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Original Research

Noninvasive Interactive Neurostimulation Therapy for the Treatment of Low-Grade Lateral Ankle Sprain in the Professional Contact Sport Athlete Improves the Short-Term Recovery and Return to Sport: A Prospective, Randomized Controlled Trial

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ABSTRACT

Ankle injuries are very common between professional athletes and recreational sports. Lateral stable ligaments injury can be treated conservatively. Noninvasive interactive neurostimulation (NIN) is a form of electric therapy that works by locating areas of lower skin impedance. The objective of this prospective, double-blinded, randomized controlled trial was to compare the results in terms of improvement of a foot functional score, lower level of reported pain, and return to sports in 2 groups of contact sport athlete affected by a grade I or II lateral ankle sprain. Patients were randomized using random blocks to the NIN program (group I) or a sham device (group II). The outcome measurements were the use of a self-reported Inability Walking Scale, patient-reported subjective assessment of the level of pain using a standard visual analogue scale, and daily intake of nonsteroidal antiinflammatory drugs (etoricoxib 60 mg). Patients were also reached by telephone at 2 and 4 months of follow-up to register their return to sport activity. Beyond baseline evaluation, follow-ups were done after 5 (1 week) and 10 sessions (2 weeks) of treatment, and then at 30 days after the end of therapy. Of the 70 athletes admitted to the study, 61 eligible patients were randomized using random blocks to group I (n = 32) and group II (n = 29). Group I patients showed better improvement in terms of functional impairment (Inability Walking Scale), reported pain (visual analogue scale), and daily intake of etoricoxib 60 mg. Athletes of group I registered a faster resuming of sport activities. This prospective, randomized trial showed NIN can improve short-term outcomes in athletes with acute grade I or II ankle sprain and that it can hasten resuming of sport activities.

Ankle injuries are very common between professional athletes and recreational sports, with an incidence in the general population of United States of 2.15 per 1000 persons each year (1). The most common injury mechanism is a combination of inversion and adduction of the foot in plantar flexion (supination). This injury mechanism can cause damage to the lateral ankle ligaments (2); most of these lesions—in particular, uncomplete tearing of ligaments—can be treated conservatively (3). In a multicenter randomized trial, Lamb et al (4) showed that after acute sprains of the ankle, initial immobilization using a soft brace or below-knee cast resulted in faster recovery than simple compression with tubular bandaging. There is also good evidence that after a short period of immobilization, functional rehabilitation is better than the traditional treatment of 6 weeks in a cast (5,6). Many possible physical therapies may be used to improve pain reduction and tissue healing, including Transfer of Energy Capacitive and Resistive therapy, laser therapy, ultrasound therapy, and other form of electric therapies (7,8).

A relatively new form of electrotherapy based on the application of noninvasive interactive neurostimulation (NIN) has been recently used for the analgesic effect on hip, knee, and ankle fractures/pain after joint replacement and for muscle skeletal pain (9–15). The manufacturer

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purports that the device works by locating areas of lower skin impedance, which generally "relate to major nerve branches, trigger points, acupuncture points, and localized areas of sympathetic skin response" (14,16). The analgesic effects of NIN are due to a distinctive electrode positioning, releasing a high amplitude/density current; the most interesting aspect of the NIN is adaptation in relation to the body (area of lower electric impedance), with the beneficial effects arising from the selective stimulation of nerve fibers A, delta, and C. In the same way, selective stimulation can also occur at the level of the corresponding spinal cord vertebral body by the action of the central nervous system (14). Literature about NIN evidences that this electric therapy is a tool available for the treatment of acute (10,11,13) and chronic (9,12,15) conditions, and, overall, it emerged that patients show a very good compliance with this therapy, because of its painless nature and of its low cost in terms of time and money (15). Acute lateral ankle sprains in the professional contact sport player may benefit using NIN, after a short time of immobilization and pain control with nonsteroidal antiinflammatory drugs (NSAIDs).

We hypothesized that the use of NIN may improve the short-term recovery and return to sport of professional contact sport player who sustained an acute grade I or II lateral ankle sprain. Accordingly, the objective of this prospective, double-blinded, randomized controlled trial was to compare the results in terms of improvement of a foot functional score, lower level of reported pain, and return to sports in 2 groups of contact sport athlete affected by an acute grade I or II lateral ankle sprain. In the first group, the use of NIN was added to a standard conservative protocol consisting of first days of rigid immobilization, ice, daily low-dose of NSAIDs, and then early mobilization. In the second group, the same protocol was adopted but NIN was simulated with a sham device.

Materials and Methods

The protocol for this investigation received formal approval from the institutional ethics committee and the study review board of the Centro Medico Erre. Patients were informed about the purpose of the study and gave informed consent to collect clinical data for scientific purposes. All rights of the enrolled subjects in the present study were protected. The study was carried out in accordance with the World Medical Association Declaration of Helsinki.

Between September 1, 2016, and June 31, 2017, athletes with a diagnosis of grade I or II lateral ankle sprain that occurred during a contact sport competition were enrolled in this trial and randomly assigned to the 2 groups. Randomization was done by a clinician not enrolled in the study using random blocks to have treatment groups equal in size and uniformly distributed and thus reduce bias and achieve balance in the allocation of participants to treatment arms. Because the study cohort was composed by 2 relatively small groups (n = < 50), smaller block sizes lead to more balanced groups by time than larger block sizes.

The inclusion criteria were as follows:

- Athletes involved in professional soccer, football, basketball, and mixed martial arts
- First episode of lateral ankle sprain occurred during sport activity (not recurrent instability or chronic sprains)
- Enrollment of patients within 48 hours after the trauma (only acute trauma)
- Clinical, ultrasound, and/or magnetic resonance imaging diagnosis of partial tear (grade I or II) of the lateral ligaments of the ankle in absence of bone edema and skin wound or sufferance
- Age > 18 years.

Exclusion criteria were as follows:

- History of recurrent ankle dislocation or presence of hyperlaxity of any joint
- Athletes who received any form of local physical therapy and NSAID in the last 2 months before the injury
- Athletes admitting anabolic steroid use
- Any limitation that could interfere with electrical stimulation (pacemaker, insulin pump, neurostimulation implants, current pregnancy, active malignancies, or inability to consent to participation in clinical research).

Selection/exclusion of patients was consistently executed by the randomizing clinician not enrolled in the study. Joint sprain evaluation was systematically done with clinical evaluation (history of acute lateral sprain during sport activity with immediate functional impairment, swelling on the lateral aspect of the ankle, absence of skin sufferance, and neurovascular impairment) and ultrasound or magnetic resonance imaging examinations showing sprain or incomplete tearing of the lateral ankle ligaments without bony involvement.

Table 1
Demographic and morphometric characteristics with baseline evaluations of self-reported scales

Characteristic	Group I, NIN (N = 32)	Group II, SHAM (N = 29)
Age (y), mean (range)	23 (18 to 43)	23 (20 to 39)
Male sex, no. (%)	18 (56.25)	15 (51.70)
Weight (kg), mean ± SD (range)	75.1 ± 13 (47 to 88)	77 ± 14 (50 to 92)
Body mass index, mean ± SD (range)	23.2 ± 4 (19 to 29)	22.9 ± 5 (18 to 30)
T0 evaluations		
Self-reported inability walking scale* (0 to 10), mean ± SD	9.1 ± 0.6	8.9 ± 0.5
VAS** (0% to 100%) (range)	88 (75 to 100)	85 (75 to 100)

Abbreviations: NIN, noninvasive interactive neurostimulation; SD, standard deviation; SHAM, sham device; VAS, visual analogue scale.
* Score ranges from 0 to 10 (higher scores indicate greater impairment).
** A higher score indicates greater impairment.

Demographic (age, sex) and morphometric (body mass index) characteristics of patients were recorded and are synthetized in Table 1.

First Phase of the Study: Immobilization and Pain Control

Independent of the allocation in one of the 2 groups, patients followed the same protocol in the first 2 weeks. The protocol consisted of an incomplete plaster cast (Dynacast® Prelude; BSN Medical, Luxembourg, Germany), a synthetic splinting system specifically incorporating fiberglass covered by a polypropylene padding) for the immobilization of the ankle and foot, restricted weightbearing (2 crutches), and NSAID therapy using etoricoxib 60 mg/d. Because of restricted weightbearing and immobilization, enoxaparin 4000 IU 1 ampoule per day was prescribed for 2 weeks. This short time immobilization of 2 weeks was given because of pain and edema control, and with the incomplete but unremovable plaster cast, athletes were obliged to respect the restricted weightbearing and immobilization.

Second Phase of the Study

Depending on allocation of the group, patients started their rehabilitation program, with gentle range of motion and the electric therapy (NIN or a sham device). The rehabilitation program was given by 2 physical therapists not blinded to the nature of the electric therapy. This is because the active and real treatment involves interactive feedback from the device to determine the optimal treatment point location. Therapists trained to correctly apply NIN can recognize a sham device, which does not give the same feedback to the operator. However, patients cannot recognize the sham device; in fact, it has the same appearance as the active NIN device and also generates similar audio/visual signals and tactile sensations of vibration.

Each session lasted 40 minutes, with the first 20 minutes given for the manual recovery of range of motion and proprioceptive exercises and the remaining 20 for the electric therapy. The 2 physical therapists were not involved in the follow-up visits.

NIN Application

The treatment protocol was settled with 5 sessions per week, 20 minutes per each session using a portable, handheld device (InterX® 5002; InterX Technologies, Richardson, TX) (14) for a total of 10 sessions (2 weeks). This device generates high-amplitude, pulsed, damped biphasic sinusoidal current that is delivered to the tissue via a pair of concentric electrodes placed in direct contact with the target area. In comparison with the InterX® 5000 device (Neuro Resource Group) (10), the InterX® 5002 uses a more advanced user interface. Using the handheld device, the electrode position is identified by scanning the target site using minimal stimulation intensity that is related to the lowest tissue impedance (Fig. 1). The handheld tool is then left stationary for the first 10 minutes, with an increasing intensity until a comfortable electrical paresthesia is reached. In the last 10 minutes, the InterX® Multiflex array electrode (Neuro Resource Group) is used (Fig. 2).

Patients allocated to the control group received the same protocol, with the use of a sham device. The protocol was repeated for 10 sessions, 5 times a week. Patients not respecting this schedule were excluded from the study.

Outcome Measurements

A researcher not involved in the protocol and blinded to the treatment consistently collected outcome measurements (double-blinded randomization). All

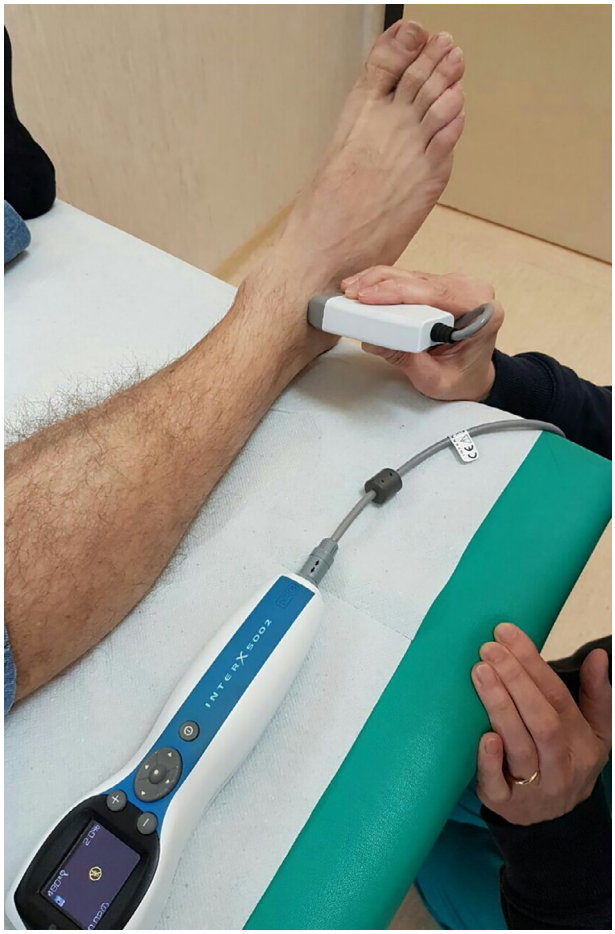

Fig. 1. The noninvasive interactive neurostimulation handheld device, with the treatment starting by scanning the target site using minimal stimulation intensity to identify the correct electrode position for the first 10 minutes. Shown with permission.

patients underwent baseline evaluations before their first treatment session (time 0 [T0]). Outcome tools included the use of a self-reported Inability Walking Scale (IWS; with a value of 0 indicating normal ability to walk and a value of 10 indicating an absolute inability to walk) patient's subjective assessment of pain using a standard visual analogue scale (VAS) and daily intake of tablets of etoricoxib 60 mg (used as the reference NSAID), calculated at the first follow-up (T1). The score of the self-reported IWS was used to produce the primary numeric outcome score. The VAS may range on a scale from 0 (no pain) to 10 (worst possible pain). The VAS has been already used for follow-up of acute ankle sprain and is defined as a reliable and sensitive measure of pain intensity in acute conditions (16). Patients who did not respect the prescription of etoricoxib 60 mg oral tablets when needed and who used other analgesics were excluded from the study.

Return to Sport

Patients were reached by telephone at 2 and 4 months of follow-up by the therapists to register their resumption of sport activities. Complications were assessed by an author blinded to the treatment (S.C.). Beyond baseline evaluation (T0), follow-ups were done after 5 (T1) and 10 sessions (T2) of treatment and then 30 days (T3) after the end of therapy.

Statistical Analysis

A linear regression was used to evaluate time progression of data, using as the independent variable times T0, T1, T2, and T3 and as the dependent variable the parameter evaluated (IWS, VAS, daily intake of Etoricoxib 60 mg tablets); the *F*-test with Bonferroni correction for multiple comparison was used to compare difference average value data of 2 groups over time. Categorical data were analyzed with Fisher's exact test. The statistical analysis was performed with SPSS software, version 16.0 (SPSS, Chicago, IL). Statistical significance was defined at the 5% ($p \leq .05$) level.

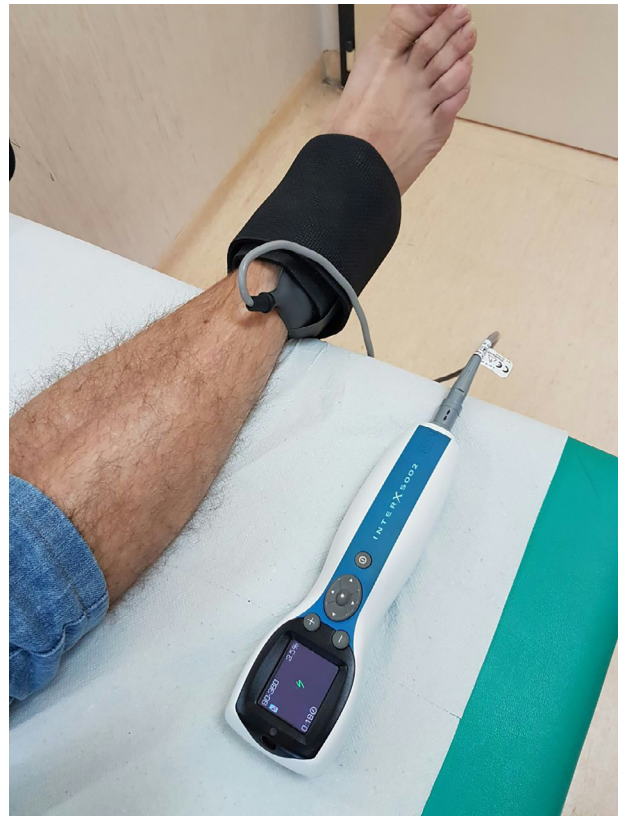

Fig. 2. The noninvasive interactive neurostimulation Multiflex array electrode is used for the second 10 minutes of treatment. Shown with permission.

Results

Of the 70 athletes admitted to the study institution during the trial enrollment period with a diagnosis of an acute grade I or II lateral ankle sprain, 6 did not fulfill the inclusion criteria and 3 were reluctant to participate. The remaining 61 eligible patients were randomized using random blocks to the NIN program (n = 32; group I) or sham device (n = 29; group II) (Fig. 3). The 2 groups were comparable for demographic and morphometric features, as well as for the considered T0 evaluations (IWS, VAS, and etoricoxib tablets; $p > .1$) (Table 1).

Outcomes

Functional Impairment (IWS)

At T0, the IWS was similar in both groups, with a mean value of 9.1 and 8.9 in groups I and II, respectively ($p > .1$). After 5 sessions of therapy or after 1 week (T1), the self-reported scale resulted 5.3 and 6.2 in the 2 groups, respectively ($p = .046$). The difference between the 2 treatment groups continued to escalate as the study proceeded, with a final result of 1.3 and 2.6 in the 2 groups, respectively ($p = .043$). These and further results are synthetized in Table 2.

Self-Reported Level of Pain (VAS)

At T0, the VAS, registered as 0 (no pain) to 10 (the worst imaginable pain), was comparable in the 2 groups, with values of 8.8 and 8.5, respectively ($p > .1$). At T1, the self-reported level of pain showed only a trend of significance ($p = .07$), with values of 7.1 and 7.4, respectively; the same was noted at T2 ($p = .058$). Finally, at T3 the result was statistically significant in favor of NIN treatment ($p = .043$). These and other results are synthetized in Table 2.

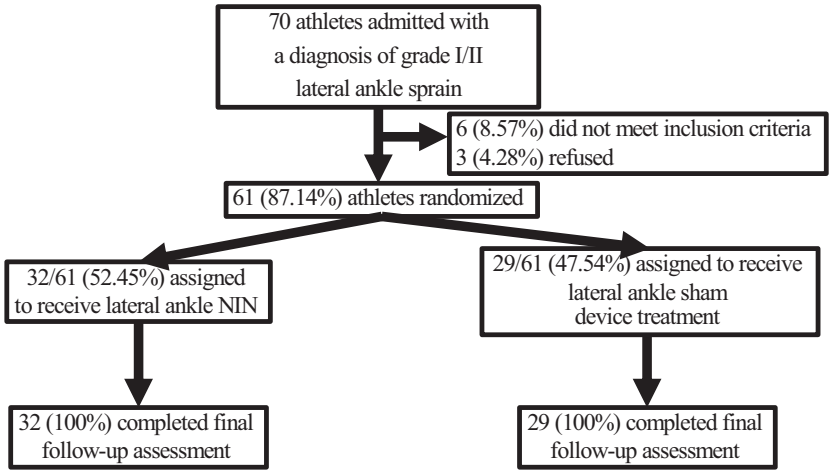

Fig. 3. Flowchart of the study. NIN, noninvasive interactive neurostimulation.

Table 2
The Inability Walking Scale, visual analogue scale, and nonsteroidal antiinflammatory drug daily intake results at the 3 follow-ups

Evaluation Scale and Coxib Intake	T1	T2	T3
IWS			
NIN	5.3	2.0	1.3
SHAM	6.2	2.8	2.6
p Value	.046	.058	0.043
VAS			
NIN	7.1	3	1
SHAM	7.4	3.7	1.7
p Value	.07	.058	.043
Etoricoxib 60 mg daily intake			
NIN	1.5	1.1	0.3
SHAM	1.4	1.3	0.6
p Value	.14	.048	.033

Abbreviations: IWS, Inability Walking Scale; NIN, noninvasive interactive neurostimulation; SHAM, sham device; VAS, visual analogue scale.

Daily Intake of Etoricoxib 60 mg

After the 2-week immobilization period, patients in both groups were taking a mean of 2 tablets of etoricoxib 60 mg, which was the maximum dosage permitted. At T1, both groups maintained a comparable dosage, with 1.5 and 1.4 tablets per day in groups I and II, respectively ($p = .14$). At T2, patients in group I reported taking a mean of 1.1 tablets compared with 1.3 tablets for group II ($p = .048$). At T3, the use decreased to 0.3 and 0.6 in the 2 groups, respectively ($p = .033$). These and other results are reported in Table 2.

Return to Sport

At 2 months' follow-up, 23 (71.87%) and 16 (55.17%) patients in the 2 groups, respectively, reported back in their sport activity ($p = .029$). At 4 months, the numbers increased to 27 (84.3%) and 24 (82.7%) patients, showing no statistical significance ($p = .09$).

Side Effects

All patients in both groups reported no discomfort during the treatment and/or transient reddening in the few hours after the treatment. No device-related complications occurred.

Discussion

The hypothesis of this double-blinded, prospective, randomized controlled study was that NIN may improve short-term recovery and return to sport of professional contact sport athletes who sustained an acute grade I or II lateral ankle sprain. The results showed this form of electric therapy contributed to a better recovery in term of functional impairment (IWS scale), a lower level of reported pain (VAS), and a lower intake of NSAIDs (etoricoxib 60 mg). Resumption of sport activities was faster in the group who received the NIN therapy, with 71.9% of patients back to sport activities at 2 months of follow-up.

This study is the first dealing with a consistent consecutive number of athletes affected by an acute ankle sprain treated with NIN. Lateral ankle sprains are a very common injury in the general population and in contact sportsman, with total societal costs much higher than most would comprehend. If we combine the direct cost for management of acute lateral ankle sprain to the costs of managing the loss of physical activity and daily working activities, it is easy to formulate the health care burden that emerges from a seemingly simple lateral ankle sprain injury (16). Physical therapies such as ultrasound treatments, laser, and capacitive and resistive energy transfer are often added to a short period of immobilization, and they should be effective, painless, and inexpensive. Recently, an innovative treatment modality that has been suggested for the conservative treatment of syndesmotic injuries is dry needling (17). Although dry needling and NIN therapy are apparently very different, both work on trigger points that correspond with the area of lower impedance, where nerve branches course close to the skin surface (18). The NIN mechanism of action is complex and only partially identified; evidence has shown that NIN therapy probably activates the gate control mechanism of pain but seems to not be the primary mechanism of pain relief, owing to the long-lasting effects and cumulative decrease in pain reported by patients (19). When skin is stimulated, its impedance changes: NIN therapy rapidly modifies the waveform and amplitude in response to these impedance changes, which allows for a significantly greater concentration (current density) of stimulation without risking harm to the skin.

The main outcomes of this study were the functional impairment calculated with the IWS and the pain level with the VAS. Both evaluations showed a positive progression of results over time in the NIN and sham device groups, with a functionally significant statistical difference emerging at each follow-up point. Overall, the T1 and T2 VAS results were better in the NIN group, even if they were not statistically significant. The daily intake of NSAID confirmed these

results. Unfortunately, in the literature, there is a lack of similar studies to compare our results and very low evidence in favor of any therapies. An important issue to consider in athletes is muscular atrophy consequent to immobilization, with some authors arguing for intermittent vascular occlusion to prevent it (20). We believe that 2 weeks of immobilization are acceptable also by the elite competitors, even if in some cases hydrotherapy and isometric strengthening exercises may be performed precociously. Nevertheless, from review of the literature, it emerges that despite their regular occurrence, management of this injury varies widely between departments and often between clinicians working in the same department. There is no gold standard method of management used universally. Instead, clinicians rely on a combination of personal experience and clinical judgment (21). This finding is true in Europe (21), and no significant treatment difference is found between grade I and grade II injuries. A review of treatments in adults suggested using the principle of functional treatment with any form of ankle brace and early mobilization to decrease the potential for long-term residual complications (22).

The use of NSAIDs is widely accepted in the conservative treatment of ankle sprain, both for pain and inflammation therapy and for the prevention of heterotopic ossification (23). Over time, NIN therapy has decreased significantly the daily intake of Etoricoxib in this prospective trial, with a maximum of 1.5 tablets per day at 1 week after the onset of the neurostimulation program and decreasing to 0.3 tablet at the final evaluation (30 days after the ending of the program). Of course, simply the use of NSAID may have influenced the final outcomes in both groups. An alternative form of antiinflammatory therapy is topical application of an NSAID gel, especially in Europe. Despite some randomized study advocated the local use of diclofenac 4% and ketoprofen spray gel for uncomplicated ankle sprain (24,25), a very recent trial found no difference between topical 1% diclofenac/3% menthol gel compared with placebo, 1% diclofenac, or 3% menthol gel in treating pain from ankle sprain (26). In our experience, we never used it simply because patients were in an unremovable plaster cast.

Resumption of sport activities is of maximum importance in professional athletes. In addition, resuming recreational activities is important in the general active population. In the first weeks after injury, the rehabilitation program in an athletic population may include hydrotherapy and isometric strengthening exercises; it may be expected that athletes with pain-free running and cutting may return to full practice and then to competition in the absence of pain or limitations after 1 week of full practice (27,28). We considered 2 and 4 months as 2 reasonable follow-ups to investigate about sport activities, and this approach is in line with what is reported for similar trial in stable syndesmotic injuries (25). We registered a considerably faster resumption of sport activities in the group treated with the NIN therapy (71.87% vs 55.17%) at 2 months; at 4 months, the numbers were similar (84.3% vs 82.7%). It can be concluded that NIN therapy may hasten early return to sport activities.

The absence of registered side effects and the low-cost and painless nature of NIN (15) improve patients' compliance to this form of electric therapy. Other forms of sport-specific rehabilitation, such as dry needling (17) or exercises under blood flow restriction (20), are not pain free and may not be readily accepted. In addition, the handheld NIN portable device may be used directly where athletes train, improving the athletes' compliance with the rehabilitation program.

A strength of our study is the strict method of patient selection. In fact, we selected only professional athletes who suffered acute grade I or II ankle sprains and treated immediately (not >48 hours after the trauma) with the proposed protocols. A potential limitation is that the final follow-up is relatively short. However, because ankle sprains are an acute and often self-limiting condition, with longer follow-up it may be difficult to attribute the healing to the treatment only, which could jeopardize the results. We empirically assumed that 30 days of follow-up are enough to study NIN effects applied to ankle sprains in athletes. Another possible limitation is that we used the self-reported IWS, and one may argue that it is an unvalidated and subjective instrument. Nevertheless, this simple scale gives the opportunity for patients/athletes to scale the severity of their injury from 0 to 10 of and their inability to walk. In the competitive athlete scenario, the inability to walk and then to train is the most important factor to be considered.

In conclusion, the results of our study showed NIN can improve short-term outcomes as walking pain free in athletes/patients with acute grade I or I ankle sprains and can hasten resumption of sport activities. We believe an early introduction of NIN therapies in sport traumatology could be a valuable tool for the rehabilitation of sports injuries.

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