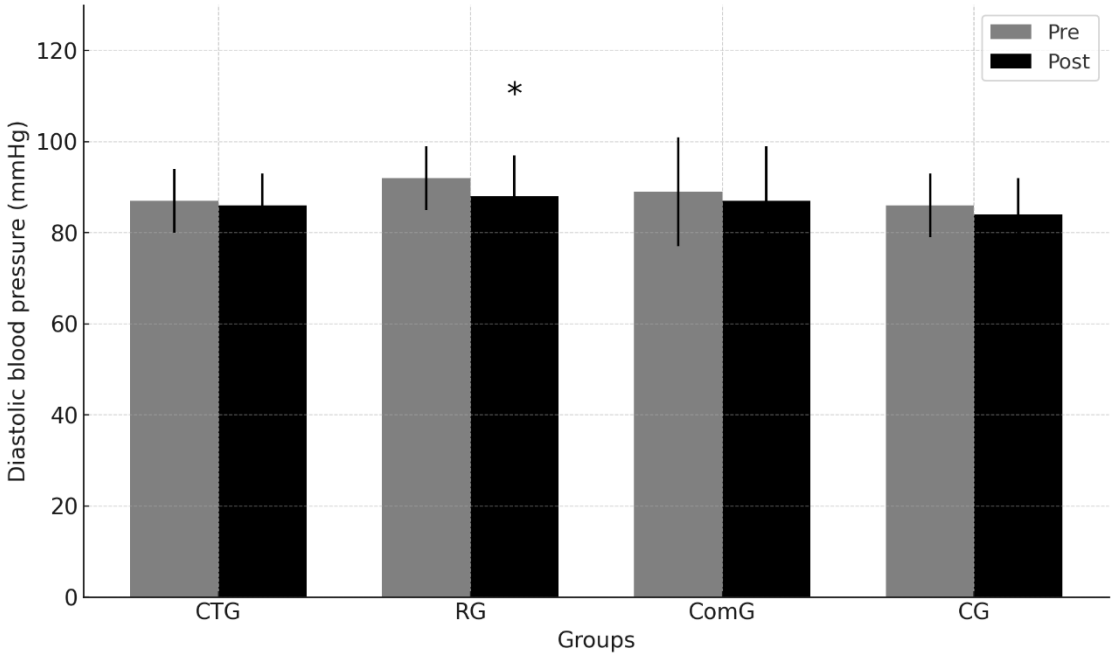


Figure 2

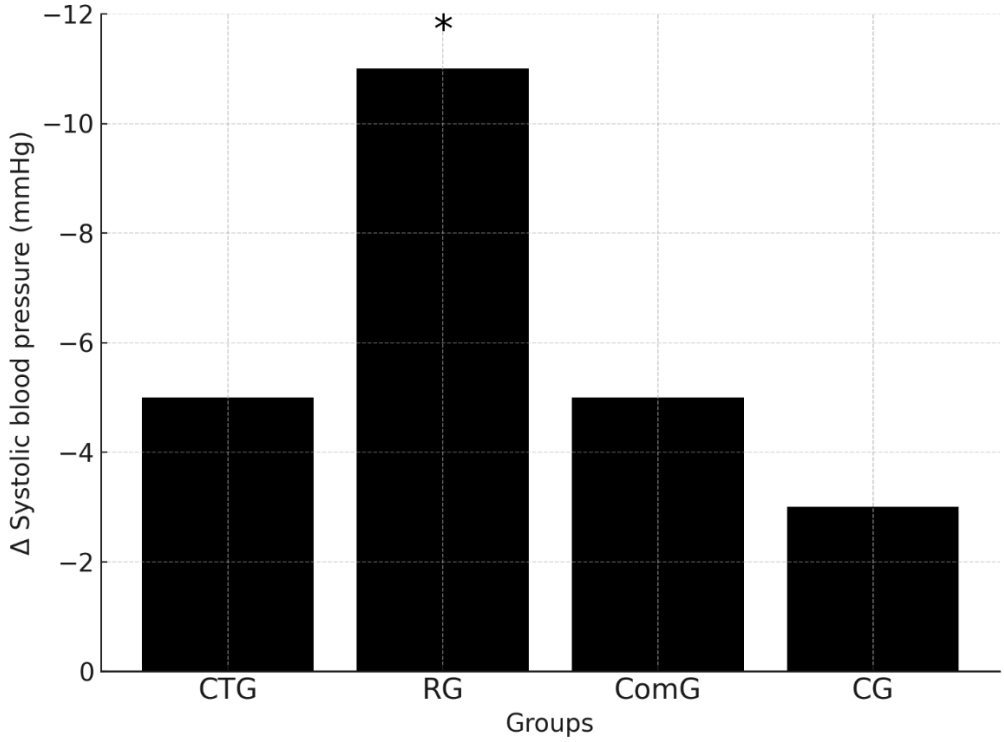


Figure 3

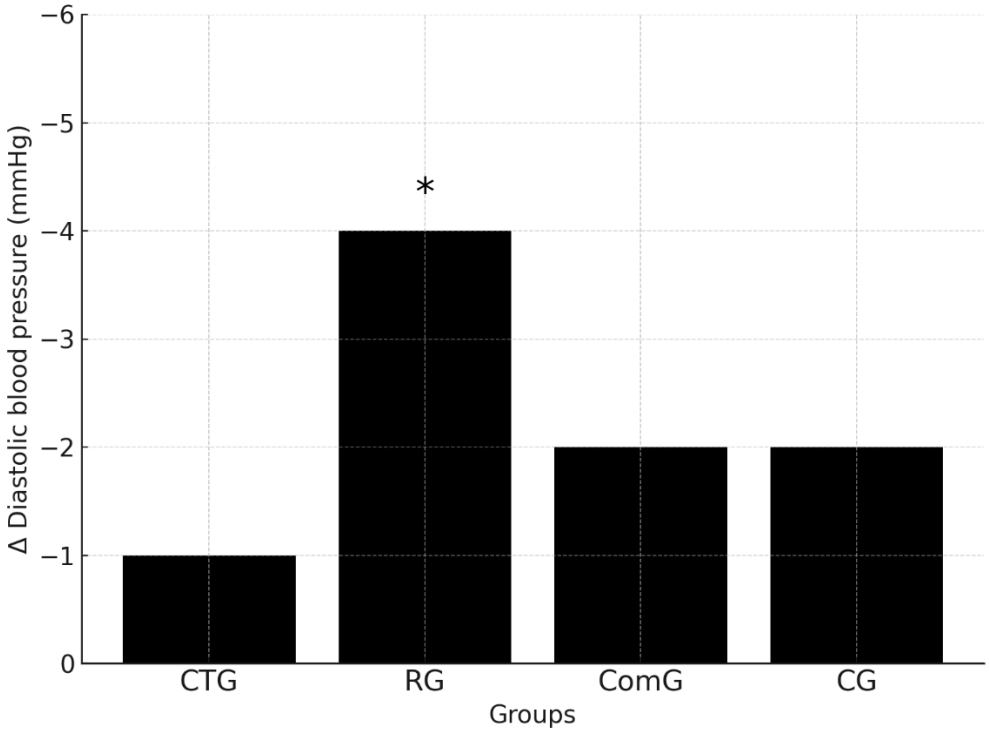


Figure 4

Table 4. Blood pressure behavior after ten low-frequency TENS sessions according to the application site

	CTG (n=10)			RG (n=10)			ComG (n=10)			CG (n=10)			p		
	Pre	Post	Δ	Pre	Post	Δ	Pre	Post	Δ	Pre	Post	Δ	Group	Time	Interaction
SBP (mmHg)	138 ± 7	133 ± 10	-5	138 ± 7	127 ± 10*	-11	146 ± 21	141 ± 19	-5	140 ± 10	137 ± 11	-3	0.179	<0.005	0.314
DBP (mmHg)	87 ± 7	86 ± 7	-1	92 ± 7	88 ± 9*	- 4	89 ± 12	87 ± 12	-2	86 ± 7	84 ± 8	-2	0.583	0.005	0.741

Legend: CTG: cervicothoracic group; RG: kidney group; ComG: combined group; CG: control group; SBP: systolic blood pressure; DBP: diastolic blood pressure; Δ: post-pre. Data presented as mean and standard deviation. Two-way ANOVA for repeated measures and Bonferroni post hoc. *p<0.05 vs pre.

Regarding autonomic control, a difference was observed over time for ComG in the low frequency component (LF) and high frequency component (HF) domains. There was no difference between the groups. The difference over time for ComG in the aforementioned domains indicates an increase in sympathetic nervous system activity and a decrease in parasympathetic activity in the supine position. In the orthostatic position, there was no change in autonomic control for either group. The full data for this outcome can be seen in Table 5.

Table 5. Behavior of autonomic control after ten low-frequency TENS sessions according to the application site

		GCT (n=8)		GR (n=9)		GCom (n=7)		p		
		Pre	Post	Pre	Post	Pre	Post	Group	Time	Interaction
LF	SP	46.2 ± 12.1	56.5 ± 10.7	50.8 ± 15.3	56.4 ± 12	39.9 ± 23.7	62 ± 15.4*	0.854	<0.005	0.166
	Orthostasis	68.2 ± 8.2	69.4 ± 11.7	47.3 ± 17.2	59 ± 18.4	58.9 ± 21.3	61.2 ± 22.5	0.134	0.121	0.324
HF	SP	49.5 ± 13.8	36.5 ± 10	33.9 ± 20.3	26 ± 14.8	38.7 ± 30.6	22.5 ± 17*	0.202	0.005	0.682
	Orthostasis	18.3 ± 8.2	18.5 ± 8.7	39.2 ± 17.9	22 ± 22	25.1 ± 24.7	24.4 ± 21.2	0.319	0.093	0.067
LF/HF	SP	0.98 ± 0.38	1.75 ± 0.86	2.27 ± 1.68	3.01 ± 1.96	3.38 ± 5.12	3.96 ± 2.21	0.071	0.298	0.992
	Orthostasis	4.85 ± 2.98	4.93 ± 2.99	2.62 ± 4.29	5.29 ± 3.55	5.59 ± 4.32	5.32 ± 4.61	0.684	0.221	0.146

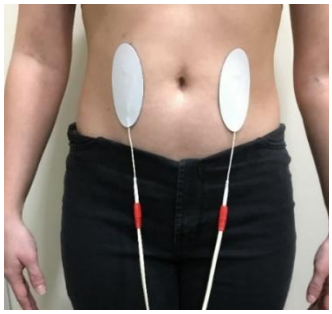
Legend: LF: low frequency component; HF: low frequency component; LF/HF: sympathovagal balance – low frequency/high frequency; SP: supine position. Data presented as mean and standard deviation. Two-way ANOVA for repeated measures followed by Bonferroni's post hoc test. *p<0.05 vs pre. Not all patients have the final assessment of autonomic control, therefore n < 10.

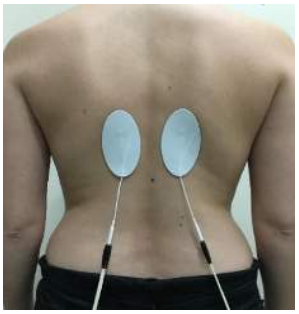
Final Considerations

Low-frequency sensory stimulation (5 Hz TENS) appears to have a positive effect on reducing blood pressure in individuals with essential hypertension when applied to the anatomical site of the kidneys. Modulation of autonomic control showed no clinically relevant changes, regardless of the site of therapy application. It should be noted that these are preliminary results (pilot study – 40 patients) and a larger sample size is needed for definitive conclusions.

Figures

1A. CTG





1B. RG

1C. ComG

Figure 1. Positioning of electrodes at the sites of application of electrical current for the different intervention groups

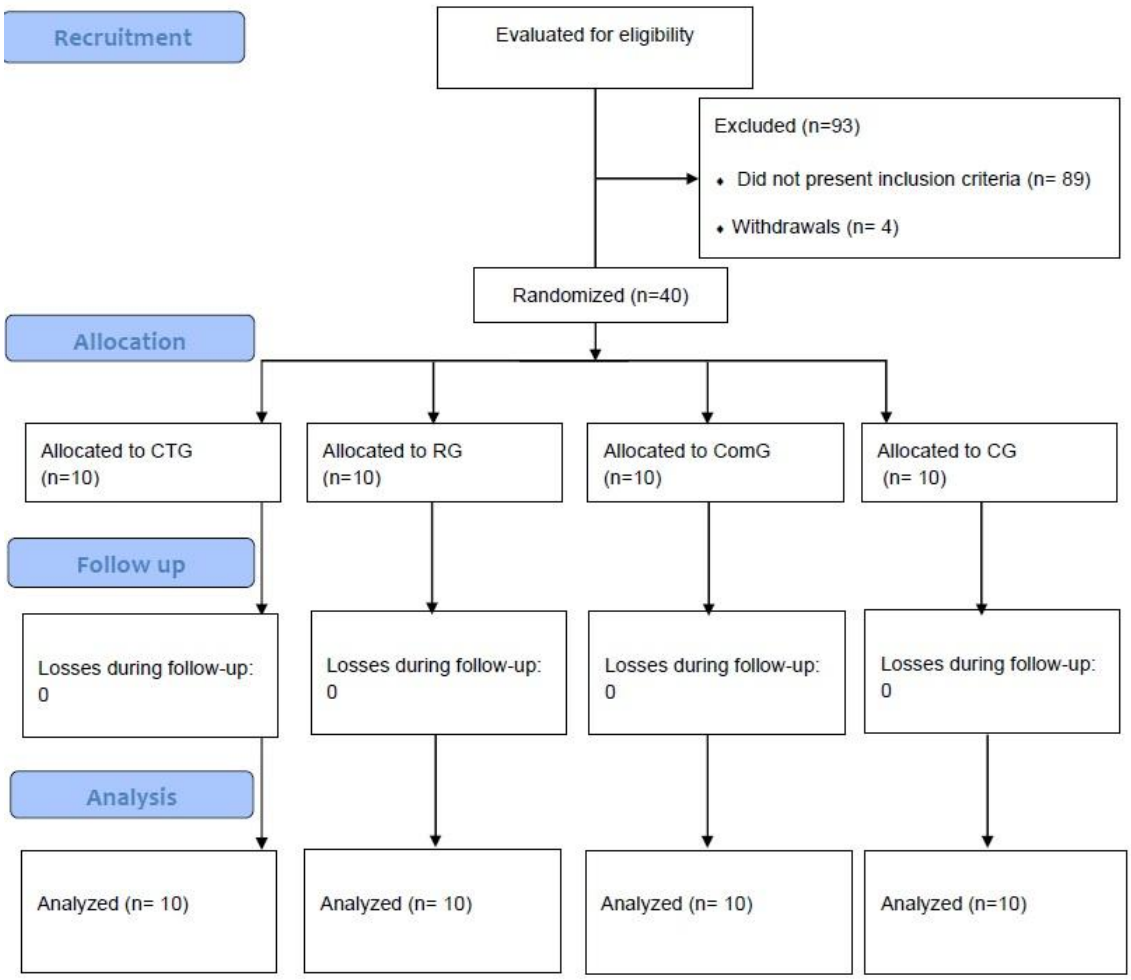


Figura 2. Fluxograma de seleção dos pacientes e composição dos grupos

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