

SHORT-TERM EFFECTS OF PERCUTANEOUS ELECTRICAL NERVE STIMULATION ON PAIN AND MUSCLE FUNCTION ON ANTERIOR CRUCIATE LIGAMENT SURGERY PATIENTS: A RANDOMIZED CLINICAL TRIAL

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Submitted to Journal:
Frontiers in Rehabilitation Sciences

Specialty Section:
Rehabilitation for Musculoskeletal Conditions

Article type:
Clinical Trial Article

Manuscript ID:
1501703

Received on:
30 Sep 2024

Revised on:
09 Apr 2025

Journal website link:
www.frontiersin.org

Scope Statement

This is a manuscript that reflects the work carried out with patients undergoing anterior cruciate ligament surgery using the minimally invasive technique of percutaneous electrical nerve stimulation, in the management of pain, strength and range of motion. The combination of conservative treatment and the experimental technique was carried out compared to conservative treatment in isolation, with long-term follow-up of the operated population, changes were observed in both groups but mainly associated with the PENS technique in the short term in relation to the decrease in the intensity of pain on the VAS Scale immediately after application, and the increase in strength in knee extension. The main findings focus on the effect of the combination of the PENS technique together with conservative rehabilitation treatment, as a therapeutic option in the management of dysfunction associated with pain and loss of strength in the post-surgical patient.

Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

Credit Author Statement

Carlos Romero Morales: Conceptualization, Formal Analysis, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing. **Fernando García Sanz:** Conceptualization, Investigation, Supervision, Validation, Visualization, Writing – review & editing. **Francisco Minaya Muñoz:** Methodology, Supervision, Validation, Visualization, Writing – review & editing. **Julio Caballero López:** Conceptualization, Data curation, Investigation, Methodology, Software, Writing – original draft. **Marcos Jose Navarro Santana:** Methodology, Project administration, Software, Supervision, Validation, Writing – original draft. **María José Díaz Arribas:** Conceptualization, Formal Analysis, Methodology, Software, Supervision, Validation, Writing – review & editing.

Keywords

ACL Rehabilitation, precutaneous electrical nerve stimulation, US guided intervention, ACL surgery, ACL function

Abstract

Word count: 246

Introduction: Anterior cruciate ligament (ACL) reconstruction surgery is associated with the presence of anterior knee pain and knee extension weakness. Percutaneous electrical nerve stimulation (PENS) is a minimally invasive technique with the objective of neuromodulating the symptoms derived from the intervention. The objective of the study is to analyze the short-term effect of the use of the PENS technique in patients undergoing ACL surgery. **Materials and Methods:** A randomized clinical trial was carried out at the CEMTRO clinic in Madrid with 70 participants (N = 70) where the effect of the PES intervention in combination with a rehabilitation program (n = 35) was compared against a control group of rehabilitation (n = 35). The study analyzed changes in pain intensity, pressure pain threshold (PPT) of the vastus medialis, vastus lateralis, quadriceps and patellar tendons, isometric knee extension strength and range of motion of the knee. **Results:** Differences were determined in the PENS group compared to the rehabilitation group immediately after the first intervention in the reduction of pain intensity through the VAS scale and in knee extension isometric strength ($p < 0.05$). Both groups showed differences after 12 weeks in the range of motion of the knee in knee flexion and extension, as well as in the PPT of the patellar tendon. **Conclusion:** The PENS intervention combined with a rehabilitation program compared to an isolated rehabilitation program showed a short-term reduction in pain intensity and an increase in isometric strength in knee extension in patients undergoing ACL surgery.

Funding statement

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Ethics statements

Studies involving animal subjects

Generated Statement: No animal studies are presented in this manuscript.

Studies involving human subjects

Generated Statement: The studies involving humans were approved by Ethics committee of Ntra. Señora del Valme Hospital Universitario (approval code: 0255-N-21) and Universidad Europea de Madrid Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Inclusion of identifiable human data

Generated Statement: No potentially identifiable images or data are presented in this study.

Data availability statement

Generated Statement: The datasets presented in this article are not readily available because **Legal restrictions due to data confidentiality**. Requests to access the datasets should be directed to **Jaime Almazan Polo**; jaime.almazan@universidadeuropea.es.

Generative AI disclosure

No Generative AI was used in the preparation of this manuscript.

In review

1 **TITLE**

2 **SHORT-TERM EFFECTS OF PERCUTANEOUS ELECTRICAL NERVE**
3 **STIMULATION ON PAIN AND MUSCLE FUNCTION ON ANTERIOR**
4 **CRUCIATE LIGAMENT SURGERY PATIENTS: A RANDOMIZED CLINICAL**
5 **TRIAL**

6 **1. INTRODUCTION**

7 Anterior cruciate ligament (ACL) rupture is a common injury typically resulting from
8 acute trauma and is often accompanied by a painful, swollen knee. It is frequently
9 associated with secondary issues such as joint instability, meniscal and cartilage damage,
10 and an increased risk of developing osteoarthritis (1,2). The incidence is estimated to be
11 49–75 cases per 100,000 person-years, imposing both socioeconomic and individual
12 burdens (3,4). Current consensus among orthopedic surgeons recommends that
13 individuals engaged in athletic activities or those with high functional demands on their
14 knees should be offered the option of ACL reconstruction surgery (5,6). Surgical ACL
15 reconstruction has been associated with improved function, reduced symptoms, and
16 enhanced quality of life compared to individuals who do not undergo surgery (7).
17 However, several studies have reported a decline in quadriceps femoris muscle strength
18 and function following ACL reconstruction, often accompanied by pain, which
19 contributes to delayed recovery of knee joint function (8–10). In this context, the
20 prevalence of anterior knee pain has been estimated to range from 5% to 19%, frequently
21 linked to an inability to achieve full knee extension during the early postoperative period.
22 This limitation is associated with quadriceps weakness and alterations in knee and lower
23 limb biomechanics (11).

24 Percutaneous electrical nerve stimulation (PENS) is a minimally invasive, ultrasound-
25 guided technique that involves delivering electrical current through a solid filament
26 needle. Ultrasound guidance ensures procedural safety and minimizes the risk of adverse
27 events associated with needling techniques applied to sensitive anatomical structures
28 (12). The primary objective of this technique is to achieve both sensory and motor
29 stimulation of peripheral nerves, with specific therapeutic goals tailored according to
30 clinical reasoning based on patient findings and symptomatology (13). The electrical
31 current applied in PENS is biphasic, with frequency ranges from 2–5 Hz to 80–100 Hz
32 and pulse durations varying from 100 to 450 ms, depending on the desired effect, stimulus
33 intensity, and patient tolerance. This technique delivers electrical stimulation through a
34 needle, typically using acupuncture needles. Although evidence supporting greater pain
35 intensity reduction with PENS is of low quality and the difference is not clinically
36 significant (14), a recent review suggests that PENS provides moderate evidence for pain
37 relief and the reduction of pain-related disability in musculoskeletal conditions (13).

38 Regarding the associated pain and loss of function after an ACL reconstruction, numerous
39 authors have focused their interventions on targeting the femoral nerve to aid in
40 postoperative pain control and facilitate the immediate restoration of quadriceps function
41 following surgery (10,15–17). The aim of the present study was to evaluate the effects of
42 a PENS of the femoral nerve added into a rehabilitation program in patients with an ACL
43 reconstruction immediately after the surgical procedure on pain, musculoskeletal pain
44 pressure threshold (PPT) alterations, the average (QMeIC) and maximum (QMIC)
45 quadriceps strength during isometric and the knee range of motion (ROM). It was
46 hypothesized that in an early postoperative stage an intervention with a femoral nerve
47 PENS in combination with a rehabilitation program could be more beneficial for the pain

48 intensity, ROM and quadriceps strength with respect to an isolated rehabilitation program
49 in patients with an ACL reconstruction.

50 **2. METHODS**

51 ***2.1. Study design***

52 The present study was a prospective, randomized, controlled clinical trial (registered at
53 ClinicalTrials.gov as NCT05606250) evaluating individuals over a 12-weeks period
54 between November 2022 and June 2023, following the Consolidated Standards of
55 Reporting Trials (CONSORT) guidelines (18).

56 ***2.2. Participants***

57 In this study, 70 individuals who undergone ACL surgery were recruited and divided in
58 two groups A and B: group A (n = 35) received the femoral nerve PENS plus the
59 rehabilitation program and group B (n = 35) who received the isolated rehabilitation
60 program. The selection criteria defined eligible subjects as those who: were aged 18-55
61 years, individuals who underwent surgical intervention of the ACL within a period of 2
62 to 6 weeks post-surgery, had a visual analog scale (VAS) pain score of at least 2 out of
63 10 points, and have no received any physical therapy. The present pain threshold ensures
64 that the participants presented a clinically relevant level of postoperative pain requiring
65 intervention, while avoiding the inclusion of individuals with minimal or no pain, which
66 could limit the ability to detect treatment-related changes. Exclusion criteria were as
67 follows: metabolic or rheumatic disease, chronic disease, prosthesis or osteosynthesis,
68 cardiac disturbances, central nervous system disease, commonly accepted
69 contraindications to invasive techniques, such as epilepsy or claustrophobia or fear of
70 needles (Figure 1).

71 All the participants recruitment and interventions were performed at CEMTRO medical
72 center, FIFA-accredited medical center and supervised through the process by a
73 reference medical doctor with more than 25 years of experience in ACL diagnosis and
74 management.

75 ***2.3. Sample size calculation***

76 Based on prior PENS research, the sample size was calculated using G*Power software,
77 considering pain intensity as the primary outcome. An a priori power analysis was
78 conducted using an F-test ANOVA for repeated measures to detect between-group
79 differences of 1.5 units, with a standard deviation of 1.75. The estimated sample size
80 required was at least 35 participants per group, accounting for a 15% dropout rate (19).

81 ***2.4. Randomization***

82 In the research study, the randomization process for dividing participants into two groups
83 was conducted using opaque envelopes. Initially, an equal number of envelopes, each
84 containing a group assignment (either Group A or Group B), were prepared separately
85 for male and female participants to ensure balanced distribution by sex. These envelopes
86 were thoroughly shuffled within each sex category to randomize the order. Participants
87 were then asked to select an envelope at the time of their enrollment in the study, without
88 any prior knowledge of the group they would be assigned to. This selection was done
89 blindly, as the envelopes were opaque and indistinguishable from one another. By
90 employing this method, the study ensured that the allocation of participants to either
91 group was completely random, free from selection bias, and stratified by sex, thereby
92 upholding the integrity and validity of the research outcomes.

93 ***2.5. Ethical considerations***

94 The study was authorized by the ethics committee of Ntra. Señora del Valme Hospital
95 Universitario (approval code: 0255-N-21) and Universidad Europea Ethics Committee.
96 The study respects the Declaration of Helsinki for human experimentation (20). All the
97 participants signed the informed consent form.

98 ***2.6. Rehabilitation program for both groups***

99 Both groups followed a 12-week rehabilitation program based on clinical practice
100 guidelines for patients after ACL reconstruction adapted to the individual needs and
101 requirements of each patient (21). The program generally consisted of the following
102 phases (Figure 3):

- 103 - Phase 1 (Weeks 0–2): 30 minutes of passive knee mobility (extension and
104 flexion), 15 minutes of neuromuscular electrical stimulation (NMES) applied to
105 the quadriceps muscle combined with isometric contractions, and 15 minutes of
106 cryotherapy
- 107 - Phase 2 (Weeks 2–6): 30 minutes of manual therapy, soft tissue mobilization and
108 active knee joint mobility, 12 minutes of cycling, 3 × 10 repetitions of isotonic
109 flexion and extension strengthening exercises, 5 minutes of proprioception
110 exercises (Initial pase), 15 minutes of NMES on the quadriceps muscle, and 10
111 minutes of stationary cycling at an intensity based on the participant's tolerance.
- 112 - Phase 3 (Weeks 6–9): Manual therapy, soft tissue mobilization and active
113 mobility exercises for the knee and associated periarticular soft tissues, 20
114 minutes of cardiovascular training (e.g., running, cycling), and advanced strength
115 and proprioception exercises (Advanced pase).
- 116 - Phase 4 (Weeks 9–12): 3 × 10 repetitions of extension, flexion, adductor, and
117 abductor muscle strength and endurance exercises, advanced coordination and

118 proprioception exercises, 15 minutes of NMES on the quadriceps muscle, and 25
119 minutes of cardiovascular training (22).

120 The rehabilitation program was implemented five times per week for all participants. To
121 ensure the reproducibility of both interventions, the Template for Intervention
122 Description and Replication (TIDieR) checklist was completed and listed according to
123 our registered protocol (23).

124 ***2.7. PENS Intervention group***

125 Participants assigned to the experimental group received two sessions of PENS targeting
126 the femoral nerve. The first intervention was administered during the initial session, with
127 data collected before the intervention (Baseline) and immediately afterward (Post-
128 Intervention 1). The second PENS intervention was performed one week later, with data
129 collected at the beginning of the session (Pre-Intervention 2) and immediately after the
130 intervention (Post-Intervention 2). In the current study, we applied the electrical current
131 with a 30x0.40 mm needle (Agupunt[®]) as close as possible to the femoral nerve. The
132 femoral nerve was US - guided with an ultrasound system (Sonoscape E2, Spain) with a
133 linear transducer of 12MHz to provide the highest accuracy for needle insertion and safety
134 for the patients. The images were collected immediately below the inguinal fold at the
135 level of the pubic tubercle, taking as reference the imaginary line between the anterior
136 superior iliac spine and the pubis to obtain the transverse view (short axis) of the femoral
137 nerve (Figure 2). Once the short axis of the femoral nerve was identified at the level of
138 the femoral triangle within the muscular lacuna, the invasive “out of plane” approach was
139 performed by inserting the needle under ultrasound guidance along the probe’s short axis,
140 with an entry angle of 90° relative to the skin. The needle's advancement was continuously
141 monitored to ensure its correct positioning along the upper and lateral peripheral edges
142 of the nerve. PENS procedure was developed with an ITO ES-160 (Ito Co. Ltd., Tokyo,

143 Japan) device, at 2Hz frequency, with 240 μ s pulse duration (24). The electrical current
144 was increased at an intensity of a visible motor response of the femoral nerve innervated
145 musculature (25) (Figure 3).

146 **2.8. Outcomes**

147 Pain intensity was assessed with a visual analogue scale (VAS), a valid, responsive, and
148 frequently used which consist in a 10 cm bidirectional straight line with two labels in both
149 edges, “no pain” and “worst possible pain” (26). Subjects were instructed to draw a
150 vertical mark on the line to indicate their pain intensity level. VAS reported an excellent
151 test-retest reliability and a minimum detectable change (MCD) of 0.08 (27).

152 PPT was assessed from 0 to 10 kg/cm² with a mechanical algometer (FDK/FDN, Wagner
153 Instruments, Greenwich, CT). The most hyperalgesic area of the vastus medialis and
154 vastus lateralis muscles and quadriceps and patellar tendons were evaluated in supine
155 position. With continuously increasing pressure, the soft tissue targeted was compressed
156 with the metal rod of the algometer. The selected threshold aimed to identify the earliest
157 indication of hyperalgesia in the targeted tissue, reflecting changes in peripheral and
158 central sensitization associated with post-surgical recovery. Participants were instructed
159 to report the exact moment at which they experienced pain. The intra-rater reliability for
160 PPT was excellent (0.93-0.97) with a MCD of 1.53-1.62 (28). This protocol is consistent
161 with previous studies that support the use of PPT as a reliable and sensitive indicator of
162 mechanosensitivity, particularly at the knee. For example, Mutlu et al. reported post-
163 intervention increases in medial knee PPT from 5.47 ± 2.99 to 7.58 ± 2.97 lb, with a SEM
164 of 0.66, MDC of 1.19, and a moderate-to-large effect size of 0.70. Similarly, Paungmali
165 et al. demonstrated excellent reliability for lumbar PPT measures (ICC = 0.99; SEM =
166 1.19), further supporting the robustness and clinical utility of single-session PPT
167 assessments in musculoskeletal populations (29).

168 Isometric muscle force was assessed with the ActivForce (AF; Activbody, San Diego
169 CA) for the knee extension.(30) Participants were placed sitting at the end of the table
170 with a belt located on the ankle of the assessed leg with a 90° degrees knee flexion ankle.
171 To assess the maximal isometric contraction of the quadriceps (QMIC) and the mean
172 contraction strenght (QMeIC), participants were instructed to perform a maximal knee
173 extension against the dynamometer for 4 seconds. Inter-examiner reliability of knee
174 extensors and flexors were 0.97 and 0.95, respectively, with a MDC of 33.09 Nm and
175 21.45 Nm for knee extensors and flexors, respectively (31). Three repetitions of each
176 measurement were performed to establish the average of the results.

177 Knee ROM was assessed using a universal goniometer with one-axis joints with two-
178 arms (one movable and one fixed arm). This procedure demonstrates excellent intra-rater
179 reliability, with intraclass correlation coefficients (ICCs) of 0.997 for flexion and 0.98 for
180 extension. Similarly, inter-rater reliability shows ICCs of 0.98 for flexion and 0.92 for
181 extension, respectively (32). All study measurements will be performed in the same
182 temporal sequence for participants in both groups and by the same evaluator, who will be
183 blinded to group allocation. The first evaluation was carried out before the first session
184 (Baseline), the second measurement after the first intervention (Post-Intervention 1), the
185 third measurement before the second intervention session one week later (Pre-
186 Intervention 2) and the fourth measurement after said session (Post - Intervention 2), and
187 finally the fifth and sixth measurement at 4 (4-weeks) and 12 (12-weeks) weeks
188 respectively.

189 **2.9. Statistics**

190 The statistical analysis was performed using the Statitstical Package for Social Sciences
191 (SPSS) v.23.0 for Windows (IBM SPSS Statistics, NY: IBM Corp.) and Jamovi v.2.3
192 (www.jamovi.org) was carried out by an independent statistician. An α error of 0.05 (95%

193 confidence interval) and a desired power of 80% (β error of 0.2) were used for all the
194 statistical tests. The Shapiro-Wilk test was used for normality assumption. For the
195 baseline comparison, the Student *t* test was used, considering the homogeneity of variance
196 following Levene's test. A two-way analysis of variance (ANOVA) for repeated measures
197 was employed to examine the intra-subject (Baseline, Post-Intervention 1, Pre-
198 Intervention 2, Post-intervention 2, 4-weeks, 12-weeks) and inter-subject
199 (treatment*group) effects for the dependent variables. The assumption of
200 homoscedasticity was assessed using Levene's test, and when this assumption was
201 violated, Welch's statistical test was applied. The assumption of sphericity was evaluated
202 using Mauchly's test, and when violated, the Greenhouse-Geisser correction was applied
203 for epsilon values > 0.75 , whereas the Huynh-Feldt correction was used for epsilon values
204 < 0.75 . Effect sizes were calculated using partial eta squared (η^2) coefficients and
205 interpreted according to the following thresholds: 0.01 (small effect size), 0.06 (medium
206 effect size), and 0.14 (large effect size). Post-hoc analyses were conducted using
207 Bonferroni's correction, adjusting the significance level to $p < 0.008$ to account for the
208 six time-point measurements.

209 3. RESULTS

210 Sociodemographic data did not statistically differ between groups ($p > 0.05$) (Table 1).
211 Pain intensity, PPT for vastus medialis and lateralis muscles, ROM and maximal
212 isometric contraction (QMIC) reported benefits with respect to the baseline but did not
213 show significant differences ($p > 0.05$) between the intervention groups (Table 2, Table
214 3). Post-hoc analysis reported for pain intensity significant group differences in favor the
215 PENS treatment immediately posterior the first intervention (Baseline vs Post-
216 Intervention 1; $p = 0.00$, $\eta^2 = 0.14$) and the week after (Baseline vs Post-Intervention 2;
217 $p = 0.003$, $\eta^2 = 0.29$), as in the comparison with the pain at 4-weeks (Baseline vs 4-

218 weeks; $p = 0.003$, $\eta^2 = 0.33$). Regarding the ROM post-hoc analyses between the
219 Baseline and 12-weeks assessments, significant differences were found in both groups
220 for the knee flexion ($p < 0.001$) and extension ($p = 0.021$). The PPT of the patellar tendon
221 showed significant differences between Baseline vs 12-weeks measurements in PENS
222 group with respect to the Control group. For quadriceps during mean isometric
223 contraction (QMeIC), significant differences were found immediately after first
224 intervention comparing PENS group (Baseline vs Post-Intervention 1) with respect to the
225 control group ($p = 0.049$) (Table 3). Despite this acute effect in strength, no interaction
226 of medium-long term effect between group * time was reported ($F = 0.16$, $p = 0.695$, η^2
227 < 0.01).

228 **4. DISCUSSION**

229 To the best of our knowledge, this is the first randomized clinical trial to evaluate the
230 effects of ultrasound-guided percutaneous electrical nerve stimulation (PENS) in patients
231 undergoing ACL reconstruction. The main finding of this study indicates that the PENS
232 group demonstrated significant short-term improvements in perceived pain intensity and
233 active knee extension isometric strength following the first intervention, compared to the
234 control group. Nevertheless, both groups exhibited beneficial effects on PPT, ROM, pain
235 intensity, and knee extension strength (QMeIC and QMIC) at the 12-week follow-up.
236 These results suggest a potential short-term advantage of PENS in reducing pain and
237 enhancing quadriceps strength immediately after the intervention.

238 **4.1.PENS outcomes on pain variables**

239 The reduction in pain observed with the combination of PENS and a rehabilitation
240 program, compared to rehabilitation alone, is an important finding in the early
241 postoperative management of pain. However, despite these initial improvements, the

242 comparison of long-term effects (12 weeks) across repeated measures (six assessments)
243 showed no significant differences between groups. This suggests that while PENS may
244 help modulate pain symptoms in the short term, its effects may diminish over time,
245 ultimately leading to similar outcomes as rehabilitation alone. Although the present study
246 provides evidence of short-term effects of PENS, the current follow-up period of 12-week
247 may be insufficient to detect long-term benefits or potential sustained neuromodulatory
248 effects on pain and muscle function. Chronic post-surgical pain and long-standing
249 quadriceps inhibition remain significant concerns in ACL rehabilitation. Therefore, future
250 studies should explore whether repeated or maintenance PENS sessions over a longer
251 period, possibly in the later stages of rehabilitation, can help reduce chronic pain
252 development and enhance long-term muscle function recovery. Additionally, assessing
253 outcomes beyond 12-week would help clarify whether the neuromodulatory mechanisms
254 triggered by PENS persist or require continued stimulation.

255 Fernández de las Peñas et al. reported findings consistent with those of our study,
256 demonstrating short-term improvements in pain, function, and pain intensity. Similar
257 effects were observed in the medium and long term in patients undergoing carpal tunnel
258 surgery compared to the PENS group (33). However, it is important to note that short-
259 term differences in their study were classified within the first three months, whereas long-
260 term follow-up extended up to 12 months. Additionally, some evidence supports the
261 effectiveness of PENS in managing chronic pain conditions, including chronic low back
262 pain, knee and ankle pain, and certain neuropathic pain syndromes (33,34). Regarding its
263 impact on pain intensity and disability, Plaza-Manzano et al. conducted a meta-analysis
264 indicating that PENS may reduce pain intensity, though its effects on disability in
265 musculoskeletal disorders appear limited (35).

266 The immediate clinical improvement of symptoms may represent the opening of a
267 therapeutic window for both pain management and the modulation of inhibition
268 phenomena observed in post-surgical processes. The biological mechanisms underlying
269 these immediate effects may involve the blockade of nociceptive input through the
270 regulation of neuroinflammation and neurogenic excitability, which are characteristic of
271 the early stages following surgery (34). Although chronic pain involves processes beyond
272 inflammation and neuroinflammation, stages of chronic neuroinflammation have been
273 observed in patients with chronic pain, such as in the case of fibromyalgia (36). The
274 presence of various neuroinflammatory mediators during post-surgical stages—along
275 with altered sensory pain modulation and glial cell activation—has been proposed as part
276 of the pathophysiology of what is defined as 'post-surgical pain.' In this context, non-
277 pharmacological interventions such as PENS or neuromodulation techniques, including
278 spinal cord stimulation, have been suggested as therapeutic strategies capable of
279 modulating pain and reducing post-surgical neuroinflammation (37). Furthermore, other
280 therapeutic approaches, such as neurodynamic mobilization—which aims to modulate the
281 nervous system through mechanical stimuli and movement—have demonstrated a
282 reduction in pain and an improvement in grip strength following the mobilization of the
283 median nerve in populations with osteoarthritis of the carpometacarpal joint(38). In this
284 context, combining therapeutic strategies that focus on modulating centrally mediated
285 pain through the stimulation of peripheral neural tissue represents a promising avenue for
286 future research in the management of post-surgical pain(39,40).

287 ***4.2.PENS outcomes in functional variables, strength and range of motion***

288 Regarding the effect of PENS on improving knee extension strength immediately,
289 previous research has documented similar results on muscle function (41,42). The effects
290 of PENS depend on both the needle's placement, determined by the topographic

291 distribution of motor and somatic axons within the nerve trunk, and the modulation of
292 electrical parameters. These parameters include pulse width, insertion site, frequency, and
293 current intensity, among others. By adjusting these factors, the motor response can be
294 tailored, offering potential advantages over techniques such as neuromuscular electrical
295 stimulation (NMES), as PENS activates motor units along the entire length of the nerve
296 rather than only superficial motor units (43–45).

297 Therefore, addressing quadriceps activation failure resulting from neural inhibition—
298 specifically identified as iatrogenic inhibition following ACL intervention—should be
299 considered a key therapeutic target in this population. The limited evidence supporting
300 the effectiveness of therapies such as transcutaneous electrical nerve stimulation (TENS)
301 or NMES in managing neural inhibition, especially when compared to other interventions
302 like cryotherapy or exercise, has been noted in the literatura (46). Moreover, direct
303 stimulation of the nerve trunk appears to provide a more effective means for restoring
304 resting motor potentials, modulating the sensitivity of articular receptors, and influencing
305 spinal and cortical excitability. However, further research is needed to determine the
306 effects of different current parameters applied through the PENS technique, with the aim
307 of optimizing motor responses to modulate iatrogenic inhibition in patients undergoing
308 ACL reconstruction. Beyond its analgesic effects, PENS also demonstrated a clinically
309 relevant capacity to enhance quadriceps activation in the immediate postoperative phase.
310 This dual impact—on both pain and neuromuscular performance—positions PENS as a
311 valuable adjunct for promoting early functional recovery through simultaneous
312 modulation of nociceptive input and facilitation of motor output.

313 *4.3 Clinical relevance*

314 The clinical relevance of these findings lies in the potential for PENS to be used as a
315 complementary strategy during the early stages of rehabilitation following ACL

316 reconstruction. The immediate reduction in pain and the enhancement of quadriceps
317 activation observed in this study suggest that PENS may serve as an effective tool to
318 facilitate early neuromuscular recovery and improve patient engagement with the
319 rehabilitation process. Its integration into standard care protocols could help overcome
320 initial barriers to movement and muscle recruitment, promoting faster progression
321 through rehabilitation phases. Moreover, the rapid onset of benefits positions PENS as a
322 valuable option for clinicians aiming to optimize early functional outcomes and reduce
323 the impact of postoperative pain and quadriceps inhibition in the short term.

324 ***4.4 Strength and limitations***

325 The following strengths and limitations should be considered in the results of this study.
326 The findings of the present study provide immediate effects on pain reduction and
327 strength recovery; thus, PENS may offer significant advantages for managing post-
328 surgical pain and addressing long-term neuromuscular deficits. Previous studies have
329 shown the effectiveness of PENS in conditions such as carpal tunnel syndrome and
330 chronic low back pain, which demonstrated sustained improvements in pain intensity and
331 functional outcomes over extended periods.(35,47). These findings suggest that PENS
332 could play a crucial role in mitigating chronic neuroinflammation and enhancing motor
333 function in patients with persistent iatrogenic quadriceps inhibition following ACL
334 surgery. The ability of PENS to modulate neuroinflammatory processes and restore motor
335 unit activation through targeted stimulation of the femoral nerve makes it a promising
336 adjunct to traditional rehabilitation protocols. In this line, this approach could prevent
337 chronic pain syndromes and optimize neuromuscular recovery in this population. Future
338 studies should investigate the integration of PENS into later phases of rehabilitation, with
339 extended treatment durations and additional nerve targets, such as the saphenous and
340 obturator nerves, to maximize therapeutic efficacy.

341 Moreover, certain limitations must be considered in research design. Firstly, the
342 limitation of the short-term effect of the PENS intervention compared to the control group
343 could call into question the real benefit between conservative management and the
344 application of an invasive approach. In this sense, a possible explanation for the lack of
345 differences observed in the medium and long term could be the limited number of PENS
346 interventions, as only two sessions were performed in the intervention group—one in the
347 first week and another in the following week after surgery. This may have been
348 insufficient to produce sustained effects over time. Therefore, further studies are needed
349 to evaluate the impact of PENS in later phases of the rehabilitation process, with a greater
350 number of applications over an extended period. Secondly, the role of different
351 psychological yellow flags in the evolution of patients, such as fear-avoidance behaviors,
352 anxiety, or psychological profile, could play an interesting role in long-term evolution
353 was not considered. Thirdly, the lack of evidence regarding the optimal dosing strategy
354 for PENS therapy must be considered. Future research comparing different treatment
355 doses (sessions per week) and stimulation parameters (frequency, pulse width,
356 application duration, and achieved response) is needed to establish more standardized
357 protocols and better determine the most effective therapeutic approach. Lastly, targeting
358 additional neural structures involved in the sensory innervation of the knee and motor
359 function of the thigh—such as the posterior branch of the obturator nerve, the saphenous
360 nerve, the tibial nerve, the genicular branches, as well as the common fibular nerve and
361 its articular branch—should be considered in future research to enhance the effectiveness
362 of the PENS technique.

363 **5. CONCLUSION**

364 The minimally invasive approach to PENS, combined with a conservative rehabilitation
365 program in patients undergoing ACL surgery, demonstrated immediate improvements in

366 pain intensity reduction and knee extension isometric strength compared to the isolated
367 rehabilitation program. However, both groups showed improvements in pain, ROM, and
368 strength over time, with no significant long-term differences between groups, except for
369 knee extension ROM. Future studies with longer intervention durations are needed to
370 further explore the effects of the PENS technique on muscle function and pain
371 management in post-surgical patients over the medium and long term.

372 **6. REFERENCES**

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572 **Table 1.** Sociodemographic Characteristics of the Study Sample.

Data	PENS (n = 35)	Control (n= 35)	P-value
Age, y	30.6 ± 9.68	30.66 ± 10.79	0.939
Weight, kg	74.26 ± 11.48	71.11 ± 13.51	0.441
Height, m	1.75 ± 0.9	1.71 ± 0.5	0.063
BMI, kg/m ²	24.17 ± 3.49	24.25 ± 3.77	0.981
Sex	Women	14 (20%)	1.000*
	Men	21 (30%)	

Frequency and relative percentage (%) as well as Chi-square test was used for was used for differences assessment between sex distribution per groups.

Table 2. Dependent variables of the study of pressure pain threshold and pain intensity in the different time phases, with means, standar devaiitonss and IC's 95% represented.

Measure	PENS (n=35)	Control (n=35)	Intrasubject Effects					
			<u>Time value</u> F; P (Eta ²)	<u>Treatment X Time</u> F; P (Eta ²)				
VAS, (0 – 10)	Baseline	2.34 ± 1.78 (1.73-2.95) a, b, c	2.51 ± 1.76 (1.91-3.12)	F = 12.39 P = 0.001 (0.154)	F = 1.51 P = 0.216 (0.02)			
	Post-Intervention 1	1.60 ± 1.31 (1.15-2.05)	2.60 ± 2.08 (1.89-3.31)					
	Pre-Intervention 2	1.54 ± 1.07 (1.18-1.91)	2.17 ± 1.62 (1.62-2.73)					
	Post-Intervention 2	1.34 ± 1.0 (1.0-1.69)	2.17 ± 1.5 (1.65-2.69)					
	4-weeks	1.17 ± 0.45 (1.02-1.33)	1.80 ± 1.30 (1.35-2.25)					
	12-weeks	1.06 ± 0.42 (0.91-1.20)	1.51 ± 0.95 (1.19-1.84)					
	VM-PPT, kg/s	Baseline	7.03 ± 1.88 (6.38-7.68)			6.43 ± 1.94 (5.76-7.10)	F = 27.61 P = 0.001 (0.29)	F = 0.16 P = 0.951 (0.01)
		Post-Intervention 1	7.11 ± 1.88 (6.46-7.75)			6.30 ± 2.01 (5.61-6.99)		
Pre-Intervention 2		7.42 ± 2.0 (6.73-8.10)	6.68 ± 2.10 (5.96-7.40)					
Post-Intervention 2		7.58 ± 1.89 (6.93-8.23)	6.79 ± 1.94 (6.13-7.46)					
4-weeks		8.44 ± 1.81 (7.82-9.06)	7.60 ± 1.94 (6.92-8.28)					
12-weeks		8.73 ± 1.51 (8.21-9.24)	7.89 ± 1.93 (7.22-8.55)					
VL- PPT, kg/s		Baseline	7.23 ± 1.72 (6.63-7.82)	6.23 ± 1.94 (5.56-6.89)	F = 25.89 P = 0.001 (0.28)	F = 0.84; P = 0.505 (0.01)		
		Post-Intervention 1	7.30 ± 1.99 (6.61-7.98)	6.02 ± 2.27 (5.31-6.87)				
	Pre-Intervention 2	7.08 ± 1.67 (6.51-7.66)	6.46 ± 2.10 (5.73-5.18)					
	Post-Intervention 2	7.52 ± 1.62 (6.96-8.08)	6.53 ± 2.09 (5.82-7.25)					
	4-weeks	8.41 ± 1.52 (7.89-8.93)	7.16 ± 2.13 (6.43-7.89)					
	12-weeks	8.70 ± 1.49 (8.19-9.21)	7.94 ± 1.77 (7.33-8.55)					
	Quadriceps tendon PPT, kg/s	Baseline	8.01 ± 1.81 (7.39-8.63)	6.93 ± 2.47 (6.08-7.78)			F = 22.69 P = 0.001 (0.25)	F = 1.07 P = 0.374 (0.02)
		Post-Intervention 1	8.22 ± 1.71 (7.63-8.81)	7.24 ± 2.45 (6.40-8.08)				
Pre-Intervention 2		8.44 ± 1.87 (7.80-9.08)	7.44 ± 2.24 (6.67-8.21)					
Post-Intervention 2		8.47 ± 1.84 (7.83-9.10)	7.64 ± 2.24 (6.86-8.41)					
4-weeks		9.00 ± 1.54 (8.47-9.53)	8.35 ± 1.95 (7.68-9.02)					
12-weeks		9.37 ± 1.36 (8.90-9.83)	9.03 ± 1.39 (8.56-9.51)					
Patellar tendon PPT, kg/s		Baseline	7.82 ± 2.07 (7.11-8.53)	7.50 ± 2.21 (6.74-8.26)	F = 11.39 P = 0.001 (0.14)	F = 1.03 P = 0.384 (0.01)		
		Post-Intervention 1	8.27 ± 2.08 (7.56-8.99)	7.52 ± 2.15 (6.78-8.26)				
	Pre-Intervention 2	8.41 ± 1.94 (7.74-9.07)	7.61 ± 2.02 (6.92-8.30)					
	Post-Intervention 2	8.69 ± 1.95 (8.03-9.36)	7.69 ± 2.08 (6.97-8.40)					
	4-weeks	9.06 ± 1.47 (8.56-9.75)	8.32 ± 1.75 (7.72-8.92)					
	12-weeks	9.35 ± 1.19 (8.94-9.75)	8.25 ± 1.95 (8.94-9.75)					

Abbreviature: VAS, visual analogue scale; VM-PPT, vastus medialis pain pressure threshold; VL-PPT; PENS, percutaneous electrical nerve stimulation.

a. Time differences from Baseline. vs Post-Intervention 1 with p-value < 0.008; b. Time differences from Baseline vs Post-Intervention 2 with p-value < 0.008; c. Time differences from Baseline. vs 4-week with p-value < 0.008; For all analyses, P < .05 (for a confidence interval of 95%) was considered statistically significant (**bold**).

Table 3. Dependent variables of the study of range of motion (ROM) and strength in the different time phases, with means, standar deviatonss and IC's 95% represented.

Measure	PENS (n=35)	Control (n=35)	Intrasubject Effects		
			<u>Time value</u> F; P (Eta ²)	<u>Treatment X Time</u> F; P (Eta ²)	
Extension ROM, (°)	Baseline	-1.14 ± 2.82 (-2.11--0.17)	-4.29 ± 5.48 (-6.17--2.40)	F = 13.02 P = 0.001 (0.168)	F = 4.58 P = 0.001 (0.063)
	Post-Intervention1	-0.46 ± 1.92 (-1.11-0.20)	-2.69 ± 4.03 (-4.07--1.30)		
	Pre-Intervention2	-0.86 ± 1.96 (-1.53--0.18)	-3.23 ± 4.62 (-4.81--1.64)		
	Post-Intervention 2	-0.57 ± 1.44 (-1.07--0.08)	-2.14 ± 3.40 (-3.31--0.98)		
	4-weeks	-0.26 ± 0.95 (-0.58-0.07)	-1.14 ± 2.78 (-2.10-0.19)		
	12-weeks	0.0 ± 0.0 (0-0)	-0.14 ± 0.85 (-0.43-0.15)		
Flexion ROM, (°)	Baseline	100.8 ± 15.75 (95.45-106.27)	100.9 ± 19.55 (94.23-107.66)	F = 168.74 P = 0.001 (0.71)	F = 2.07 P = 0.121 (0.03)
	Post-Intervention 1	104.6 ± 16.64 (98.88-110.32)	106 ± 17.23 (100.11-111.95)		
	Pre-Intervention 1	110.9 ± 12.28 (106.73-115.16)	108.1 ± 14.01 (103.30-112.32)		
	Post-Intervention 2	113.6 ± 12.47 (109.32-117.88)	113.6 ± 13.89 (108.83-118.37)		
	4-weeks	128.9 ± 8.90 (125.86-131.97)	125.8 ± 10.7 (122.13-129.53)		
	12-weeks	135.0 ± 6.73 (132.74-137.37)	136.51 ± 6.3 (134.33-138.70)		
Q-MIC, (Nw)	Baseline	149.1 ± 80.2 (121.54-176.66)	149.6 ± 81.1 (121.78-177.52)	F = 132.25 P = 0.001 (0.66)	F = 0.75 P = 0.511 (0.01)
	Post-Intervention 1	173.6 ± 71.7 (149.10-198.24)	161.5 ± 91.99 (129.97-193.17)		
	Pre-Intervention 2	182.9 ± 78.6 (155.94-209.95)	185.4 ± 95.73 (152.57-218.34)		
	Post-Intervention 2	211.2 ± 79.1 (184.02-238.38)	203.1 ± 89.47 (172.44-233.91)		
	4-weeks	251.9 ± 84.77 (222.86-281.11)	233.99 ± 89.26 (203.32-264.65)		
	12-weeks	315.4 ± 82.98 (286.97-343.98)	298.5 ± 108.5 (261.28-335.86)		
Q-MeIC, (Nw)	Baseline	100.1 ± 55.38 (81.17-119.21)	104.5 ± 61.58 (83.35-125.66)	F = 123.78 P = 0.001 (0.65)	F = 0.16 P = 0.695 (0.01)
	Post-Intervention	123.6 ± 52.65 (105.53-141.70)	116.3 ± 71.21 (91.91-140.83)		
	Pre-Intervention 2	138.2 ± 66.08 (115.54-160.94)	136 ± 78.55 (109.11-163.07)		
	Post-Intervention 2	154 ± 64.64 (131.81-176.22)	153.6 ± 74.72 (128.01-179.35)		
	4-weeks	188.7 ± 72.97 (163.70-213.83)	175.64 ± 77.55 (149.01-202.28)		
	12-weeks	232.5 ± 65.88 (209.87-255.13)	215.6 ± 86.37 (185.95-245.29)		

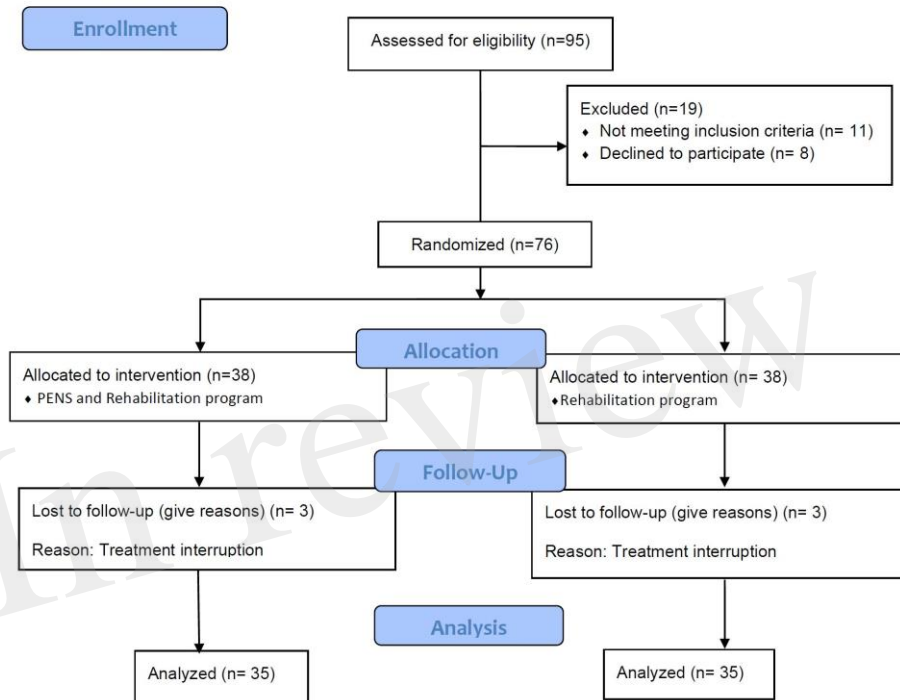
Abbreviature: Q-MIC, quadriceps maximal isometric contraction; Q-MeIC, quadriceps mean isometric contraction; PENS, percutaneous electrical nerve stimulation.

586 **Figures**

587 **Figure 1.** Flowchart of the Study According to the CONSORT 2010 Statement.



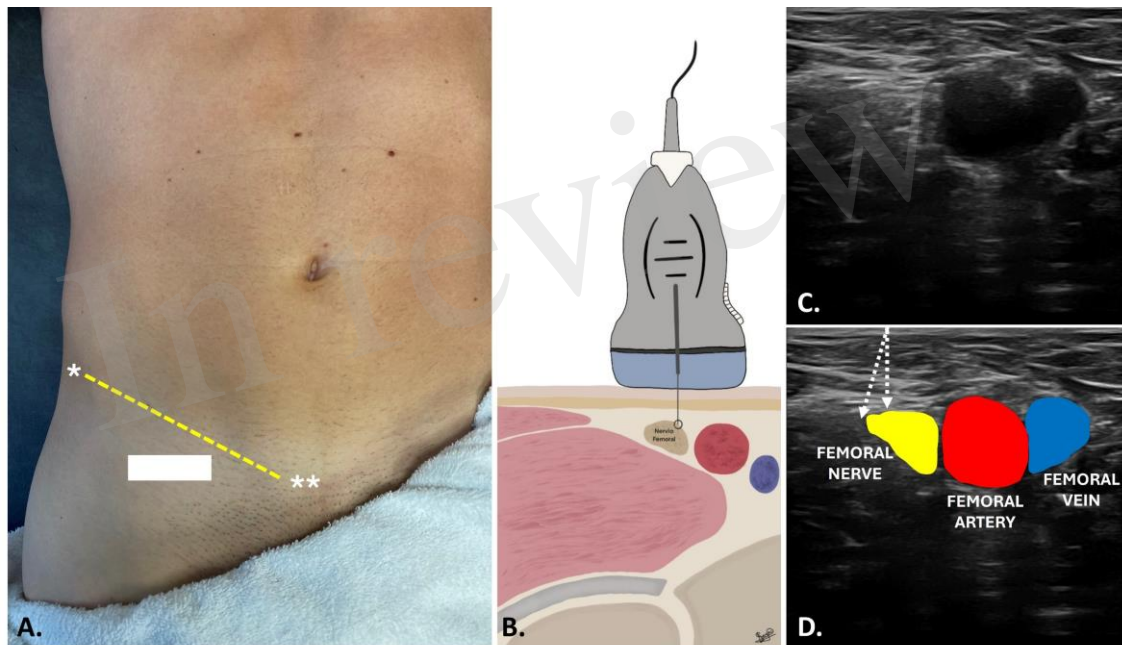
CONSORT 2010 Flow Diagram



588

589

590 **Figure 2.** Location of the ultrasound probe and visualization of the femoral nerve for the
591 femoral nerve invasive approach. A., Location of the probe below the inguinal fold at the
592 level of the pubic tubercle (**), below the imaginary line between the anterior superior
593 iliac spine (*); B., Representation of the peripheral placement of the needle in relation to
594 the position of the femoral nerve with respect to the femoral vascular structures (C., and
595 D.). The needle entry approach was performed "out of plane" by passing the needle over
596 the lateral edges of the perineurium (white dashed arrows showing the needle positioning)
597 at the lateral or superior border of the nerve.



599 **Figure 3.** Summary of the Study Groups: Rehabilitation Protocols for the Intervention (PENS + Rehabilitation) and Control (Isolated
 600 Rehabilitation) group.

INTERVENTION GROUP: PENS + REHABILITATION PROGRAM	CONTROL GROUP: ISOLATED REHABILITATION PROGRAM
<p style="text-align: center;">PHASE 1 (0 – 2 weeks)</p> <ul style="list-style-type: none"> - Passive Knee Mobilization (30') - NMES + Quadriceps muscle activation (15') - Cryotherapy (15') - PENS femoral nerve. Electrical current parameters: Frequency = 2Hz; Pulse duration = 240µs; Intensity = Patient's tolerance + quadriceps motor response; Interventions: Week 1 + RP; Week 2 + R 	<p style="text-align: center;">PHASE 1 (0 – 2 weeks)</p> <ul style="list-style-type: none"> - Passive Knee Mobilization (30') - NMES + Quadriceps muscle activation (15') - Cryotherapy (15')
<p style="text-align: center;">PHASE 2 (2 – 6 weeks)</p> <ul style="list-style-type: none"> - Manual Therapy, Soft Tissue Mobilization + Active mobility of the knee, muscle activation (30') <ul style="list-style-type: none"> - Cycling (12') - 3x10 isotonic flexion + extension strengthening exercises <ul style="list-style-type: none"> - Propicepcion training/exercises (5') (Initial phase) - NMES + Quadriceps muscle activation (15') 	
<p style="text-align: center;">PHASE 3 (6 – 9 weeks)</p> <ul style="list-style-type: none"> - Manual Therapy, Soft Tissue Mobilization + Active mobility of the knee, muscle activation <ul style="list-style-type: none"> - Cardiovascular training such as cycling or running (20') - Strengthening and propiception trainig/exercises (Advanced phase) 	
<p style="text-align: center;">PHASE 4 (9 – 12 weeks)</p> <ul style="list-style-type: none"> - 3x10 strengthening and endurance exercise (Thigh muscle: adductor, quadriceps, hamstring) <ul style="list-style-type: none"> - Propiception and coordination training/exercises (Advanced phase) <ul style="list-style-type: none"> - NMES (15') - Cardiovascular training (25') 	



CONSORT 2010 Flow Diagram

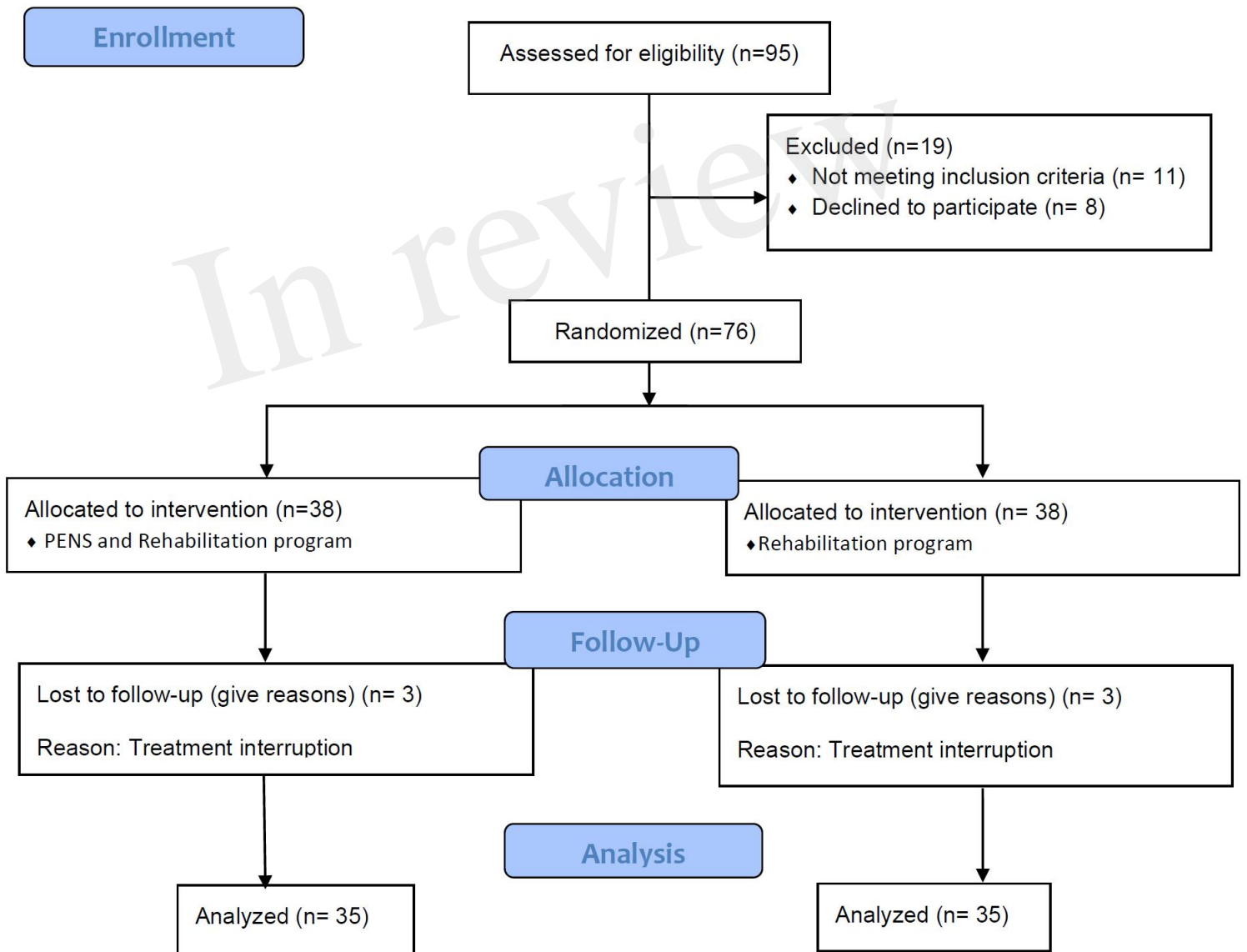


Figure 2.JPEG

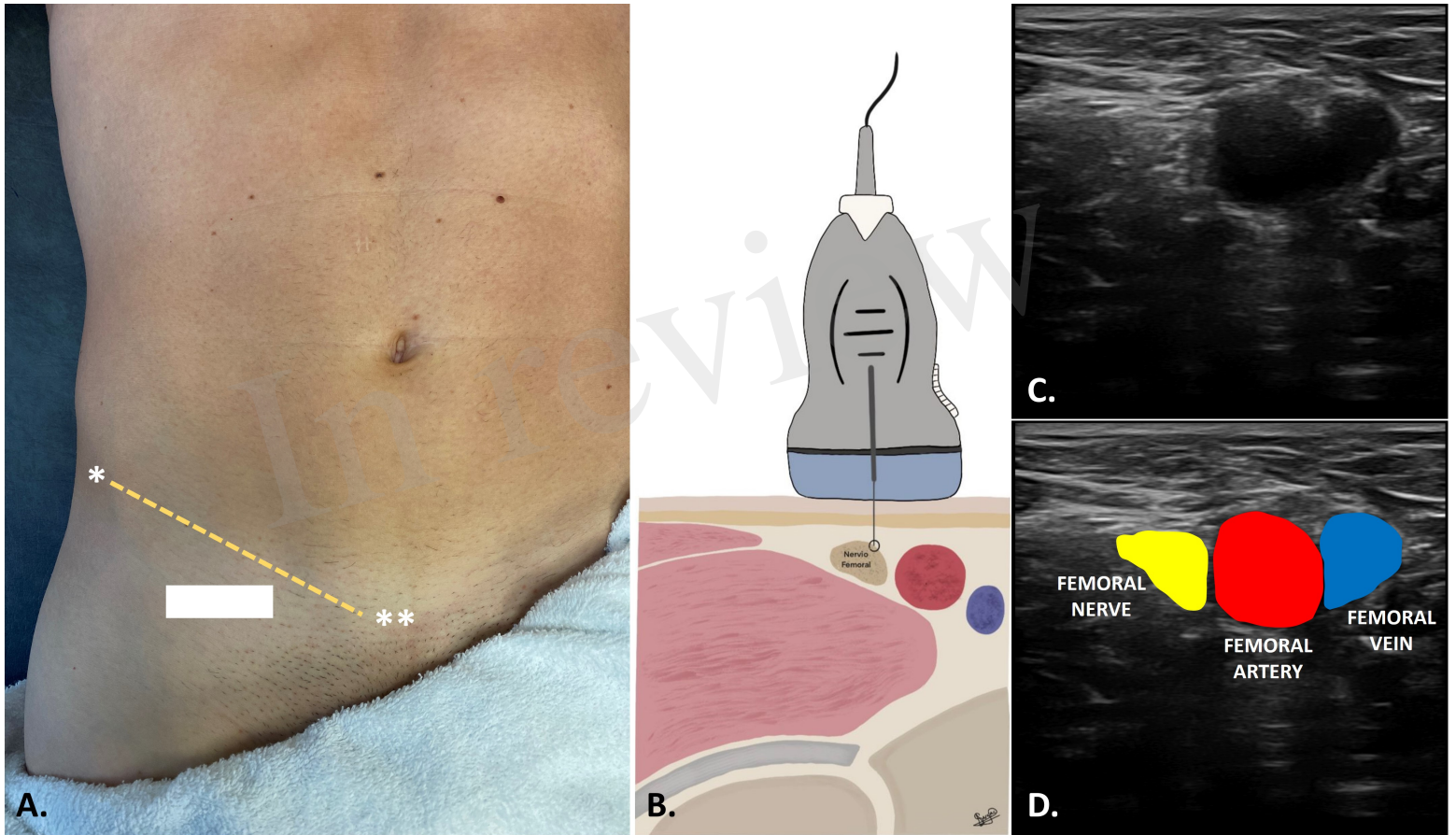


Figure 3.JPEG

INTERVENTION GROUP: PENS + REHABILITATION PROGRAM	CONTROL GROUP: ISOLATED REHABILITATION PROGRAM
PHASE 1 (0 – 2 weeks)	PHASE 1 (0 – 2 weeks)
<ul style="list-style-type: none"> - Passive Knee Mobilization (30') - NMES + Quadriceps muscle activation (15') - Cryotherapy (15') - PENS femoral nerve. Electrical current parameters: Frequency = 2Hz; Pulse duration = 240µs; Intensity = Patient's tolerance + quadriceps motor response; Interventions: Week 1 + RP; Week 2 + R 	<ul style="list-style-type: none"> - Passive Knee Mobilization (30') - NMES + Quadriceps muscle activation (15') - Cryotherapy (15')
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