

Research Article

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Acetic Acid Iontophoresis and Ultrasound Effectiveness on Calcifying Tendonitis of the Shoulder, Elbow, Wrist, Hip, Knee and Ankle: A Non-Randomized Multicenter Control Trial.

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Abstract

Objective: To conduct a prospective Multicentre Quasi-experimental before-and-after study (Non-Randomized Control Trial) to demonstrate the effectiveness of Acetic Acid Iontophoresis and Ultrasound in the treatment of Calcifying Tendonitis (CT) of the shoulder, elbow, wrist, hip, knee and ankle.

Material and methods: Prospective, multicentre, quasi-experimental before-after intervention study, to 91 patients who attended to both Rehabilitation Departments, at Santísima Trinidad's General Foundation Hospital, Salamanca-Spain and at Santa Cristina's University Hospital, Madrid-Spain, from June-2014 to October-2016.

Outcome Measures: 1) pain: measured by Visual Analogical Scale (VAS); 2) Calcification size: in millimetres (mm), both measured radiologically at the beginning/end of treatment.

Intervention: Iontophoresis with 5% acetic acid at 4,7mA x 10 minutes and continuous Ultrasound 1W/cm² /1MHz x 5 minutes over calcification.

Results: Mean age 55.08±11.62 years (n = 91). Female 70% (n = 64). At the shoulder, Supraspinatus tendon was the most affected (91.5%; n = 65) followed by Subscapularis (8.5%; n = 9). Other affected tendons were gluteus medium and gluteus minimum at the hip (n=9, 10%), Achilles (n=3; 3%). CT at the elbow (triceps tendon) and at the wrist showed similar frequencies (n=2; 2%). CT of the quadriceps tendon inserted at the patella was the most uncommon (n=1; 1%). Average number of sessions: 20. Treatment showed a significant amelioration of pain (p<0.05) in all patients. Calcification size diminished significantly in all treated tendons (p<0.05), except for wrist and Achilles.

Conclusion: CT is more common in middle-aged women. It affects insertional tendons at different articulation sites. Iontophoresis with 5% Acetic Acid and Ultrasound is a safe, simple and inexpensive technique capable to reduce pain and calcification on the shoulder, elbow, wrist, hip, knee and ankle. This study shows a level of evidence II-1 and grade of recommendation B that allows us to postulate Acetic Acid iontophoresis and ultrasound as an effective treatment in CT.

Keywords: Iontophoresis; Ultrasound; Calcifying tendonitis; Shoulder pain; Physical therapy

Abbreviations: CT: Calcifying Tendonitis; VAS: Visual Analogical Scale; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; mm: Millimeters; MRI: Magnetic Resonance Imaging

Introduction

Calcifying tendonitis (CT) is defined as the deposit of hydroxyapatite within tendons and tendon sheaths. It occurs in up to 3% of adults and is the cause of 40-54% of painful shoulder

symptoms [1-3]. The etiology of CT is considered multifactorial, playing degeneration an important role. Certain tendons are particularly vulnerable to CT. These include elements of the

rotator cuff, Achilles, Patella, forearm extensors, biceps brachia and tibialis posterior tendon [4]. CT etiology and pathogenesis remain unclear [4] and is still a matter of controversy [5]. In 1872 Duplay described CT as a cause of shoulder pain. Degenerative changes, hypovascularization of the rotator cuff, metabolic abnormality and overuse have been suggested as possible causes for calcification of the tendon tissue [3]. According to Uthoff & colleagues [5,6], the deposition of calcium apatite crystals within the substance of the tendon is not a degenerative process but one that is actively mediated by cells in a viable tendon.

Three stages with clinical/histological/radiological correlation are described, and sometimes overlap:

- a. pre-calcification: tenocyte metaplasia and chondrocyte transformation;
- b. calcification:
 - A. Formative (reservoir of vesicles in matrix),
 - B. Resorptive (spontaneous resorption by macrophages/multinucleated cells by phagocytosis);
- c. post-calcification: collagen remodeling and tendon repair [7].

The clinical picture in CT is highly variable. There are asymptomatic patients (incidental radiological finding), patients with chronic pain and patients in acute painful crisis, mainly associated to the resorptive phase [8]. The diagnosis is clinical and radiological [8]. CT treatment is initially conservative and depends on its evolutionary stage [8].

In most of the cases, CT is a self-limiting condition, in which the calcification spontaneously resorbs after a period of a few years or is treated successfully conservatively [5,9]. In the formative and resting phases of the disease, if conservative measures fail and the patient presents with progressive symptoms interfering with daily living activities, removal of calcific deposits may be indicated [5,6]. Conservative treatment includes NSAIDs (non-steroidal anti-inflammatory drugs), physiotherapy, and electrotherapy (micro waves, short waves, TENS, ultrasounds, iontophoresis, interferential and pulsed electromagnetic therapy) [8]. Fernández-Cuadros et al. [8] have demonstrated recently that different electrotherapy techniques are useful reducing pain but not the calcification on CT patients.

Iontophoresis with acetic acid is a safe, common and cheap treatment and it was for decades the only option available, capable of acting over the calcification [8]. However, there is only a few clinical studies that support its effectiveness [10,11]; some of them are even controversial [12,13]. In a recent article, Fernández-Cuadros et al. [7] have stated the effectiveness of acetic acid iontophoresis and ultrasound on CT of the shoulder, but to the best of author's knowledge, there is no report on its effectiveness in other tendons apart from the rotator cuff. The objective of the study is to demonstrate the effectiveness of Acetic Acid Iontophoresis and Ultrasound on CT of the shoulder,

elbow, wrist, hip, knee and ankle; through a non-randomized multicentre control trial, which gives a good level of evidence-based medicine.

Material and Methods

Design

Prospective, not randomized, multicentre, quasi-experimental before-after control trial.

Patients

The study included 91 patients diagnosed clinically and radiologically with shoulder, elbow, wrist, hip, knee and ankle CT who attended to either the Rehabilitation Department, at Santísima Trinidad's General Foundation Hospital, in Salamanca-Spain, or the Rehabilitation Department, at Santa Cristina's University Hospital, in Madrid-Spain, from June 2014 to October 2016 (28 months).

a. Inclusion criteria

- i. All patients with clinical and radiological diagnostic of CT derived to the Rehabilitation Departments (from Traumatology, Rheumatology, Familiar Medicine, etc.);
- ii. older than 18 years;
- iii. who accepted the proposed treatment and firmed consent;
- iv. With pain greater than 3 on the Visual Analogical Scale (VAS).

b. Exclusion criteria

- v. Any patient with electrical devices (pacemaker, electrical stimulator) which constitute formal contraindication to electrotherapy treatment;
- vi. Intolerance or allergy to acetic acid, erythema or burn caused by the treatment;
- vii. Osteoarthritis, inflammation or infection on the respective articulation;
- viii. Cancer or any other severe or mental diseases.

Evaluation

Socio-demographic data (age, sex, occupation, laterality, dominance, occupation), *personal history* (diseases, pacemakers, electrical stimulator), and *radiological characterization of calcification* (formative/resorptive) were obtained. The treatment protocol was approved by the ethical committee of both Hospitals, and patients were given Informed Consent.

Outcome Measures:

- 1) pain: measured by Visual Analogical Scale (VAS);
- 2) Calcification size: in millimetres (mm); both evaluated radiologically at the beginning/end of treatment (Figure 1).

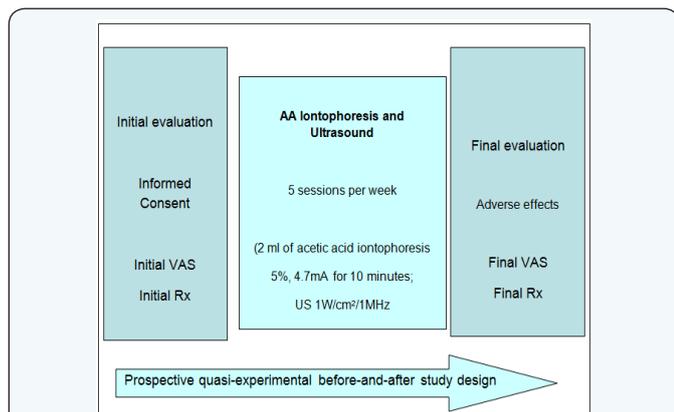


Figure 1: Latency times.

Abbreviations: VAS: Visual Analogical Scale; Rx: Posterior Anterior Plain Radiography. AA: Acetic Acid; US: Ultrasound; W: Watts; MHz: mega Herz

Protocol applied at the Department of Rehabilitation at Santa Cristina's University Hospital (Madrid-Spain), and at Santísima Trinidad's Foundation Hospital (Salamanca-Spain). The study ran from January 2014 to October 2016.

Intervention: All diagnosed patients were given 5% Acetic Acid Iontophoresis, 2cc dropped into a gauze and placed on a moistened cation (negative electrode), on the anterior aspect of the affected tendon. The anion (positive electrode), also moistened, was placed at a distance of 10cm from the cation, to allow the passage of current flow. Both damp cloth coated electrodes were attached with a belt, allowing full contact, in order to avoid the risk of burning. A 4.7mA galvanic current was applied for 10 minutes.

Subsequently, continuous Ultrasound to an intensity of 1W/cm²/5 minutes and a 1MHz frequency was applied over the affected tendon to promote drug absorption and to decrease pain [11]. To perform the treatment protocol, two European Medical Devices were used:

- For Iontophoresis, ENDOMED 581^{LD} (EnrafNonius® CE 0197), located both in Salamanca-Spain and Madrid-Spain, were used;
- For Ultrasound, SONOPULS 490 (EnrafNonius® CE 0197), both located on Salamanca-Spain and Madrid-Spain, were used.

Follow-up: Periodic reviews were performed (every 10 days) to assess pain and radiological change in size and/or disappearance of calcification by radiological evaluation. The minimum clinically significant change for pain measured by VAS corresponds to 1 point; it is considered a significant improvement if the change is greater than 3 points [14,15]. The radiographic measurements of the calcification were made in millimetres (mm), on 100%- size, posterior anterior plain radiographs of the affected articulation, assessing the calcification in its longest axis. If there was more than one calcification, the full measure corresponded to the sum of these calcifications measured

separately [7,10].

The effectiveness of treatment with iontophoresis considering the result variable “size of calcification” is valued as follows:

- Cured/success (calcification diminishing more than 75% or total disappearance);
- Improved (decreased calcification between 25-75%);
- Failure (if calcification decreased less than 25% or not disappearance). Clinical improvement included decreased pain (measured by VAS), the disappearance of the painful manoeuvres and functional mobility recovery.

Statistical analysis: SPSS ® 20.0 statistical package was used. For the analysis of quantitative descriptive variables, averages were used; while for qualitative variables, percentages and frequencies were used. To contrast the quantitative variables, paired T-test was used; while for qualitative variables, the chi [2] test was used. The level of significance used was 95% (p<0.05).

Results

A total of 91 patients were recruited for this non-randomized quasi-experimental multicenter-control-trial. 81 patients corresponded to Santísima Trinidad's General Foundation Hospital and 10 patients corresponded to Santa Cristina's University Hospital. The most common affected tendons were those from the rotator cuff (n=74, 82%). The supraspinatus tendon was the most affected (n=65, 91.5%), followed by the subscapularis tendon (n=9, 8.5%). The second most common affected tendons were gluteus medium and gluteus minimum at the hip (n=9, 10%). The third affected tendon was Achilles (n=3; 3%). CT at the elbow (triceps tendon) and at the wrist showed similar frequencies (n=2; 2%). Finally, CT of the quadriceps tendon inserted at the patella was the most uncommon (n=1; 1%) (Figure 2).

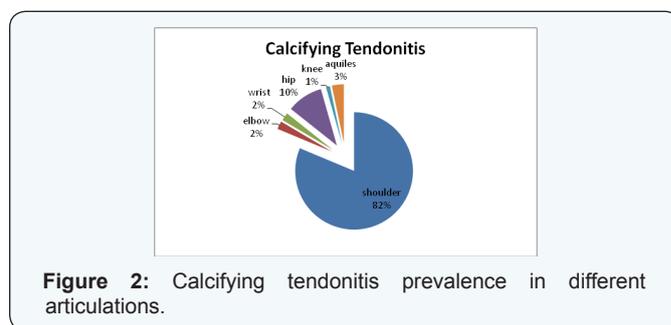


Figure 2: Calcifying tendonitis prevalence in different articulations.

The mean age of the sample was 55.08 ± 11.62 years. As for gender, women were more affected (n=64; 70%), than men (n=27; 30%). The mean time of pain in elbow, wrist, Achilles, knee, hip and shoulder CT were 2.5, 3.5, 4.7, 2, 11.1 and 5.1 months respectively. All patients received between 20-25 sessions of 2% Acetic Acid Iontophoresis and Ultrasound treatment. To be

more precise, in CT of the shoulder, elbow, wrist, hip, knee and Achilles, a total of 20.1, 25, 20, 23.8, 20 and 20 sessions were applied respectively (Table 1). Considering Pain as an outcome measure (measured by VAS), all of the patients diminished pain significantly. In CT of the elbow, pain decreased from 9.5 to 3 (p=0.0489). In CT of the wrist, pain diminished from 8 to 1.41

(p=0.0169). In CT of the Achilles tendon, pain reduced from 8 to 2.6 (p=0.0185). In CT of the knee, pain fall from 5 to 0 (p=0.0000). In CT of the hip, pain dropped from 7.3 to 1.8 (p=0.0020). In CT of the shoulder, pain lowered from 7.4 to 2.6 (p=0.0000) (Table 1).

Table 1: Change in Pain (measured by VAS) and in calcification (measured by radiographies) at the beginning and at the end of intervention (Acetic Acid Iontophoresis and Ultrasound).

Localization	Session	VAS-1	VAS-2	p	Rx-1	Rx-2	p
Elbow (n=2)	25	9,5±0,7	3±1,41	0,0489	11±1,41	2,5±3,54	0,0248
Wrist (n=2)	20	8±1,41	2,5±0,7	0,0169	10±7	5±2,83	0,3440
Achilles (n=3)	20	8±2,6	3±2,6	0,0185	7,6±2,8	5,3±1,41	0,3356
Knee (n=1)	20	5±0	0±0	0,0000	8±0	0±0	0,0000
Hip (n=9)	23,8	7,3±1,8	2,8±1,9	0,0020	10,3±6.8	5,3±3,3	0,0488
Shoulder (n=74)	20,1	7,4±1,3	2,6±1,9	0,0000	9,6±6,2	3,5±4,3	0,0000

With regard to the change in millimeters (mm) of the calcification, all of the patients showed a decrease in the size of calcification, although only significant for elbow, knee, hip and shoulder CT. The radiological change in wrist and Achilles CT was not significant. In CT of the elbow, calcification decreased from 11 to 2.5 mm (p=0.0248). In CT of the wrist, calcification diminished from 10 to 5 mm (p=0.3440). In CT of the Achilles tendon, calcification reduced from 7.6 to 5.3 mm (p=0.3356). In CT of the knee, calcification fall from 8 to 0 mm (p=0.0000). In CT of the hip, calcification dropped from 10.3 to 5.3 mm (p=0.0488). In CT of the shoulder, calcification lowered from 9.6 to 3.5 mm (p=0.0000) (Table 1).

When the radiological change is considered as a measure of success rate, in three possible scenarios:

- i. Cured (if calcification disappeared or diminishes more than 75%),
- ii. Improved/diminished (if calcification reduced size between 25-75%) and
- iii. Failure/the same (if calcification reduced less than 25%); a total of 48% of patients were cured (n=44); 30% of patients diminished calcification (n=27) and 22% of patients failed (n=20) (Figure 3).

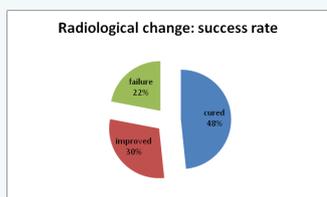


Figure 3: Radiological change in calcification as a measure of success rate, after intervention (Acetic Acid Iontophoresis and Ultrasound).

Cured: calcification size disappeared or diminished more than 75%,
 Improved: calcification size diminished between 25-75%
 Failure: Calcification diminished less than 25% or not disappeared at all.

If the radiological changes on different CT tendons are analyzed, the results in success rate are quite similar (Figure 4). If we considered only two variables:

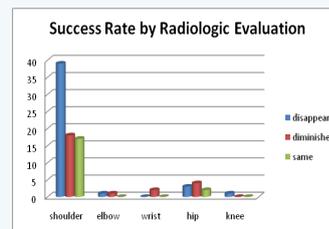


Figure 4: Radiological change in calcification as a measure of success rate, after intervention (Acetic Acid Iontophoresis and Ultrasound) considering three possible scenarios (disappear/diminished/same) in the different tendons.

Disappear/cured: calcification size disappeared or diminished more than 75%
 Diminished/improved: calcification size diminished between 25-75%
 Failure/the same: Calcification diminished less than 25% or not disappeared at all.

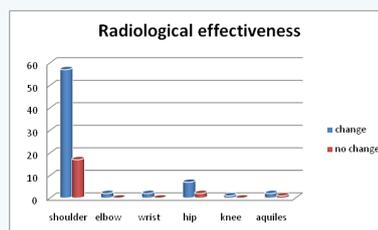


Figure 5: Radiological change in calcification as a measure of success rate, after intervention (Acetic Acid Iontophoresis and Ultrasound) considering change/not change as two scenarios in the different tendons.

Change: calcification size diminished more than 25%
 No change: Calcification diminished less than 25% or not disappeared at all.

- a) The change in radiological calcification (calcification size reduction greater than 25%) or

b) Not change (calcification size reduction lower than 25% or not reduction at all); 5% Acetic Acid Iontophoresis was capable to produce a change in CT in all of tendons treated (Figure 5).

Discussion

The use of Acetic Acid Iontophoresis with or without Ultrasound in the treatment of CT (mainly CT of the shoulder) is been for years the most frequently applied therapeutic modality in Rehabilitation Wards. However, there is a paucity of studies that support its use [7,10,11]; even, there are other classic and conflicting studies (Perrón, Leduc) [13,14]. To the best of authors' knowledge, this is the first study that supports the use of Acetic Acid Iontophoresis and continuous Ultrasound in the treatment of CT of the shoulder and other tendons (elbow, wrist, hip, knee and ankle), with demonstrable scientific evidence and with a sample number higher than those previous studies [7,10-14].

CT is a common, painful, disabling disease, which produces great socio economic impact [16], great demand and high use of resources [17] and labor absenteeism [8], being pain the leading cause of disability due to loss of mobility [8]. In this study, 9.8% of patients (n = 9) had limited mobility. Some authors argue that pain could remain in 50% of cases up to a year after onset [14], while others claim that CT could evolve spontaneously toward healing between 3 and 10 year [18]; this fact worsens patients' quality of life in their personal, family and work aspects [8]. CT is common in middle-aged working patients (between 30-50 years) [7,8,16], as it was in the present trial (55 years). CT is more common in women [8,16,19-21], including our study (n=64, 70%). The presences of CT on other articulations different from the shoulder are rare. Only a few case reports make note of these infrequent presentation (CT at the hip and at Achilles tendon). To date, there are neither reports on prevalence nor clinical outcomes on CT of the wrist, elbow or patella (Figure 6).

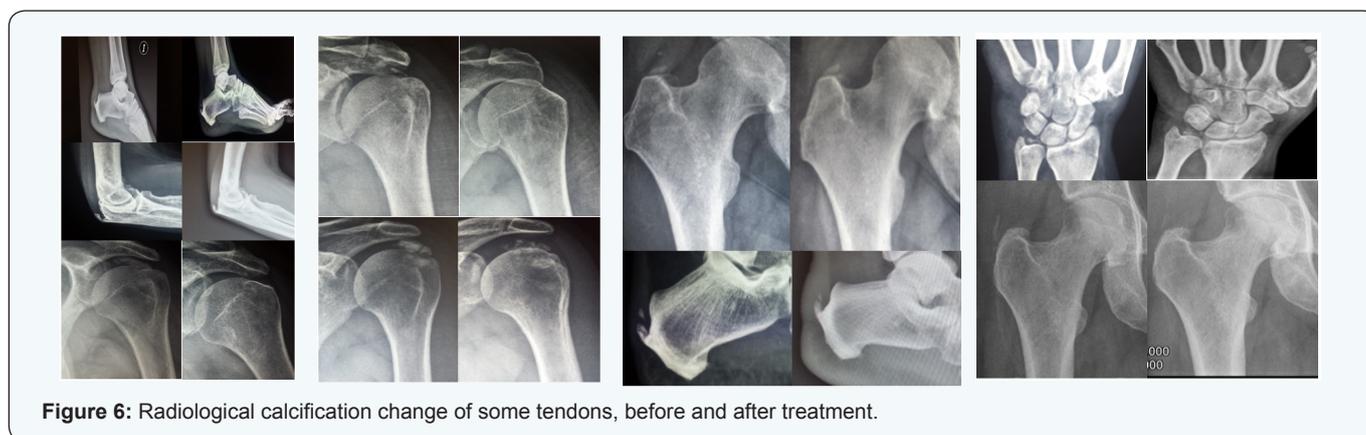


Figure 6: Radiological calcification change of some tendons, before and after treatment.

Calcific tendinopathy involves the substance of the tendon and is particularly common in the rotator cuff (shoulder) [5]; whereas insertional calcific tendinopathy involves the deposit of calcium at the enthesis, affecting predominantly the Achilles tendon, the common extensor tendon at the elbow, the gluteus medium and minimum at the greater trochanter and the patellar tendon [5]. Indeed, most of CT occurs at the insertion of the tendon, and it is related to the degree of force transmitted to the tendon [4]. CT is related to a degenerative change, which is commonly seen in the Achilles, the rotator cuff, the patella and the extensor carpi radialis brevis (tennis elbow) [4]. The location of tendons affected by CT in decreasing order of frequency includes the shoulder, hip, elbow, wrist and knee [1]. This totally coincides with the prevalence of the present trial.

In the case of CT of the shoulder, the supraspinatus tendon is the most affected, followed by infraspinatus and subscapularis tendon [8,10,20,22,23]. In our trial supraspinatus and subscapularis were the affected tendons of the rotator cuff, this coincides with previous similar studies [7,8,23]. The radiological diagnosis of CT is made by radiography or ultrasound. MRI is only indicated in cases of suspected association with muscle/

tendonpathology [7,8]. The various radiological classifications agree that the type I corresponds to located deposits, well-defined contours, dense texture and homogeneous consistency; whereas type II corresponds to scattered deposits, not-well-defined contours, cloudy consistency and heterogeneous texture [10]. This radiological characterization is important because type II (resorptive) has a better prognosis than type I (formative) [8].

CT treatment is controversial. A recent article has demonstrated the effectiveness of different Rehabilitation techniques to reduce pain but not the calcification on shoulder CT [8]. Until now, the only option used in the treatment of calcification was acetic acid iontophoresis. However, there are only three classic studies that assess their effectiveness; one favorably (Rioja-Toro) [11], and two unfavorably (Perrón and Leduc) [14,15]. In fact, Leduc and Perrón stated that acetic acid iontophoresis produced neither relief in pain nor decreased in calcification size. Recently, two different studies, conducted by Chico-Alvarez and Fernández-Cuadros have demonstrated that Acetic Acid Iontophoresis produced relief in pain and decreased in calcification size in CT of the shoulder [7,10]. However, to the

best of our knowledge, there are only some case reports on the effectiveness of this treatment on CT in gluteus medius and minimum tendon [24] and in Achilles tendon [25], with promising results. Meanwhile, there is no report on the effectiveness on elbow, wrist or knee CT. There subsides the importance of this multicenter non-randomized before-and-after control trial.

Iontophoresis is a noninvasive technique that increases the penetration of transdermal substances (drugs) through the skin layers (epidermis, dermis and hypodermis) in a controlled manner and with the help of the application of electric current, based on physical-chemical principles of attraction and repulsion of charges [26]. Its most common applications are: 1) calcifying tendinitis and 2) myositis ossificans (with acetic acid as a therapeutic agent) [27]. This technique is cheap because of the economic use of topical medications and because the electrotherapy equipment has decreased in size and has become more accessible due to low-production-costs [28].

The application of Ultrasound to the skin increases its permeability and facilitates diffusion of different drugs/substances into the skin. This transport is called sonophoresis [29]. Low frequency sonophoresis works synergistically with iontophoresis; Le et al. [30] used Ultrasound 10 minutes prior to the application of iontophoresis with good results. Psaki and Carrol (in 1955) [14,15,31] introduced acetic acid iontophoresis as an effective treatment in shoulder CT. Kahn [31] postulated that insoluble calcium carbonate precipitates could become soluble salts of calcium acetate, which could favor the reabsorption of the calcification: $\text{CaCO}_3 + 2\text{H}(\text{CaH}_3\text{O}_2)_2 = \text{Ca}(\text{C}_2\text{H}_3\text{O}_2)_2 + \text{H}_2\text{O} + \text{CO}_2$. Furthermore, the use of ultrasound for their mechanical and thermal effects could help disintegrate and reabsorb calcification due to increase in local vascularization [11].

The proposed study protocol (2cc of 5% acetic acid Iontophoresis at 4.7mA x 10 minutes, followed by continuous ultrasound 1W/cm²/1MHz x 5 minutes) [7] differs from those of Rioja-Toro [11] (3cc of 5% acetic acid iontophoresis for 20min at 4.7mA plus ultrasound 1.5W/cm²), Perron [12] (5% acetic acid iontophoresis (not specified amount) at 5mA x 20 minutes followed by ultrasound 0.8W/cm² x 5 minutes), Leduc [13] (5% acetic acid iontophoresis, 20cc at 5mA x 15-20 minutes without ultrasound) and Chico-Alvarez (5% acetic acid iontophoresis (not specified amount) at 4.7mA for 20 minutes without ultrasound) [1].

The average number of sessions in our series was 20 (from 10 to a maximum of 40 sessions). The criterion to continue or discontinue treatment was the radiological evolution. Perrón treated his patients for 9 sessions (3 sessions / week for 3 weeks) [12]. Leduc treated them for 10 sessions (3/week the first two weeks, and then weekly for 4 weeks) [13]. Rioja-Toro treated his patients for 40 sessions (5 times a week) and evaluated them

at 20 and at 40 sessions [11]. Chico-Alvarez treated his patients between 15 and 30 sessions depending on the radiological evolution (5 times a week) [10]. The failure from the protocols of Perrón and Leduc were probably because 9 and 10 sessions were insufficient to get the desired goals (to reduce pain and calcification size). That would explain why Rioja-Toro, Chico-Alvarez and Fernández-Cuadros have gotten such a success in their studies (the greater the sessions, the better success).

To the best of our knowledge, the present study supports the highest number of patients published up-to-date. The importance lies in the difficulty of prospectively collect such a number of patients. Perrón [12] studied 21 patients; Leduc [13] 36 patients, Rioja-Toro [11] recruited 34 patients; Chico-Álvarez [10] studied 25 patients for each control group, and Fernández-Cuadros 44 patients [7]. We recruited 91 patients in a two years prospective study (28 months). The present study has demonstrated that Acetic Acid Iontophoresis is effective in diminishing pain and size of calcification not only in CT of the shoulder (as Fernández-Cuadros [7] and Chico-Alvarez stated) [10], but for the first time in CT of other articulations (elbow, wrist, hip, knee and ankle). This find is in accordance with a recent Systematic Review and a Meta-Analysis, which sustains that Iontophoresis is effective in the treatment of pain for musculoskeletal disorders [32].

Methodologically, a quasi-experimental before and after study (or Non-Randomized Control Trial) is considered an intervention intended to evaluate the impact of an intervention. It is more simple and cheaper than a Clinical Trial. It is the only way to perform a study when ethical problems or feasibility to perform randomization come to light. This pretest-posttest design is considered "intra-subject" study, there is only one group, and therefore the observations are made before and after the intervention. No randomization is feasible since only a group is studied. However, as this is an experimental study, it gives a good level of based-evidence. The Canadian Task Force on Preventive Health Care gives this studies an II-1 level of evidence [33,34].

Study Limitations

An important limitation of the study is the absence of control group. This is mainly due to the limited number of cases. In fact, 28 months-follow-up was needed to collect such a sample. As the effectiveness of acetic acid Iontophoresis on CT is for decades recommended, and all patients accepted the treatment, it was not ethical to deny the intervention. A quasi-experimental before and after intervention study (also referred to as a non-randomized control trial) is applied in this specific situation, to solve the lack of control group, and to give clinical based evidence. We encourage researchers to conduct studies like ours to reproduce our findings, and to increase consistency and demonstrable clinical-based-evidence, given the encouraging results observed in this study.

Conclusion

CT is more common in middle-aged women. It affects insertional tendons at different articulation sites. Iontophoresis with 5% Acetic Acid and Ultrasound is a safe, simple and inexpensive technique capable to reduce pain and calcification on the shoulder, elbow, wrist, hip, knee and ankle. This study shows a level of evidence II-1 and grade of recommendation B that allows us to postulate Acetic Acid Iontophoresis and Ultrasound as an effective treatment in CT.

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Conflict of interest

The authors declare no conflict of interest. We certify that no party having a direct interest in the results of the research supporting this article has or will confer a benefit on us or on any organization with which we are associated AND, if applicable, we certify that all financial and material support for this research (eg, NIH or NHS grants) and work are clearly identified in the title page of the manuscript. The legal/regulatory status of the device(s) that is/are subject of this manuscript is/are not known by the author(s).

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