quantum experimental	**FINAL REPORT**	**Date**	4-01-2017
		N. of pages	46
		Protocol code	QTM/WND-0215

RANDOMIZED DOUBLE-BLIND CLINICAL TRIAL TO EVALUATE THE EFFICACY OF A HANDHELD TENS PEN IN THE TREATMENT OF ACUTE OR CHRONIC MUSCULOSKELETAL PAIN

Protocol code: QTM/WND-0215

Sponsor: WINDIRECT, S.L.

INDEX

1. GENERAL INFORMATION

Title: Randomized double-blind clinical trial to evaluate the efficacy of a handheld TENS pen in the treatment of acute or chronic musculoskeletal pain.

Protocol code: QTM/WND-0215

Sponsor data

WINDIRECT, S.L.
C/ Córcega, 299, 5º 3ª I
08008 Barcelona
Spain

Principal Investigator

Juan Francisco Abellán

Investigation Site

Hospital General Universitario Morales Meseguer

Study duration

- Total duration of study: 8 months
- Recruitment: 6 months
- Treatment: 28 days
- Results and final report: 1 month

Independent Ethics Committee (IEC)

IRB Hospital General Universitario Morales Meseguer

Contract Research Organization (CRO)

Quantum Experimental, S.L.
C/ Carril de la Condesa Nº 58, office 505
30010 Murcia, Spain

2. BACKGROUND AND STUDY JUSTIFICATION

The International Association for the Study of Pain (IASP), (2) defines pain as *an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.* There are two kinds of pain, acute and chronic. The acute pain is a predominant symptom or manifestation of tissue injury, chronic pain is considered a disease in itself. Chronic pain persists for a period longer than three months and often it is difficult to treat. It can cause major problems to the patient and it has a negative impact on their quality of life.

Chronic pain is classified in oncological and non-oncological. Both can be nociceptive (somatic or visceral) and neuropathic.

In scientific literature there is a broad consensus that pain is a complex and multifactorial phenomenon that depends on the interaction of physiological, psychological and sociocultural factors. Inconclusive differences in pain perception or manifestation, related to ethnic or racial conditions in adults and children have been described (12, 13, 14).

There are studies that show differences in pain perception by gender, highlighting the revision published in 2009 about prevalence of chronic pain in representative samples from different countries of our socioeconomic environment. In seven out of ten studies included, the differences between men and women were statistically significant.

Different types of pain based on its causation, characteristics and approach have been conceptualized. In 1994 IASP published a classification of chronic pain, which included a complete taxonomy and different definitions; both are subject to periodic revision and updates, (16).

The following table shows the common causes of chronic pain, (4):

Table1. Common causes of chronic pain

Musculoskeletal pain	Joint pain (arthritis and arthrosis) Spinal pain: lumbar, cervical Muscle pain (myofascial pain syndromes and muscular pain) Oncological pain with musculoskeletal affectation
Neuropathic pain	Herpes zoster and post-herpetic neuralgia Neuralgia of peripheral nerves Painful diabetic neuropathy Complex regional pain syndromes Pain from nerve injury Post-amputation pain and phantom limb
Mixed pain	Radicular pain of spinal pathology
Chronic visceral pain	
Vascular pain	
Somatoform pain	

The pain from musculoskeletal injuries is one of the most common reasons for disability. In addition, these injuries can create functional impairment, disrupt sleep and mood, and this cannot be completely solved with currently available therapies which enable the incorporation of additional treatment options to potentially improve outcomes of care.

Recent research has examined the use of an adjuvant transcutaneous electrical nerve stimulator (TENS) for pain treatment.

In 1965, Melzack and Wall introduced "gate-control theory" about an electrical current that affects nerve fibers. This stimulation causes the release of endorphins in the hypothalamus which gives relief from pain especially that of musculoskeletal origin. Following this theory more clinical trials were carried out. All of them showed positive results regarding the effect of pain relief. Based on this technology the studied device is a handheld, wireless TENS electrical stimulator.

This trial is going to examine specifically if the addition of a protocol transcutaneous electrical nerve stimulation (TENS) therapy (handheld TENS pen) will have a beneficial impact on pain caused by acute and chronic musculoskeletal injury.

The types of pain covering acute or chronic musculoskeletal injury for this study are the following:

- Neck and shoulders: neck tension syndrome, cervical syndrome, torticollis and frozen shoulder.

- Arms and elbow: epicondylitis (tennis elbow), epitrocleitis (golfer's elbow), tenosynovitis in extensor (elbow bursitis), radial tunnel (radial nerve by repeated movements of the arm), wrist tendinitis (rotator cuff syndrome and sprained wrist).
- In the hand and wrist: carpal tunnel syndrome; ulnar tunnel syndrome; Clerk syndrome.
- In the spine: back pain, acute lower back pain, acute lumbar pain.
- In the lower limbs: Achilles tendinitis; knee bursitis
- Arthritis, osteoarthritis, rheumatism

Bibliography

2. Unidad de Cirugía Mayor Ambulatoria. Estándares y Recomendaciones. Agencia de Calidad del SNS. Ministerio de Sanidad y Consumo. 2008.

4. Unidad de Pacientes Pluripatológicos. Estándares y Recomendaciones. Agencia de Calidad del SNS. Ministerio de Sanidad y Política Social. 2009.

12. Green CR, Anderson KO, Baker TA, Campbell LC, Decker S, Fillingim RB, et al. The unequal burden of pain: Confronting racial and ethnic disparities in pain. Pain Med 2003; 4: 277-294.

13. Anderson KO, Green CR, Payne. Racial and ethnic disparities in pain: causes and consequences of unequal care. J Pain. 2009;10:1 187-204.

14. Flores G; Committee On Pediatric Research Technical report--racial and ethnic disparities in the health and health care of children. Pediatrics. 2010.

15. Fillingim RB, King CD, Ribeiro-Dasilva MC, Rahim-Williams B, Riley JL. Sex, Gender, and Pain: A Review of Recent Clinical and Experimental Findings. J Pain. 2009; 10: 447- 485.

16. International Association for the Study of Pain. Task Force on Taxonomy. Classification of Chronic Pain, Second Edition, edited by H. Merskey and N. Bogduk, IASP Press, Seattle, 1994.

3. OBJECTIVES OF THE TRIAL

3.1. Main objectives

- To evaluate the efficacy of the handheld TENS pen for the relief of **acute pain** of moderate/severe intensity associated with musculoskeletal disorders compared with a placebo.
- To evaluate the efficacy of the handheld TENS pen for the relief of **chronic pain** of moderate/severe intensity associated with musculoskeletal disorders compared with a placebo.

3.2.Secondary objectives

- To compare the efficacy of the handheld TENS pen for the relief of acute pain associated with musculoskeletal diseases versus chronic pain.
- To compare the modifications that the handheld TENS pen produces in the administration of analgesic medication versus a placebo for both chronic and acute pain associated with musculoskeletal disorders.
- To evaluate the modifications that the handheld TENS pen produces in the quality of life of patients with musculoskeletal disorders compared to a placebo.
- To evaluate the safety and tolerability of the handheld TENS pen.

Definition

The International Association for the Study of Pain (IASP) defined pain as "*an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage*"

Classification of pain according to duration

Acute pain: Initially acute pain was simply defined in terms of duration, but now it is defined as *"an unpleasant and complex experience with cognitive and sensory factors that occur in response to tissue trauma*".

In contrast to chronic pain, with acute pain there is a significant correlation between the intensity of pain and the trigger disease and it gradually reduces until it disappears, once the healing of the underlying injury occurs.

Chronic pain: Defined as "*pain that extends for over 3 or 6 months from the appearance or extending beyond the period of healing of tissue damage, or is associated with a*

chronic medical condition". Other features of chronic pain in addition to the time factor, are that sometimes the possibilities to identify the causal pathology is low. It can be insufficient to explain the presence and intensity of the pain, and there can be a poor response to standard treatments.

Intensity of moderate/severe pain: Equivalent to a score higher than 4 on the visual analog scale of pain intensity.

Type of medication

Control medication (scheduled): Medication prescribed by the doctor on a schedule in order to keep the individual the least amount of time with pain.

Rescue medication: Medication prescribed by the doctor to be used by the patient on demand at times when the intensity of the pain makes neccesary its use

4. TRIAL DESIGN

4.1.Trial design

This is a multicenter, randomized, placebo-controlled, parallel, double-blind clinical trial.

In this trial, stratified randomization was done depending on the duration of the pain associated with musculoskeletal disorders experienced by the patients. Therefore, **strata are acute pain and chronic pain.**

In each stratum the patient allocation was performed to one treatment group in a 1:1 ratio. Furthermore the relationship between the number of patients in the experimental group and the placebo group was also be 1:1.

Figure 1 shows the scheme of the trial design.

During the visit 0 or selection visit the patients were recruited. After informed consent was signed they were randomized. This visit could be made during the 15 days prior to the initiation of treatment.

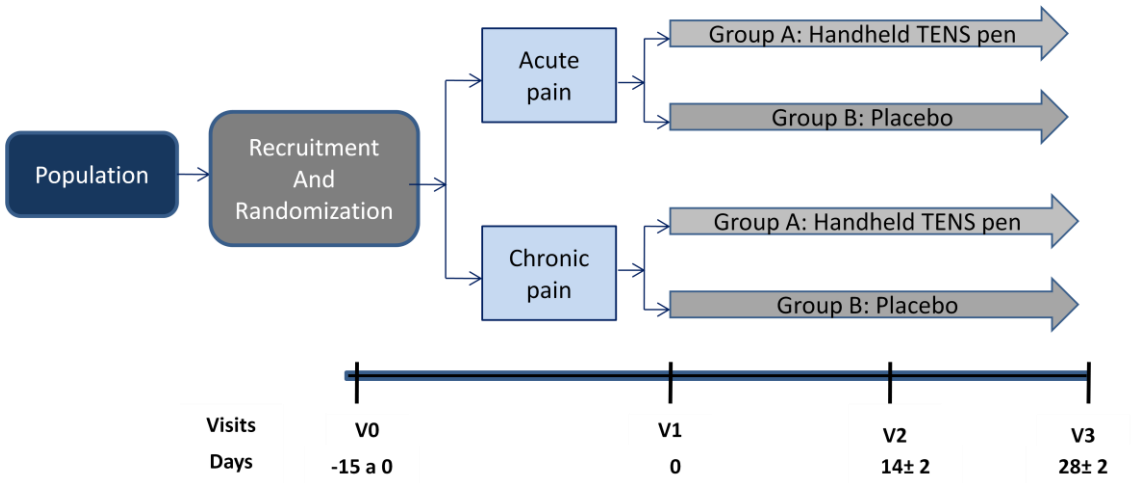

Figure1.Clinical Trial Design

Visit 1, which corresponds to day 0 of the study, it is the baseline and could coincide with the screening visit. From this visit, treatment with investigational medical devices was initiated.

Visit 2 and 3 correspond to day 14 and 28 of the study, respectively. In all visits, the patients had to go to the research centre to carry out the study procedures.

Treatment groups:

Experimental group (A): Handheld TENS pen

Placebo group (B): placebo

The clinical trial is double blind so that neither the researchers nor the patients know which group they have been assigned to. This is intended to reduce to a minimum the subjectivity of patients and researchers and reduce the bias in the interpretation of results.

This clinical trial was carried out in the Morales Meseguer Hospital (reference centre) and 3 primary care centres in which the researchers developed their activity. In this study they were employed by the Public Health Service of Murcia. In addition, these researchers included patients from other private clinics where the prevalence of acute pain was greater in respect to the reference hospital.

This design is justified by the need to cover as representative a sample as possible of the study population.

4.2. Trial Variables

4.2.1. Primary endpoint

The primary endpoint of efficacy is the intensity of the pain of musculoskeletal origin. To measure the intensity of the pain, the visual analogue scale (VAS) was used. VAS is a line of 10 cm graded numerically from 0 to 10 in which the patient marks pain intensity of 0-10 considering that 0 is "nothing" and 10 is "intolerable". The distance in centimetres or millimetres, from the point of "no pain" marked by the patient is the pain intensity. Studies show that the value of the scale reliably reflects the intensity of pain and its evolution. Therefore it is used to assess the intensity of pain experienced by a person over time.

A value less than 4 in the VAS means mild or mild to moderate pain, a value between 4 and 6 implies the presence of moderate to severe pain, and more than 6 implies the presence of severe pain.

The assessment of pain relief by VAS was done by two methods:

Daily analysis of the variable: Pain was measured by VAS each morning before administering any pain medication and before the application of the investigational device.

Analysis during the use of the device throughout the study: When the subject decided to use the device, they had to measure the intensity of pain using the VAS, before the device application and two minutes after its use. These measurements were performed each time the individual used the device throughout the day.

4.2.2. Secondary variables

- Demographic variables: age and sex.
- Clinical variables: disease process that causes pain, duration of pain, location, basal intensity, type of pain (acute or chronic)
- Concomitant analgesic medication.
- Daily use of the device. Number of times the device is used daily. The evolution of this variable will be analyzed throughout the observation period.
- Quality of life. The quality of life will be measured by the EQ-5D scale. They apply at baseline and at the final visit.
- The safety and tolerability of the product will be assessed by analysis of adverse events detected and recorded throughout the study.

4.3. Measures to minimize or avoid bias

4.3.1. Randomization

Patients who were candidates to be included in the study were selected consecutively assigning a selection number.

Once it had been verified that the patient met all inclusion criteria and none of the exclusion criteria and they had signed the informed consent form, the patients were assigned to one or another study group (placebo or experimental) by stratified randomization.

4.3.2. Masking techniques and blinding

As explained above, this is a double blind study. So, the placebo had identical characteristics and the same appearance as the medical device under investigation but no activity. Both were manufactured by the sponsor.

4.4. Description of investigational products

Experimental product:

Portable piezoelectric stimulator based on transcutaneous electrical nerve stimulation (TENS) with EC Nº 94387

The device is a handheld, wireless TENS electrical stimulator, ergonomically designed with a pen-like shape to fit to the hand and allow for easy use. Externally, it consists of an electrically-insulating casing, with at one end an actuator button, and at the other end a contact electrode. In the middle of the device is a metal contact ring that earths the device.

The device is intended for pain relief and works on the basis of transcutaneous electrical nerve stimulation. It device generates low-energy electrical impulses which is posited to result in pain relief through the same biological mechanism as that of other TENS devices.

The device produces an electrical output through the depression of the actuator button by the user. This results in the generation of a low energy electrical output, which is conducted through the negative electrode to the user's skin at the site of application of the device. The device is a complete unit and does not require any additional

accessories. It is designed for use directly by the end-user.

Therapeutic group: Medical Device Class IIa

Category:

4- Electro/mechanic products
12- Products that use radiation for diagnostics
GMDN (Global Medical Device Nomenclature):
35372- Stimulator, electrical, analgesic, peripheral nerve, transcutaneous

Patents: EP1194107 A1/WO2001001920 A1

How to use: The individual holds the device in their hand with their fingers placed firmly around the metal ring. The thumb should be free to press the activation button. The tip of the device is placed directly onto the painful area and the button is pressed 30 to 40 times.

Placebo Product:

The placebo device is identical in external form to the genuine medical device and is comparable in weight. However, the placebo unit emits no electrical impulse whatsoever.

Instead, upon depression of the activating button, the metallic tip of the device protrudes by approximately 1-2mm from the unit casing. This brings the tip into contact with the user's skin, or presses more deeply into clothing. Upon release of the button, the tip recedes back into the casing. The intention is to give an impression to the user that the placebo device is active (while having no therapeutic benefit) and obstructing the user from discerning the placebo from the genuine article.

The following paragraphs apply to both the experimental and the placebo product.

How to use: The individual holds the device in their hand with their fingers placed firmly around the metal ring. The thumb should be free to press the activation button. The tip of the device is placed directly onto the painful area and the button is pressed 30 to 40 times.

4.5. Acquisition, packaging and labelling of medication

The sponsor was responsible for the manufacturing, mask, coding and product supply of

both the experimental and the placebo devices.

Investigational products (IPs) were properly labelled according to the Guide to Good Manufacturing of medicines for human and veterinary use.

4.6. Storage and dispensation

The sponsor was responsible for sending the investigational product to the Hospital where it was stored at the appropriate temperature and humidity conditions (Temperature: -20ºC to +50ºC, relative humidity: 10% to 95%).

Investigators gave the investigational product to the patient explaining in detail how to use it and showing them a demonstration video. In addition, patients could read the instructions for use included in the device box.

4.7. Identification of data to be recorded in the CRF

The Case Report Form (CRF) for this study is a printed document, which was designed to collect and transmit to the sponsor / CRO all the information required in the protocol for each subject of the study.

In the CRF, patients were identified solely with their randomization code and no information that might reveal the identity of the patient was collected.

The data recorded directly in the CRF (considering it as a source document) are the results of the VAS pain intensity, the quality of life questionnaire EQ-5D and concomitant medication.

4.8. End of the study

End of the study was considered the day of the final visit of the last patient included.

5. SELECTION AND WITHDRAWAL OF PATIENTS

5.1. Definition of the study population

Subjects who fulfill all inclusion criteria and none of the exclusion criteria which are listed below:

Inclusion Criteria

- Patients age equal to 18 years old or above
- Patient that meet the following criteria:

- Acute or Chronic pain
- Moderate or severe pain intensity. The assessment of baseline pain intensity should be taken after a minimum of 4 hours after the last dose of regular analgesic.
- Pain caused by musculoskeletal disease of any etiology except bone fracture.

Exclusion Criteria

- Pain caused by bone fracture
- Patients in analgesic treatment with opioid derivatives included in the group of strong opioids, drugs of the third step according to the pain ladder of the World Health Organization (WHO): Morphine, Oxycodone, Oxycodone-Naloxone, Fentanyl, Hydromorphone, Tapentadol, and Buprenorphine.
- Injuries involving hospitalization or surgery for treatment in the area that has the pain.
- Any contraindication for use of electrical stimulation, including history of epilepsy, cardiac arrhythmias, pacemaker or other implantable programmable device.
- Pregnant women or women of childbearing potential not using effective contraception (Complete abstinence from sex, surgical sterilization (tubal ligation), implanted or injectable hormonal contraceptives and oral contraceptives are considered effective contraception). This reliable contraception must be maintained throughout their participation in the study.
- Participation in another clinical trial in the three months preceding the study.
- Lack of will or inability to comply with the procedures of clinical trials.

Criteria for withdrawal.

The investigator could remove a patient from the study if they considered that the patient could no longer meet all the requirements thereof or if any of the procedures was possibly harmful to the patient. The data already gathered about the retired patients is retained and used for analysis, but no new data for the study after the withdrawal was collected.

6. STATISTICS

6.1. Statistical methodology

Descriptive study of the variables

Quantitative variables were expressed as mean, median, standard deviation, confidence interval 95% and the minimum and maximum values. This description was made for the total sample and for each of the study groups.

The qualitative variables were presented in tabular form including absolute and relative frequencies for both treatment groups and the global population.

Comparative study between groups

The homogeneity of the population at baseline with respect to demographic variables, medical history and other clinical parameters was analyzed at baseline. For quantitative variables t-student comparisons took place between the two groups of the study (placebo and experimental). The qualitative variables were analyzed by a homogeneity test based on the Chi-square distribution when it was possible and by Fisher exact test values otherwise.

The evolution of these variables was analyzed using a linear mixed model with the following factors for efficacy analysis: dependent variable (VAS results after application) inter-subject factor (treatment group), co-variable (VAS results before application) and random variable (subjects).

This model was used for other variables: dependent variable (increase of VAS results, number of daily use of device), inter-subject factor (treatment group) and random variable (subjects).

All comparative analysis was done considering all population and after that, the two strata (acute and chronic pain) were compared against each other.

The level of significance used in all statistics test was alpha =0,05

Statically analysis was performed with SPSS 21.0 computer software.

7. RESULTS

102 patients have been included in this study. 51 patients suffered from chronic pain

and 52 patients suffered from acute pain.

16 patients were withdrawn due to different causes (withdrawal of consent, non-compliance with the protocol, compliance with same exclusion criteria....), so 86 patients have been analysed in this study. 38 patients suffered from chronic pain and 48 patients suffered from acute pain.

Table 1 shows the distribution of patients by treatment group.

Table 1. Distribution of patients according to the type of pain

		Pain		Total
		Acute	Chronic	
Treatment	Experimental	29	20	49
	Placebo	19	18	37
Total		48	38	86

7.1. Demographic variables

The collected demographic variables are age and sex.

7.1.1. Age

Table 2 shows the patient's age per treatment group.

No statistically significant differences were found when comparing the age of the study groups (experimental and placebo) in the total population. The strata analysis shows that there are no differences between placebo and experimental groups. So, the study population was homogeneous in relation to the age.

Table 2. Age (mean and SD) and P between group in each stratum and total population

Pain	Treatment	Mean	Standard Deviation	N	P
Acute	Experimental	45.93	12.66	29	0.54
	Placebo	48.42	15.16	19	
Chronic	Experimental	48.70	11.45	20	0.13
	Placebo	54.61	12.10	18	
Total study population	Experimental	47.06	12.13	49	0.12
	Placebo	51.43	13.92	37	

7.1.2. Sex

The distribution by sex in both groups is homogeneous (table 3) since no significant

difference has been found between treatment groups.

Table 3. Number of men and women in each treatment group

			Sex		P
			Men	Women	
Treatment	Experimental	Number	13	36	0.551
		% inside group	26.5%	73.5%	
	Placebo	Number	12	25	
		% inside group	32.4%	67.6%	
Total		Number	25	61	
		% inside group	29.1%	70.9%	

7.2. Clinical variables

The distribution of patients related to the type of pain (acute or chronic) as well as the study group (experimental and placebo) in which they were randomized is shown in table 1.

According to the clinical variables measurement at baseline, 45.3% of the study population suffered moderate pain while 54.7% suffered severe pain (table 4).

The distribution of the intensity of pain into treatment groups is homogeneous since no significant differences between them were found.

Table 4. Distribution of patients according to the intensity of pain: Moderate and severe

			Intensity of pain		Total
			Moderate	Severe	
Treatment	Experimental	Number	21	28	0.593
		% inside group	42.9%	57.1%	
	Placebo	Number	18	19	
		% inside group	48.6%	51.4%	
Total		Number	39	47	
		% inside group	45.3%	54.7%	

The distribution of patients based on the type of pathology that they presented as well as the study group in which they were randomized, are shown in tables 5 (acute pain group) and 6 (chronic pain group).

Table 5. Type of pathology in acute pain stratum

	Treatment		Total
	Experimental	Placebo	
Chondromalacia patella	1	0	1
Muscle contracture	4	3	7
Sprain	0	2	2
Multiple contusions	1	1	2
Worsening arthrosis	3	7	10
Carpal tunnel syndrome	2	0	2
Subacromial Syndrome	1	1	2
Acute tendinopathy	17	5	22

Table 6. Type of pathology in chronic pain stratum

	Treatment		Total
	Experimental	Placebo	
Arthrosis	7	7	14
Kyphoscoliosis	1	0	1
Muscle Contracture	2	1	3
Herniated disc	1	2	3
Poliomyelitis sequelae	0	1	1
Carpal tunnel syndrome	0	1	1
Myofascial Syndrome	6	4	10
Tendinopathy	2	2	4

The distribution of patients according to the location of the pain presented by the subjects as well as the study group in which they were randomized is shown in tables 6 (acute pain) and 7 (chronic pain).

Table 6. Distribution of patients according to the location of the acute pain

	Treatment		Total
	Experimental	Placebo	
Cervical spine	2	3	5
Dorsal column	3	2	5
Lumbar spine	2	3	5
Shoulder	4	3	7
Elbow	8	1	9
Wrist	3	2	5
Hand	1	0	1
Knee	3	4	7
Ankle	0	1	1
Foot	2	0	2

Table 7. Distribution of patients according to the location of the chronic pain

	Treatment		Total
	Experimental	Placebo	
Generalized	1	2	3
Vertebral column	2	1	3
Cervical spine	4	0	4
Dorsal column	4	2	6
Lumbar spine	2	6	8
Shoulder	1	2	3
Elbow	1	0	1
Wrist	0	1	1
Hand	0	1	1
Knee	5	3	8

7.3. Efficacy analysis. Visual analogue scale (VAS)

7.3.1. Baseline

The analysis of VAS score at baseline shows that no statistically significant differences among treatment groups were found (table 8) when we analyse the total study population. The same result was obtained when we compare the results of the VAS score between experimental and placebo groups in the acute and chronic pain strata respectively (tables 9 and 10).

Therefore, we can say that the study population was homogeneous in terms of the VAS score variable at baseline. This means that the treatment groups can be compared related to VAS score variable with each other throughout the study.

Table 8. Mean and standard deviation of the baseline VAS score for total study population

	Treatment	N	Mean	SD	P
VAS	Experimental	49	6.735	1.1691	0.233
	Placebo	37	6.417	1.2716	

Table 9. Mean and standard deviation of the baseline VAS score for acute pain stratum

	Treatment	N	Mean	SD	P
VAS	Experimental	29	6.693	1.0351	0.071
	Placebo	19	6.112	1.1119	

Table 10. Mean and standard deviation of the baseline VAS for chronic pain stratum

	Treatment	N	Mean	SD	P
VAS	Experimental	20	6,795	1,3667	0,901
	Placebo	18	6,739	1,3789	

7.3.2. Comparing the VAS score between treatment groups

In order to compare the VAS score among treatment groups, we have analysed the **differences between the VAS score before and after use**. Firstly, we have calculated these differences for total study population and then we have done the same analysis for acute and chronic pain strata, respectively. Finally, we have compared the results of the calculated differences between experimental and placebo groups.

Total study population

In general, a decrease of VAS score has been found after using the medical device, taking the VAS score before use as a reference. This decrease is observed in the experimental and placebo groups.

However, when we compare the reduction of the VAS score between treatment groups (experimental and placebo) we find that the decrease in the VAS score in the experimental group (1.0 ± 1.3) is statistically greater ($p<0.001$) than in the placebo group (0.4 ± 0.7) (figure 2).

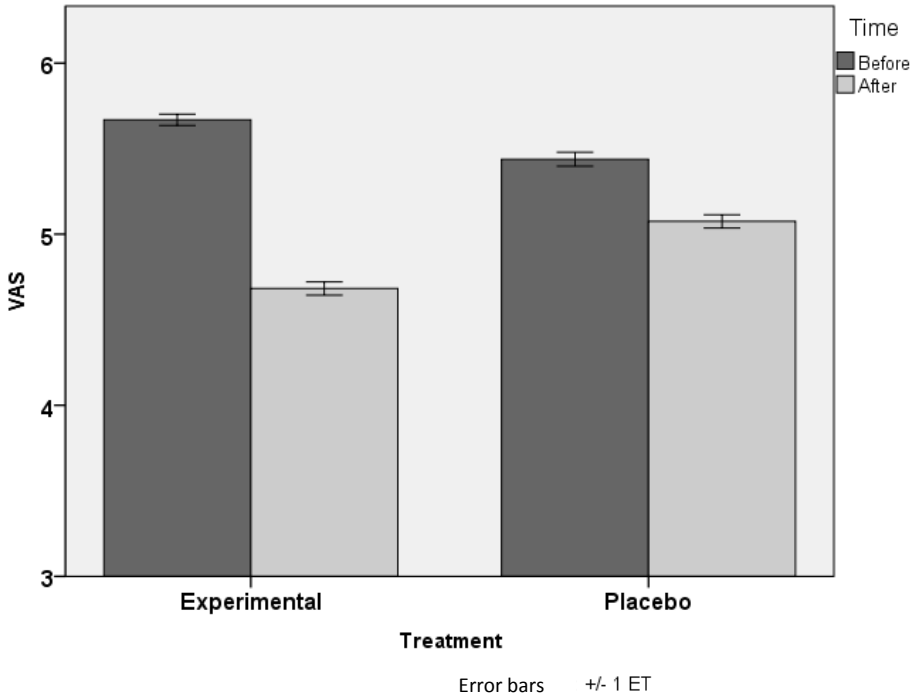

Figure 2. The VAS score before and after using the device for experimental and placebo groups taking in account the total study population

Therefore, we can conclude that the efficacy of the handheld TENS pen in relieving general musculoskeletal pain have been shown

Acute pain stratum

The analysis of the VAS score before and after use in the acute pain stratum shows a similar behaviour to that experienced by the total study population. After using the experimental device, patients felt statistically significant ($p<0,044$) pain relief compared with the placebo. So, experimental and placebo groups experienced a decrease of 1.1 ± 1.4 and 0.6 ± 0.9, respectively, in the VAS score (Figure 3) in the acute pain stratum.

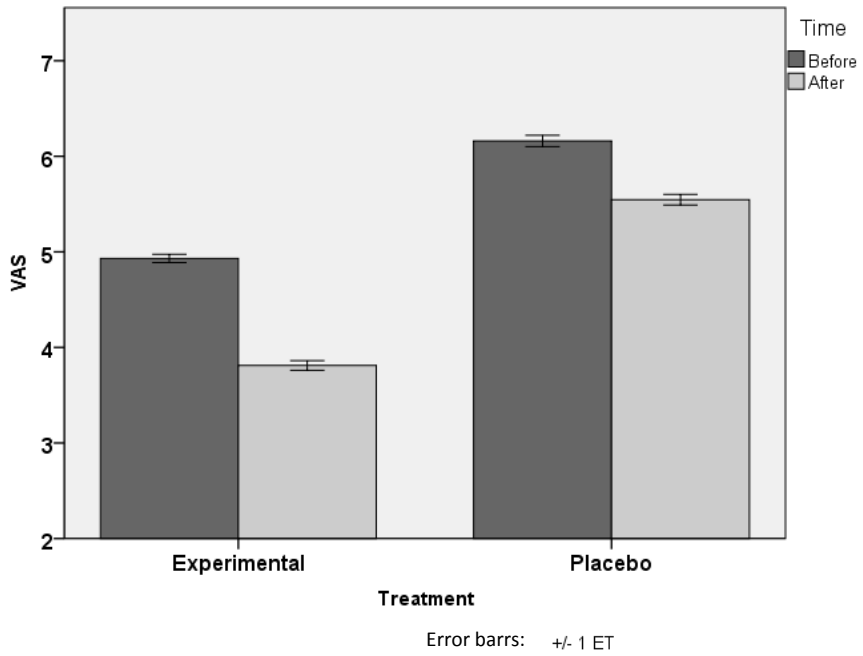

Figure 3. Acute pain stratum.VAS score for experimental and placebo groups before and after using the device.

Therefore, we can conclude that the efficacy of the handheld TENS pen in relieving acute musculoskeletal pain have been shown

Chronic pain stratum

From analysis of the VAS score decrease in chronic pain stratum, (figure 4) a statistically significant decrease ($p<0.01$) in the VAS score in the experimental group (0.8 ± 1.2) in relation to the placebo group (0.2 ± 0.5) can be seen.

Therefore, we can conclude that the efficacy of the handheld TENS pen in relieving chronic musculoskeletal pain have been shown

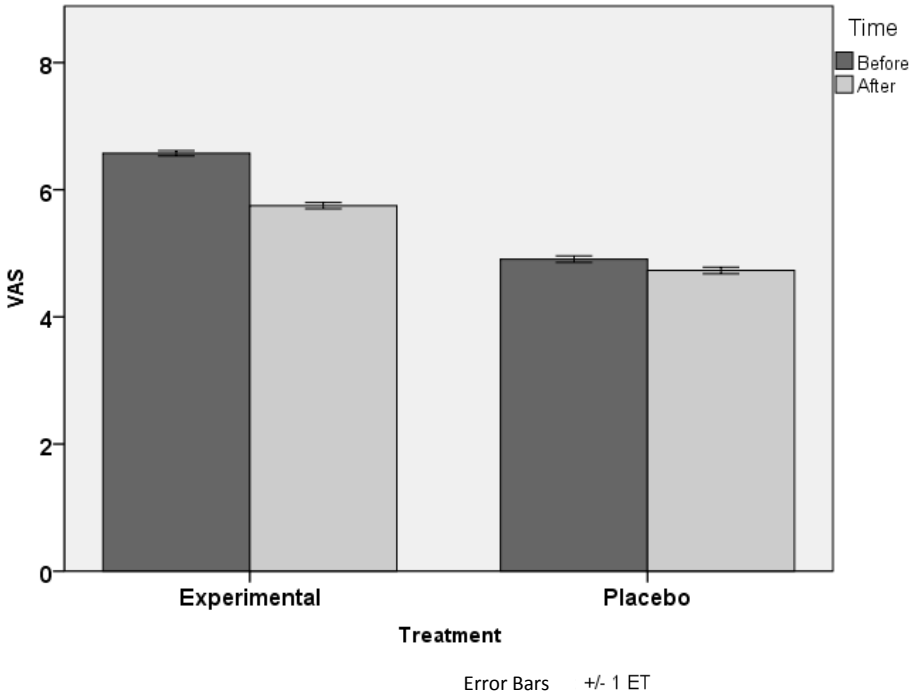

Figure 4. Chronic pain stratum.VAS score for experimental and placebo groups before and after using the device

Table 11 displays that the VAS scores showed by the acute pain stratum, before and after the use of the device, were 4.9 ± 2.1 and 3.8 ± 2.4, respectively, in the experimental group. While the placebo group experienced VAS scores from 6.2 ± 1.9 to 5.5 ±1.8 before and after the device use, respectively.

As table 11 also shows, the chronic pain stratum experienced VAS scores from 6.6 ±1.8 to 5.7 ± 2.1, before and after using the experimental device, respectively, while the VAS scores in the placebo group were 4.9 ± 2.0 and 4.7 ± 2.5 before and after using the device, respectively.

Table 11. Mean and standard deviation of VAS score before and after use in total study population and in acute and chronic pain groups

Pain	Treatment		VAS Before	VAS After	P
Acute	Experimental	Mean	4.9	3.8	0.044*
		SD	2.1	2.4	
	Placebo	Mean	6.2	5.5	
		SD	1.9	1.8	
Chronic	Experimental	Mean	6.6	5.7	0.01*
		SD	1.8	2.1	
	Placebo	Mean	4.9	4.7	
		SD	2.0	2.0	
Total Study Population	Experimental	Mean	5.7	4.7	0.001*
		SD	2.1	2.5	
	Placebo	Mean	5.4	5.1	
		SD	2.1	2.0	

*Statistically significant ($p<0.05$)

7.3.3. Temporary evolution of the daily VAS scores

In order to study the temporary evolution of the VAS scores, we have calculated the daily average differences of VAS scores before and after use for the study period (28 days). Then, we have compared the daily calculated values among experimental and placebo groups for total study population as well as for acute pain and chronic pain strata.

Total study population

a) Daily decrease of VAS score

The results show a daily decrease of VAS score after the device use.

From comparison of the study groups, we can observe that the daily VAS score reduction in the experimental group is significantly greater ($p<0.001$) than in the placebo group.

Therefore, the efficacy of the device was maintained for 28 days (length of the study) (figure 5) when considering the total study population.

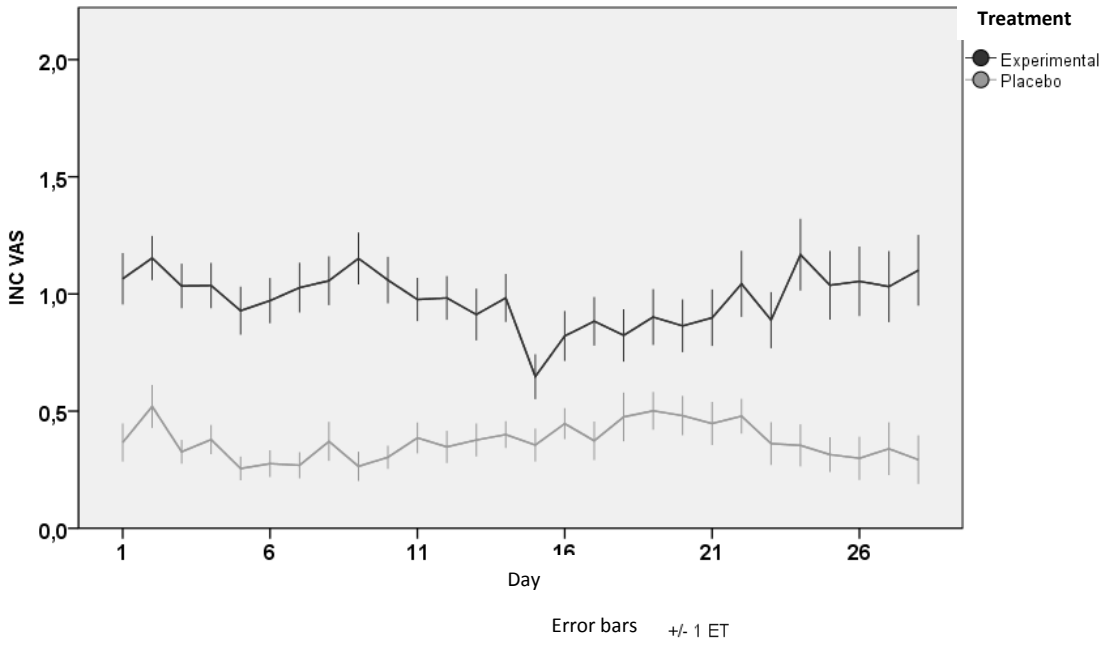

Figure 5. Daily decrease of VAS scores after device use. Total population.

As figure 5 shows, the daily VAS score decrease remains constant throughout the study (p=0.682) in the experimental group. Therefore, the use of the experimental device relieves the pain in the same manner every day for 28 days independent of pain type.

b) Daily decrease of VAS score before the experimental device use.

Regarding the VAS scores **before the experimental device use**, figure 6 shows that there is a significant decrease of this score over the days (p <0.001). In this way, the VAS score on the first and 28 days was 6.2 ± 1.8 and 5.2 ± 2.1 points on baseline and 28 days respectively.

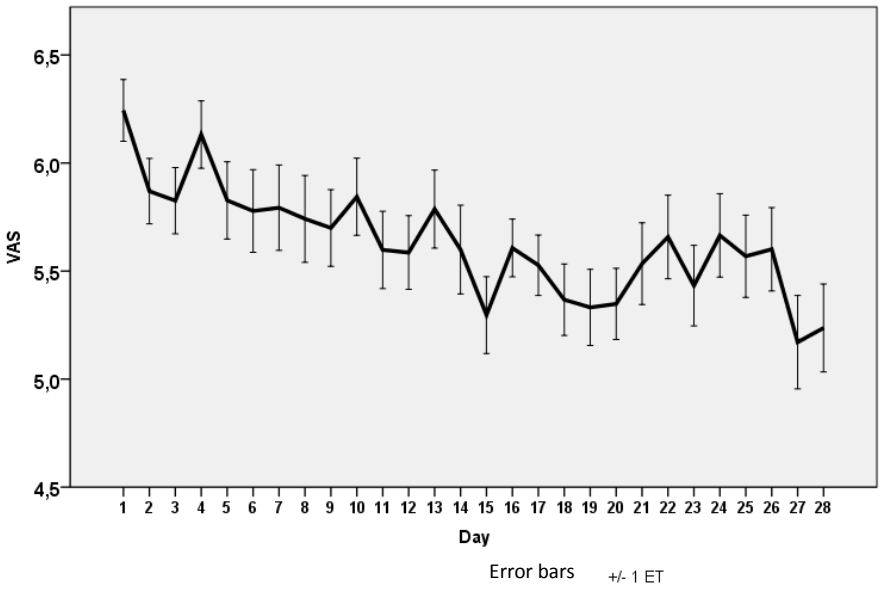

Figure 6. Temporary evolution of the VAS score obtained before the use of the experimental device. Total population

So, the handheld TENS pen efficacy remains constant over a 28-day period in alleviating general musculoskeletal pain. Furthermore, the pain relief is the same for each day of the treatment.

Acute pain stratum

a) Daily decrease of VAS score

Figure 7 shows the daily decrease of the VAS score in the acute pain stratum.
Results show that the decrease of the VAS score in the experimental group is statistically higher than that obtained in the placebo group for days 1 and 5 and shows a tendency to a greater decrease ($p < 0.1$) on days 17, 18, 23, 24, 25, 26, 27 and 28.

As can be seen in figure 7, the decrease of the VAS score in the experimental group does not remain constant throughout the study ($p < 0.030$) showing greater decrease on days 2, 5, 6, 8, 9, 10, 11, 22, 24, 25, 26 and 28 ($p < 0.05$) with respect to the first day of the study. Therefore, the decrease in pain intensity resulting from the use of the experimental device is greater in the days after the first use for acute pain.

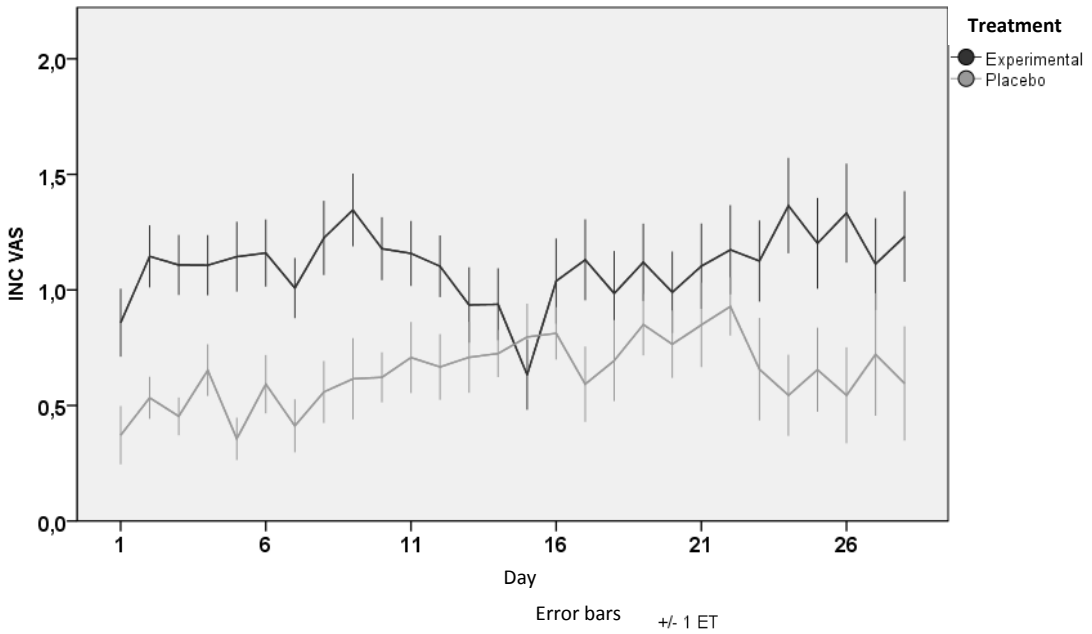

Figure 7. Daily decrease of VAS scores after device use. Acute pain group

b) Daily decrease of VAS score before the experimental device use

The temporary evolution of the VAS score before the use of the experimental device shows that there was a significant decrease throughout the study ($p < 0.001$). In this way, the VAS score was 5.9 ± 1.5 and 4.7 ± 2.2 points at baseline and at 28 days, respectively (figure 8).

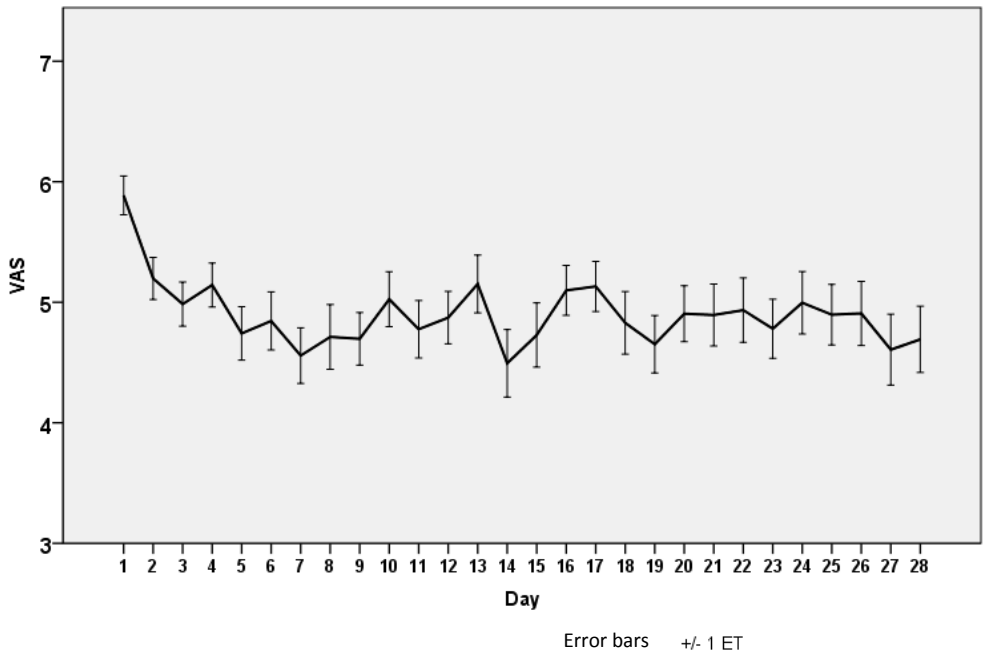

Figure 8. Temporary evolution of the VAS score obtained before the use of the experimental device. Acute pain stratum

Chronic pain group

a) Daily decrease of VAS score

Results show that there is a decrease in the VAS score after using the device by the chronic pain stratum. When comparing the daily decrease in the VAS score after application of the device between the placebo and the experimental groups, we observed that this is statistically higher ($p<0.05$) in the experimental group than that obtained in the placebo group for 1, 2, 3, 4, 14 and 28 days and shows a tendency to a greater decrease ($p <0.1$) on days 7, 8, 9, 10, 11, 12 and 25 (figure 9).

Referring to figure 9, we can see that the VAS score decrease experienced by the experimental group is not constant ($p <0.001$). We observe a daily minor decrease in VAS scores compared to the first day ($p<0.05$) except on days 2, 7 and 14. Therefore, the decrease in the intensity of pain after the use of experimental device is lower on the days after the first day in the chronic pain stratum.

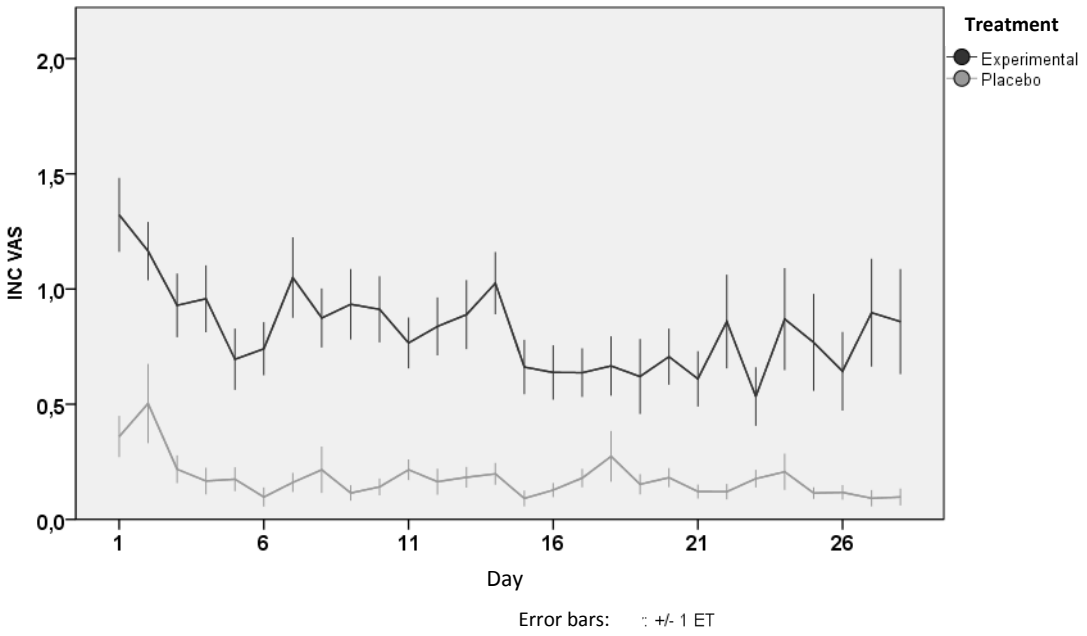

Figure 9. Daily decrease of VAS scores after device use. Chronic pain group

b) Daily decrease of VAS score before the experimental device use

Figure 10 shows that the temporary evolution of the VAS scores before the use of the experimental device does not change significantly during the study.

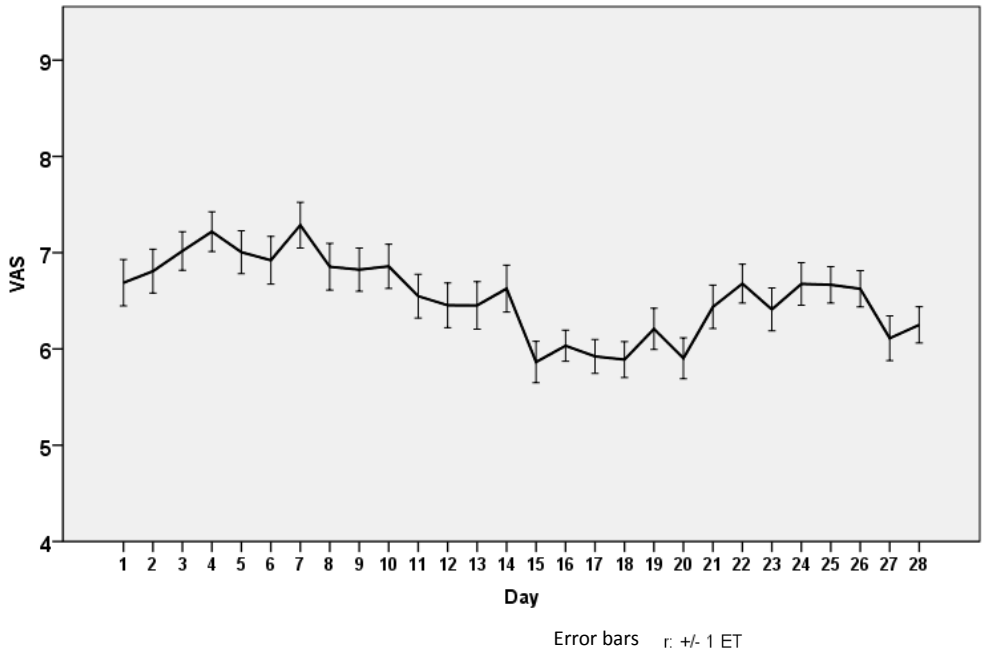

Figure 10. Temporary evolution of the VAS score obtained before the use of the experimental device. Chronic pain group.

7.3.4. First use

FIRST DAY OF USE

<u>Comparison of the VAS score before and after the first use of the device on the first day</u>

From comparative analysis between the VAS score before and after the first use of the experimental device significant differences were found ($p<0.05$). However, these differences are not significant in the placebo group. This fact is observed when we consider the total study population or each stratum separately (table 12).

However, when we compare the changes in VAS scores obtained from the first use between the experimental and the placebo groups no significant differences are observed (table 12). This is applicable to the total study population as well as to acute and chronic pain strata.

Table 12. VAS scores before and after the first use

Pain	Treatment		VAS Before	VAS After	P Time	P Time x Treatment
Acute	Experimental	Mean	5.9	5.4	0.009	0.072
		SD	1.6	1.8		
	Placebo	Mean	6.0	5.8	0.259	
		SD	1.5	1.6		
Chronic	Experimental	Mean	6.4	5.4	0.001	0.408
		SD	2.0	2.3		
	Placebo	Mean	6.3	5.9	0.240	
		SD	1.8	1.8		
Total study population	Experimental	Mean	6.1	5.4	0.001	0.079
		SD	1.8	2.0		
	Placebo	Mean	6.2	5.9	0.099	
		SD	1.6	1.7		

FIRST DAILY USE

Comparison of daily VAS scores before and after the first daily use of the device.

Table 13 shows the results of the global VAS scores before and after the daily first use of the device.

As table 13 shows, significant differences ($p<0.05$) have been found between the experimental and placebo groups with respect to the global decrease of the VAS score after the first daily use. These differences appear considering the total population and considering any of the strata.

Significant differences ($p<0,05$) have been found between the moment before and after using the device for the first daily use in all study groups but there are greater differences in experimental groups with respect to the placebo.

Table 13. VAS scores before and after the daily first use.

Pain	Treatment		VAS Before	VAS After	P Time	P Time x Treatment
Acute	Experimental	Mean	5.0	3.9	0.001	0.001
		SD	2.1	2.2		
	Placebo	Mean	5.5	5.0	0.001	
		SD	2.1	2.0		
Chronic	Experimental	Mean	6.2	5.0	0.001	0.001
		SD	2.0	2.2		
	Placebo	Mean	4.7	4.5	0.001	
		SD	2.0	2.0		
Total study population	Experimental	Mean	5.5	4.3	0.001	0.001
		SD	2.1	2.3		
	Placebo	Mean	5.1	4.7	0.001	
		SD	2.1	2.0		

Temporary evolution of the VAS scores after first daily use

Total study population

a) Daily decrease of VAS score

The analysis of the temporary evolution of VAS scores decrease after the first daily use is shown in figure 11. This graph illustrates that the decrease of the VAS score in the experimental group is statistically higher than that obtained in the placebo group on most days and, therefore, the experimental device decreases pain intensity in the first application of the day more effectively than the placebo device in the majority of the 28 days of use.

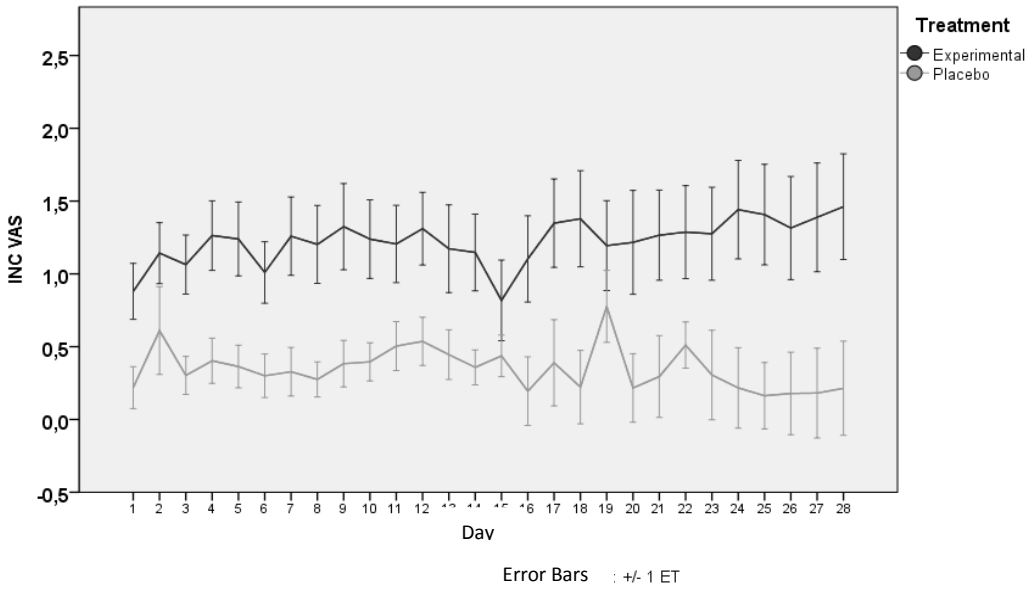

Figure 11. Decrease in the VAS score of the daily first use. Total study population

The results for VAS scores decrease after the first daily use of the experimental device indicate that they are constant and, therefore the decrease in pain intensity resulting from the use of the experimental device is equal throughout the 28 days of application for the total study population.

b) Daily decrease of VAS score before the experimental device use

On observation of the temporary evolution of the VAS score before the first use of the experimental device, it does not change for 28 days (figure 12).

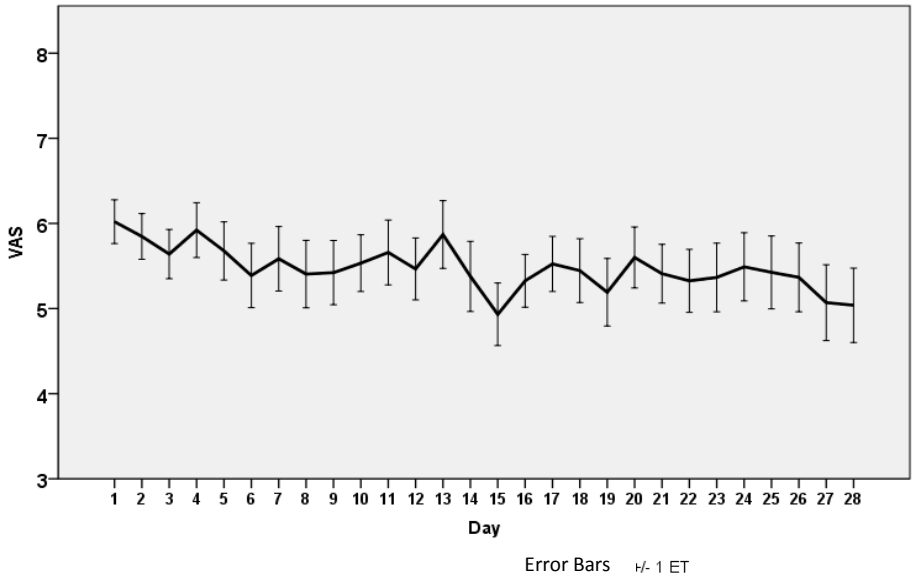

Figure 12. Temporary evolution of the VAS score obtained before the first use of the experimental device. Total study population

Acute pain stratum

a) Daily decrease of VAS score

The comparative results between the daily VAS scores after using the experimental and placebo device do not show significant differences in any days. Therefore, we cannot say that the experimental device reduces the intensity of pain in the first application of the day more effectively than the placebo device during the 28 days of application (figure 13) for the acute pain stratum.

As figure 13 shows, the VAS scores decrease after using the experimental device remains constant for 28 days.

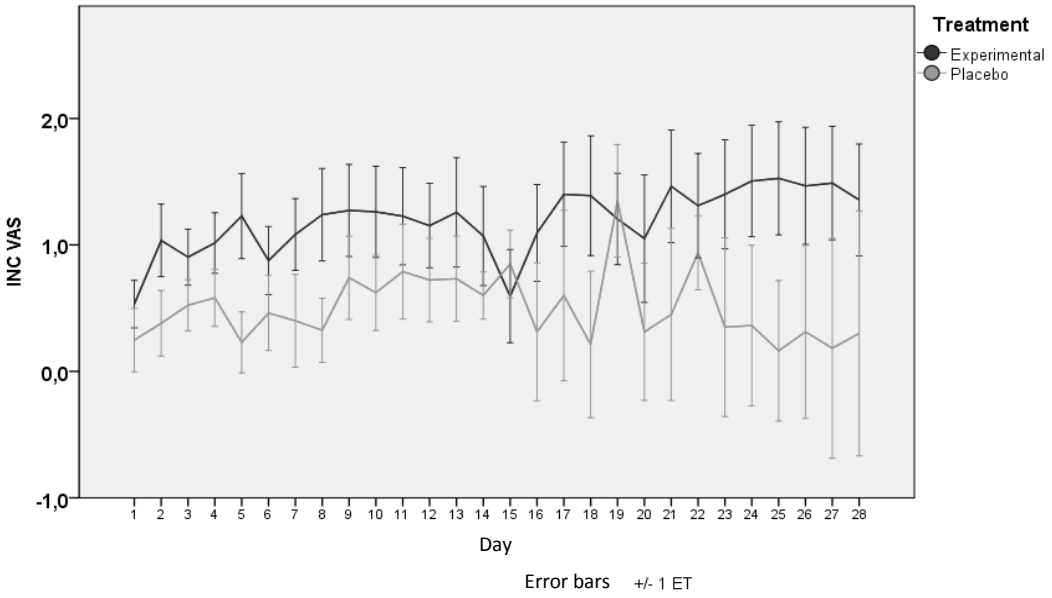

Figure 13. Decrease in the VAS score of the daily first use. Acute pain stratum

b) Daily decrease of VAS score before the experimental device use

From the temporary evolution of the VAS score before the first daily use of the experimental device, we can support that this variable does not change throughout the 28 days (figure 14).

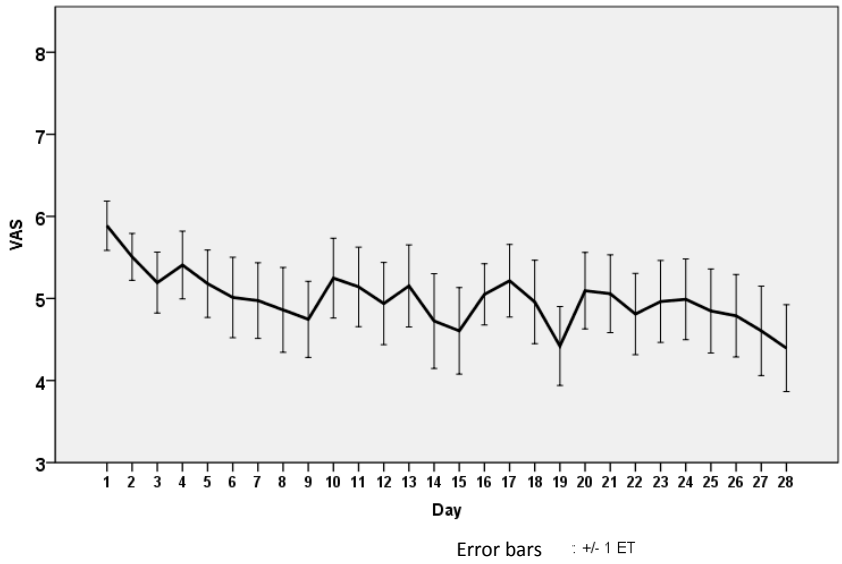

Figure 14. Temporary evolution of the VAS score obtained before the first use of the experimental device. Acute pain stratum

Chronic pain stratum

a) Daily decrease of VAS score

The results of the VAS score decrease after the first daily use of the experimental device are statistically higher ($p<0.05$) than those obtained after using the placebo device. Therefore, the experimental device decreases pain intensity in the first use of the day more effectively than the placebo device in the majority of the 28 days of application (figure 15).

As figure 15 illustrates, the decrease of the VAS scores are maintained constantly during the study for the experimental group. Therefore, the decrease in pain intensity resulting from the application of the experimental device is the same throughout the 28 days of use in the chronic pain stratum.

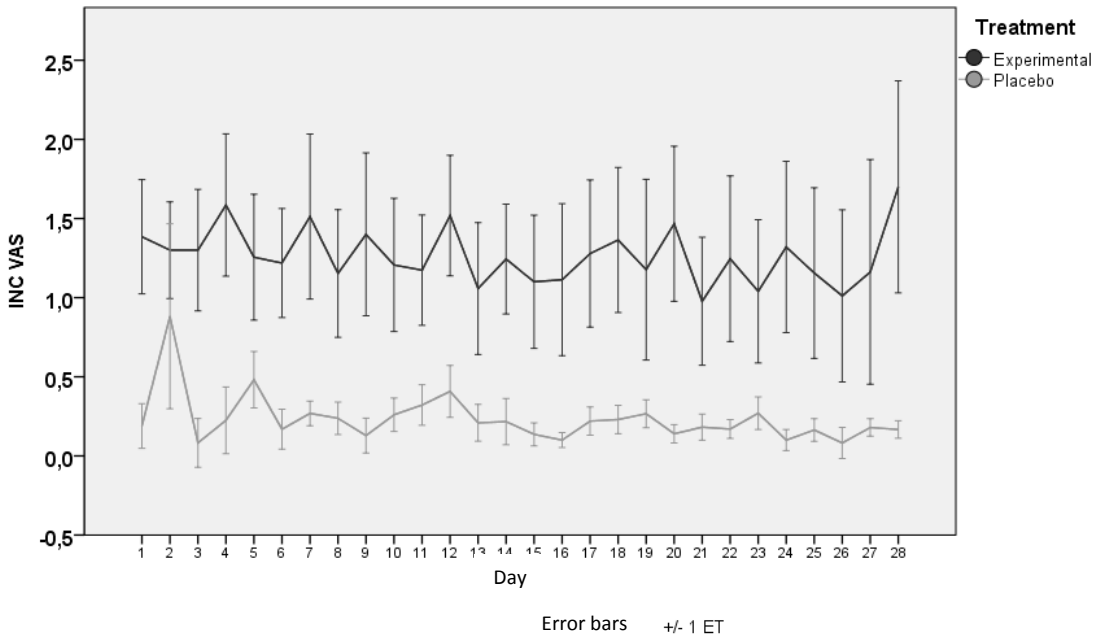

Figure 15. Decrease in the VAS score of the daily first use. Chronic pain stratum

b) Daily decrease of VAS score before the experimental device use

Regarding the temporary evolution of VAS scores before the first use of the experimental device, we have observed that there are no modifications of this score with the passage of days (figure 16).

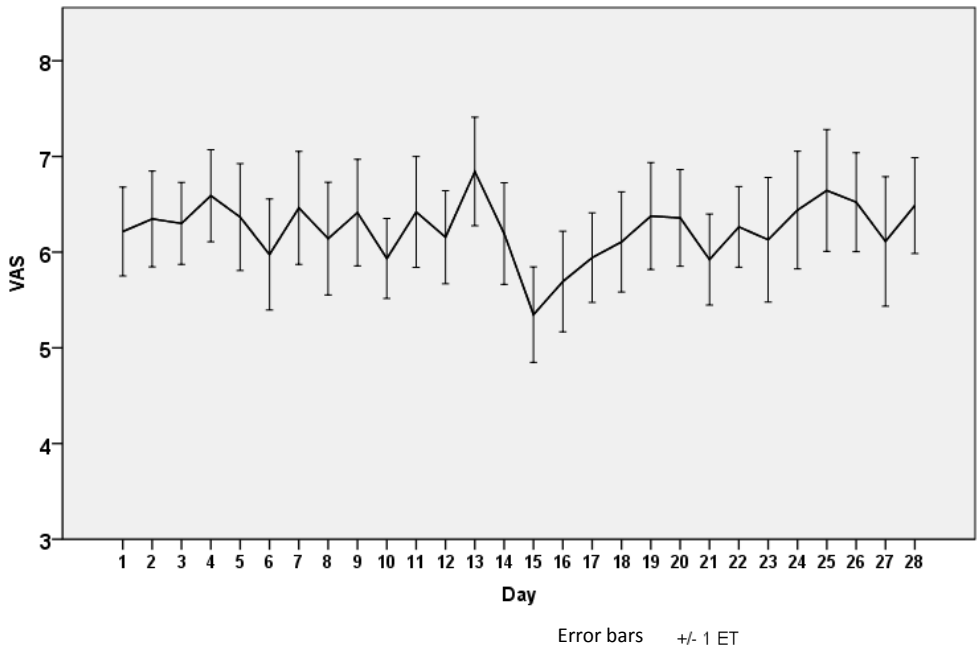

Figure 16. Temporary evolution of the VAS score obtained before the first use of the experimental device. Chronic pain stratum

7.4. Daily use of the device

Table 14 shows the average number of days that the patients used the device in acute and chronic strata as well as in total study population.

Table 14. Number of days in which the device was used for acute and chronic strata. Mean and standard deviation.

Pain	Treatment	Mean	SD	P Treatment
Acute	Experimental	3.68	2.248	0.64
	Placebo	3.84	3.304	
Chronic	Experimental	4.60	4.121	0.56
	Placebo	3.84	2.836	
Total study population	Experimental	4.05	3.156	0.73
	Placebo	3.84	3.040	

The comparative analysis of this variable shows that there is no statistically significant difference between the study groups (experimental and placebo) nor between the days of use of the device.

Patients used the experimental device the same number of times per day than those who used the placebo device.

There are no variations in the number of times that the subjects used the device during 28 days. So, during the study period, the experimental and placebo devices were used the same number of times.

We can see the same results for the total population and for acute and chronic pain strata (figures 17, 18 and 19).

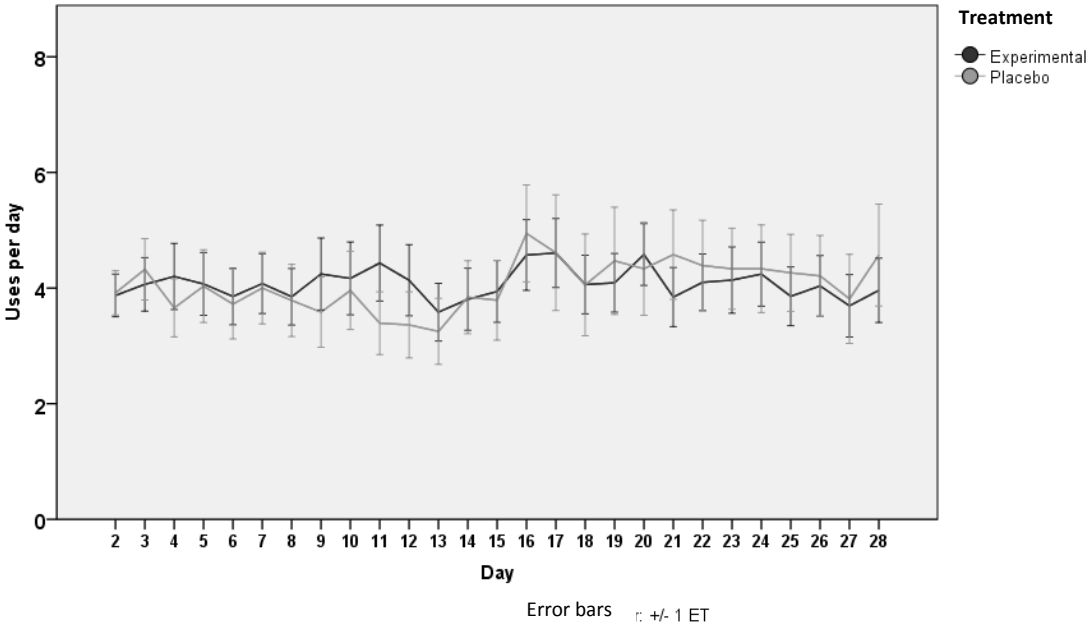

Figure 17. Use per day of the device. Total population

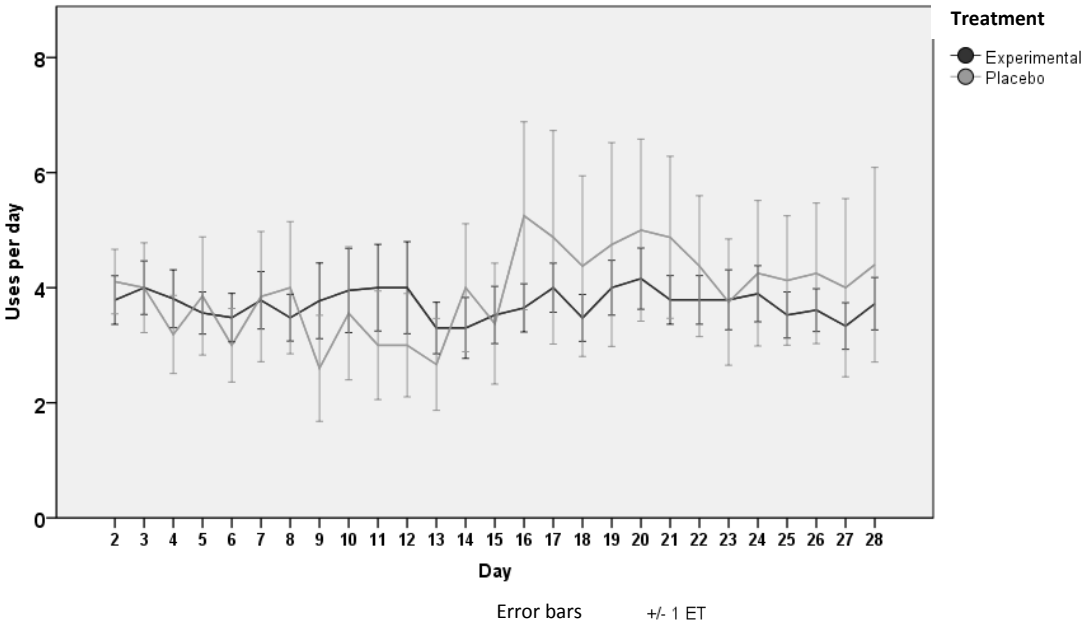

Figure 18. Use per day of the device. Acute pain stratum

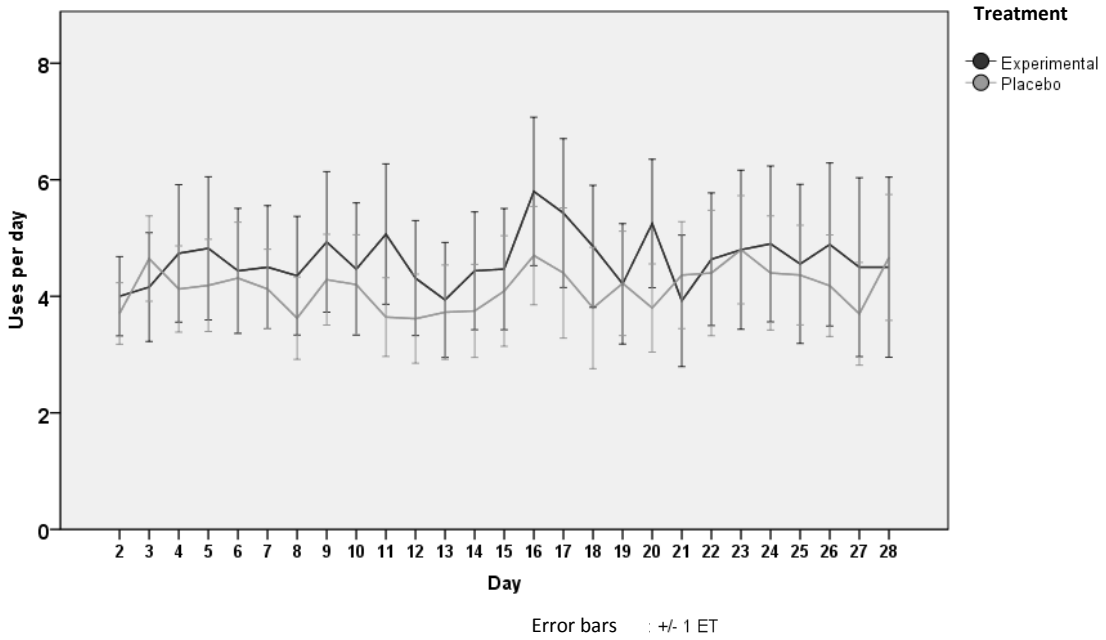

Figure 19. Use per day of the device. Chronic pain stratum

7.5. Use of rescue medication.

Before starting the study, 42.9% of the subjects who used the experimental treatment (acute pain 27.6% and chronic pain 65.0%) and 29.7% who used the placebo treatment (acute pain 15.8% and chronic pain 44.4%) used rescue medication (Table 15).

There were no significant differences between the experimental and placebo groups at baseline in relation to the use of rescue medication for the study population overall as well as for each stratum.

Table 15. Use of rescue medication

Pain	Treatment	Baseline	Follow-up	P Time x Treatment
Acute	Experimental	27.6%	3.6%	0.012
	Placebo	15.8%	10.5%	
Chronic	Experimental	65.0%	65.0%	0.318
	Placebo	44.4%	33.3%*	
Total study population	Experimental	42.9%	29.2%	0.858
	Placebo	29.7%	21.6%	

As table 15 shows, rescue medication was used in 29.2% of subjects in the experimental group (acute pain 3.6% and chronic pain 65.0%) and 21.6% of those who were in the placebo group (acute pain 10.5% and chronic pain 33.3%) (Total p = 0.431; acute pain p = 0.338; chronic pain p <0.05). The percentage of subjects suffering from chronic pain that used rescue medication in the experimental group was significantly (p <0.05) higher than in the placebo group. However, this difference was not appreciated in the group of patients with acute pain or in the general group.

The percentage of subjects with acute pain that used rescue medication during the study decreased significantly with respect to the baseline when they used the experimental device compared to the placebo device. However, patients with chronic pain did not reduce the use of rescue medication.

7.6. Quality of life questionnaire.

The quality of life was measured by the EQ-5D questionnaire which was answered at baseline and at the final visit.

EQ-5D is a generic instrument for measuring health-related quality of life that can be used in both relatively healthy individuals (general population) and in groups of patients with different pathologies. The individual themselves value their health, first in levels of gravity (descriptive system) and then in a visual analogue scale of more general evaluation. A third element of the EQ-5D is the index of social values that is obtained for each health status (question) generated by the questionnaire. So, the index of social values is the evaluation of health status.

7.6.1. Assessment of health status by the variable: pain / discomfort level.

The percentage of subjects who responded positively to each level of the pain / discomfort (none, moderate and extreme) at baseline and at the final visit was analysed for total study population and for acute and chronic pain strata separately.

Total population

The temporary evolution for this variable showed these results (table 16):

- Both the experimental and placebo groups experienced an increase in the percentage of subjects who answered with the level "none" and this rise was the same for the two groups.
- There was a decrease in the percentage of subjects who answered with the level "moderate" in the placebo group but the percentage was constant in the experimental group. No significant differences were observed in this different evolution ($p < 0.09$).
- There was a decrease in the percentage of subjects who answered with the level "extreme" in both groups. Significant differences were observed in this decrease being the decrease occurring in the experimental group ($p < 0.003$) greater.-

Table 16. pain/discomfort level for total population

Pain/discomfort level	Treatment	Initial	Final	P Time x Treatment
None	Experimental	0%	30.4%	0.318
	Placebo	2.7%	30.0%	
Moderate	Experimental	55.1%	60.9%	0.09
	Placebo	70.3%	50.0%	
Extreme	Experimental	44.9%	8.7%	0.003
	Placebo	27.0%	20%	

Acute pain stratum

We have analysed the temporary evolution of pain/discomfort level for acute pain stratum and we have seen (table 17):

- The percentage of subjects who answered with the level "none" increased in both groups (experimental and placebo). This rise is the same for both groups.
- The percentage of subjects who answered with the level "moderate" decreased in both groups. Significant differences between groups were observed being the decrease occurring in the placebo group ($p < 0.04$) greater than in experimental group.
- The percentage of subjects who answered with the level "extreme" decreased in the experimental group. However the percentage did not change in the placebo group. Significant differences were observed in this different evolution ($p < 0.001$).

Table 17. pain/discomfort level for acute pain stratum

Pain/discomfort level	Treatment	Initial	Final	P Time x Treatment
None	Experimental	0%	37.0%	0.107
	Placebo	5.3%	43.8%	
Moderate	Experimental	69.0%	55.6%	0.04
	Placebo	78.9%	37.5%	
Extreme	Experimental	31.0%	7.4%	0.001
	Placebo	15.8%	18.8%	

Chronic pain stratum

We have analysed the temporary evolution of pain/discomfort level for chronic pain stratum (table 18):

- The percentage of subjects who answered with the level "none" increased in both groups (experimental and placebo). This rise is the same for both groups.
- The percentage of subjects who answered with the level "moderate" incresed in the experimental group while this percentage was constant in the placebo group. Significant differences were observed in this different evolution ($p < 0.023$).
- The percentage of subjects who answered with the level "extreme" decreased in both groups. The decrease occurring in the experimental group was significantly greater than in the placebo group ($p < 0.003$).

Table 18. pain/discomfort level for chronic pain stratum

Pain/discomfort level	Treatment	Initial	Final	P Time x Treatment
None	Experimental	0%	21.1%	0.788
	Placebo	0%	14.3%	
Moderate	Experimental	35%	68.4%	0.023
	Placebo	61.1%	64.3%	
Extreme	Experimental	65%	10.5%	0.003
	Placebo	38.9%	21.4%	

7.6.2. Evaluation of health status: Index of social values.

The index of social values goes from 0 to 100 being 100 the best health status.

The analysis of the social values index significantly increased in placebo ($P<0.001$) and in experimental ($p<0.002$) groups considering the total population.

The comparative between groups shows that there are not significant differences. However, a tendency to greater increase for the experimental group (p=0.064) was observed (figure 20).

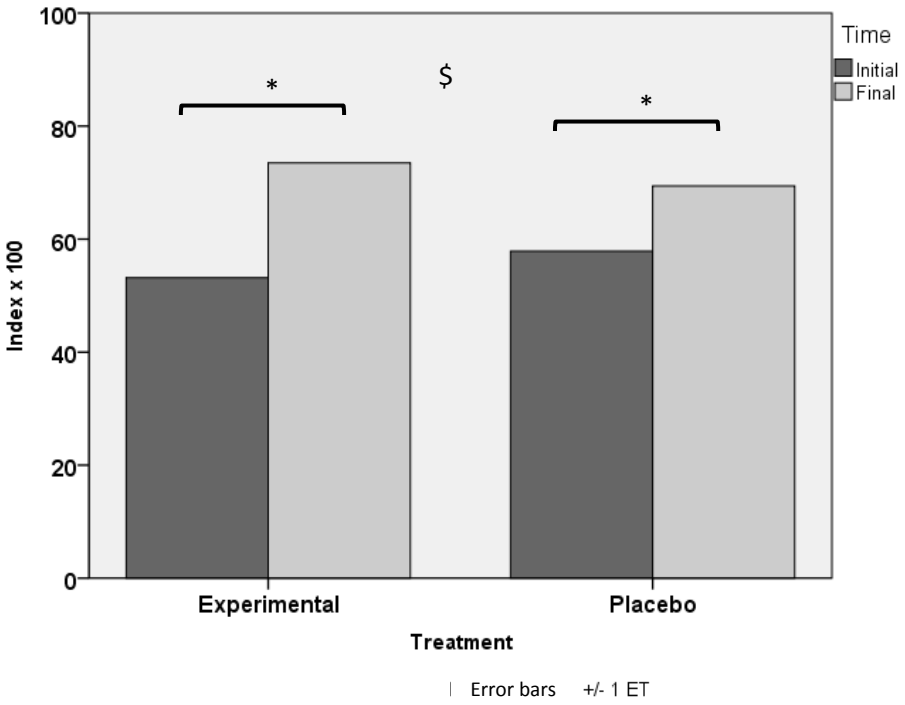

Figure 20. Index of social values used for the evaluation of health status. Total population
*p<0.05= differences between baseline and final visit
$p<0.1 =differences between groups when evolution is analysed

Results of social values index for acute and chronic pain status are shown in figure 21 and 22 respectively.

The social values index significantly increased in patients who suffer acute pain both in the experimental and placebo groups (p<0.001 and p<0.014, respectively). However, the comparative of the temporary evolution of social indexes does not show differences between the placebo and experimental groups.

As figure 22 illustrates, patients with chronic pain experienced a significant increase of the social values index when they used the experimental device (p<0.001). In addition, significant differences were found between the experimental and placebo groups due to the significant increases (p<0.042) in social values index experienced by the experimental group.

Table 19 shows the average of social value indexes and p values.

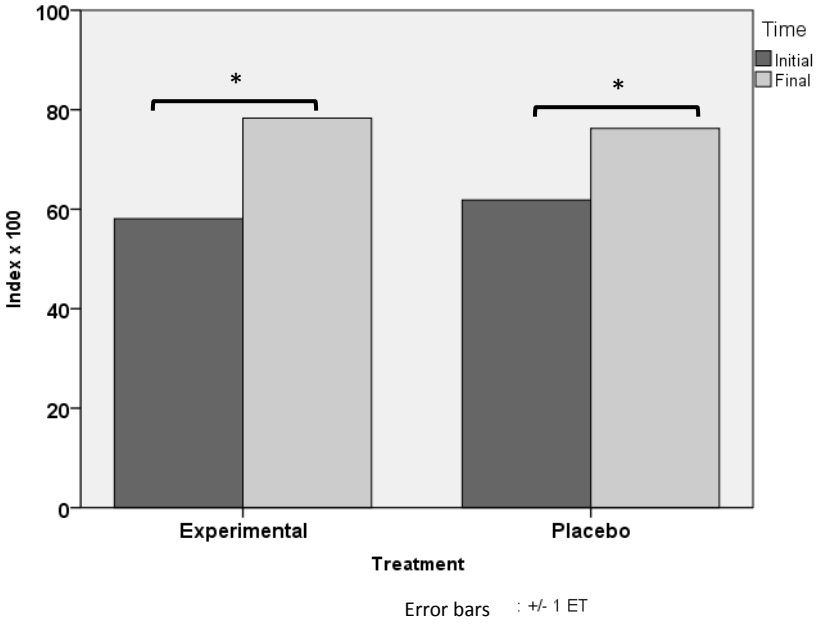

Figure 21. Index of social values used for the evaluation of health status. Acute pain stratum
*p<0.05= differences between baseline and final visit

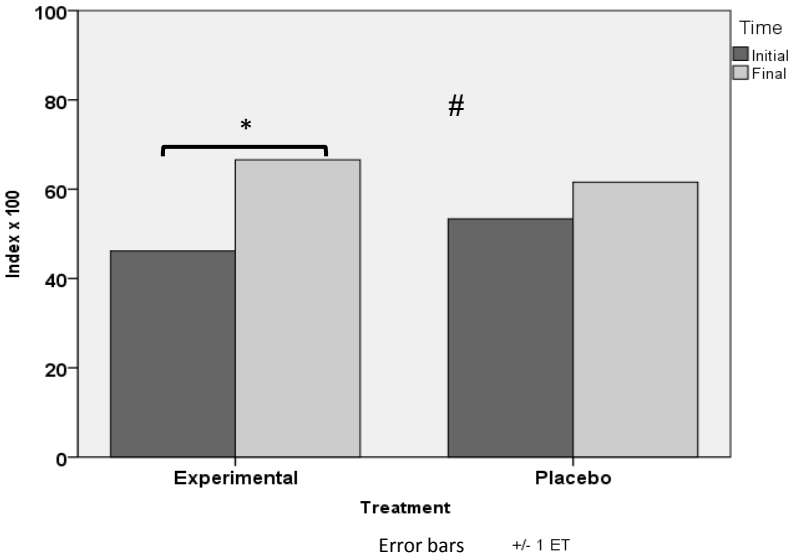

Figure 22. Index of social values used for the evaluation of health status. Chronic pain stratum
*p<0.05= differences between baseline and final visit
# p<0.05 =differences between groups when evolution is analysed

Table 19. Mean and SD of social values index

Pain	Treatment	Time	Mean	SD	P Time	P Time x Treatment
Acute	Experimental	Baseline	52.3	20.1	0.001	0.416
		Final	75.1	19.8		
	Placebo	Baseline	55.7	20.6	0.014	
		Final	71.5	26.7		
Chronic	Experimental	Baseline	44.5	23.7	0.001	0.042
		Final	56.7	22.4		
	Placebo	Baseline	44.1	18.2	0.068	
		Final	62.6	26.1		
Total study population	Experimental	Baseline	49.1	21.7	0.001	0.064
		Final	67.5	22.6		
	Placebo	Baseline	50.1	20.0	0.002	
		Final	67.2	26.3		

8. TOLERANCE AND SAFETY

The safety of the investigational medical device was assessed by recording the adverse events (AEs) during the study, that is, from baseline to final visit.

Signs and symptoms corresponding to side effects related or not related to the medical device were collected and described to document the tolerance to the device.

Only two patients suffered an adverse event related to the experimental device. These events were described as erythema on the skin surface after the device application. The symptoms disappeared after the patients stopped using the device.

Therefore, we can say that the experimental device is safe and was well tolerated by 97.67% of the study population.

9. CONCLUSIONS

The efficacy of the handheld TENS pen, used on demand for 28 days, has been evaluated both for the relief of general musculoskeletal origin pain as well as for acute and chronic pain of the same origin in particular, and it has been found that:

The following conclusions were drawn from the data evaluation and analysis of this study:

1. The handheld TENS pen is effective in relieving general musculoskeletal pain

2. The handheld TENS pen is effective in relieving acute musculoskeletal pain

3. The handheld TENS pen is effective in relieving chronic musculoskeletal pain

4. The handheld TENS pen efficacy remains constant over a 28-day period in alleviating general musculoskeletal pain. Furthermore, the pain relief is the same for each day of the treatment.

5. The handheld TENS pen reduces the acute and chronic musculoskeletal pain intensity daily as well as the general and acute musculoskeletal pain that patients feel each day before using the device.

6. The handheld TENS pen produces greater relief of acute musculoskeletal pain on most days compared to the first day of use.

7. The first application of the treatment provides pain-relieving effects in patients with general musculoskeletal pain and especially for patients with both acute and chronic pain. However, the effect of the first application has not reached the level of "statistical significance".

8. During treatment, the first daily application is effective for general musculoskeletal pain relief as well as for the relief of acute and chronic pain in particular.

9. The handheld TENS pen improves the quality of life of the subjects reducing the perception of pain in the case of general musculoskeletal pain and especially for patients with both acute and chronic pain and increasing the subjective evaluation of health status in individuals with chronic pain.

10. The use of the handheld TENS pen is safe and well tolerated

11. The handheld TENS pen reduces the use of rescue medication for patients with acute pain

12. 83% of individuals with chronic pain who used the handheld TENS pen felt that their pain had gone from severe to moderate or none.