Hyaluronic Acid injections for Chronic Tennis Elbow

Gershon Zinger (GershonZinger@gmail.com)
Shaare Zedek Medical Center
Alexander Bregman
Shaare Zedek Medical Center
Ori Safran
Hebrew University of Jerusalem
Shaul Beyth
Hebrew University of Jerusalem
Amos Peyser
Shaare Zedek Medical Center

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Abstract

Background

For most patients, tennis elbow (TE) resolves within six months of onset. For those with persistent and painful TE, nonsurgical treatment options are limited. Thousands of studies have tried to find effective treatment for TE, but usually fail. In this study, we test the hypothesis that injections with hyaluronic acid (HA) are effective at treating chronic pain from TE.

Methods

Patients with a minimum of six months of pain from TE were randomized equally into one of two groups, injection with HA or saline control, and followed for one year. Outcome measures included Visual Analogue Score (VAS pain), the shortened disabilities of the arm, shoulder and hand questionnaire (QuickDASH) and patient rated tennis elbow evaluation (PRTEE).

Results

Seventeen of the 18 HA-injected patients (94%) completed the study. The average age was 51.9 years and 10 were male. Patients had an average of 28.1 months of pain before entering the study. VAS in the HA group improved from a baseline of 76.4 to 14.3 at 12 months. All 17 patients in the HA group showed VAS improvement above minimal clinically important difference (MCID) of at least 18. PRTEE improved from 67 to 28.1. QuickDASH improved from 53.7 to 22.5. To our knowledge, this improvement is greater than can be seen in any other non-surgical treatment for TE.

Conclusions

HA injections showed significant success in pain relief by three months. Patients continued to improve for the 12-month duration of the study. This study indicates that patients with chronic lateral epicondylitis may benefit from injections of hyaluronic acid rather than having to undergo surgery.

Background:

Tennis elbow (TE) is a widespread and painful condition. Although thousands of articles have been published on the treatment of TE, there is almost no effective non-surgical treatment. Traditional non-operative treatment for TE often starts with therapy and non-steroidal anti-inflammatory medication. These treatments have not proven effective.[1)] Local treatment commonly includes injection with steroid which, in double-blinded controlled studies, have shown to give only temporary relief.[2–4)] Other less common substrates for injection have included autologous blood, plasma rich platelets (PRP) and

Botulinum, none of which have proven effective. Autologous blood has limited evidence in the literature.[5–6] Botulinum has shown partial benefit, but only temporary and with the potential side effect of paresis.[7] PRP has been tried for over ten years with limited success, and a recent review actually recommended against using PRP as a treatment for TE.[8]

Tennis elbow is considered to be self-limiting so that in 80% of patients the symptoms resolve within six to twelve months.[9] However, for those with persistent and painful TE, the data supporting successful non-operative options is limited. Recent studies have evaluated injection of hyaluronic acid (HA) for tendinosis[10–13], specifically for tennis elbow[14–15], and have shown promising results. Dong *et al.*,[16] in a comprehensive review of injection therapy for tennis elbow, searched 1,636 titles and reviewed 27 randomized controlled trials (RCTs) that met their criteria. With regards to pain score, hyaluronate injections were superior to all other treatments, but they noted that more study was needed. Most of the studies done to date using HA included different enthesopathies in the same study and have limited follow-up. The one exception is a published level 1 study in which HA injections for tennis elbow showed promising results.[15] However, this study was limited to patients who were racquet sport athletes, which is not the etiology for most patients who present with TE. The purpose of the current study was to expand the population to see if HA was effective in the general population and not limited to competitive racquet sport athletes. We prospectively evaluated the efficacy of HA injections for the treatment of chronic tennis elbow.

Methods:

This study was designed according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[17] This clinical trial was prospective, randomized and blinded. The trial was registered at ClinicalTrials.gov (NCT02258295) before IRB approval. After meeting inclusion and exclusion criteria, patients were randomized in a 1:1 ratio into one of two treatment arms, HA injection (HA group) versus saline control (Saline group). All the patients were recruited and evaluated at a single center, an academic referral facility. Randomization was done using a table provided by our statistician created by a randomization program in blocks of thirty. All patients in the study were consented prior to randomization. The research assistant would reveal to the injecting physician the material to be used after consent was obtained. Each patient was given a full explanation of the procedure including the possibility of getting a saline injection. They were given a copy of the signed informed consent. Admission of the patient into the study was recorded in the medical records.

Inclusion/Exclusion Criteria:

The criteria for diagnosis included pain and tenderness at the lateral epicondyle worse with resisted wrist or finger extension (with the elbow in the extended position). Inclusion criteria were age over 18 years, chronic pain defined as six months or longer, and pain (average pain over the past week when using the hand) on the Visual Analogue Score (VAS) scale of 50 or greater (out of 100).

Exclusion criteria included elbow steroid injection less than three months prior to starting the study, prior elbow surgery, inflammatory condition like rheumatoid arthritis or lupus, and allergy to birds, feathers or egg products. If the patient had complaints of pain and significant tenderness on exam in the area of the radial neck, then a component of radial tunnel syndrome was assumed and those patients were excluded from study. Patients with pain from other areas such as the radio-capitellar joint or medial epicondyle were also excluded.

Blinding:

All injections were performed using syringes that were masked and numbered. The patient was blinded from knowing which material was used. Although the physician injecting was not blinded, a separate physician, blinded to the material, performed follow-up visits.

Injections:

Injections of HA or saline were the only treatment for the study duration. Patients were not referred for therapy and no other interventions or treatment were recommended. This study used Intragel (IBSA Institut Biochimique, Lugano, Switzerland). The formulation has a molecular weight averaging 800-1200 KDaltons and concentration of 16mg per 2cc.

The senior author (GZ) performed all injections. The injections were performed in a similar fashion for both HA and Saline groups. First, the point of maximum tenderness at the lateral epicondyle was identified and marked. After local preparation with alcohol, 1cc of lidocaine 1% was placed both superficially and deep into the tendon substance. Using a separate and pre-loaded syringe, 2cc of either HA or saline was injected using a fanning technique into the area of maximal tenderness approximately 1cm distal to the lateral epicondyle. Each participant was injected three times, two weeks apart. When planning the study, we reviewed all the clinical studies to date and the number of injections done were between one to six per patient. The primary reason we chose three was prior experience. We have been injecting patients since 2011 with HA. Before starting this study, we did a quality survey of the patients injected and found that nearly all patients had two to three injections each until their pain was essentially resolved. We chose two weeks apart because prior research had two to three week intervals.

Additional Treatment:

Patients were not referred for any additional treatment during the study period. Most had tried therapy and injections prior to enrollment. Patients were asked about other interventions during the follow-up period (six and 12 months after HA injections) and no additional treatment was reported.

Demographic Data:

General demographic data included age, sex, handedness, type of work, symptomatic side, and if they participated in racquet sports (Table 1).

Table 1

Categorical (Chi square test for Gender, Fishers test for others - for comparisons between groups) **and Continuous** (T-tests and Wilcoxon for normal and non-normal distributions) **Baseline Characteristics by Group: HA versus Saline.**

Parameter	Category	Group HA N (%)	Group Saline N (%)	P-Value
Age (years)*	Age	51.9 (SD 10.6)	52.9 (SD 8.9)	0.800
Gender	Female	7 /17 (41.2)	3 /13 (23.1)	0.297
	Male	10 /17 (58.8)	10 /13 (76.9)	
Handedness	Left	1 /17 (5.9)	1 /14 (7.1)	1.00
	Right	16 /17 (94.1)	13 /14 (92.9)	
Occupation	Manual	3 /17 (17.6)	4 /14 (28.6)	0.115
	Office	13 /17 (76.5)	6 /14 (42.9)	
	Retired	1 /17 (5.9)	4 /14 (28.6)	
BMI	BMI	25.9 (SD 3.2)	27.1 (SD 4.1)	0.463
Painful side	Left	8 /16 (50.0)	7 /14 (50.0)	1.00
	Right	8 /16 (50.0)	7 /14 (50.0)	
Pain Duration (months)	Pain Duration	28.1 (SD 22.0)	51.4 (SD 59.9)	0.936

* T Test

HA – Hyaluronic Acid

PRTEE – patient-rated tennis elbow evaluation

QuickDASH – Quick Disabilities of the Arm, Shoulder and Hand Score

VAS – Visual Analog Score

Parameter	Category	Group HA N (%)	Group Saline N (%)	P-Value
VAS Pain (In the past week how much pain do you feel when gripping something - on average?)	VAS Pain	76.4 (SD 12.1)	72.1 (SD 11.9)	0.348
PRTEE Score	PRTEE	67.0 (SD 14.6)	71.9 (SD 14.5)	0.357
QuickDASH	QuickDASH	53.7 (SD 18.90	58.8 (SD 13.1)	0.408
Racquet sports	No	15 /17 (88.2)	13 /14 (92.9)	1.00
	Yes	2 /17 (11.8)	1 /14 (7.1)	
* T Test				
HA – Hyaluronic Acid				
PRTEE – patient-rated tennis elbow evaluation				
QuickDASH – Quick Disabilities of the Arm, Shoulder and Hand Score				
VAS – Visual Analog Score				

Outcome Measures:

The primary outcome measure was the VAS for pain when asked, “What is the average pain you experienced the past week while gripping or actively using your hand?” Secondary outcome measures included the brief form of the disabilities of the arm, shoulder, and hand (QuickDASH)[18)] and the patient rated tennis elbow evaluation (PRTEE).[19)] Outcome measures were collected at baseline, three months, six months and one year from the initial injection. Patients were encouraged to return for clinical evaluation for each visit but some preferred to respond to telephone or email outcome questionnaires.

The QuickDASH is an 11-question short version of the longer 30-question DASH. The score ranges from 0 (no disability) to 100 (most severe disability). The PRTEE is a 15-question survey that evaluates pain and function on a 10-point VAS. The score ranges from 0 (no pain and maximum function) to 100 (maximum pain and minimum function). Therefore, the best score for the QuickDASH and the PRTEE are both 0.

Primary endpoint:

The primary endpoint was reduction of the VAS pain at three months from the initial injection.

Secondary endpoints:

Secondary outcomes included differences for HA for VAS pain at six and 12 months and for PRTEE and QuickDASH at 3-, 6- and 12-months post-injection. We also calculated 25% reduction in VAS pain from baseline for HA versus saline to allow comparison to Peerbooms et al. 2010[20] results from PRP injection.

Power of study and statistical analysis:

One of the few prospective studies on HA done to date was performed by Petrella *et al*.[15] They evaluated treatment of chronic HA in racquet sport athletes using a total of two HA injections one week apart. They used pain VAS as their primary endpoint. Using standard deviation data from their study we calculated the sample size needed to power this study. With the null hypothesis that the HA group would improve relative to the control (by VAS 18 or greater) at 3 months post-injection, the significance level, $\propto$ set at 0.05 and power at 80% (1-β)=0.20, computed 29 patients per group to allow comparison to the saline placebo. Unfortunately, the inclusion and exclusion criteria were so restrictive that enrollment was slower than anticipated. Specifically, the requirement for only chronic, no component of radial tunnel syndrome and no recent steroid injections limited the number of suitable patients. In the end, we stopped the study at 35 patients, with 18 in the HA group.

Differences in baseline characteristics were assessed with Fisher's test for categorical variables and T-test or Wilcoxon tests for continuous variables, depending on the distribution of the data. The T-test was used to t for differences in outcome measures.

Results:

The enrollment period was from January 18, 2017 to December 3, 2018, and the study period continued for one year from the final injection until December 2019. At the end of the 12-month study period, only eight of the 17 enrolled control patients (47%) returned for follow-up. Although we attempted to contact these patients, we were not able to reach them to have them return for follow-up evaluation. We presume that these patients sought other treatment, possibly for persistent pain, but this could not be verified. Since we could not analyze the information from the saline-treated patients, we did not include their information in the analysis. Therefore, this study should be considered as a prospective study describing the effects of HA injections for chronic TE patients.

In contrast to the saline injected group, 17 of the 18 patients enrolled in the HA group returned for follow-up appointments for the full year of the study. The single patient lost in the HA group did not return for their first 3-month follow-up and was not counted in the outcome measures.

Demographic data were collected at the initial visit after randomization and were equivalent (Table 1). Although six months was the minimum duration of pain to be included in the study, the average pain

duration was 28.1 (SD 22) months. There were no complications noted in any of the patients in the study, including no subcutaneous atrophy, infection, or pain flare from the injection.

Primary Outcome:

The VAS pain improved in the HA group from baseline of 76.4 (SD 12.1) to 42.6 (SD 25.5) at three months (p=0.001).

Secondary Outcomes:

Pain Measures (using last carry forward):

The average pain in the HA group continued to improve over time (Figure 2). The average VAS improved 12 months after treatment in the HA group from 76.4 (SD 12.1) to 14.3 (SD 11.9), (p<0.001).

Additional VAS pain reduction measures:

MCID (minimal clinically important difference)

All 17 patients in the HA group showed VAS improvement above MCID of at least 18.[21)]

25% reduction

Using Peerbooms et al. 2010[20)] criteria of 25% or more improvement, when evaluated at 12 months, all 17 patients in the HA group met that criterion.

QuickDASH

The QuickDASH improved over time (Figure 3), HA from 53.7 (SD 18.9) to 22.5 (SD 17.1) (p<0.001) at 12 months. This average difference of 31.2 is above the MCID of 14.[22)]

PRTEE

The PRTEE improved over time (Figure 4). HA improved from 67.0 (SD 14.6) to 28.1 (SD 15.8) at 12 months (p<0.001). Poltawski *et al.*[23)] evaluated the MCID for the PRTEE and reported that 37% improvement correlated with “much better” or “completely recovered”. In the HA group, 14 of the 17 patients met this criterion.

Both the QuickDASH and the PRTEE measure pain and function. The PRTEE is considered a more specific measure for tennis elbow and theoretically would be more sensitive to changes when evaluating patients limited by TE. In this case, both measures improved since patients improved in both groups with less pain and more function.

Discussion:

The results of this prospective study show that HA injections were effective at relieving pain and improving function in patients with chronic TE. Despite an average of more than two years of pain, the VAS score improved from 76.4 to 14.3. The saline group was not compared to the HA group since it was considered an unreliable comparator.

A patient with chronic tennis elbow has few proven options other than surgery. Coombes *et al*.[2] performed a systematic review using eight databases and identified 3,824 trials of peritendinous injections for tendinopathy. Forty-one studies met their inclusion criteria. Other than injections of sodium hyaluronate, there was no intervention that gave more than temporary relief.

Steroid injections continue to be the most common treatment and PRP has become popular despite insufficient scientific support. In a prospective, double blind randomized clinical trial of 64 patients with less than six months of pain, Lindenhovius *et al*.[3] concluded that steroid injection did not affect the self-limited course of lateral elbow pain. Most of the literature on PRP contains case reports or case series.[2, 24–25] One exception is the study by Peerbooms *et al*. [20] who report their results from a randomized double-blinded study comparing PRP to steroid injection with one-year follow-up. They defined successful treatment as 25% or better improvement in VAS scores compared to baseline. They calculated 73% success in the PRP group versus 100% found in this study using HA.

In a review of the English language literature, we found eleven relevant studies that evaluated HA for tendinopathies. Three used HA for lateral epicondylitis,[14–15,26] three for the rotator cuff, [10–12] one for the Achilles,[13] and one was an animal study.[7] Three studies evaluated HA injection for multiple tendinopathies.[28–30] All the studies described here showed some benefit from HA injection but were of varying quality, did not limit treatment to chronic tennis elbow and most had only short-term follow-up. The study by Gaughan *et al*.[27] offers an understanding of the pathomechanism for HA improvement. Horses had a flexor tendon defect created when injection with HA compared to methycellulose with the contralateral limb serving as control. After killing the animals eight weeks after the injection they found histological evidence of HA treated limbs with reduced inflammatory cells, improved tendon structure and fewer adhesions.

Petrella *et al*.[15] performed a blinded prospective randomized clinical trial of hyaluronate versus saline injection. They included 331 racquet sport athletes with chronic (>3 months) lateral epicondylitis. They measured VAS pain in addition to four other outcome measures. The results showed improved pain with grip in the HA treated group with VAS scores that improved from baseline of 9.8 to 2.9 at one year.

Saline Control:

We tried to contact the lost patients and offer them treatment with HA or at least determine why they did not return, but they would not respond to either phone or email contact, which we purposely limited to two efforts each. We can only speculate as to the reasons for the high saline drop-out compared to the low-drop out for the successfully treated HA group.

There is some evidence that saline for TE may not be a true placebo but might also have therapeutic benefits. It therefore might not be the ideal comparator. Gao *et al*. [31] and Acosta-Olivo *et al*.[21] performed meta-analysis of the effect of saline injection for tennis elbow. They evaluated only prospective, randomized studies that had minimum follow-up of a year. They concluded that improvement seen with saline injection is not a placebo effect but rather that saline injections provide real therapeutic benefit.

Surgery:

Although the focus here is to compare HA injection to other non-surgical treatments, it is worth comparing the results here to surgical treatment. Ruch *et al*.[32] compared pre-op to post-op open treatment of tennis elbow after failed conservative treatment. The average VAS pain score improved from 4.6 to 2.3. Pierce *et al*.[33] did a recent systematic review of open, arthroscopic and percutaneous techniques. They note that VAS pain at final follow-up was 1.9, 1.4 and 1.3 respectively. These results compare to our results with HA injection of VAS pain score that improved from 7.6 to 1.4.

Merits and Limitations:

This study strength is the prospective design with one-year follow-up and with all injections by the same examiner. Another strength was the blinding of the patient and the evaluator.

The many patients lost to follow-up in the Saline group limited this study in having a placebo group for comparison. However, as noted, saline may have some therapeutic benefits of uncertain duration and may not be the ideal placebo control. In addition, given our strict inclusion and exclusion criteria, there was lower than targeted patient recruitment. However, the HA group showed significant improvement using all measures.

Conclusions:

We conclude that, based on this prospective study with one year of follow-up, HA proved effective at treating chronic TE. Other than the pain of injection, there were no negative side effects observed from HA injection over the course of the study. We feel that despite the limitation of this study, there is a large benefit and minimal risk that favor injecting HA for chronic tennis elbow. However, we recommend that a larger study with an appropriate placebo control should be performed. Tennis elbow as well as other enthesopathies remain difficult to treat. We hope this study stimulates further research in this important area to investigate the use of HA injections to treat this painful condition.

Abbreviations

CONSORT
Consolidated Standards of Reporting Trials
HA
hyaluronic acid
IRB

institutional review board
QuickDASH
shortened disabilities of the arm, shoulder and hand questionnaire
MCID
minimal clinically important difference
PRP
plasma rich platelets
PRTEE
patient rated tennis elbow evaluation
TE
tennis elbow
VAS
visual analogue score

Declarations

Ethics approval and consent to participate: Research involving human participants complied with institutional, national and international guidelines. This study was approved by our institution IRB Committee (Shaare Zedek Medical Center), approval number 160/14 July 2015.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: GZ planned the study, analyzed the results, and wrote the manuscript. AB performed all the blinded follow-up examinations. OS and SB helped to plan the study, recruit patients, and evaluate the results. AP helped to plan the study and analyze the results.

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Figures

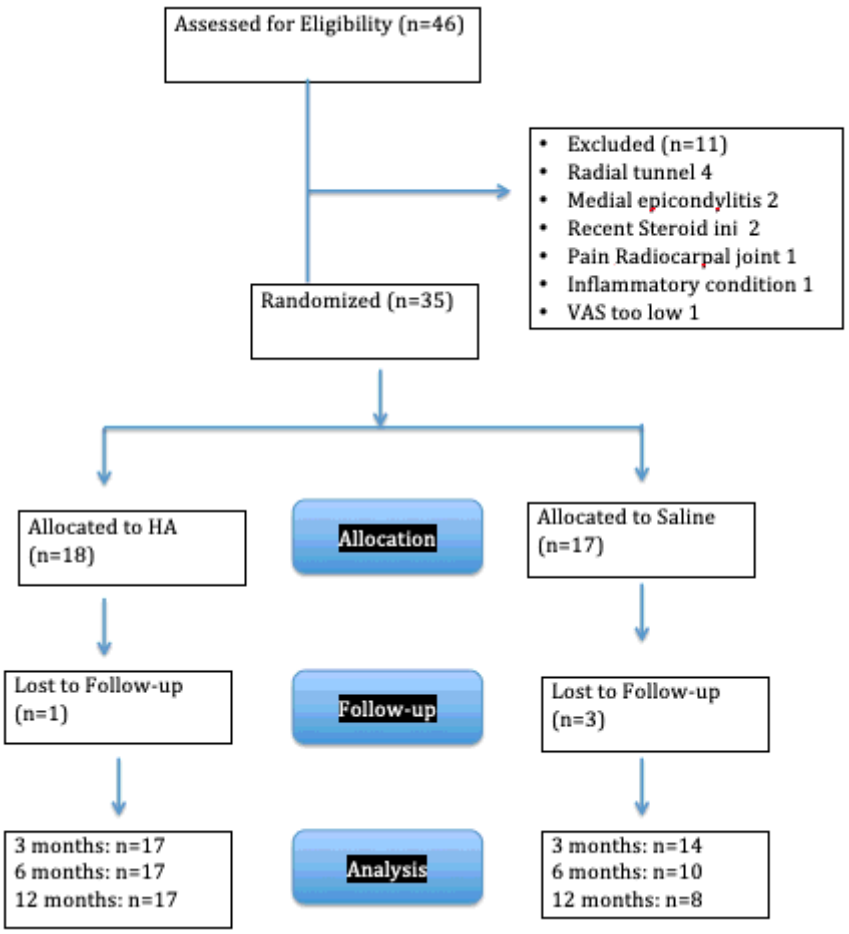

Figure 1

Flow Diagram

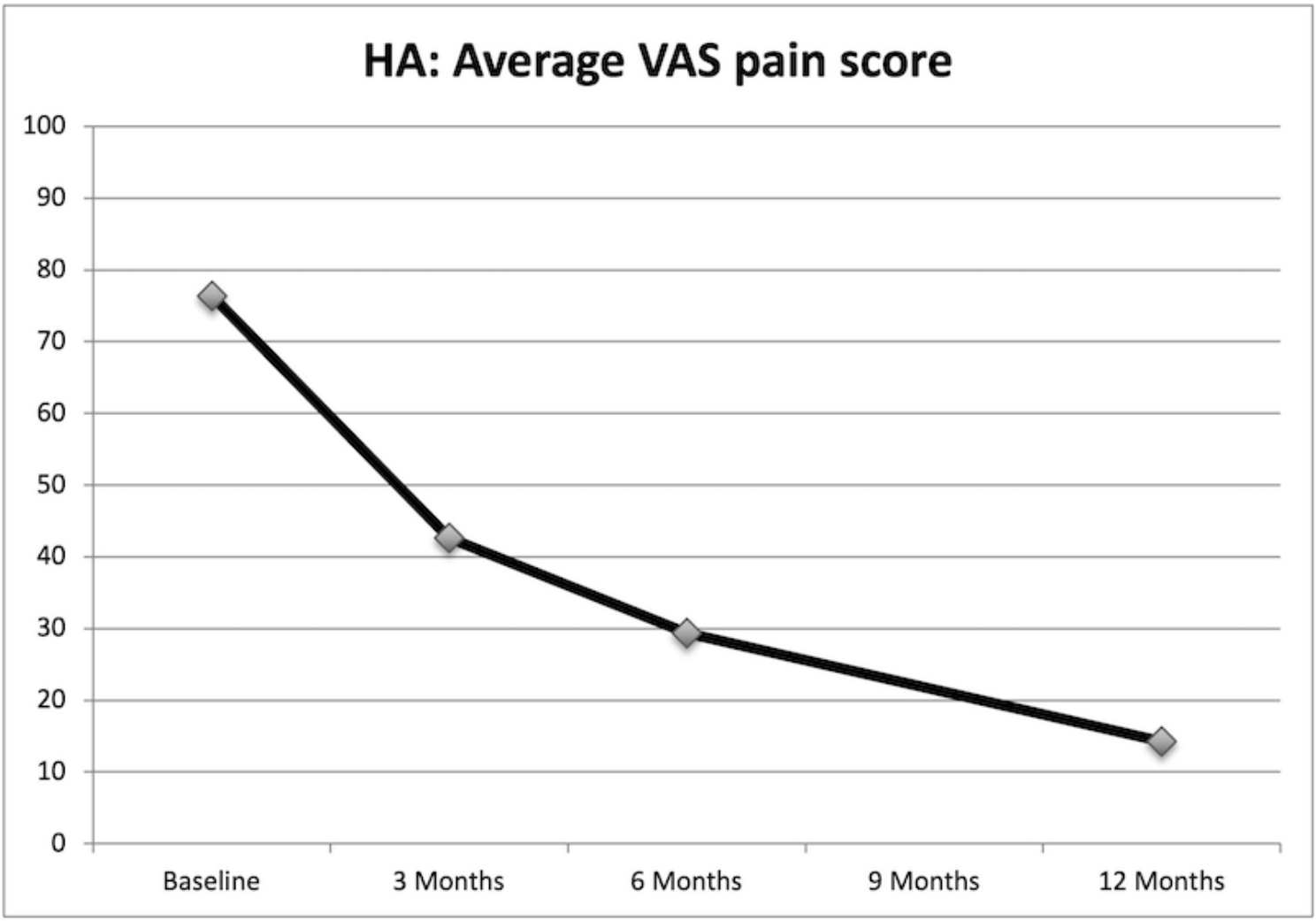

Figure 2

Average VAS pain levels

Figure 3

Average QuickDASH

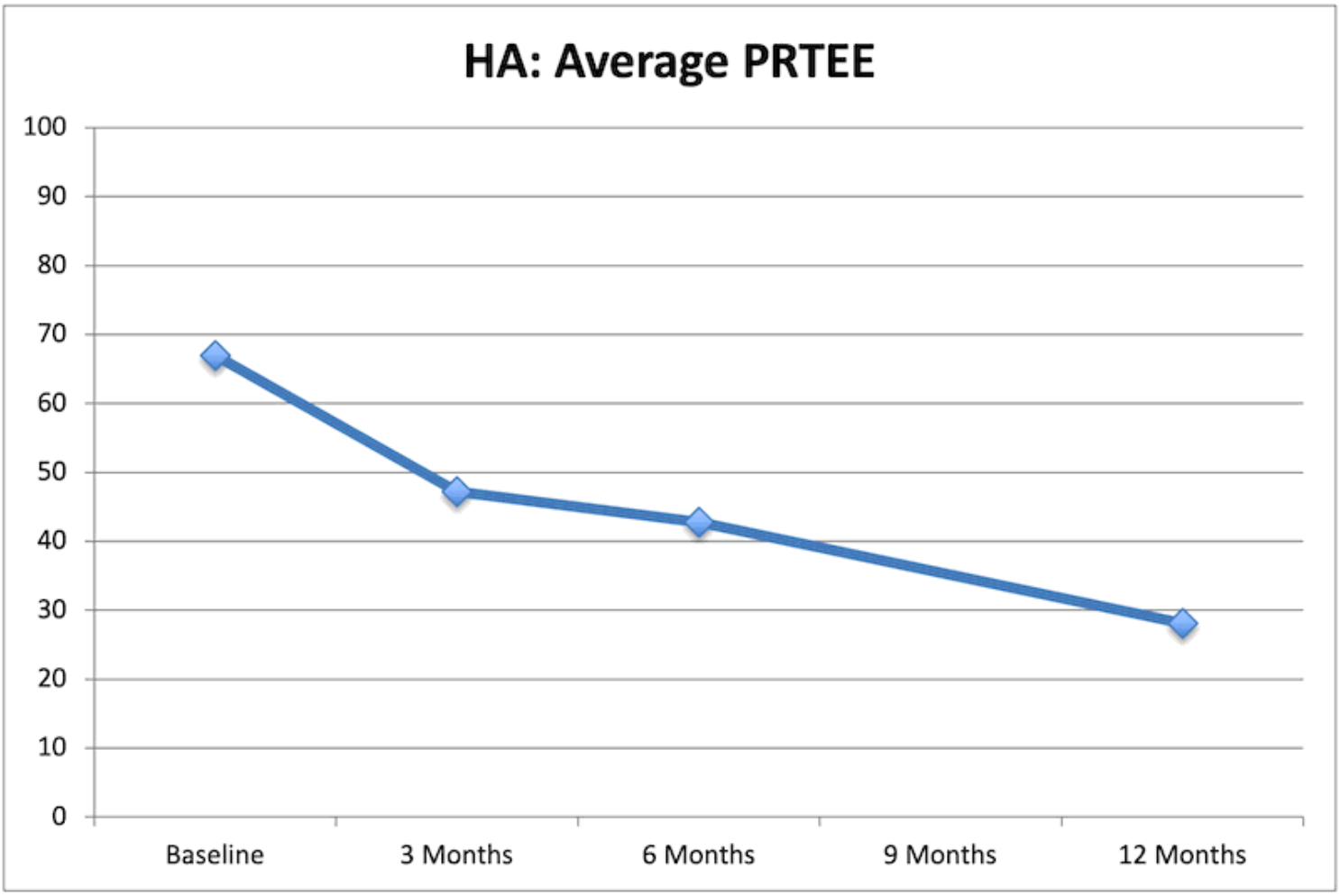

Figure 4

Average PRTEE combined (pain and function)

Supplementary Files

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- CONSORT2010Checklist.doc