Efficacy of hypertonic dextrose infiltrations for pain control in rotator cuff tendinopathy: systematic review and meta-analysis

Arias-Vázquez PI[1], Tovilla-Zárate CA[1], González-Graniel K[1], Burad-Fonz W[2], González-Castro TB[3], López-Narváez ML[4], Castillo-Avila RG[5], Arcila-Novelo R[6]

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ABSTRACT

Introduction. Our study aimed to assess the efficacy of hypertonic dextrose infiltrations (HDI) for pain control in individuals with rotator cuff tendinopathy and to assess the characteristics of the treatment and the presence of side effects or adverse reactions through a systematic review and meta-analysis.

Methods. The search for the articles was performed in the electronic databases PUBMED, EMBASE, SCOPUS, SCIELO, DIALNET and Google Scholar, published up to August 2020. The keywords used were "prolotherapy" or "proliferation therapy" or "hypertonic dextrose infiltrations" or "hypertonic dextrose injection" and "Rotator Cuff" or "Rotator Cuff Injury" or "Rotator Cuff Tear" or "Rotator Cuff Tendinosis" or "supraspinatus". The effectiveness of HDI was expressed as standardized mean difference (*d*) and 95% CI.

Results. In the pooled analysis, HDI were an effective intervention to reduce long-term pain in patients with rotator cuff tendinopathy when compared to controls; furthermore, in the individual analyses, HDI were more effective in the short, medium and long terms than non-invasive treatments, and more effective in the long-term than infiltrations with local anesthetics. On the other hand, HDI were not more effective than injections with corticosteroids or PRP. Finally, no complications or serious adverse events were observed when HDI were used.

Conclusions. We found that HDI reduced long term pain in individuals with rotator cuff. HDI could be an alternative to non-invasive treatments when no favorable results can be achieved. However, due to the small number of studies included in this meta-analysis, new studies are necessary to clarify the efficacy and safety of this intervention.

Keywords: Hypertonic dextrose; Prolotherapy; Infiltrations; Shoulder; Cuff rotator.

1. División Académica Multidisciplinaria de Comalcalco, Comalcalco, Tabasco, México; Universidad Juárez Autónoma de Tabasco
2. Centro Médico Olympia, Cancún, México
3. Universidad Juárez Autónoma de Tabasco, División Académica de Ciencias de la Salud, Villahermosa, Tabasco, México; División Académica Multidisciplinaria de Jalpa de Méndez, Jalpa de Méndez, Tabasco, México
4. Hospital General de Yajalón, Secretaría de Salud. Yajalón, Chiapas, México
5. División Académica de Ciencias de la Salud, Villahermosa, Tabasco, México; Universidad Juárez Autónoma de Tabasco;
6. Universidad Autónoma de Yucatán, Mérida Yucatán, México

INTRODUCTION

The pathology of the rotator cuff has been considered as the main cause of pain and disability of the shoulder[1]. The prevalence of injuries of the rotator cuff tendons ranges from 6% to 30%, increasing progressively with age[1]. For the treatment of this pathology conservative modalities are commonly used including anti-inflammatory drugs[2], physical therapeutic modalities [(3)], exercise programs [(4)], intra-articular and subacromial infiltrations[5, 6] and surgical procedures[7, 8].

Regarding the different infiltration treatments, the most widely used is the application of corticosteroids[5]. Other infiltrations include the use of plasma rich in platelets (PRP)[5,6,9], hyaluronic acid[5, 10], hypertonic dextrose[5, 6], botulinum toxin[5], mesenchymal cells of bone marrow[6, 11] and a mixture of oxygen - medicinal ozone[12].

On the other hand, injection therapy with sclerosing agents or irritant substances has been used for decades as a complementary treatment for chronic musculoskeletal conditions. Dr. George Hackett defined the term prolotherapy in the 1950s[13, 14]; this term involves injections of a solution with sclerosing agents or irri-

tating properties in the ligament-bone or tendon-bone areas or the intra-articular space, performed repeatedly at established intervals[13, 14]. The most common prolotherapy agent used in the clinical practice is the hypertonic dextrose solution at concentrations ranging from 12.5% to 25%, applied as intra-articular and/or extra-articular infiltrations on ligament and tendon insertions, to favor the repair processes of the affected tissues[13, 14]. Hypertonic dextrose prolotherapy has been reported to be effective for treating knee osteoarthritis where it has been reported to be more effective than infiltrations with local anesthetics, as effective as infiltrations with hyaluronic acid, ozone or radiofrequency, and less effective than PRP without side effects[15]. When used for treating tendinopathies of the lower limb it has been reported to be a safe and effective treatment for Achilles tendinopathy, plantar fasciitis and Osgood-Schlatter disease[16, 17]. When hypertonic dextrose has been used for treating upper limb pathologies such as hand osteoarthritis, lateral epicondylitis and rotator cuff disease, clinical studies have reported positive results without side effects[17, 18]. However, HDI remains a controversial therapy for treating rotator cuff tendinopathy and it is classified as a complementary therapy. Therefore, the objective of our study was to perform a systematic search of clinical studies that used HDI in patients with rotator cuff pathology, to analyze its efficacy in pain control, the characteristics of the treatment and the presence of side effects or adverse reactions through a meta-analysis.

METHODOLOGY

The methodology used was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[19] for the presentation of systematic review and meta-analysis.

METHODS AND SEARCH STRATEGY

Articles of interest were identified in electronic databases using a search period up to August 2020. The databases used were PUBMED, EMBASE, SCOPUS, SCIELO, DIALNET and gray literature as Google Scholar. The search terminology included the MESH terms (and entry terms) "prolotherapy" or “proliferation therapy” or "hypertonic dextrose infiltrations" or "hypertonic dextrose injection" and "rotator cuff" or "rotator cuff injury" or “rotator cuff tear” or “rotator cuff tendinosis” or "supraspinatus", as well as multiple combinations between these terms.

The search of eligible studies was performed without language restrictions. After searching in the databases above mentioned, a hand search of the reference list in the articles and reviews was conducted to find additional eligible studies.

TYPES OF STUDIES

This review included randomized controlled trials (RCTs) and observational studies (cases-controls, series of cases) that used HDI as a therapeutic intervention for the treatment of pain in individuals with rotator cuff tendinopathy. In the RCTs HDI were compared against physiotherapy, exercise programs or against other infiltrations (placebo or other therapeutic substances). We excluded reviews, one-case reports, studies of shoulder pathologies other than rotator cuff tendinopathy or unspecified pathologies. The studies selected had to describe in detail the interventions carried out, forms of evaluation and their results.

PARTICIPANTS

The selected studies included patients with rotator cuff tendinopathy and met the following criteria:

- Adults of at least 18 years of age.
- Clinical and imaging (ultrasonography or magnetic resonance imaging) diagnosis of rotator cuff tendinopathy (tendinosis, partial tear or full-thickness tear).
- Presence of pain and functional alterations of more than 3 months of evolution.
- Participants treated with HDI and compared with other interventions.

TYPE OF INTERVENTIONS

The selected studies included patients with rotator cuff tendinopathy who were treated with HDI and compared with other interventions.

The criteria for the type of interventions used in the patients of study groups were:

- One or more treatment sessions with HDI (at a concentration greater than 10%).
- The infiltrations applied in the rotator cuff tendons insertion and/or intratendinous application in the focal area in case of rupture and/or in subacromial or intra-articular space.
- The infiltrations performed following the anatomical technique or under ultrasound guidance.
- Patients in the control groups were treated with physiotherapy, exercise programs or infiltrations of other substances.

- Co-interventions were allowed as long as they were uniform in all groups.

EVALUATION OF THE RISK OF BIAS AND THE METHODOLOGICAL QUALITY OF THE INCLUDED STUDIES

Two researchers independently assessed the methodological quality and risk of bias of each included study. The evaluation of the clinical trials was based on the Cochrane Handbook for Systematic Reviews recommendations, version 5.1[20]. The assessment of the risk of bias in non-randomized observational studies was performed using the ROBINS-I tool[21]. The rating of the level of evidence for therapeutic studies was determined for each study using the scale of the American Society of Surgeons[22].

EVALUATION OF ELIGIBILITY AND DATA EXTRACTION

Two researchers independently examined titles, abstracts and full texts, then determined the eligibility of each study. Disagreements were solved by consensus through the opinion of a third researcher. For eligible studies, data were extracted independently and included: study design, risk of bias, clinical configuration, characteristics of the participants, characteristics of the interventions, results, duration of follow-up and adverse events.

The efficacy of HDI in pain control was established as the primary endpoint. Pain control was measured by the visual analog scale (VAS) and was included in the quantitative analysis.

The evaluation of the improvement in function, the characteristics of the treatment and the adverse effects were established as secondary endpoints and were described in the qualitative analysis according to the data provided in the included studies. Improvement in function was measured in terms of validated function scales such as Shoulder Pain and Disability Index (SPADI), American Shoulder and Elbow Surgeons Standardized (ASES) and Disability of Arm and Shoulder Score (DASH).

The follow-up time was evaluated in the short (≤ 6 weeks), medium (12 weeks) and long terms (≤ 24 weeks).

STATISTICAL ANALYSIS

For the evaluation of RCTs, studies were grouped according to the follow-up time. The effectiveness of HDI in control pain were expressed as standardized mean difference (d) and 95% CI. The standardized mean difference was calculated comparing the study group versus (vs.) the comparison group. Heterogeneity across studies was measured using Q statistic and inconsistence index I2. When p (Q) was <0.10, the presence of heterogeneity was considered. When I2 > 50% large heterogeneity was determined; when I2 = 25-50% moderate heterogeneity was considered, and when I2 < 25% absence of heterogeneity was determined. The publication bias was evaluated by Begg's funnel plots graphically and Egger's test quantitatively. For Begg's funnel plots an asymmetry was considered as a significant presence of bias. For the Egger's test, the significance was fixed as p <0.05. The meta-analysis was performed using EPIDAT 3.1 Software.

To evaluate the characteristics of the treatment and adverse effects, they were summarized in descriptive measures, according to the data provided in the included studies.

RESULTS

A total of 116 citations were identified and 63 duplicates were excluded. Titles and abstracts of the remaining 53 studies were read; then, 24 studies that contained animal models, other tendinopathies, editorials, comments and others were also excluded. Of the 29 remaining studies, 21 were additionally excluded for the following reasons: review studies (n = 16), studies of shoulder pathologies other than rotator cuff tendinopathy (n = 3), as well as one-case reports (n = 2). Finally, six clinical trials [23-28] and two observational studies[29,30] were eligible for inclusion in this systematic review. The flowchart of the systematized search is shown in Figure 1.

The final six RCTs selected included 157 individuals with rotator cuff tendinopathy treated with HDI, performed in the tendon insertion area or in the focal area of rupture of the rotator cuff tendons and/or in subacromial or intra-articular space, while 236 controls were treated with exercise programs or infiltrations with corticosteroids, lidocaine, platelet-rich plasma or saline solution. Regarding the observational studies, 78 individuals with rotator cuff tendinopathy were treated with HDI performed with the same characteristics, using 53 controls.

Of the RCTs included in the qualitative analysis, two studies showed a low risk of bias[23, 26], three had a moderate risk of bias[24,25,27] and one of them showed a high risk of bias[28]. The two observational studies included in the qualitative analysis showed a moderate

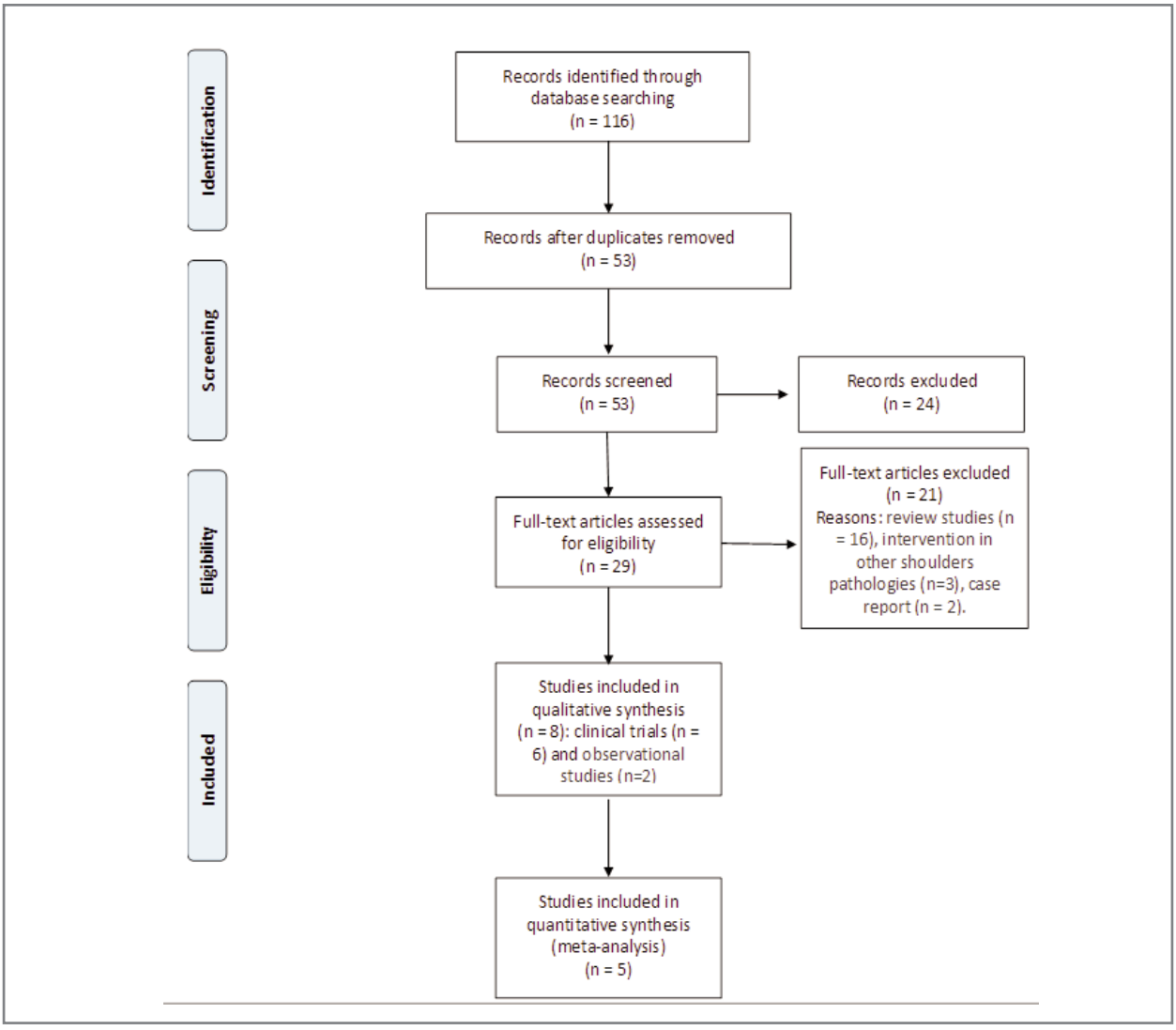

FIGURE 1. Flow diagram of the systematic review

risk of bias[29,30]. Only RCTs with low or moderate risk of bias were included in our quantitative analysis. The design characteristics and the risk of bias assessment of the included studies are summarized in Table I, Figure 2 and Figure 3.

In the five RCTs included in the quantitative analysis[23-27], all the groups studied were treated uniformly with an exercise program as a co-intervention. Similarly, in these studies the use of NSAIDs during treatment or follow-up was restricted; the use of analgesics such as acetaminophen or tramadol was allowed in case of post-infiltration pain.

The characteristics of the intervention and results of each study included are reported in Table II and III.

META-ANALYSIS OF THE EFFICACY OF INFILTRATIONS WITH HYPERTONIC DEXTROSE FOR PAIN CONTROL IN ROTATOR CUFF PATHOLOGY

In the five clinical trials included in this meta-analysis[23-27], the treatment with HDI was compared with other interventions such as infiltration with local anesthetics[23,27], exercise programs[24], infiltration with corticosteroids[25, 27], infiltration with saline solution[26] and infiltrations with platelet-rich plasma[27]. The meta-analysis was performed by time of follow-up and expressed it in terms of standardized mean difference.

Short–term follow-up: In the pooled analysis, no statistically significant difference in pain reduction was found when comparing HDI vs. controls (d = -0.045,

TABLE I. CHARACTERISTICS OF THE STUDY DESIGN

Author	Year	Sample size	Study Design	Allocation	Blinding	Level Evidence
Bertrand et al. (23)	2016	47 patients with chronic tendinopathy of rotator cuff (tendinosis, partial tear or full-thickness tear) confirmed by ultrasonography , over 3 months evolution.	Experimental, Prospective, longitudinal, Clinical trial.	Randomized to 3 treatment groups.	Blinding of participants, personnel who applied the treatment and the evaluation of the results was performed.	I
Seven et al. (24)	2017	120 patients with chronic tendinopathy of rotator cuff (tendinosis or partial tear) confirmed by magnetic resonance imaging and ultrasonography, over 6 months evolution.	Experimental, Prospective, longitudinal, Clinical trial.	Randomized to 2 treatment groups.	Blinding of and the evaluation of the results was performed. Blinding of the personnel who applied the treatment and of the participants is not possible given the difference between the types of intervention.	II
Cole et al. (25)	2018	36 patients with chronic tendinopathy of the supraspinatus (tendinosis or partial tear <50%) confirmed by ultrasound, over 3 months of evolution.	Experimental, Prospective, longitudinal, Clinical trial.	Randomized to 2 treatment groups.	Blinding of participants and the evaluation of the results was performed.	II
Lin et al. (26)	2018	31 patients with chronic supraspinatus tendinopathy (tendinosis or partial tear), confirmed by ultrasound, over 6 months evolution.	Experimental, Prospective, longitudinal, Clinical trial.	Randomized to 2 treatment groups.	Blinding of participants, personnel who applied the treatment and the evaluation of the results was performed.	I
Sari et al. (27)	2019	120 patients with chronic tendinopathy of rotator cuff (tendinosis or grade I partial tear), confirmed by magnetic resonance imaging, greater than 3 months of evolution.	Experimental, Prospective, longitudinal, Clinical trial.	Randomized to 4 treatment groups.	Blinding of participants and personnel who applied the treatment.	II
George et al. (28)	2018	12 patients with tendinopathy of supraspinatus tendinosis or partial tear) confirmed with ultrasound, with symptoms greater than 6 months of evolution.	Experimental, Prospective, longitudinal, Clinical trial.	Randomized to 2 treatment groups.	It was not reported whether the Blinding of participants, personnel and the evaluation of the results was performed.	III
Lee et al. (29)	2015	110 patients with chronic tendinopathy of rotator cuff (tendinosis, partial tear or full-thickness tear), confirmed by ultrasonography or magnetic resonance imaging, over 3 months evolution.	Observational, Retrospective Case-Controls study.	Not randomized.	Not Blinding.	III
Trebinjac et al. (30)	2015	21 patients with chronic tendinopathy (tendinosis, partial tear or full-thickness tear) of rotator cuff, confirmed by magnetic resonance imaging, over 6 months evolution.	Observational Retrospective Case records study.	Not randomized.	Not Blinding.	IV

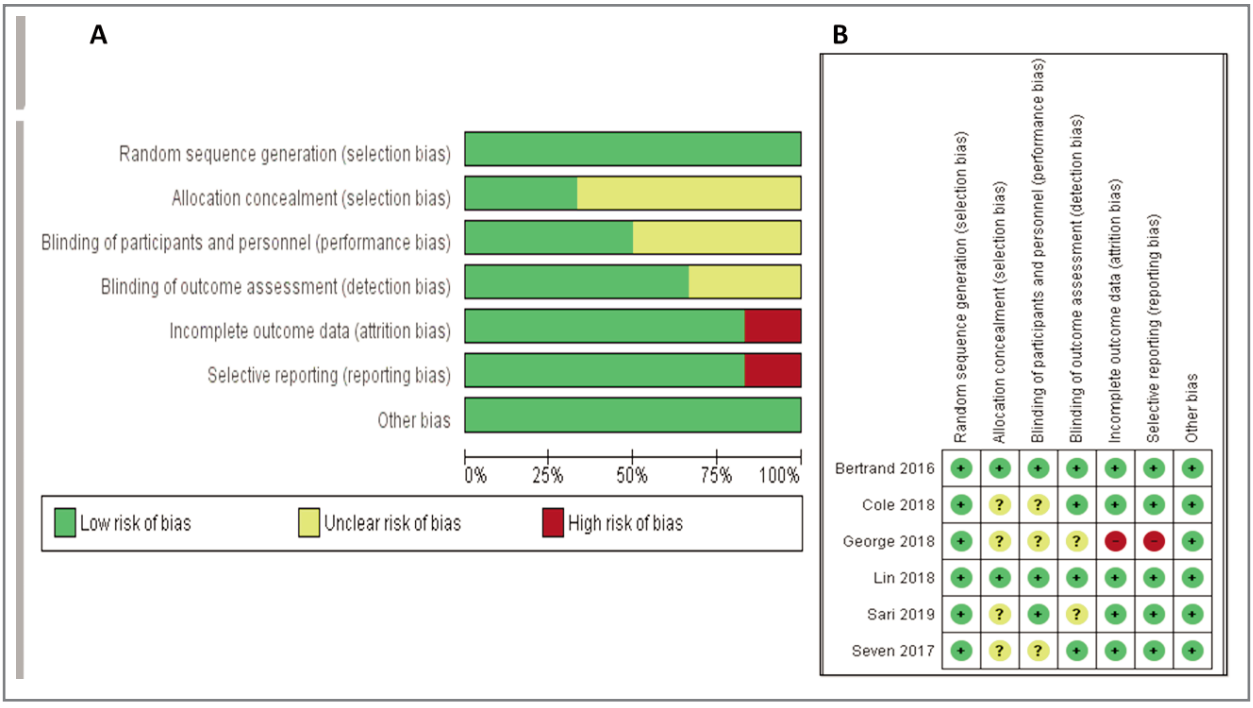

FIGURE 2. Risk of bias graph of the clinical trials included in the systematic review

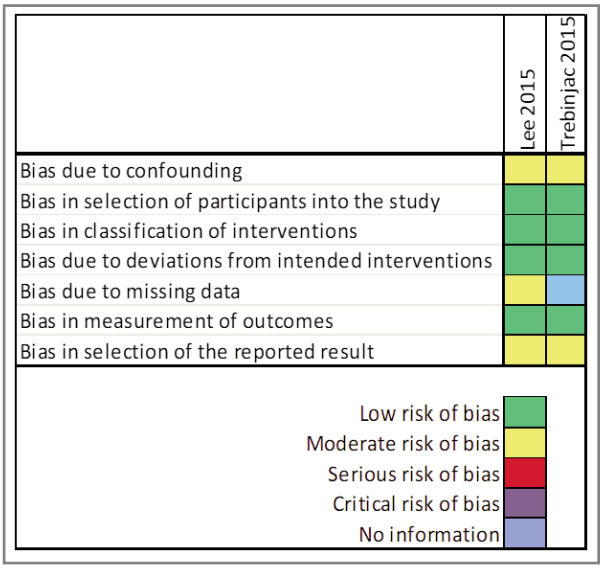

FIGURE 3. Risk of bias assessment of the observational studies included in the systematic review

95% CI -0.712 to 0.622, p (z)>0.896, I^2=89.22). However, in individual analyses, statistically significant differences were found: in the study by Seven *et al.*[24], a mean difference was found in favor of the HDI group when compared with exercise programs. Similarly, in the study by Cole *et al.*[25] a mean difference was found in favor of the HDI group when compared with corticosteroid infiltrations. On the other hand, in the study by Sari *et al.*[27], the mean difference was in favor of corticosteroid infiltrations (Figure 4A).

Medium–term follow-up: In the pooled analysis, no statistically significant difference in pain reduction was found when comparing HDI *vs.* controls (d = -0.009, 95% CI -0.448 to 0.430, p(z)>0.968, I^2=80.32). In individual analyses, responses similar to those found in short–terms were observed. In the Seven *et al.*[24] and Cole *et al.*[25] studies, the mean differences were found in favor of the HDI groups, while in the study by Sari *et al.*[27] the observations were in favor of the group who received corticosteroid infiltrations (Figure 4B).

Long–term follow-up: In the pooled analysis, the results showed that HDI had a significant effect on reducing pain in individuals with rotator cuff pathology (*d* = -2.810, 95% CI -4.468 to -1.153, p <0.001, I^2=97.86). In individual analyses, the mean difference was found in favor of the groups that used HDI in the studies of Seven *et al.*[24] and Bertrand *et al.*[23]. None of the studies found a mean difference that favored the control groups (Figure 4C).

TABLE II. CHARACTERISTICS OF INTERVENTIONS, EVALUATIONS, RESULTS AND SIDE EFFECTS

<table>
<tr><th>Study</th><th>Intervention</th><th>Evaluations and results</th><th>Side effects</th></tr>
<tr><td>Bertrand et al. (23)</td><td>DX GROUP: 27 patients (average age 53.8 years). Treated with 3 sessions of multi injections with 25% dextrose to the insertion of tendons of the rotator cuff, at monthly intervals + exercise program.
ALD GROUP: 20 patients, average age 51.1 years, treated with 3 sessions of injections with lidocaine/solution saline in the insertion of tendons rotator handle + exercise program.
ALS GROUP: 27 patients, average age 49 years, treated with 3 sessions of subcutaneous injections with lidocaine/solution saline + exercise program.</td><td>The primary evaluations were pain in the shoulder with the VAS at the beginning, 12 and 36 weeks of follow-up.
VAS
DX / ALD / ALS
Basal: 7.3 (0.4) / 6.9 (0.5) / 6.9(0.4)
12 weeks: -3.0(0.51) / -2.7(0.7) / - 2.7(0.6)
36 weeks: -2.9(0.6) / -1.8(0.7) / -1.3(0.6)</td><td>Pain was reported during and after injection as only side effects or adverse reactions.</td></tr>
<tr><td>Seven et al. (24)</td><td>DX GROUP: 60 patients, average age 50.1 years, treated with 6 sessions of multi injections with hypertonic dextrose to the insertion of tendons of the rotator cuff, under ultrasound guidance + protocol of exercise at home.
EX GROUP: 60 patients, average age 46.3 years, treated with exercise program.</td><td>They evaluated pain in the shoulder measured with VAS and SPADI at the beginning, 6, 12, 48 weeks of follow-up.
VAS
DX / EX
Basal: 7.85 (1.29) / 7.36 (1.38)
6 weeks: 3.35 (1.67) / 4.39(1.92)
12 weeks: 2.35 (1.98) / 4.00 (2.11)
48 weeks: 0.89 (1.64) / 3.77(2.12)
SPADI
DX / EX
Basal: 74.76(18.54) / 68.62 (20.4)
6 weeks: 31.30(14.19) / 41.97(16.42)
12 weeks: 16.12(12.82) / 37.25(20.32)
48 weeks: 7.66(10.68) / 34.94(19.14)</td><td>Minor adverse reactions such as pain, inflammation and hypotension occurred.
No severe adverse reactions were reported in any patient.</td></tr>
<tr><td>Cole et al. (25)</td><td>DX GROUP: 17 patients, average age 51 years, treated with an injection in the hypoechoic or anechoic areas of the supraspinatus tendon (one injection), under ultrasound guidance, at a rate of 0.5ml per zone, of a 25% dextrose solution + exercise program.
CT GROUP : 19 patients, average age 46 years, treated with an infiltration in the subacromial bursa adjacent to the supraspinatus tendon, under ultrasound guidance, of 2ml of a combination of 40mg of methylprednisolone acetate and 1% lidocaine + exercise program.</td><td>Pain was assessed when performing activities above the head with a numerical scale from 0 to 4, at 6,12 and 24 weeks of follow-up.
PAIN
DX / CT
Basal: 2.3(0.2) / 2.6(0.2)
6 weeks: 2.1 (0.2) / 2.4(0.2)
12 weeks: .9(0.2) / 2.1 (0.3)
24 weeks: 1.7(0.2) / 1.7(0.3)</td><td>It is not mentioned if there were side effects or adverse reactions in patients.</td></tr>
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TABLE II. CONTINUATION

<table>
<tr><th>Study</th><th>Intervention</th><th>Evaluations and results</th><th>Side effects</th></tr>
<tr><td>Lin et al. (26)</td><td>DX GROUP: 16 patients, average age 46.2 years, treated with an injection of 5ml of 20% dextrose in the area of supraspinatus insertion, under ultrasound guidance, + exercise program.
SS GROUP: 15 patients, average age 48.6 years, treated with an infiltration of saline solution (SS) in the areas of supraspinatus insertion, under ultrasound guidance, + exercise program.</td><td>Pain was evaluated with VAS and SPADI, at the beginning, 2 and 6 weeks of follow-up.
PAIN
DX: Basal 5.56 (0.81); 2 weeks 4.63 (0.62); 6 weeks 5.13(0.72)
SS: Basal 5.33 (0.82); 2 weeks 5.21 (0.69); 6 weeks 4.87(0.64)
VAS
DX: Basal 60.50(7.87); 2 weeks 52.69 (10.05); 6 weeks 61.56 (4.58)
SS: Basal 65.00 (2.68); 2 weeks 62.27(12.82); 6 weeks 60.00(4.9)</td><td>Minor adverse reactions occurred.
No severe adverse reactions were reported in any patient.</td></tr>
<tr><td>Sari et al. (27)</td><td>DX GROUP: 30 patients, average age 52.1 years, treated with one subacromial injection with 5ml. of 20% dextrose under ultrasound guidance + protocol of exercise.
PRP GROUP: 30 patients, average age 52.1 years, treated with one subacromial injection with 5ml. of platelet-rich plasma under ultrasound guidance + protocol of exercise.
CT GROUP: 30 patients, average age 52.1 years, treated with one subacromial injection with 5ml. of triamcinolone acetónide (40mg) under ultrasound guidance + protocol of exercise.
AL GROUP: 30 patients, average age 52.1 years, treated with one subacromial injection with 5ml. of lidocaine and solution saline under ultrasound guidance + protocol of exercise at home.</td><td>Pain and Functionality was evaluated with VAS and ASES scale at the beginning and at 3,12,24 weeks of follow-up:
VAS
Basal: DX 5.9 (.88); PRP 5.63 (1); CT 5.63 (.93); AL 5.47 (.86)
3 weeks: DX 4.37 (1.16); PRP 4.83 (.95); CT 2.43 (1.81); AL 4.23 (1.48)
12 weeks: DX 4.27 (1.36); PRP 3.9 (.99); CT 3.53 (1.41); AL 3.87 (0.97)
24 weeks: DX 3.1 (1.52); PRP 2.57 (1.19); CT 3.77 (1.41); AL 3.2 (1.19)
ASES
Basal: DX 45 (9.4); PRP 46.2 (8.6); CT 40.1 (8.8); AL 47.2 (7.4)
3 weeks: DX 52.4 (11.2); PRP 46.1 (7.9); CT 60.7 (11.4); AL 55.6 (10.5)
12 weeks: DX 56.1 (9.6); PRP 55.7 (7.9); CT 58.1 (9.03); AL 58.8 (8.8)
24 weeks: DX 60.3 (11.4); PRP 63.8 (11.9); CT 55.6 (11); AL 60.2 (11.9)</td><td>It is not mentioned if there were side effects or adverse reactions in the patients treated.</td></tr>
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TABLE II. CONTINUATION

<table>
<tr><th>Study</th><th>Intervention</th><th>Evaluations and results</th><th>Side effects</th></tr>
<tr><td>George et al. (28)</td><td>DX group: 7 patients (mean age 60 years) treated with one dextrose injection (at 12.5%), just in the focal area of tendinosis or rupture under ultrasound guidance.
PH GROUP: 5 patients (mean age 58 years) treated with conventional physiotherapy.</td><td>Pain and Functionality was evaluated with subscore pain DASH and total score respectively, at the beginning and at 12 weeks of follow-up:
DASH subscore Pain
DX / PH
Basal: 3.29 / 3.20
12 weeks: 1.86 / 2.40
DASH total score
DX / PH
Basal: 60.14 / 56.86
12 weeks: 43.89 / 46.68</td><td>It is not mentioned if there were side effects or adverse reactions in the treated patients.</td></tr>
<tr><td>Lee et al. (29)</td><td>DX group: 57 patients; average age of 54.1 years, treated with 4 (3 - 8) dextrose infiltrations (10ml. at 16.5%) in supraspinatus and subscapular tendons, at intervals every 2 - 4 weeks.
CL Group: 53 patients, average age of 55.8 years who continued with the same conservativ treatment previously established.</td><td>Pain was evaluated with VAS and functionality with SPADI, before treatment and 48 weeks after the application of the same.
VAS
DX / CL
Basal: 6.3 (1.0) / 6.1 (1.2)
48 weeks: 2.7(1.0) / 4.6(1.4)
SPADI
DX / CL
Basal: 69.4(9.2) / 67.6(9.4)
48 weeks: 43.8 (11.6) / 51.1(14.4)</td><td>It is not mentioned if there were side effects or adverse reactions in the treated patients.</td></tr>
<tr><td>Trebinjac et al. (30)</td><td>21 patients; average age of 47.8 years, treated with 6 intra – articular dextrose injections, (6 ml at 25%) and extra - articular (1 ml per dextrose point at 15%), at monthly intervals.</td><td>Pain was evaluated with VAS and functionality with SPADI before treatment and 48 weeks after the application of the same.
VAS / SPADI
Basal: 8.14 (1.2) / 76.99 (13.6)
48 weeks: 2.29(2.8) / 20.84 (23.06)</td><td>It is not mentioned if there were side effects or adverse reactions in the treated patients.</td></tr>
</table>

Abbreviations: ALD = deep local anesthetics, ALS= subcutaneous local anesthetics, DX: dextrose, EX= Exercise, SS= solution saline, CT= corticosteroid, AL= local anesthetics, PRP= platelet-rich plasma, PH= Physiotherapy, CL= Control. SPADI = Shoulder Pain and Disability Index, VAS=Analog Visual Scale. ASES= American Shoulder and Elbow Surgeons Standardized, DASH: Disability of Arm and Shoulder Score.

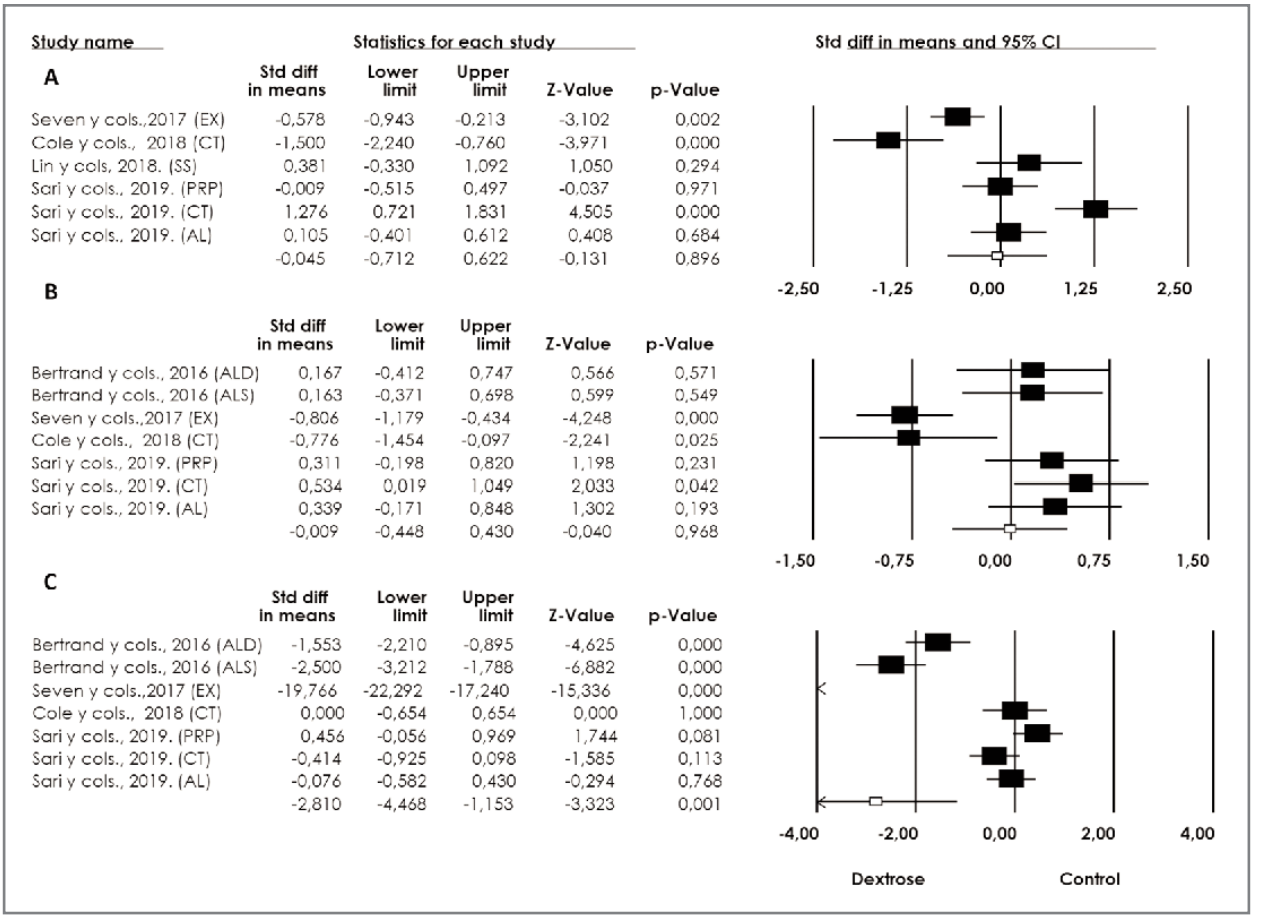

FIGURE 4. Forest plot: A) Short-term, B) Medium-term, C) Long-term.

REVIEW OF OBSERVATIONAL STUDIES

In the observational studies, Lee *et al.*[29] reported statistically significant reduction of pain and improvement of function in the HDI group compared with conservative treatments in long-term follow-up. Similarly, Trebinjac *et al.*[30] reported a series of cases treated with HDI with statically significant pain reduction and function improvement in the long-term.

CHARACTERISTICS AND DOSAGE OF HYPERTONIC DEXTROSE TREATMENT

Four studies[23,24,29,30] performed treatment schemes with multiple sessions and multi-injections in the insertion of the rotator cuff tendons; other studies[25,26,28] only used a single intratendinous application in the focal area of rupture under ultrasound guidance. Sari *et al.*[27] performed a single subacromial infiltration.

In the included studies, the number of sessions varied from 1 to 8 per participant, while the application frequency was every 2 to 4 weeks. On the other hand, the concentrations of dextrose used varied from 12.5 to 25%, with a mode of 25%.

ADVERSE REACTIONS AND SIDE EFFECTS

Three trials[23,24,26] where participants received HDI reported minor adverse reactions such as pain during or after application, inflammation after application and one study reported hypotension during treatment. The rest of the studies did not mention if there were adverse reactions.

DISCUSSION

EFFICACY OF INFILTRATIONS WITH HYPERTONIC DEXTROSE IN THE TREATMENT OF ROTATOR CUFF TENDINOPATHY

A recent review already evaluated the role of HDI in

TABLE III. SUMMARY OF THE CHARACTERISTICS AND PROPERTIES OF THE INFILTRATIONS USED FOR THE TREATMENT OF PATIENTS WITH ROTATOR CUFF TENDINOPATHY IN THE STUDIES INCLUDED IN THE REVIEW.

Treatment modalities	Mechanism of action	Effects on pain control	Adverse effects	Possible advantages	Possible disadvantages
Corticosteroid infiltration Lin MT et al. (5) Cole et al. (25) Sari et al. (27) Cook et al. (40) Ramírez et al. (41) Ji et al. (42)	Anti-inflammatory effect.	Short term.	Pain during application. Probable deleterious effects to the tendon if repeated infiltrations are carried out. Possibility of systemic side effects.	Usually the application scheme involves a single injection intra-articular or in the subacromial space.	Its application is limited to very few sessions to avoid adverse effects. Intratendinous application is not recommended.
Local anesthetic infiltration Bertrand et al. (23) Sari et al. (27) Caracas et al. (37) Cook et al. (40)	Inhibitor of nociceptive activity and slight anti-inflammatory effect.	Short term.	Pain during application.	It can be applied intra-articularly, in the subacromial space or in the enthesis of the tendon.	Possible effect only in the very short term.
Hypertonic dextrose infiltration Lin MT et al. (5) Bertrand et al. (23) Seven et al. (24) Cole et al. (25) Lin et al. (26) Sari et al. (27) George et al. (28) Lee et al. (29) Trebinjac et al. (30) Catapano et al. (31) Kin et al. (38) Ahn et al. (39) Pelt et al. (45)	Trophic effect on the tendon.	Long term.	Pain during and after application.	It can be applied intra-articularly, in the subacromial space, in the enthesis of the tendon or intratendinous. Multiple sessions can be applied, which could be useful in refractory cases.	The schemes applied involve multiple injections in the same session.

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TABLE III. CONTINUATION

Treatment modalities	Mechanism of action	Effects on pain control	Adverse effects	Possible advantages	Possible disadvantages
Platelet-rich plasma infiltration Lin MT et al. (5) Chen et al. (9) Sari et al. (27) Pauly et al. (43) Dhurat et al. (44)	Trophic effect on the tendon.	Long term.	Pain during and after application.	It can be applied intra-articularly, in the subacromial space or intratendinous. Perhaps it is the infiltration modality with the greatest regenerative potential.	Complexity and variability in preparation technique.

the management of rotator cuff tendinopathy; however, it only performed qualitative analyses[31]. In our review, more recent studies were added and we additionally performed quantitative analyses to clarify the efficacy of HDI.

In the pooled analysis, we found that HDI were more effective for reducing pain than others treatments used in controls in a long-term follow-up. This observation is similar to the results of the meta-analysis by Lin *et al.*[5], who reported that HDI are an effective intervention for long-term pain control in individuals with rotator cuff tendinopathy (nevertheless, that meta-analysis only included one study where HDI were used). The same long-term symptomatic effects were reported in the observational studies[29,30].

The study by Seven *et al.*[24] compared HDI *vs.* exercise programs, and found that HDI was more effective in reducing pain in short, medium and long-terms in the individual analysis. Non-invasive therapeutic strategies are widely used for the treatment of rotator cuff tendinopathy[32]. It has been reported that oral anti-inflammatory drugs are effective for reducing pain only in the short term, but they do not improve function[2]. Likewise, physiotherapy modalities are frequently used for the treatment of rotator cuff tendinopathy; nevertheless, it has been reported that some of them such as the transcutaneous electrical stimulation[33] and therapeutic ultrasound[34] are not more effective than placebo for the control of pain and improvement of function, while others such as laser therapy have shown a small beneficial effect[3,35]. Therapeutic exercise probably represents the most effective non-invasive therapeutic modality for the treatment of rotator cuff tendinopathy[4,36]. No previous meta-analysis has reported a direct comparison between HDI *vs.* exercise programs; the results of our meta-analysis suggest that HDI are more effective in the short, medium and long terms than exercise programs and could be an alternative when exercise strategies fail. However, this comparison was only carried out in one study, so it should be taken with reserve.

Some studies directly compared HDI *vs.* infiltrations with local anesthetics[23,27]. In the individual analyses in the short and medium terms, no significant differences were reported between the groups. However, in the long term however, the individual analysis of the study by Bertrand et-al. showed significant differences in favor of the group treated with HDI[23]. A previous meta-analysis[5] reported that HDI are an effective intervention for the long-term control of pain in individuals with rotator cuff tendinopathy, based on the compari-

son between HDI and local anesthetic infiltrations. These results suggest that in the short and medium terms HDI and local anesthetics infiltrations have the same effect in patients with rotator cuff tendinopathy. However, in the long term, the effect of local anesthetics is lost, while the benefit achieved with HDI persists. Local anesthetics have been proposed to have analgesic and anti-inflammatory effects in addition to their anesthetic effect[37], which could explain its short-term therapeutic effect. Hypertonic dextrose on the other hand, has been proposed to have a mechanism of action based on the increase of fibroblast proliferation, collagen production and extracellular matrix in the treated tendons[38,39], which could explain why its efficacy is maintained in the long-term.

Two studies directly compared HDI *vs.* conventional infiltrations with corticosteroids[25, 27]. In the individual analyses, the study of Cole *et al.*[25] reported statistically significant pain reduction in the short and medium terms in favor of HDI, but not in the long term. On the other hand, the study by Sari *et al.*[27] reported a statistically significant reduction of pain in favor of corticosteroid infiltrations in the short and medium terms, but in the long-term there was no difference between groups. No previous meta-analysis has reported a direct comparison between HDI *vs.* corticosteroid infiltrations. Other meta-analyses have reported that corticosteroid infiltrations are an effective intervention for pain control and function improvement in the rotator cuff tendinopathy when compared with placebo[5] or local anesthetics[40]; however, it was observed that the improvement only lasted <6 weeks. Corticosteroids are probably the most used infiltration in individuals with shoulder rotator cuff tendinopathy but its use has been related to deleterious effects on the tendon in addition to its contraindication in some patient with comorbidities. Basic studies have reported that infiltrations with corticosteroids could be associated with an increase of cellular apoptosis in the infiltrated tendon[41] and could facilitate the NF-KB signaling, which is involved in the pathogenesis of rotator cuff tears[42], which contrasts with the trophic effects that hypertonic dextrose can have on the tendon[38,39]. When comparing HDI vs. corticosteroids infiltrations in individuals with rotator cuff tendinopathy, further studies are required to clarify whether HDI represents an alternative to infiltrations with corticosteroids when there is a contraindication for their application.

Sari *et al.*[27] compared HDI *vs.* infiltrations with PRP and in the individual analyses found no significant differences between both groups in the short, medium and long terms. No previous meta-analysis reported a direct comparison between HDI *vs.* PRP infiltration. Others meta-analysis reported that PRP infiltrations were effective for reducing pain and improving function in long-term follow-up when compared with corticosteroids[9]. In basic studies it has been reported that in vitro applications of PRP favor tissue repair and increase the proliferation of rotator cuff tenocytes[43], similar to the effects previously described for hypertonic dextrose[38, 39]; nonetheless, the application of PRP implies greater complexity in its preparation and the results vary considerably[44]. Although HDI appear to have the same efficacy as PRP infiltrations to reduce pain in the long-term, these observations come from a single study and more studies are necessary to corroborate these results.

Regarding the characteristics of the treatment, studies with multiple sessions and multi-injections[23,24,29,30] showed greater benefits with statistically significant improvement in favor of the groups treated with HDI. On the other hand, studies[25, 28] that only included one treatment session (intratendinous) did not find greater clinical improvement in comparison with control groups. Multiple sessions and multi-injection schemes appear to be necessary to obtain clinical benefit in patients with rotator cuff tendinopathy. Previous recommendations suggest between 3 to 6 treatment sessions as well as multi-injection schemes involving at least the insertion area of the rotator cuff tendons and subacromial or intra-articular space[45].

Regarding the side effects and/or adverse reactions, pain during or after the application was the most frequently observed. None of the treated individuals reported serious complications such as infections or allergic reactions; nevertheless, not all studies reported adverse effects or complications.

A comparative table was made, which summarizes the mechanisms of action, effects on pain control, possible advantages, disadvantages and adverse effects, of the types of infiltration used for the treatment of rotator cuff tendinopathy in the included studies (Table III).

It is important to mention possible limitations of the present study. Although the studies included in the quantitative analysis showed a good methodological quality design and low or moderate risk of bias, the small number of studies included, the small number of individuals treated in each study and the lack of standardization in the application techniques most have influenced the results and its consistency.

CONCLUSIONS

The results of this systematic review and meta-analysis indicate that HDI are an effective treatment for control pain in long-term follow-up of individuals with rotator cuff tendinopathy. Therefore, it can be concluded that HDI were more effective than non-invasive treatments in the short, medium and long terms, as well as more effective than the use of local anesthetics in long term. HDI were not more effective than PRP and its efficacy comparing with corticosteroid infiltrations is not yet clear. On the other hand, HDI did not show complications or serious adverse effect. Despite the favorable results, the small number of studies included in our meta-analysis as well as their heterogeneity are the main limitations to draw definitive conclusions and good quality RCTs are required.

CORRESPONDENCE TO
Carlos Alfonso Tovilla-Zárate
Universidad Juárez Autónoma de Tabasco
División Académica Multidisciplinaria de Comalcalco, Ranchería Sur, Cuarta Sección
C.P. 86650, Comalcalco, Tabasco, México.
E-mail: alfonso_tovillaz@yahoo.com.mx

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