High-Volume Image-Guided Injections in Achilles and Patellar Tendinopathy in a Young Active Military Population

A Double-Blind Randomized Controlled Trial

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Background: Chronic Achilles and patellar tendinopathy are a significant burden in physically active populations. High-volume image-guided injection (HVIGI) proposes to strip away associated neovascularity, disrupt painful nerve ingrowth, and facilitate rehabilitation.

Purpose: To investigate the efficacy of HVIGI with and without steroid relative to placebo.

Study Design: Randomized controlled trial; Level of evidence, 1.

Methods: A total of 62 participants were recruited between May 25, 2016, and March 5, 2020. Participants were men aged 18 to 55 years with Achilles or patellar tendinopathy of at least 6-month chronicity that had not improved with nonoperative management (including physical therapy and shockwave therapy), with ultrasound evidence of neovascularization, tendon thickening, and echogenic changes. They were assigned to the following groups: control (3 mL of subcutaneous 0.5% bupivacaine), HVIGI (10 mL of 0.5% bupivacaine and 30 mL of normal saline, ultrasound-guided between tendon and underlying fat pad), or HVIGI with steroid (HVIGIwSteroid; 0.25 mL of 100 mg/mL hydrocortisone). Clinicians and assessors were blinded. All participants were supervised through a pain-guided progressive loading program for 6 months postinjection. The main outcome measures were the Victoria Institute of Sport Assessments (VISA) for Achilles and patellar tendinopathy and the visual analog scale (VAS) for pain at 6 months postinjection.

Results: The VISA score improved by a mean of 22.8 points (95% CI, 10.4-35.3 points; effect size [ES], 1.51) in the control group (n = 21), 18.6 points (95% CI, 9.1-28.0 points; ES, 1.31) in the HVIGI group (n = 21), and 18.5 points (95% CI, 3.4-33.6 points; ES, 0.88) in the HVIGIwSteroid group (n = 20). VAS pain improved by a mean of 15 points (interquartile range [IQR], –38.75, 8 points; ES, 0.39) in controls, 13 points (IQR,–34.0, 3.75 points; ES, 0.47) in the HVIGI group, and 27 points (IQR,–38.0, –1.0 points; ES, 0.54) in the HVIGIwSteroid group. The main effects were significant for time ($P < .001$) but not group ($P \geq .48$), with no group × time interaction ($P = .71$). One participant was lost to follow-up from each group, multiple imputation was used for missing data points. No adverse events occurred.

Conclusion: Study findings did not demonstrate superiority of HVIGI over control injection.

Registration: EU Clinical Trials Register (EudraCT: 2015-003587-36).

Keywords: tendinopathy; high-volume image-guided injection; randomized controlled trial; rehabilitation; sport and exercise medicine

Achilles and patellar tendinopathy are prevalent conditions among populations exposed to frequent mechanical loading. The incidence of Achilles tendinopathy during 6-month initial military training in the United Kingdom has been reported as 1.4%.[31] Both of these lower limb tendinopathies frequently result in persistent symptoms that require ongoing management over several months.[21,23]

Pain in such chronic cases interferes with activities of daily living and sports and occupational activities.[23] Best practice management has progressive loading within a pain

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monitoring framework at its core.[5] Sufficient healthy tendon adaptation to reduce symptoms can take several months, during which load dosage and intervals between sessions need to be carefully controlled to maintain net gains in type 1 collagen.[20]

Several adjunctive treatments, including laser, extracorporeal shockwave therapy, and topical glyceryl trinitrate, have demonstrated limited success, mostly in the short to medium term.[24] Injectable therapies, including peritendinous corticosteroid, which offers short-term benefit only, have also been proposed.[7] Platelet-rich plasma and autologous blood injections initially showed promising results in case series, but when these were subsequently tested in several randomized controlled trials (RCTs), they were found to be no better than the controls in improving pain and function.[3,9,10] Injection of polidocanol, a sclerosant, is a technically difficult procedure targeting the neovascularity seen in degenerative tendinopathy directly. Repeated injections are required, and an RCT has shown a small effect at 4 months compared with control.[13]

High-volume image-guided injection (HVIGI) has a similar mechanism of action targeting the neovascularity visible on ultrasound Doppler. Using mechanical stripping[27] and potential toxicity from local anesthetic,[33] HVIGI is proposed to reduce hypersensitive substance P–positive nerve fibers.[17] There have been several case series investigating the effect of HVIGI in Achilles and patellar tendinopathy showing positive results. Initially, these mostly included steroid in the injectate,[6,14,28] although there have now been similar results without the addition of steroid.[18,19,36] A higher volume of at least 50 mL has been shown to be more effective than a lower volume of around 30 mL in consecutive case series.[37] Two RCTs have been published to date, both in Achilles tendinopathy. One RCT compared the results of HVIGI with steroid (HVIGIwSteroid) to a placebo injection and platelet-rich plasma in a 3-arm study of 60 participants.[4] Boesen et al[4] showed a superior effect of HVIGIwSteroid compared with sham placebo at interim points of 6 weeks and 3 months, but the trend in improvement was not sustained at 6 months. Another RCT showed no effect of HVIGI without steroid versus a placebo sham control at 6 months in 80 participants.[32]

The aim of this study was to test the efficacy of HVIGI. Further, in a 3-arm clinical trial design, HVIGI was compared with and without the addition of corticosteroid, an element that has not been investigated to date via RCT. It was hypothesized that participant outcomes after HVIGI would be superior to those of control and that the outcomes of HVIGI without steroid would not differ from those of HVIGIwSteroid.

METHODS

Study Design

A double-blind RCT was conducted at a single site (a tertiary referral center) according to a protocol approved by the UK Ministry of Defence research ethics committee and UK Medicines and Healthcare Products Regulatory Agency clinical trial authorization. The full protocol is available online.[1] All participants gave written informed consent.

The research question arose from patient-reported unmet needs expressed to the clinician authors of the current study during routine clinical care. Patients were not formally involved in the formulation of the research question or study design. The scientific and ethical review process conducted by independent committees before study commencement included lay members. Resulting changes included more accessible language used in participant information, clarification of time commitments, and the implications of being in the control group. This included the offer of the intervention, if appropriate, after the trial period. Public engagement was conducted by a Ministry of Defence press release, including a patient interview broadcast on Forces TV, with the aim of promoting recruitment to the trial and offering a point of contact for interested parties. A lay summary was emailed to all participants to coincide with the publication of the current study.

The study participants were recruited between May 25, 2016, and March 5, 2020. With the agreement of the trial management group, the study sponsor (UK Defence Medical Services) made the executive decision to stop the study in 2020 after continued delivery of the protocol became unfeasible as a result of the coronavirus-2019 (COVID-19) pandemic and in the knowledge that the minimum power calculation had been reached.

Participants

UK military male patients with either Achilles or patellar tendinopathy persistent over 6 months; with unresolved symptoms after best-practice routine clinical management,[1] including physical therapy and extracorporeal shockwave therapy; aged 18 to 55 years; and with ultrasound evidence of neovascularization, tendon thickening, and echogenic changes were included in the study. Diagnosis was confirmed by a sport and exercise medicine consultant (P.B.) and a physical therapist (J.W.). A high-frequency linear array 6- to 15-MHz transducer was used with a Logic 9 ultrasound scanner (GE Medical Systems

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Ethical approval for this study was obtained from the Ministry of Defence (MoD) research ethics committee (reference No. 684/MODREC/15).

Ltd). As per routine clinical examination, the consultant first oriented herself to tendinopathic areas using grayscale before power Doppler ultrasound to identify neovascularization. Further detail on the grading of this baseline assessment was as per secondary outcome measures described below and identical to the technique previously reported by the research team.[35] Female patients, patients with a concurrent alternate lower limb diagnosis, using anticoagulant medication, or having had previous tendon surgery or injection to the affected limb were excluded. Plantaris involvement in Achilles tendinopathy, insertional Achilles tendinopathy, tears, and partial tears were also treated as alternate diagnoses. Patients with patellar tendinopathy were also carefully examined to exclude patellofemoral pain syndrome (PFPS).

Randomization and Masking

Randomization in equal ratio and blocks of 9 was achieved via selection of sealed preprepared envelopes by an independent administrator. Treating clinicians were blinded to this process and did not have access to the case report forms or trial master list. The chief investigator (R.M.B.-D.) prepared injection syringes checked by a nurse or other physician not involved in the trial. Double data entry to restricted-access spreadsheets was undertaken by the chief investigator and administrator only. The independent medical officer and pharmacy had access to the trial master list as part of the data and safety monitoring protocols, with the pharmacy retaining hard copies of prescriptions.

Fully blinding the control injection (bupivacaine only) to the clinician performing the intervention was not possible because of the small volume of injectate (3 mL of local anesthetic) and difference in procedure; neovessels were not targeted under ultrasound guidance. However, as per the protocol described, at follow-up visits the treating clinicians had no access to any data reminding them of group assignments. The study physical therapist (J.W.) was fully double-blinded throughout. The 2 treatment arms (bupivacaine + saline; bupivacaine + hydrocortisone + saline) were fully blinded to clinicians and participants, as the volumes delivered were equal and identical in technique. The steroid used did not appear opaque in the syringe maintaining clinician blinding. Clinicians and participants were shielded from syringe preparation. To assess blinding at trial completion, we asked participants if they thought they were randomized to any individual trial arm, if they thought they received either an HVIGI or the control, or if they were unsure.

Procedures

Participants were randomized to 1 of the following 3 injection groups:

1. Low-volume (3 mL) peritendinous local anesthetic (control group): 0.5% bupivacaine (3 mL = 15 mg)
2. HVIGI group: 0.5% bupivacaine (10 mL = 50 mg) + 30 mL of saline
3. HVIGIwSteroid group: 0.5% bupivacaine (10 mL = 50 mg) + 100 mg/mL of hydrocortisone (0.25 mL = 25 mg) + 29.75 mL of saline

Before the intervention, the consultant performed a diagnostic ultrasound. In addition to other factors described in the secondary outcomes, neovascularization was identified. Under ultrasound guidance, a 21-gauge needle was placed between the anterior aspect of the Achilles tendon and Kager's fat pad or posterior aspect of the patellar tendon and Hoffa's fat pad at the area of maximum neovascularization (often associated with the greatest anterior-posterior diameter) (Figure 1A). Connecting tubing attached using a Luer lock (Becton Dickinson, Sweden) to a 10-mL syringe was then connected to the needle. Under instruction of the consultant, the assistant then delivered the contents of the syringe to separate the fat pad from the tendon. During the procedure, the needle was reoriented to ensure maximum separation of 2 layers (Figure 1B). Another 10-mL syringe then replaced the empty syringe until 40 mL of injectate had been delivered. In each case, the first syringe contained the local anesthetic with or without an additional 0.25 mL of corticosteroid. This was then followed by three 10-mL syringes of saline, with a final fifth syringe of 2.75 to 3 mL (depending on whether or not the first syringe contained steroid) to allow for the blind space in the connecting tubing. In all injections, an aseptic technique was used. After the procedure, the consultant rescanned the tendon, ensuring disappearance of neovascularization (Figure 1C). The patient was also asked to rate the pain experienced during the procedure on a visual analog scale (VAS; 0 = no pain, 100 = maximum pain).

As a safety measure, all participants received a card detailing that they may have been treated with any of the combinations used in the study.

During the follow-up period, all participants were advised to continue with a pain-guided progressive loading program. Oversight was maintained by the study physical therapist. All participants were progressed along an incremental pathway of rest (initially 5 days); isometric (phase 1), isotonic (phase 2), and heavy slow (phase 3) resistance; and then elastic activities including plyometrics and return to running (phase 4) according to symptoms. Additional details on the physical therapy prescription, including progression criteria between phases and microcycling of activity type, are included in the published protocol.[1] A logbook was issued to all participants for them to record activity and compliance (Supplemental Material 1). A target score $\leq$30 of 100 was used for pain during prescribed loading.[21] The same target score ($\leq$30/100) was not to be exceeded for resting pain the following day to avoid continual overload and net collagen degradation.[20] Participants were asked to refrain from seeking alternative treatments during the trial and to record completed rehabilitation sessions along with ongoing symptoms in the logbook.

After completion of the trial, the details of which combination above was prescribed were added to the patient

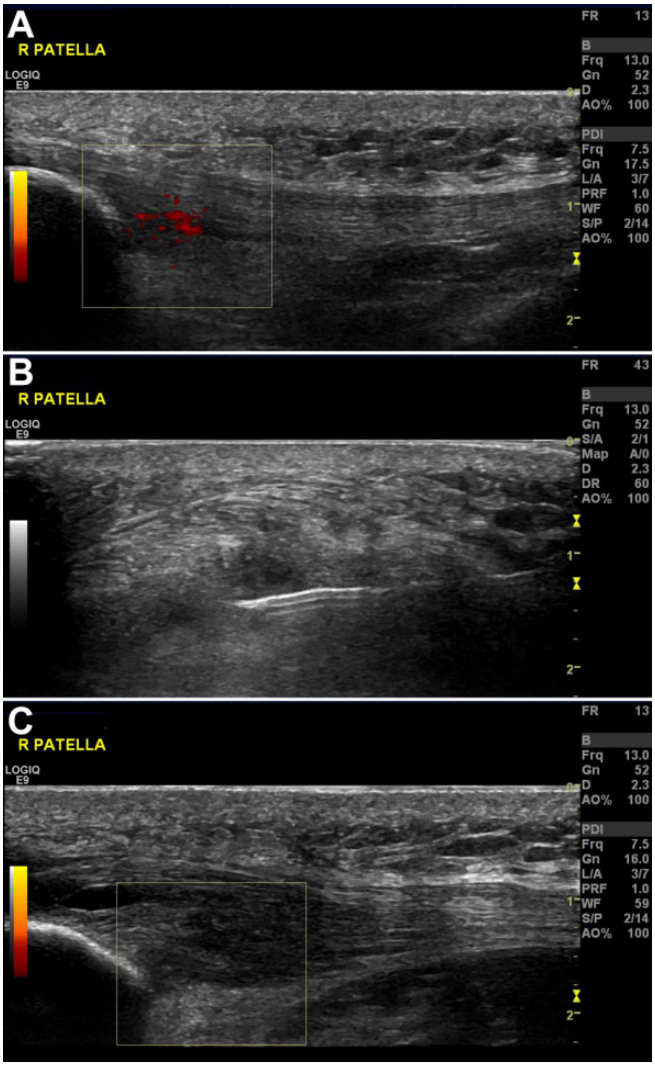

Figure 1. (A) Patella tendon with neovascularity associated with the hypoechoic area of tendinopathy arising from the deep proximal fibers. (B) The tendon in the transverse section with the Doppler box switched off to preserve the frame rate during the procedure; the needle is seen in-plane between the tendon and the Hoffa fat pad. (C) A repeat scan at the end of the procedure with the Doppler box back on, confirming disappearance of the Doppler activity.

notes at the 6-month follow-up appointment by the treating consultant once informed by the chief investigator.

Outcomes

Outcome measures were taken at baseline and at 6-week and 3-, 6-, and 12-month follow-up visits. Primary outcomes were the validated Victoria Institute of Sport Assessment–Achilles (VISA-A)[30] or Victoria Institute of Sport Assessment–Patella (VISA-P)[34] scores for pain and function and the 100-point VAS pain on the day of review at 6 months. The respective VISA scales include 6 structured questions relating to pain and function (worth 10 points each), with 2 further questions relating to participation in activities (worth 10 and 30 points); scores range from 0 (most severe) to 100 (no symptoms on direct questioning).

Secondary outcomes were VISA-A or VISA-P scores for pain and function and VAS pain on day of review at 6 weeks and 3 and 12 months (with unblinding at 6 months); the degree of neovascularization, as measured using the modified Ohberg score and maximum tendon diameter at 6 weeks and 3 and 6 months[35]; the functional activity assessment (FAA) score, which was validated in a military population, at 6 weeks and 3, 6, and 12 months; and strength and balance testing, as assessed by the study physical therapist at 6 weeks and 3 and 6 months.[29] The secondary outcome measure strength and balance assessments were the small knee bend (SKB) score, which was graded from 0 (good) to 5 (poor), as previously described by the research team,[2] and 5-repetition maximum calf raise and leg extensions for Achilles and patellar tendinopathies, respectively.[1] Adherence to the rehabilitation program was also scored using a percentage measure. The study physical therapist multiplied out the number of sets and repetitions recorded in the patient logbook mentioned earlier and then divided the result by the total number prescribed using this proportion multiplied by 100 to arrive at the final score.

We formulated a detailed protocol for significant adverse events and suspected unexpected serious adverse reactions occurring from the time of written informed consent and start of trial treatment until 6 months postcessation of trial treatment.[1] None were reported. An independent data monitoring committee (IDMC) was appointed in accordance with national research ethics service guidance and the DAMOCLES study group recommendations[8] and included an independent statistician. The chief investigator analyzed and made available accruing data, the protocol deviation log, and significant event reports before the IDMC meeting at 6 monthly intervals. The IDMC chair inspected all locked stores containing case report forms and audited the transfer to spreadsheets. As set out in its charter, the IDMC made recommendations to the sponsor, who retained executive decision making on stopping the trial. A summary in the form of a Developmental Safety Update Report was sent annually to the Medicines and Healthcare Products Regulatory Agency.

Statistical Analysis

The effect size (f) was calculated along with the overall predicted sample size calculation using G*Power (University of Dusseldorf) based on the minimum clinically important difference for VISA-P (12.6; SD, 18.4) and combined with an α level of .05 and power of 0.8 in an a priori power calculation for repeated-measures, between-factors analysis of variance (ANOVA).[1] A minimum of 60 participants were required to power the study.

Descriptive data were compared between groups. Parametric assumption checks were made using the Shapiro-Wilk and Levene tests, and 1-way ANOVA was used to check for statistical differences that may have occurred by chance at baseline. Where data did not meet parametric assumptions or were ordinal, the Kruskal-Wallis H test was

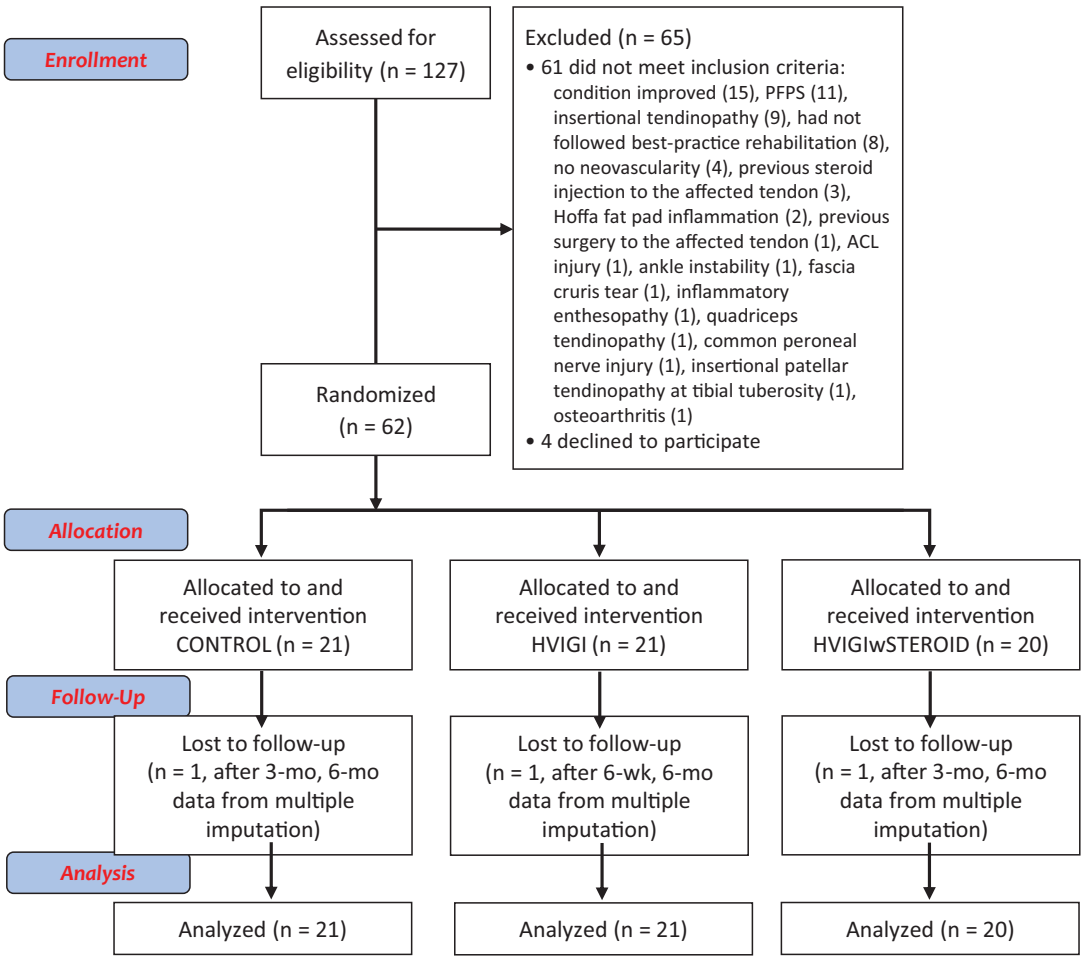

Figure 2. CONSORT (Consolidated Standards of Reporting Trials) flow diagram of participant progression through to 6-month follow-up. ACL, anterior cruciate ligament; HVIGI, high-volume image-guided injection; HVIGIwSTEROID, high-volume image-guided injection with steroid; PFPS, patellofemoral pain syndrome.

used. The adherence to rehabilitation score was considered but did not require use as a covariate.

The primary outcome data were compared between groups at baseline and 6 months. For primary and secondary outcome measures, a repeated-measures, between-factors ANOVA (time × intervention) was used to look for significant difference. Groups were then compared against each other using post hoc Bonferroni-corrected pairwise comparisons using SPSS software Version 27 (IBM Corp), and effect sizes were calculated. Where parametric assumptions were violated, the between-group analysis was conducted on the residuals using the Kruskal-Wallis *H* test. Within-group Bonferroni-corrected comparisons were also made between follow-up time points, and baseline with effect sizes were calculated. Where parametric assumptions were violated, the Friedman test was used in place of repeated-measures ANOVA.

A protocol deviation log was kept so that unanticipated trends could be analyzed. The proportion of missing data was recorded with reasons where possible. Missing data were handled using multiple imputation calculated using SPSS. A minimum of 5 imputations were calculated using the automatic method, with interim result data for the missing variables used as predictors (Supplemental Material 2). Results for completed cases were compared with those based on multiple imputation.

RESULTS

A total of 127 participants were screened, and 62 participants (n = 17, Achilles; n = 45, patellar tendinopathy) were enrolled in the study between May 2016 and March 2020. Patient flow and reasons for exclusion are documented in Figure 2; the most common reasons for exclusion were insertional Achilles tendinopathy (n = 9) and predominant PFPS (n = 11). Three participants were lost to follow-up because of work commitments (n = 2) or loss of contact (n = 1). A comparison of participant characteristics indicated no significant baseline differences between groups (Table 1).

Over the 6-month trial period, 5 participants did not progress beyond phase 1, 10 patients completed phase 2, 40

TABLE 1
Comparison of Baseline Characteristics of the Study Groups[a]

	Control, n = 21	HVIGI, n = 21	HVIGIwSteroid, n = 20	P^b
Age, y	30.7 ± 6.9	33.8 ± 6.0	33.7 ± 7.5	.26
Height, m	1.79 ± 0.09	1.78 ± 0.07	1.81 ± 0.07	.41
Weight, kg	91.8 ± 15.4	89.6 ± 10.4	94.5 (88.5, 100.5)	.82
BMI	28.5 ± 3.8	28.1 ± 2.8	28.3 ± 2.5	.90
Chronicity, mo	18 (5.3, 30.8)	18 (13.5, 22.5)	18.5 (12, 25)	.47
Achilles tendinopathy	5	5	7	n/a
Patellar tendinopathy	6	16	13	n/a
Maximum tendon diameter, mm				
Achilles only	7.6 ± 0.64	6.6 ± 0.61	7.9 ± 2.4	.44[c]
Patella only	8.8 ± 1.8[d]	9.4 ± 1.5	8.3 (7.1, 9.5)	.16
Neovascularity (MOS)	4 (3.4, 4.6)	4 (3.5, 4.5)	4 (3, 5)	.50
Functional activity assessment	3 (2, 4)	2 (1.5, 2.5)	2 (1.5, 2.5)	.05
VISA score	38.3 ± 14.5	43.5 ± 11.9	43.2 ± 18.3	.47
VAS pain	35.2 ± 23.5	28.2 ± 20.0	35.7 ± 22.3	.47
Small knee bend	3 (2, 4)	3 (2, 4)	3 (1.6, 4.4)	.82
Strength, kg				
Achilles only	53.0 ± 42.3	88.8 ± 8.5[e]	94.2 ± 25.0[f]	.09[c]
Patella only	28.3 ± 12.4	32.3 ± 12.5	35.0 ± 10.1[g]	.33
Smoking, pack-years	0 (–1.6, 1.6)	0 (–4.4, 4.4)	4 (–0.4, 8.4)	.06

[a]Data are presented as mean ± SD, median (interquartile range [first quartile, third quartile]) where a statistic was not normally distributed or ordinal, or No. of participants. BMI, body mass index; HVIGI, high-volume image-guided injection; HVIGIwSteroid, high-volume image-guided injection with steroid; MOS, modified Ohberg score; n/a, not applicable; VAS, visual analog scale; VISA, Victoria Institute of Sport Assessment.
[b]One-way analysis of variance for normally distributed variables; Kruskal-Wallis *H* for nonnormally distributed variables.
[c]Variances not homogeneous.
[d]n = 15 not 16 (unable to determine because of position of calcification in 1 patient).
[e]n = 4 not 5.
[f]n = 6 not 7.
[g]n = 12 not 13 (unable to attempt for 1 patient because of pain).

patients completed phase 3, and 4 completed phase 4, with no difference between groups ($\chi^2_{(2)} = 1.13$; $P = .57$). Adherence to prescribed rehabilitation did not differ between groups ($\chi^2_{(2)} = 0.008$; $P = .99$). No adverse events were reported.

There was a significant main effect for improvement in VISA scores over time ($F_{(1,56)} = 67.4$; $P < .001$) but not for group ($F_{(2,56)} = 0.74$; $P = .48$), and there was no group × time interaction ($F_{(2,56)} = 0.35$; $P = .71$). Bonferroni-corrected within-group pairwise comparisons indicated that the improvements in VISA were significant in all groups from 3 months onward. Multiple imputation did not alter the significance of the results (Table 2).

VAS pain did not meet parametric assumptions (Supplemental Material 2). There was no difference in residual (change from baseline) VAS pain ($\chi^2_{(2)} = 0.20$; $P = .905$) between groups. Across all groups, VAS pain was reduced at follow-up ($z = 3.84$; $P < .0005$), Bonferroni-corrected within-group pairwise comparisons were significant for the HVIGI group ($z = 2.89$; $P = .023$) and HVIGIwSteroid group (z = 3.27; $P = .007$) but not the control group ($z = 2.45$; $P = .086$).

The additional interim data points for VISA and VAS pain were considered secondary outcome measures and are represented in Figure 3, A and B, respectively.

There was a significant main effect for time for neovascularity grade using the modified Ohberg score ($\chi^2_{(3)} = 26.79$; $P < .0005$) across all groups but no difference in residual (change in neovascularity) between groups ($\chi^2_{(2)} = 1.84$; $P = .40$). Although within each group there was a significant main effect for time ($P \leq .014$), no Bonferroni-corrected pairwise comparisons were significant (Figure 3C).

Maximum tendon diameter is reported in the patella subgroup only because of the small numbers in the Achilles subgroup. There was a significant main effect for time ($\chi^2_{(3)} = 8.25$; $P = .041$) across all groups with Bonferroni-corrected post hoc tests, indicating a significant pairwise difference between baseline and 6-month data ($P = .042$). There was no difference in residual (change in diameter) between groups ($\chi^2_{(2)} = 0.30$; $P = .86$) and no significant main effect for time within any of the 3 groups ($P \geq .14$) (Figure 3D).

The SKB score improved across all groups ($\chi^2_{(3)} = 58.91$; $P < .0005$), but there were no differences in residual (change in SKB) between groups ($\chi^2_{(2)} = 3.67$; $P = .16$). Bonferroni-corrected post hoc tests indicated significant reductions at 6 months in the control group ($d = 0.65$; $P < .0005$) and HVIGIwSteroid group ($d = 0.50$; $P = .012$) and at 3 months ($d = 0.51$; $P = .011$) and 6 months ($d = 0.64$; $P < .0005$) in the HVIGI group (Figure 3E).

Strength data are reported in the patella subgroup only because of the small numbers in the Achilles subgroup. There was a significant main effect for time across all

TABLE 2
Primary Outcome Measures at Baseline and Follow-up[a]

Group	Baseline[b]	6-mo Follow-up[b]	MD (95% CI)	P_{Adj}	ES
VISA[c]					
Control				**<.001**	1.51
Per protocol	37.0 ± 13.4	59.8 ± 16.7	22.8 (10.4-35.3)		
Pooled imputations	38.3	60.7	22.4		
HVIGI				**<.001**	1.31
Per protocol	43.3 ± 12.1	61.9 ± 16.0	18.6 (9.1-28.0)		
Pooled imputations	43.5	63	19.5		
HVIGIwSteroid				**.011**	0.88
Per protocol	44.3 ± 18.2	62.8 ± 23.3	18.5 (3.4-33.6)		
Pooled imputations	43.2	62.5	19.3		
VAS pain[d]					
Control	30 (7.8, 52.3)	15 (–4.4, 34.4)	–15 (–38.75, 8[e])	.086	0.39
HVIGI	23 (7.6, 38.4)	10 (3.8, 16.3)	–13 (–34.0, 3.75[e])	**.023**	0.47
HVIGIwSteroid	34 (16.5, 51.5)	7 (–10, 24)	–27 (–38.0, –1.0[e])	**.007**	0.54

[a]VISA met parametric assumptions for 2-way analysis of variance (ANOVA); VAS pain did not. Bolded P values indicate a statistically significant difference between baseline and 6-month follow-up ($P < .05$). Adj, Bonferroni corrected pairwise comparison; ES, effect size; HVIGI, high-volume image-guided injection; HVIGIwSteroid, high-volume image-guided injection with steroid; MD, mean difference; VAS, visual analog scale; VISA, Victoria Institute of Sport Assessment.

[b]Data are presented as mean ± SD or median (interquartile range [first quartile, third quartile]).

[c]Significant main effect for time ($F_{(1,56)} = 67.367$; $P < .001$) but not group ($F_{(2,56)} = 0.744$; $P = .480$); no group × time interaction ($F_{(2,56)} = 0.352$; $P = .705$) (2-way ANOVA).

[d]No difference in residual VAS pain ($\chi^2_{(2)} = 0.20$; $P = .905$) between groups (Kruskal-Wallis H). Across all groups, VAS pain was reduced at follow-up ($z = 3.845$; $P < .0005$).

[e]First quartile, third quartile for residual.

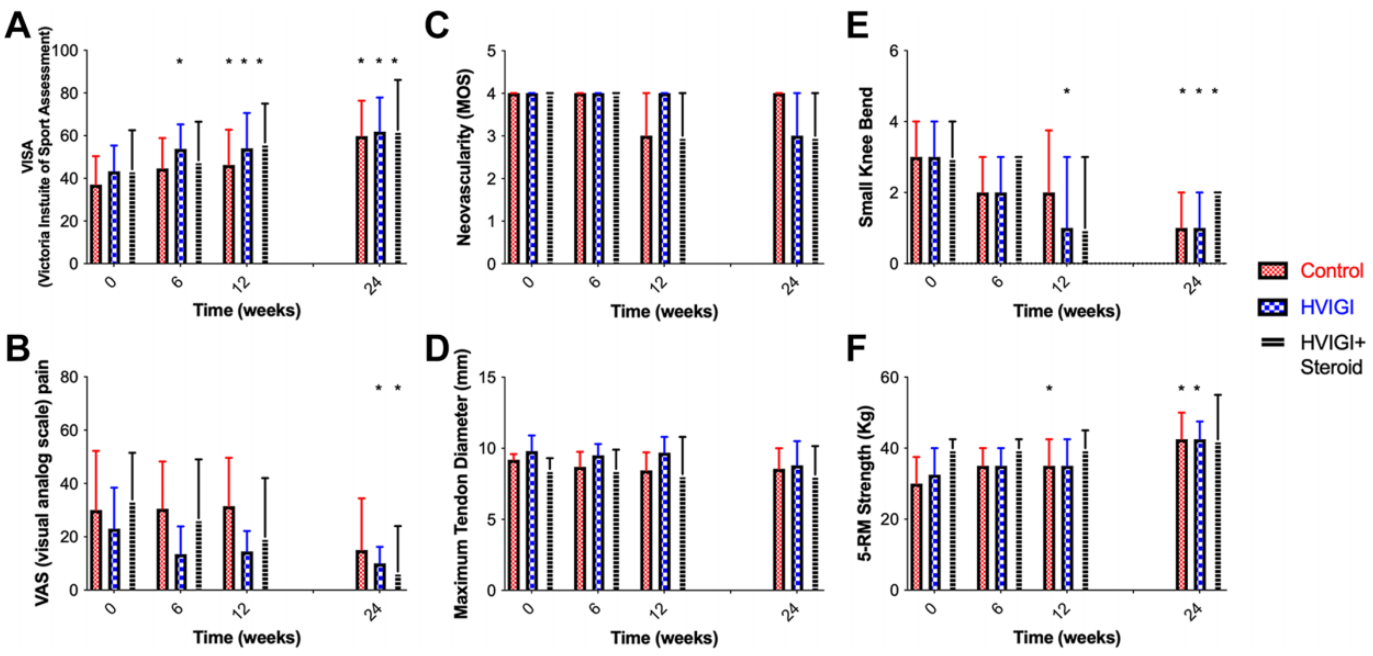

Figure 3. (A and B) Primary and (C-F) secondary outcome measures by study group. All outcomes demonstrated significant main effects for time ($P \leq .041$) but none for group, with no group × time interactions ($P \geq .16$). Error bars indicate SD from the group mean or interquartile range around the median, according to parametric testing (see text). Data for the maximum tendon diameter and 5-repetition maximum (5-RM) strength are for patellar tendinopathy cases only. *Bonferroni-corrected significant difference compared with baseline ($P < .05$). HVIGI, high-volume image-guided injection; MOS, modified Ohberg score.

groups ($\chi^2_{(3)} = 55.64$; $P < .0005$) but no difference in residual (change in strength) between groups ($\chi^2_{(2)} = 2.98$; $P = .23$). Bonferroni-corrected post hoc tests indicated significant increases in strength from baseline at 3 months ($d = 0.53$; $P = .022$) and 6 months ($d = 0.81$; $P < .0005$) in the control group and at 6 months only in the HVIGI group ($d = 0.69$; $P = .001$) (Figure 3F).

There were no differences in FAA across all time points ($\chi^2_{(3)} = 0.55$; $P = .91$) and no difference in residual (change in FAA from baseline to 6 months) between groups ($\chi^2_{(2)} = 1.50$; $P = .47$).

The VAS pain score on injection did not differ between groups ($\chi^2_{(2)} = 2.68$; $P = .26$) with medians of 25 (interquartile range [IQR], –8.3, 58.3), 39 (IQR, 20.8, 57.3), and 46.5 (IQR, 23.4, 69.6) in the control, HVIGI, and HVIGIwSteroid groups, respectively.

Of the 59 available participants who attended the 6-month follow-up where unblinding occurred, 52 participants (88%) said they had no idea which injection they had. Two participants thought they had the control injection; 1, HVIGI without steroid; 3, HVIGIwSteroid; and 1, HVIGI of either description. Of these, only 3 participants were correct in identifying their interventional group.

VISA, VAS pain, and FAA data were collected at 12 months. Three control group participants, having completed the study, elected to undergo an HVIGI at 6 months, and last observation was carried forward to 12 months. Three participants who remained under clinical care were followed up in the clinic, 6 responded via email, and 38 responded via telephone, 3 participants withdrew during the trial period, and another 9 were not contactable and therefore lost to follow-up. Twelve-month VISA data were not normally distributed in either the HVIGI or HVIGIwSteroid group ($W_{(16\text{-}17)} \leq 0.88$; $P \leq .032$). There was no difference in residual (compared with baseline) VISA ($\chi^2_{(2)} = 3.25$; $P = .20$) at 12 months, with a median of 68 (IQR, 52.5, 83.5) in the control group (n = 17), 84 (IQR, 69.5, 98.5) in the HVIGI group (n = 17), and 80.5 (IQR, 64.6, 96.4) in the HVIGIwSteroid group (n = 16). VAS pain was also not normally distributed at 12 months across all groups ($W_{(16\text{-}17)} \leq 0.85$; $P \leq .011$). There was no difference in residual (compared with baseline) VAS pain ($\chi^2_{(2)} = 0.75$; $P = .69$), with a median at 12 months of 12 (IQR, –6.8, 30.8) in the control group (n = 17), 2 (IQR, –3, 7) in the HVIGI group (n = 17), and 8 (IQR, 1.1, 14.9) in the HVIGIwSteroid group (n = 16). There was no difference in residual (compared with baseline) FAA ($\chi^2_{(2)} = 4.06$; $P = .13$), with a median at 12 months of 2 (IQR, 1, 3) in the control group (n = 17), 2 (IQR, 1.5, 2.5) in the HVIGI group (n = 17), and 2 (IQR, 1.6, 2.4) in the HVIGIwSteroid group (n = 16).

DISCUSSION

The results of this double-blind RCT showed that neither an HVIGI with nor one without steroid resulted in significant differences in pain and function outcome measures at the 6-month follow-up compared with a sham-control injection. All outcomes demonstrated significant main effects for time but none for group, with no group × time interactions. Inspection of the graphed interim secondary data indicated a pattern of accelerated reductions in pain in the HVIGI without steroid group at 6 weeks and 3 months, but this was not statistically significant. Further differences in pain and function at 12 months were not significant.

As there were no differences in the secondary outcome measures, including neovascularity and tendon thickness, the results of this study do not support the proposed mechanistic effect that HVIGI achieves in disrupting associated painful nerve fibers. This is despite the confirmation of disappearance of Doppler activity at the end of each interventional procedure. One theory is that neovascularity remains after the procedure but is not immediately visible because of compression. Further neovascularity at the 6-week interim follow-up was not significantly reduced compared with baseline.

The study findings are in line with those of van der Vlist et al,[32] who also prescribed progressive loading to all patients in their RCT comparing HVIGI without steroid to placebo. The current study also included a 12-month follow-up and third trial arm to compare HVIGI with and without steroid. The lack of group differences across both studies, conducted using similar methods, in conjunction with the success of the control group in the current study, supports the use of pain-guided progressive loading as the mainstay of treatment. RCT evidence has demonstrated the superiority of progressive loading to eccentric loading in patellar tendinopathy.[5] Note that the current study recruited participants who had already followed progressive loading as part of their initial routine clinical care. Further, the exclusion criteria were strictly applied so that patients who had not genuinely attempted progressive loading were not recruited (n = 8). How to replicate the clinical improvements after similar therapy in a controlled trial setting is worthy of further hypothesis generation and investigation.

The current study did not mirror significant reductions in pain and function scores after HVIGIwSteroid, as demonstrated by the RCT of Boesen et al[4] at 6 weeks and 3 months compared with the sham control. The reason for this could be a result of our strictly pain-titrated loading prescription and generally more conservative approach to progression. In the study of Boesen et al, participants were permitted to return to running after 10 days, which may have amplified short-term group differences. It is noted that in an RCT in patellar tendinopathy, peritendinous steroid injection (1 mL of 40-mg/mL methylprednisolone) showed significant improvement at 12 weeks that trended higher than eccentric loading and heavy slow resistance training but regressed to baseline at 6 months. Improvements in the comparator groups were maintained.[16] Taken together in the medium to long term, the control of pain levels in tendinopathy is a priority, but careful load prescription rather than injectable therapy may result in more enduring improvements. This may be particularly true for more chronic cohorts, such as the current study (18 months' duration), characterized by long-established degenerative mechanisms.[24] Degenerative mechanisms are less likely than acute inflammatory processes to respond to treatment targeting inflammation, such as peritendinous steroid,

which has been implicated in tendon rupture.[11,12,15] Steroid cannot, therefore, be recommended as a first-line treatment in the target population of the current study.

Participants who returned with the acceptable pain levels described were encouraged to progress via the pathway providing they continued to meet load tolerance test criteria.[1] This approach may seem counterintuitive to clinical patients,[23] but the structured, well-supervised, and logged continuation of loading would likely explain improvements in a population who had previously not responded to physical therapy.

The aims for future work should be to optimize service delivery to support physical therapy as demonstrated, with a focus on patient education, and to improve objective outcome measures to enhance patient experience and compliance.

Limitations

Limitations of the current study include the number of participants at the lower end of the target range for recruitment because of continuation becoming unfeasible after the onset of the COVID-19 pandemic. It may be argued that the study has made an assumption in pooling data across 2 diagnoses in Achilles and patellar tendinopathy, but there is rationale and precedent for doing so.[26] Nonetheless, a larger sample would have allowed for a subgroup analysis that would be underpowered on the existing data.

A greater limitation may be the imprecision of using the VISA score in a heterogeneous population not defined by 1 particular sport or activity.[22] As 40 of 100 points are awarded for participation of the individual's "sport," construct validity may be affected depending on how participants choose to define their activity.[25] A participant who can play a round of golf without pain may participate fully and score 40 points, whereas if they interpreted the question as the ability to run, they may score 0. Furthermore, in this study, specific participant activity was limited by instructing participants not to engage in any activity other than that prescribed to the 6-month follow-up. This may have made interpretation of the participation question hypothetical or introduced a ceiling effect. Participants may have changed the activity on which they based the final question, affecting the reliability and responsiveness. There are a number of possible solutions to this, with the simplest being to ensure consistency with participant understanding of which sport they are scoring or the development of more sensitive questionnaires, as well as objective measures of tendon health.

CONCLUSION

This double-blind RCT showed that neither an HVIGI with nor one without steroid resulted in significant differences in pain and function outcome measures at the 6-month follow-up compared with a sham-control injection in participants with either chronic Achilles or patellar tendinopathy, who underwent a 6-month pain-guided progressive loading program. However, across all groups, there were significant improvements.

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