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Evaluation of the efficiency of an ultrasound-supported infiltration technique in patients with tennis elbow applying the ITEC medical device: a multicenter study

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Background: The treatment of lateral epicondylitis remains unsatisfactory in certain cases. The aim of this study is to investigate the efficiency of an ultrasound-guided infiltration combined with fenestration of the extensor tendon postulating a 50% reduction in pain on exertion within 6 months.
Methods: In a prospective, nonrandomized, multicenter study design, 68 patients with chronic lateral epicondylitis and symptoms lasted for at least 6 weeks were included. Each hospital has been assigned for Traumeel (A), autologous whole blood (B), or dextrose (C) in advance. Preinterventional, 6 weeks, 12 weeks, 6 and 12 months after infiltration, patient-related outcome parameter, and dorsal wrist extension strength were documented. Preinterventional (obligate) and after 6 months (optional) radiological evaluation (magnetic resonance imaging) was performed.
Results: The Visual Analog Scale showed a significant reduction after 6 months in all groups (A. 4.8-2.5, B. 6.2-2.3, C. 5.8-2.4). Similar results could be observed with Subjective elbow value, Disabilities of Arm, Shoulder, and Hand Score, Mayo Elbow Performance Score, and Patient Rated Tennis Elbow Evaluation. The loss of strength could be completely compensated after about 6 months. Magnetic resonance imaging did not fully reflect clinical convalescence. Re-infiltrations were sometimes necessary for final reduction of symptoms (A = 11, B = 8, C = 4). Switching to surgical intervention was most frequently observed in group C (A = 2, B = 1, C = 5). In 14.5% of the cases, no improvement of the symptoms could be achieved with this method.
Conclusion: The primary hypothesis of a significant long-term pain reduction of at least 50% could be achieved regardless of the medication chosen.

The treatment of lateral epicondylitis (LE) is multifaceted but remains unsatisfactory in certain cases. Physiotherapy, orthotic treatment, a “wait and see strategy”, and surgical interventions emphasize the complexity of the treatment variety.[14] Infiltration therapy can be an important part of the cascade.[15] In addition to the choice of medication, accurate application is an indispensable prerequisite for the success of the therapy. Keijsers et al already showed a 60% misapplication intra-articularly instead of the proper infiltration of the tendon attachment of the extensor carpi radialis

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Local ethics committee (Charité—University of Berlin) approval was obtained (registration number: EA4/228/17).
All patients gave consent to be included in this study.

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brevis (ECRB) tendon and postulated an ultrasound-supported technique.[11] Cutaneous penetration as such also seems to have a relevant influence on the healing tendency. With the description of the "peppering" technique, Altay et al already proved that the injection technique with multiple punctures has a relevant advantage over conventional infiltration therapy, independent of the applied medication.[1]

The choice of the injection fluid to be applied also has a relevant impact on the healing process. Corticosteroids act at the cellular level by inhibiting cytokinesis and proinflammatory factors, thereby enabling a reduction in inflammation, neo-vascularization, and tendon thickness.[18] However, meta-analyses point to a short-term effect with a possible rebound phenomenon after 6 weeks.[6] The application of platelet-rich plasma (PRP) or autologous whole blood has been shown to be promising, however controversial in a variety of studies. The intention of the treatment is to support natural tendon healing by generating growth factors such as PDGF, IGF-1, VEGF, and TGF-ß1.[23]

Prolotherapy is based on infiltration of osmotic or chemotactic stimulants such as dextrose or polidocanol. The iatrogenically delivered inflammatory stimulus induces fibroblast growth and collagen synthesis, resulting in vigorous tendon repair.[20]

Traumeel, which belongs to the homeopathic formulary, is also widely used in the treatment of musculoskeletal tendopathies in Europe.[22] The healing mechanism results from the interaction of the individual components, which have been used in isolation for pathological entities of the musculoskeletal system such as pain (atropa) and hematoma (arnica).[22]

The objectification of therapy success is usually defined by patient-reported outcome measures (PROMs). With the introduction of the "Minimal Clinical Important Difference" (MCID), statistically significant results are relativized in terms of clinical importance. Therapy for LE was considered effective if the average difference in score results between baseline and follow-up exceeded the following MCIDs: 1.5 points for the Visual Analog Scale (VAS); 16 points for Disabilities of Arm, Shoulder, and Hand Score (DASH); 11 points for Patient Rated Tennis Elbow Evaluation (PRTEE); and 15 points for Mayo Elbow Performance Score (MEPS).[19]

The aim of this multicenter study is to analyze the efficiency of a standardized, ultrasound-controlled infiltration therapy of patients with chronic LE using different injection fluids (Traumeel, dextrose, autologous whole blood). Based on the "Dutch" protocol, presented by Keijers et al the "Instant Tennis Elbow Cure Device" (ITEC Medical, Enschede, Overijssel, The Netherlands) consisting of a table with an attached injection arm was used.[12] The ECRB tendon can be perforated using the device, after an ultrasound measurement has been performed to determine the depth of the tendon. The device contains an injection disposable with 12 small needles, which are arranged in a 3×4 formation and adapted to the anatomy of the ECRB. It was hypothesized that a possible summation effect of the tendon fenestration and the administered medication would lead to a reduction of 50% pain on exertion within 6 months with objectification by improved dorsal wrist extension. Furthermore, it was questioned, whether the efficiency depends on the applied substance and if there were any differences concerning their mode of action. In addition to pain reduction, the number of infiltrations required and the conversion rate to surgical intervention are decisive in this regard. Finally, it was investigated whether this technique enables a long-term pain relief or whether a rebound effect occurs similar to the use of corticosteroids.[6]

Materials and methods

The study protocol was approved by the local ethics committee (registration number: EA4/228/17).

Study design and participants

The prospective, multicenter, nonrandomized cohort study included patients with clinically and radiologically confirmed chronic LE. Patients were recruited via the specialist consultations of 3 hospitals with focus on shoulder and elbow, whereby each hospital was assigned an application arm in advance (A: Traumeel, B: autologous whole blood, C: dextrose). In addition to the confirmed clinical appearance, the following criteria had to be met for positive inclusion: The duration of symptoms had to be at least 6 weeks after unsuccessful conservative treatment. In particular, no infiltration therapy should have been performed before inclusion in the study. The existing pathology was clinically confirmed by the presence of positive pressure pain over the radial epicondyle as well as a positive Cozen and Maudsley's test. Only study participants with an age between 18 and 65 years were included. There must be an unremarkable X-ray except for possible calcification in the extensor tendon region. Patients with previous infiltration therapy or surgery, subsequent fractures conditions, or with a systemic rheumatologic disease were excluded. Allergies to the substances to be applied as well as bilateral occurrence and medial epicondylitis were also among the exclusion criteria. For each application arm (A: Traumeel, B: autologous whole blood, C: dextrose), the inclusion of 20 patients was planned according to a performed power analysis.

Protocol

Five follow-ups were defined including preinterventional inclusion (T0), 6 weeks (T1), 12 weeks (T2), 6 months (T3), and 1 year (T4) after infiltration according to the schematic representation in Fig. 1. For each included patient, detailed documentation of epidemiological data (age, occupation, sports, handedness, affected side, duration of discomfort) before study inclusion was done. The details of the infiltration, such as the infiltration depth and re-infiltrations, if necessary, were also documented. Potential complications of the intervention were recorded, specified, and documented at each patient contact. The grip strength was measured with a hand dynamometer or a commercially available force-measuring device (IsoforceControl EVO2; Herkules Kunststoff AG, Oberburg, Switzerland) by performing dorsal wrist extension in 3 repetitions. Mean value was included as percentage of the healthy opposite side. Radiological imaging included a standardized postero-anterior and lateral radiograph of the elbow joint. The initial native magnetic resonance imaging (MRI) examination was performed on an extended and supinated arm. PROMs (VAS, Subjective Elbow Value [SEV], MEPS, DASH, and PRTEE), which address the elbow joint in general and the pathology specifically, were documented at each examination time point.

Device and infiltration technique

Primarily, the tendon thickness of the ECRB tendon was determined by ultrasound. Depth measurement takes place perpendicularly from the skin to the middle of the tendon, at half the distance epicondyle—radial head. The infiltration of the affected arm was performed using the Instant Tennis Elbow Cure (CE 621544; ITEC

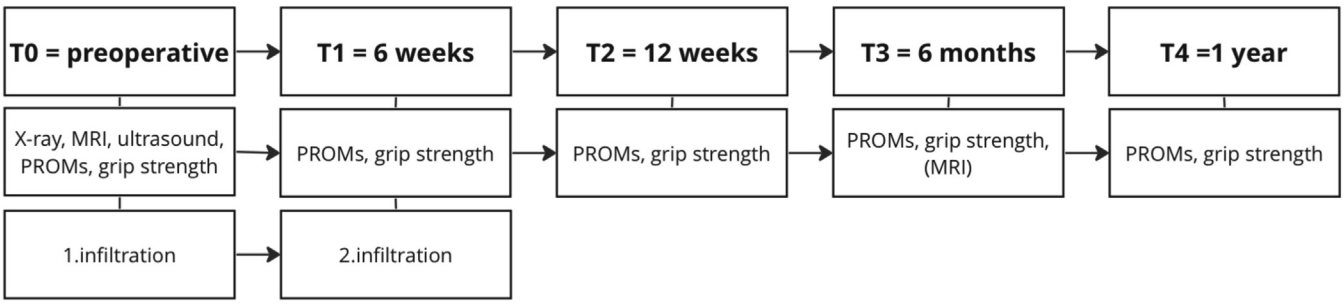

Figure 1 Flow chart presenting study design. *MRI*, magnetic resonance imaging; *PROMs*, patient-reported outcome measures.

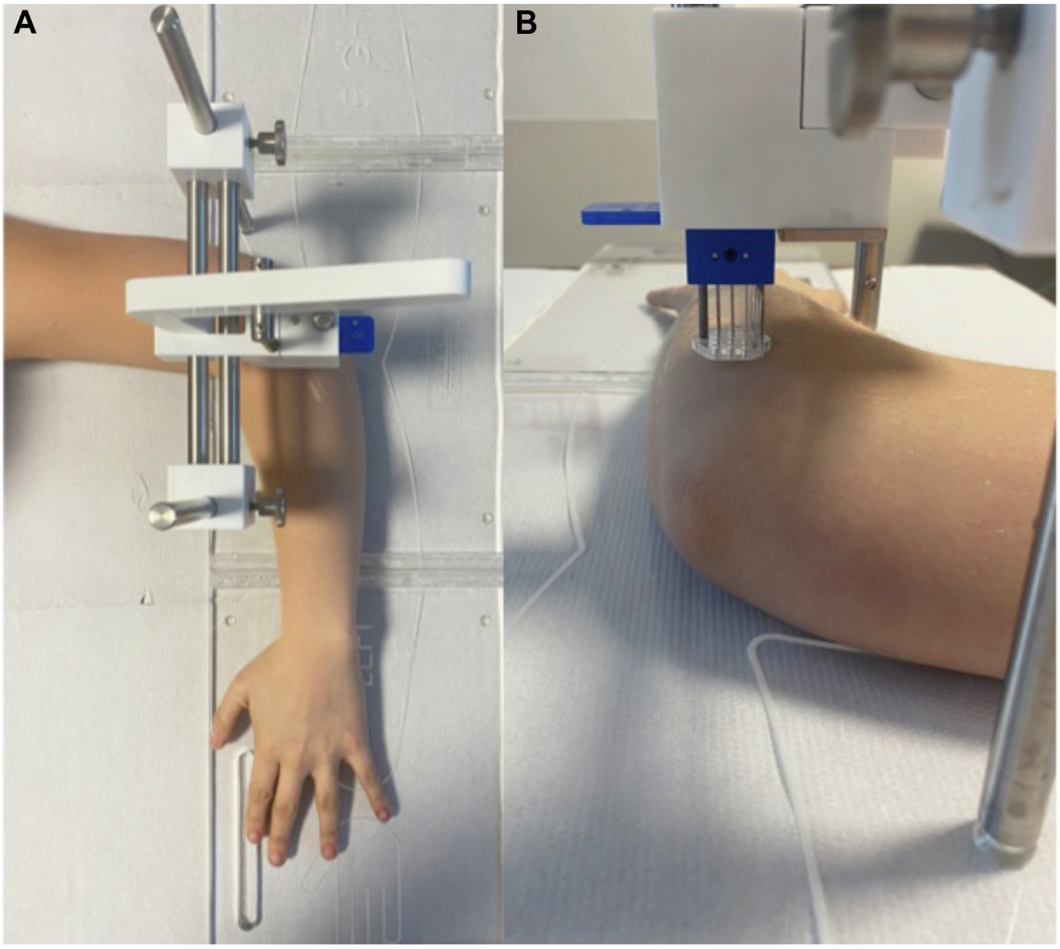

Figure 2 (**A**) Demonstration of the ITEC medical system; (**B**) Positioning of the arm in the device with view of the needle patch.

Medical, Enschede, Overijssel, The Netherlands), consisting of injection table ITEC-id with a depth adjustment screw and injection disposable ITEC-id. This has a fluid injection port through which the respective injection fluid is applied (Fig. 2).

The arm was then positioned in 90° flexion in the elbow joint and 90° abduction in the shoulder in the marked area inside the device. Local anesthesia is not used, contrary to the initial description, not to falsify the determined perforation depth and to negate possible interactions with the local anesthetic. Subsequently, percutaneous perforation with the aid of the associated needles is performed. The infiltration is triggered by pressing down the device lever and allows an application of 12 drops corresponding to a total volume of 0.4 mL (Fig. 2). The respective infiltration could be repeated once after 6 weeks if the therapy was not successful enough.

Outcome measurements

Primary outcome parameter

The primary outcome parameter was defined as a 50% reduction (VAS) on exertion within 6 months in dependence of the applied injection fluid. The objective stress test was a dorsiflexion of the wrist with the elbow joint extended.

Secondary outcome parameters

The secondary end points were defined as the reduction in VAS on exertion at 6 weeks, 12 weeks, 6 months, and 1 year postintervention. At T1-T4, PROMs (DASH, MEPS, PRTEE, SEV) and grip strength were measured. The primary and secondary outcome parameters were correlated with the respective follow-up dates T1-T4 and the corresponding application arm. Randomization for a particular application arm was not possible in this setting, as 1 application substance is administered by 1 hospital at a time.

Comparison with historical group

The generation of a control group with singular infiltration of corticosteroids was waived for ethical reasons in view of the proven possibility of tendon degeneration and the rebound phenomenon described.[6,29] Instead, a comparison was made with a historical control group presented by Bisset et al with a nearly identical study design.[3] The double-blinded randomized controlled trial investigated the effectiveness of physiotherapy compared to the "wait and see" strategy and cortisone infiltrations over a period of 52 weeks with defined follow-up points. This involved the inclusion of 198 study participants (aged 18-65 years) with a clinical diagnosis of LE. Sixty-five patients received cortisone infiltration. Patients had a minimum duration of complaints of 6 weeks and were not undergoing any therapy until the time of study inclusion. The inclusion criteria and the follow-up times were identical to those in the present study. The outcome parameters included a strength measurement and the VAS related to the past week.[3] The visualization scale of pain was collected on a scale from 0 to 100 in the study by Bisset et al so that it was divided by 10 in the present study for better comparability.[3]

Calculation and statistics

The REDCap system (Research Electronic Data Capture; Vanderbilt University, Nashville, TN, USA) was used for data collection, which enables central digital data entry by the participating hospitals. The data were exported anonymously as a CSV or Excel file. Only patients with complete datasets were considered in REDCap.

The sample size for the analysis of variance (ANOVA) for the primary variable VAS pain was a priori calculated considering the expected effect size, power, and design effect with G*Power (Version 3.1.9.2; Heinrich Heine Universität, Düsseldorf, Germany). An effect size of f = 0.416 was assumed, derived from a study by Bisset et al, which examined the effects of injections on pain after 6 months, among other factors.[3] Therefore, with an alpha risk of 0.05 and a statistical power of 0.8, a sample size of 60 (20 patients in each of the 3 groups) is required to detect significant differences in a 1-way ANOVA design at 6 months of follow-up.

The evaluation of the demographic data, infiltration depth, pain duration, and the PROMs was carried out by descriptive statistics with indication of the mean value with standard deviation. The Shapiro-Wilk test was used to test for normal distribution. To determine the significance level, the Kruskal-Wallis test or X^2 test was used for the categorical, independent variables (gender, injured hand, dominant elbow affected, trauma, employment, manual work, clinical appearance) at T0. For metric measurement scale levels (age, pain duration, infiltration depth), the evaluation was carried out using single-factor ANOVA. For the evaluation of the patient-related outcome parameters (VAS, SEV, DASH, MEPS, and PRTEE) and for the grip strength, the Mixed Model Repeated Measurements analysis was used including the 3 application groups over the examination time points T0-T4.

To analyze occupational activity as a potential factor influencing recovery, the occupations were divided into 4 groups and coded with a number (0 = no occupation; 1 = desk occupation; 2 = manual occupation; 3 = occupation not clearly assigned to the previous categories). To analyze this nominal characteristic with the metric variables such as SEV, VAS, and their respective changes, the Eta coefficient was calculated.

The correlation between MRI findings (Walz stage) and pain (VAS) were correlated using the Kendall-Tau-b test, as it is based on a comparison of a metric with an ordinal variable.

Statistical analysis was performed using GraphPad Prism Version 8.0 (GraphPad Software, San Diego, CA, USA) and SPSS (IBM SPSS Statistics 25; IBM Corp., Armonk, NY, USA). A P value < .05 was considered significant.

Results

Participant flow and follow-up

According to the inclusion criteria, 68 patients were included. Primarily, group A included 22 patients, group B 26, and group C 20 patients. Incomplete initial datasets and a possible interaction with an independent therapy regime for another pathology led to the final group sizes of (A) 20, (B) 22, and (C) 20. The final group numbers, taking into account therapy conversion or dropouts, are shown in Fig. 3. The mean age was 47.4 ± 7.0 years (A: 48.6 ± 7.6; B: 48.1 ± 5.9; C: 45.6 ± 7.1), with 34 males and 28 females in the patient population (A 13:7, B 9:13, C 12:8). The dominant side was affected in a total of 42 patients (corresponding to 67.7%). In group A, the dominant arm was affected in 12 of 20 patients (60.0%), in group B in 15 of 22 (68.2%), and in group C in 15 of 20 (75.0%). The average duration of symptoms before inclusion in the study was 11.4 ± 16.7 months (A: 13.9 ± 15.6; B: 14.5 ± 22.6; C: 5.6 ± 3.3). The full demographic data are shown in Table I.

Baseline characteristics (=T0)

At intervention inclusion, there was no significant difference in age, gender distribution, and depth of infiltration between the 3 treatment groups.

Regarding the duration of complaints, there was a significant difference between the treatment groups with a shorter duration of complaints for group C (P < .05) (Table I), whereby the overall duration of complaints was significantly longer than the minimum duration of 6 weeks.

With regard to the PROMs, there were no significant differences for the score results SEV and PRTEE in contrast to VAS, DASH, and MEPS. Despite the statistical significance, the clinical differences are rather secondary when considering the MCID of the individual parameters ($MCID_{literature}$/$MCID_{study}$: DASH 15.8/13.3, MEPS 15/7.39). The VAS showed 0.1 points above the MCID ($MCID_{literature}$/$MCID_{study}$: 1.5/1.6).

Primary outcome parameter (T1-4)

The baseline (T0) VAS score was 5.1 for the total patient population (A: 4.2; B: 5.8; C: 5.3). There was a significant reduction in pain of >50% in all 3 treatment arms at T3 (A: 1.7, B: 1.4, C: 1.5). Overall, a mean reduction of 69.8% within 6 months (A: 60.0%; B: 75.2%; C: 71.1%) was demonstrated, thus verifying the primary hypothesis. At the 1-year follow-up (T4), the mean score of the entire population was 0.8 (A: 1.1; B: 0.6; C: 0.7). Over the entire

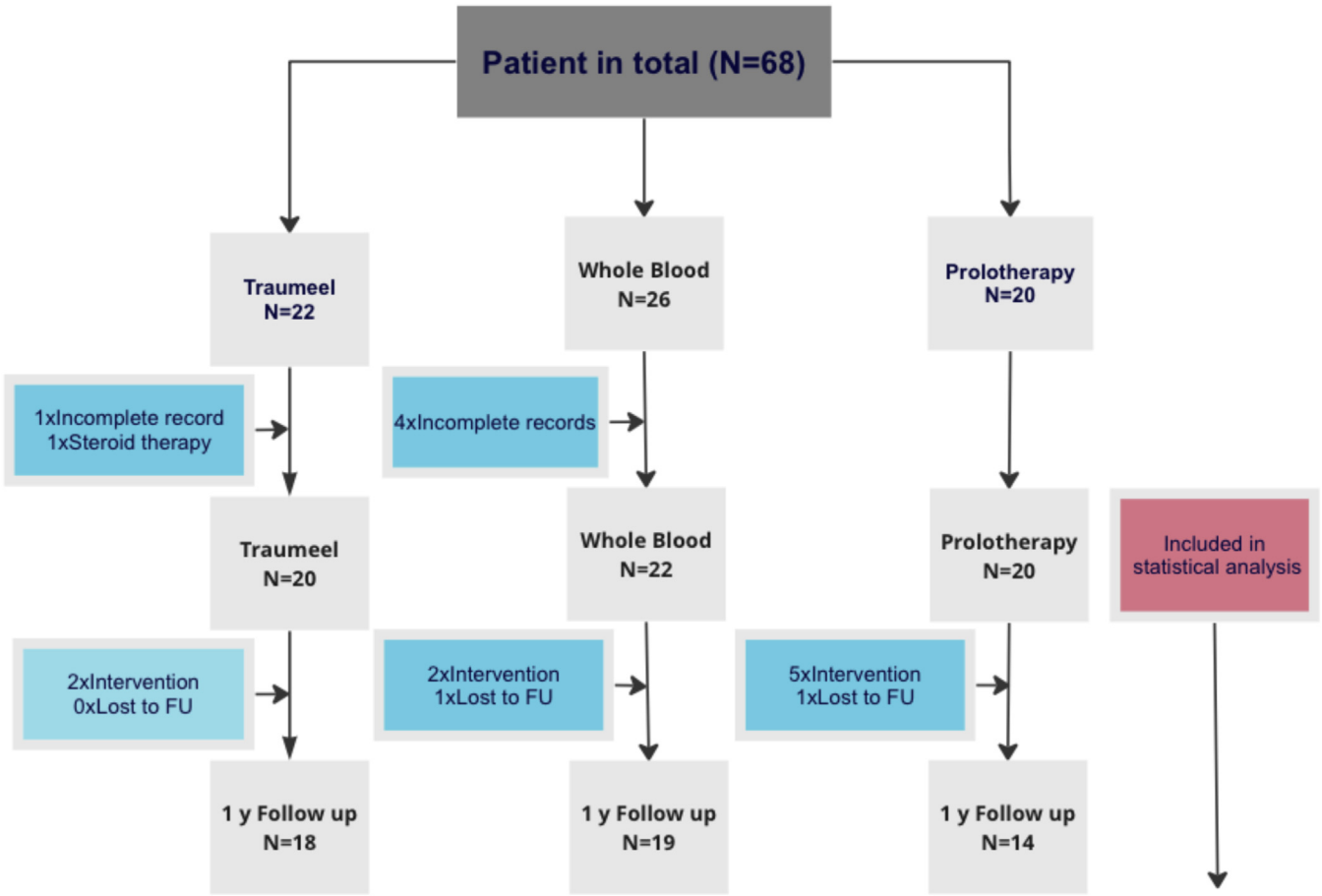

Figure 3 Representation of patient inclusion including follow-up and drop out.

Table I
Demographic data.

Characteristics	Traumeel	Whole blood	Prolotherapy	*P*
Demographic data (N)	20	22	20	
Age (y)	48.6 ± 7.6	48.1 ± 5.9	45.6 ± 7.1	ns
Gender (m/f)	13:7	9:13	12:8	ns
Duration of pain (mo)	13.9 ± 15.6	14.5 ± 22.6	5.6 ± 3.3	*
Injured hand (N) (r/l)	12:8	15:7	16:4	
Dominant elbow affected (%/100)	60.0	68.2	75	
Trauma (%/100)	54	35	35	
Employment (%/100)	100	97	90	
Manual work (%/100)	54	42	45	
Infiltration depth (mm)	5.5 ± 1.0	6.7 ± 2.0	5.9 ± 0.0	ns
Clinical appearance (N)	20	22	20	
DS Epicondylus (%/100)	95.0	100.0	100.0	ns
Cozen test (%/100)	95.0	100.0	100.0	ns
Maudsley test (%/100)	90.0	81.8	100.0	ns
PROMs (N)	20	22	20	
SEV (%)	47.2 ± 15.9	51.4 ± 18.7	54.8 ± 10.1	ns
VAS (points)	4.2 ± 1.6	5.8 ± 2.1	5.3 ± 1.3	*
PRTEE (points)	39.7 ± 12.9	43.8 ± 17.5	49.0 ± 14.4	ns
DASH (points)	64.5 ± 16.2	66.6 ± 17.5	77.8 ± 9.8	*
MEPS (points)	64.5 ± 8.9	68.6 ± 10.3	61.3 ± 13.8	*
Grip force (% healthy upper extremity)	74.6 ± 29.3	66.0 ± 36.2	55.9 ± 12.2	ns

PROMs, patient-reported outcome measures; *SEV*, subjective elbow value; *VAS*, visual analog scale; *DASH*, disabilities of arm, shoulder, and hand score; *PRTEE*, patient rated tennis elbow evaluation; *MEPS*, mayo elbow performance score.
*$P \leq .05$.

period, all groups showed a significant reduction in pain perception from T0-T4 (A-C, $P < .05$). In the mixed model measurement analysis, there is no significant difference between the groups from the sixth week onwards with regard to the course over the entire observation period. The detailed results are listed in the Table II and Figs. 4 and 5.

Table II
Results T0-T4 for PROMs and grip strength (mixed model repeated measurements analysis).

	VAS (pts)			SEV (%)			DASH (pts)			MEPS (pts)			PRTEE (pts)			Grip strength (%)		
	Mean 1	Mean 2	*P*	Mean 1	Mean 2	*P*	Mean 1	Mean 2	*P*	Mean 1	Mean 2	*P*	Mean 1	Mean 2	*P*	Mean 1	Mean 2	*P*
T0																		
Traumeel vs. Whole Blood	4.15	5.76	*	47.15	51.36	ns	64.45	66.59	ns	64.50	68.64	ns	39.65	43.82	ns	74.55	66.00	ns
Traumeel vs. Prolotherapy	4.15	5.29	*	47.15	54.75	ns	64.45	77.75	†	64.50	61.25	ns	39.65	48.90	ns	74.55	55.85	*
Whole Blood vs. Prolotherapy	5.76	5.29	ns	51.36	54.75	ns	66.59	77.75	*	68.64	61.25	ns	43.82	48.90	ns	66.00	55.85	ns
T1 6 w																		
Traumeel vs. Whole Blood	3.05	2.92	ns	58.40	67.73	ns	48.30	48.77	ns	75.25	77.73	ns	27.10	22.27	ns	80.65	86.76	ns
Traumeel vs. Prolotherapy	3.05	3.56	ns	58.40	66.94	ns	48.30	70.50	†	75.25	64.44	ns	27.10	40.17	ns	80.65	80.28	ns
Whole Blood vs. Prolotherapy	2.92	3.56	ns	67.73	66.94	ns	48.77	70.50	‡	77.73	64.44	†	22.27	40.17	*	86.76	80.28	ns
T2 12 w																		
Traumeel vs. Whole Blood	2.03	1.91	ns	65.78	80.77	ns	45.83	39.45	ns	79.72	83.64	ns	20.72	13.77	ns	95.06	85.76	ns
Traumeel vs. Prolotherapy	2.03	2.46	ns	65.78	76.11	ns	45.83	58.06	ns	79.72	74.44	ns	20.72	28.56	ns	95.06	84.67	ns
Whole Blood vs. Prolotherapy	1.91	2.46	ns	80.77	76.11	ns	39.45	58.06	*	83.64	74.44	ns	13.77	28.56	ns	85.76	84.67	ns
T3 6 m																		
Traumeel vs. Whole Blood	1.66	1.42	ns	84.72	84.14	ns	39.50	33.33	ns	87.78	87.86	ns	15.72	10.05	ns	100.80	93.60	ns
Traumeel vs. Prolotherapy	1.66	1.51	ns	84.72	82.81	ns	39.50	46.25	ns	87.78	86.25	ns	15.72	15.94	ns	100.80	94.50	ns
Whole Blood vs. Prolotherapy	1.42	1.51	ns	84.14	82.81	ns	33.33	46.25	ns	87.86	86.25	ns	10.05	15.94	ns	93.60	94.50	ns
T4 12 m																		
Traumeel vs. Whole Blood	1.04	0.61	ns	83.72	92.05	ns	34.11	28.90	ns	90.83	92.5	ns	9.28	5.60	ns	98.76	97.05	ns
Traumeel vs. Prolotherapy	1.04	0.73	ns	83.72	86.60	ns	34.11	38.07	ns	90.83	94.33	ns	9.28	9.33	ns	98.76	101.20	ns
Whole Blood vs. Prolotherapy	0.61	0.73	ns	92.05	86.60	ns	28.90	38.07	ns	92.50	94.33	ns	5.60	9.33	ns	97.05	101.20	ns

PROMs, patient-reported outcome measures; *VAS*, visual analog scale; *SEV*, subjective elbow value; *DASH*, disabilities of the arm shoulder and hand; *MEPS*, Mayo elbow performance score; *PRTEE*, patient rated tennis elbow evaluation.
*$P \leq .05$.
†$P \leq .01$.
‡$P \leq .001$.

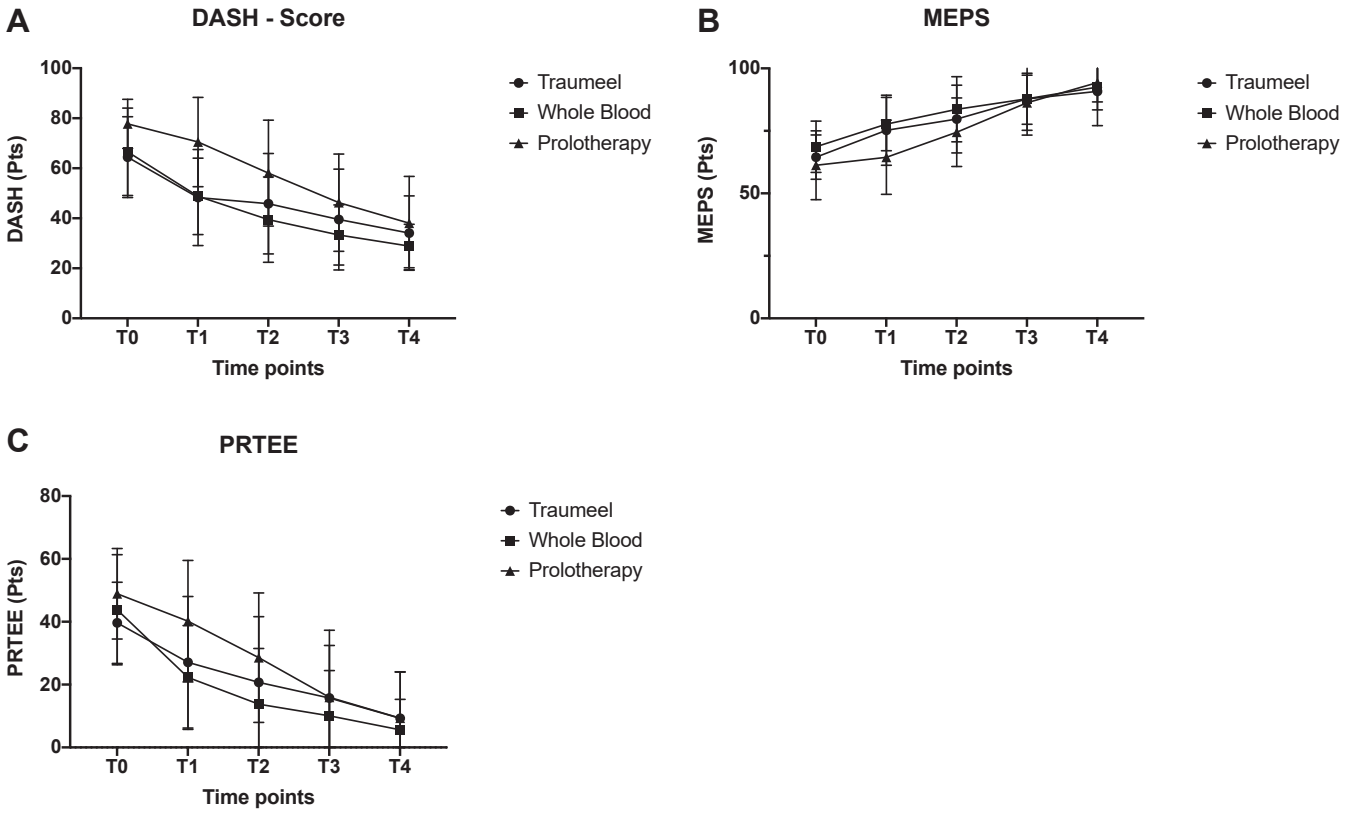

Figure 4 Graphical presentation of the outcome parameters DASH (**A**), MEPS (**B**), and PRTEE (**C**) for T0-T4 (mean/SD). *DASH*, disabilities of the arm shoulder and hand; *MEPS*, Mayo elbow performance score; *PRTEE*, patient rated tennis elbow evaluation; *SD*, standard deviation.

Secondary outcome parameter

The SEV significantly reflects complaints reduction numerically from T0 to T4, in analogy to the VAS progression. Both the averaged value of the entire patient population and the individual treatment groups showed a significant increase in SEV over the treatment period. The average of the entire patient population at study inclusion (T0) was 51.1 (A: 47.2, B: 51.4, C: 54.8). At mid-year follow-up (T3), the SEV was 84.0 (A: 84.7, B: 84.1, C: 82.8). Over the entire period, all groups showed a significant increase in SEV from T0 to T4

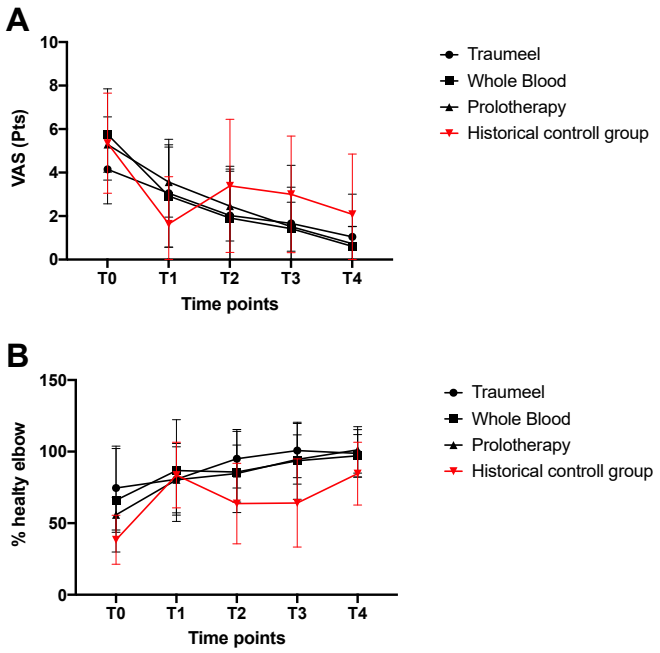

Figure 5 Graphical presentation of the outcome parameters VAS (**A**) and grip strength (**B**) (T0-T4) (mean/SD), compared to a historical patient group with corticosteroid treatment according to Bisset et al (mean/SD).[3] *VAS*, visual analog scale; *SD*, standard deviation.

(A-C, $P < .05$). The MEPS and DASH score as elbow-specific scores also showed highly significant results regarding pain reduction and functionality of the affected elbow joint. The PRTEE score, specially designed for the pathology of epicondylitis, confirms the treatment success of all 3 forms of application with a likewise significant progression from T0 to T4 (A-C, $P < .05$).

The grip strength results averaged 65.5% compared to the healthy extremity at the time of study inclusion (A: 74.5%; B: 66.0%; C: 55.8%). After 6 weeks, an increase in strength on 82.7% of the opposite side was observed in the total patient population (A: 80.6%, B: 86.8%, C: 80.2%). At the 12-week follow-up, the strength of the affected side averaged 88.4% of the opposite side (A: 95.1%, B: 85.8%, C: 84.7%). At the 1-year follow-up, the measured strength in the total cohort was 98.8% of the healthy side (A: 98.7%, B: 97.1%, C: 101.2%). Over the entire period, all groups showed a significant increase in strength with alignment to the existing strength of the unaffected limb (A-C, $P < .05$). The complete detailed information is presented in Table II and Figs. 4 and 5.

Group comparisons

PROMs

Taking the MCID into account, there are only minor differences between the application groups. A clear superiority of a drug cannot be formulated, only a tendency toward a faster onset of action of autologous whole blood. With regard to PROMs (SEV, MEPS) and grip strength, there is no significant difference between the groups and the course over time. DASH and PRTEE show better results for autologous whole blood compared to prolotherapy from T1 onwards including the MCID aspect (Fig. 5, Table II).

Comparison with historical group

According to the explanations in the method section, the comparison of the results for the outcome parameters VAS and grip strength was carried out in comparison with a patient group after conventional cortisone treatment. For both items, there was an improvement over the entire timeline similar to our patient cohort, but the rebound effect was only confirmed for the VAS at week 6 postintervention in the historical group. In a weakened form, this is also reflected for the strength development between the sixth and 12th postintervention week in the reference group (Fig. 5).

Repetition infiltration and therapy conversion

In some patients, a second infiltration using the same standardized procedure was necessary to achieve a final relief in symptoms. This was performed in case of persistent complaints according to the study protocol at the first follow-up (6 weeks after the original intervention) with the same medication at the previously measured depth. A total of 23 re-infiltrations were performed (N = A 11 [55%], B 8 [36%], C 4 [20%]). Patients with a wish for a second infiltration had an average VAS of 4.3 points (vs. total 3.2 points), SEV of 53.9 (vs. total 64.4%), and PRTEE of 39.0 points (vs. total 29.2 points) at the time of re-infiltration.

In total, 9 patients underwent therapy conversion toward surgical intervention (14.5%) with the highest proportion in group C (Table III). Patients, who have opted for surgical therapy, had a SEV of 42.5%, VAS of 3.0 points, and PRTEE score of 42.5 on average. The comparison of the mean values of the entire T0 population with the mean values of the therapy converters does not show a targeted failure pattern with missing significances (Table IV). No complications were reported during the entire follow-up period.

Radiological parameters

The initial X-ray showed calcification of the extensor insertion in a total of 8 patients (corresponding to 12.9%) (N = A: 3; B: 1; C: 4) with otherwise unremarkable radiographic findings.

The MRI evaluation of the degree of tendinopathy was based on the Walz classification system.[27] With 60 initial MRI images (100%) (inclusion of 2 patients without initial MRI), the following distribution pattern (N) was found: Grade 0 = 1 (2%), Grade 1 = 21 (35%), Grade 2 = 37 (62%), and Grade 3 with evidence of complete rupture in N = 1 (2%). Optional follow-up MRI was performed in 31 patients (51%) with proportionate radiological signs of regeneration (Grade 0 = 3 [10%], Grade 1 = 21 [67%], Grade 2 = 7 [23%], Grade 3 = 0 [0%]). In summary, the comparison of preinterventional to postinterventional MRI showed a

Table III
Re-infiltration and switching to surgery.

	N	Lost of follow-up	Re-infiltration			Change to surgery			
			Traumeel	Whole blood	Prolotherapy	(In total)	Traumeel	Whole blood	Prolotherapy
T0	62	-	-	-	-	-	-	-	-
T1	59	1	11	8	4	1	0	0	1
T2	56	0	-	-	-	3	2	0	1
T3	53	1	-	-	-	3	0	1	2
T4	52	0	-	-	-	2	0	1	1

Table IV
Comparison between T0 mean (total) vs. T0 mean (converter).

	VAS (pts)		P	SEV (%)		P	DASH (pts)		P	MEPS (pts)		P	PRTEE (pts)		P	Strength (%)		P
	(Mean)	(Mean_Conv)		(Mean)	(Mean_Conv)		(Mean)	(Mean_Conv)		(Mean)	(Mean_Conv)		(Mean)	(Mean_Conv)		(Mean)	(Mean_Conv)	
Traumeel	4.15	6.10	ns	47.15	36.50	ns	64.45	50.00	ns	64.50	62.50	ns	39.65	37.00	ns	74.55	108.50	ns
Whole blood	5.76	4.40	ns	51.36	47.50	ns	66.59	68.00	ns	68.64	62.50	ns	43.82	60.00	ns	66.00	90.50	ns
Prolotherapy	5.29	5.80	ns	54.75	42.00	*	77.75	80.60	ns	61.25	54.00	ns	48.90	56.40	ns	55.85	52.40	ns

SEV, subjective elbow value; *VAS*, visual analog scale; *DASH*, disabilities of arm, shoulder, and hand score; *PRTEE*, patient rated tennis elbow evaluation; *MEPS*, Mayo elbow performance score.
* $P \leq .05$.

decrease by one Walz stage in 12 patients, while no difference could be detected image morphologically in 18 patients. The Kendall-Tau test showed a weak correlation of the Walz stage with the recorded VAS at the respective time of examination (correlation coefficient 0.185, $P < .05$).

Influence factors

The therapy success thus appears to be independent of the duration of the preintervention pain (SEV) by missing correlation (Pearson test, correlation coefficient −0.061, $P > .05$).

Furthermore, no correlation between occupation and severity of pain at T0 (Eta: VAS 0.17, SEV 0.27) and duration of pain post-intervention (T1-T4) could be proven (Eta: VAS 0.23, SEV 0.18).

Discussion

The aim of this multicenter study was to test the efficiency of a standardized ultrasonographic confirmed infiltration method for the therapy of chronic LE following the published protocol of Keijsers et al.[12] The technique of needling was combined with the application of an injection fluid to potentiate the advantages of tissue stimulation with the spectrum of action of the applied medication. The primary hypothesis of a significant long-term pain reduction of at least 50% could be achieved regardless of the medication chosen. Applications of Traumeel, autologous whole blood, and dextrose with different modes of action related to the regeneration of musculotendinous pathologies were used. The most effective reduction of symptoms was achieved with the application of autologous whole blood. Here, a pain reduction of 75.2% of the initial value was reached, followed by dextrose (reduction of 71.1%) and Traumeel (reduction of 60.0%). Consideration of the other outcome parameters (SEV, PRTEE, MEPS, DASH score) did not show a clear superiority of a stimulus, although the onset of effect after 6 weeks was significantly faster in patients treated with autologous whole blood. Restoration of strength over time tended analogously to the functional scores and underlined the improved functionality of the affected elbow joint in the long-term course, also independent of the medication. Switching to surgical intervention as an important indicator of treatment failure is most common in the dextrose treatment group (5/62). In contrast, patients with Traumeel and autologous whole blood treatment have the highest proportion of re-infiltrations (A: 55 %, B: 36%, C: 20%), so some bias by the practitioner cannot be excluded. No patient underwent surgical therapy after re-infiltration.

The total proportion of patients who did not respond to infiltration therapy in the presence of chronicity was 14.5%. The relatively good results of this study could be explained by the accumulated effect of needling and the medication applied.

A rebound effect 6 weeks after infiltration for the outcome parameter pain is only evident in the case of the historical comparison group. In the present patient population, the phenomenon of a renewed worsening of symptoms after 6 weeks cannot be shown for all outcome parameters surveyed, which may emphasize the regenerative character of this therapeutic approach in contrast to an immunosuppressive therapy with cortisone.

There is some evidence in the literature for the success of needling as a therapy option with few complications.[25,26] The needling pad, consisting of 12 needles, mimics the repetitive, percutaneous fenestration of the tendon origin and thereby initiates the regeneration process by means of hemorrhage and fibroblastic proliferation. In a meta-analysis of 320 patients, Navarro-Santano et al attribute a positive effect to the treatment method in terms of pain reduction and efficient strength development in

the short term, even if they only classify the evidence as moderate.[17]

The assumption was built up that the combination of percutaneous fenestration and the respective application of a medication would potentiate the effect. The largest basis for discussion here is certainly the use of Traumeel. Traumeel (Tr14) is an injection solution consisting of 12 botanical and 2 mineral substances, whereby the individual components are attributed anti-inflammatory, antiedematous, antiexudative properties, but their mode of action has not yet been fully clarified in detail.[21] Jordan et al demonstrate that the natural combination of the components unfold their anti-inflammatory efficacy via promoting specialized proresolving mediators that act as immunoresolvents.[9] The efficacy with regard to the therapy of tennis elbow has so far only been analyzed in non-randomized observational studies to our knowledge and at least does not prove any inferiority to nonsteroidal anti-inflammatory drugs.[2] The results of this study are all the more surprising, with significant pain reduction, positive strength development, and improvement in functionality. The extent to which this effect must be attributed to the accumulative effect of needling remains the goal of further investigations.

The healing potential of osmotically active substances such as dextrose has been reviewed by Zhu et al in a recent meta-analysis.[30] Despite a long history of using, the inclusion of a total of 8 randomized controlled trials also shows the rather weak scientific evidence here. The pooled results for one study characteristic at least suggest that after 12 weeks there is superiority for VAS, PRTEE, and DASH compared to active (injection solutions, exercise, manual therapy, dry needling, ESWT, laser) or inactive (no treatment) control groups.

The use of PRP or autologous whole blood for the treatment of musculotendinous and degenerative articular pathologies has become very popular, although studies on its efficiency are inconsistent. In an earlier meta-analysis, Krogh et al postulated a possible superiority of PRP and autologous whole blood over cortisone infiltrations.[15] Subsequent meta-analyses, including a Cochrane analysis, cannot unanimously support this and only confirm the absence of adverse effects.[5,10,24,28] Based on animal models, these injections may modulate tendon injury healing.[7] The controversy regarding the use of autologous blood is unfortunately also evident in the combined use with the ITEC device.[4,8] Braaksma et al negate an efficient pain reduction after 3 months while Goorens et al underpin the effectiveness of this procedure. Both studies also included patients who had received corticosteroid therapy beforehand, which may have increased the risk of heterogeneity and thus led to the different results.[4,8]

Overall, the results of our study population suggest that combined application is an effective treatment option for chronic LE. The efficacy appears comparable to cortisone administration without the negative catabolic characteristics of corticosteroids. The lack of rebound phenomenon after 6 weeks in the present patient population could be interpreted as indicating that the success is not due to a suppressive but rather regenerative healing approach.

The present study shows some limitations. A potential confounding factor is the lack of a control group in the sense of a single needling therapy without medication or only saline application. Due to this, the influence of pure needling on the therapy efficiency cannot be evaluated. Instead, the comparison with a historical evaluation by Bisset et al was used as a control group, as a planned cortisone infiltration was omitted for ethical reasons with evidence-based indications regarding disadvantages of this form of therapy.[3] Following Keijsers et al's study protocol, a group without medication application is planned here, so that these results can still provide information about the possible potential of needling.[12] The lack of randomization for a medication cannot exclude bias by the practitioner here. The indication for re-infiltration or switching to surgical therapy is not clearly defined and is up to the decision of the therapist. It is also questionable how much influence the increased attention and care of the study team during the follow-up examinations has on the subjective pain perception of the patients. A comparison with a placebo intervention would be helpful here, but difficult to implement.

Conclusion

The ITEC medical device with the possibility of variable application of medication represents an alternative treatment method for chronic LE due to the summation effect of needling and the respective administration of a medication. The results show a long-term effective pain reduction without evidence of side effects. Yet, the effect of needling without administration of a medication or only saline is still to be evaluated. With 14.5% treatment failures, there is no absolute guarantee of success here either and further alternatives must be explored. The use of autologous blood products still shows inconsistent results with regard to the literature, but pursues a promising idea with the biological regeneration approach. Initial work on the use of adipose-derived mesenchymal stromal cells in tendinopathies points to the future of this approach.[13,16]

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