

Topical polidocanol application in combination with static stretching in tendinopathies: a prospective pilot study

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Summary

Background: Highly operator-based injection therapy with vasosclerosing and anesthetic polidocanol is used for tendinopathies. This pilot-study evaluates the topical application of polidocanol gel.

Methods: Prospective case series. 39 patients with tendinopathies (14 Achilles, 14 patella, 11 wrist extensors) with a symptom duration > 6 months were included. Polidocanol and static stretching were the therapy in the first 2 weeks, while static stretching was continuously performed for 6 months. Clinical outcome was evaluated with VISA-A, VISA-P and DASH Scores and sonographically with B-Mode (B-Mode), Power Doppler (PD) and Shearwave Elastography (SWE). **Results:** 22 patients clinically improved (>+10 score points), 11 patients were without improvement (<+ 10) and 1 patient worsened during 6 months. The VISA-A Score increased in average 19 points from 56 to 75 ($p < 0.01$), VISA-P Score increased 13 points from 59 to 72 ($p < 0,01$) and the DASH-Score decreased 20 points from 40 to 20 ($p < 0,01$). SWE correlates better than B-Mode or PD with symptom improvement.

Conclusion: The combination of static training and topical polidocanol application seems to be

successful in the treatment of tendinopathies. Further RCT studies need to evaluate the efficiency of topical polidocanol application. SWE is a more sensitive tool to describe symptom development than PD or B-Mode. Level of evidence: IV.

KEY WORDS: Achilles, epicondylitis, patella, shear wave elastography, tendinopathy, ultrasound.

Introduction

Most common tendinopathies (TP) are at the Achilles, patella and wrist extensor tendons.

Neovascularisation as a pathogenic model in chronic TPs

The pathogenesis of chronic TPs is not fully understood, but it is based on overuse combined with various individual risk factors resulting in both disturbance of tendon extracellular matrix levels and decrease of tenocytes cell numbers^{1,2}. A posttraumatic inflammatory response is present with leucocytes suppressing *in vitro* Type 1 collagen synthesis, which might be a stimulus for catabolic and pro-inflammatory mediators³. According to the Iceberg Theory of Abate relative overload leads to micro ruptures, followed by the over-expression of Vascular Epithelial Growth Factor (VEGF)⁴. As a result, VEGF stimulates the synthesis of matrix metalloproteinases (MMPs) with an imbalance of MMPs and tissue inhibitors of MMPs, leading to degradation of the extracellular matrix consecutively decreased collagen strength and a predisposition of further micro ruptures^{2,5}. Secondly, VEGF induces neovascularization (neoV) covered by nerve fibers, which can be activated by local cytokines as well as by cholinergic and sympathetic innervation of these peripheral nerves⁶. Even if nerve supply differs by tendon region, in a painful tendon free nerve endings are remarkable high concentrated². In symptomatic tendons neoV is a common finding in Power Doppler Ultrasound with corresponding angiogenesis in histological preparations, but "it is difficult to know if this neoV represents genuine neoangiogenesis"⁷. In general neoV is seen as a pathological vascular ingrowth in the symptomatic tendon, but there also exists opinion that the pain and the whole pathogenetic model are not totally based on neoV⁸. Therefore, in addition to the neurovascular ingrowth further aspects like synthesis rates of gluta-

mate, substance P and calcitonin gene related peptide also play a role in TP. Increased levels of these substances provoke a neurogenic-mediated inflammation. Working together, both neurogenic-mediated inflammation and neoV are seen as an inappropriate healing process with neoV being a result of the inflammatory response⁷. At this point pain just gets present. As a result, this pilot study concentrates on a therapeutical approach to reduce neoV and the accompanied nerve fibers in order to reduce pain and break through the cascade of tendinopathy⁴.

Invasive and non-invasive treatments

Conservative treatment options of TP are eccentric exercises, extracorporeal shock wave therapies or injection therapies with high-volume injections, platelet-rich plasma, corticosteroids or polidocanol⁹. A Cochrane Review evaluating RCT studies of various injection therapies in AT draw the conclusion that there is no sufficient evidence for a routine injective use^{9,10}. Consequently, non-invasive topical applications could be a further option as an independent home-based standard medication to the already established NSAIDs or nitroglycerine¹¹. In general, there is a high interest and acceptance in patients for a topical rather than a systemic medication, ease of use and an attempt for an alternative to NSAIDs. In that sense, a natural based oxygen oil with an unknown active component showed significant effects in acute tendinopathies compared to a placebo¹². Concerning conventional active pharmaceutical ingredients, Frizziero et al. examined a betamethasone plaster in elbow tendinopathy significantly reducing the VAS score by twice with a 12 hour application compared to a placebo¹³. Furthermore, there is a growing interest of alternative options like nutraceutical supplements e.g. curcumin, which inhibits neoV and apoptosis in addition to an antioxidant effect showing good results in animal models¹⁴.

Polidocanol as a causal treatment option

Polidocanol is a sclerosing, antipruritic and anesthetic agent. Injected, it is mainly used for sclerosing varices in the lower extremities, while in psoriasis it is cutaneously applied¹⁵. In solution polidocanol molecules are mainly enclosed in a micelle, while free molecules are surface-active and attach to the endothelial wall causing a disintegration and denaturation; thus thrombocytes get adherent causing a sclerosing effect¹⁶. Antipruritic effects could be explained by inhibiting unmyelinated C-nerve fibers. Polidocanol should induce ischemia to reduce the neural coat of the vessels and to break through the pathologic healing process¹⁷. Alfredson and Öhberg introduced an injection technique for Achilles TP, which was subsequently used in patella and wrist extensors tendons^{18,19}. Using Power Doppler sonography polidocanol should be injected intravascularly directly into the neoV. Nevertheless, extravascular injection is also effective, most likely by ischemic effects on nerve fibers¹⁷. The results of the injection technique were

good. In patella TP the VISA- Score increased of 26 points during 1 year²⁰. In the Achilles tendon VAS score reduces from 75 to 7²¹ and in wrist extensors from 75 to 34²². Whereas, in a further study by van Sterkenburg 50% of Achilles TP patients had a poor outcome, which might be explained by the retrospective study design without consistent use of VISA-A Scores²³. However, as Alfredson has written “the method is technically demanding, very much operator-dependent with a long learning curve, making it less suitable for general use”²⁴. Therefore this pilot-study investigates the topical application of polidocanol in combination with static stretching to avoid operator-based disadvantages and to provide a general, non-invasive form of topical application without technical devices. In contrast to injection therapy where the active agent is directly applied to the area of interest the quantitative absorption of the skin needs to be considered. Concerning Polidocanol or related substances, just 2% of the topically applied amount penetrates the human skin^{15,25}. Furthermore, the absorption rate of the amphiphil polidocanol through the Stratum corneum of the skin might be enhanced by allantoin, which is as an ingredient of the product (Thesit ®) used in this study and in general meliorates skin penetration. Unfortunately, no data exist which scientifically quantify a possible increase of the 2% absorption rate by different galenic mechanisms or allantoin. It is our understanding that polidocanol has to penetrate the skin without any support by cutaneous transport carriers.

Materials and methods

Study design

We chose a prospective case series study as a study design. The investigation was approved by the ethical committee of our medical faculty (EK 267/12) and meets the ethical standards of the Declaration of Helsinki and the MLT Journal²⁶. All volunteers provided written informed consent to participate.

Inclusion and exclusion criteria

In total, 36 patients were included: 14 patients with Achilles, 11 with patella and 11 with wrist extensors TP (Table I). All patients experienced pain or discomfort while participating in their sports or at work.

They suffered from chronic TP of the patella, Achilles or wrist extensor tendons for at least 6 months and were pre-diagnosed and treated individually non-successfully by physicians previously with various therapies. Diagnosis was confirmed by clinical history and tests, pain questionnaire and sonographic examination.

To focus on severe tendinopathies, 9 eligible patients with low symptomatic (>80 VISA-A/P; <20 DASH) were excluded. Other exclusion criteria were inability to perform stretching exercises, local cortisone injection in the last 6 months, previous surgery or rupture of the tendon, rheumatic diseases and medication with fluoroquinolone.

Table I. Patient characteristics in entire cohort.

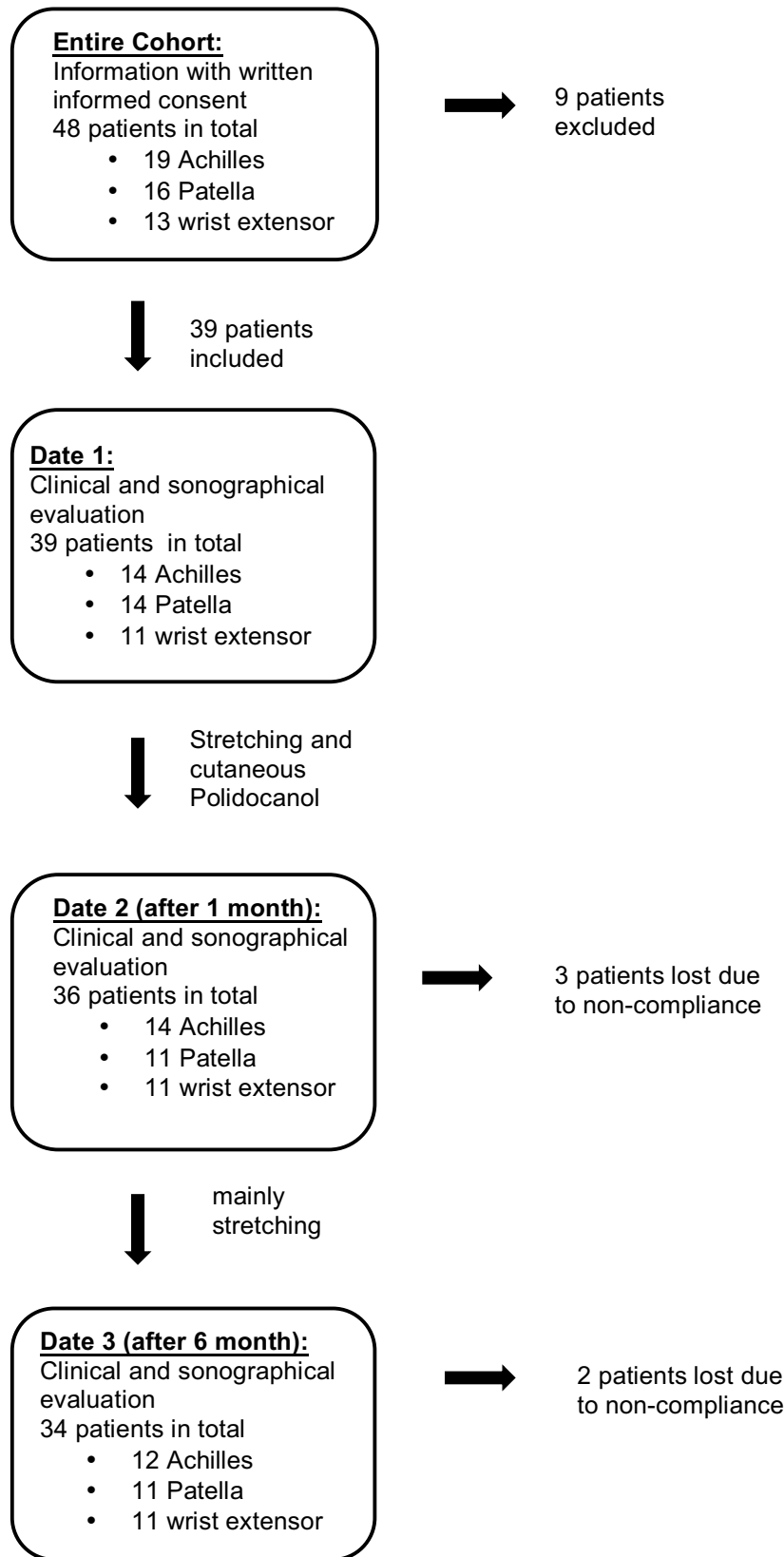
Characteristics	Achilles (n=14)		Patella (n=11)		Wrist extensor (n=11)	
Sex	♀ 5	♂ 9	♀ 0	♂ 11	♀ 6	♂ 5
Age	50 ± 13 (31-69)		26 ± 5 (20-40)		49 ± 15 (24-70)	
Side of affected tendon						
Left	10		7		3	
Right	8		7		9	
Symptom duration in months						
Mean	24		30		20	
Median	12		11		9	
Min.- max.	6 - 84		6 - 102		24 - 70	
Previous therapeutic approaches						
Mean	3,86		3,75		4	
Cryotherapy	9		11		5	
NSAID	8		11		8	
Cortisone	1		2		2	
Professional physiotherapy	10		11		7	
Shock wave	3		0		3	
Acupuncture	3		1		1	
Bandage	2		11		11	
Activity-loading						
Mean hours/week	4,5		8		1,68	
Recreational sport	11		1		3	
Amateur sport	0		10		0	
Work related	0		0		4	
Level of pain						
In rest	2		5		4	
During palpation	11		10		9	
During activity	10		13		9	
After activity	9		12		8	

Study design

There were 3 scheduled assessment visits: at the beginning (0 month), after 1 and 6 months. At every visit patients were examined clinically by two independent

physicians (Flowchart I).

The therapy consisted of two elements: static stretching exercises and cutaneous polidocanol application. In the first two weeks patients used polidocanol gel,



Flowchart I: Study design.

performed stretching exercises and did not participate in sports. After two weeks patients could individually slowly start loading and continue a load level depending upon pain (scale 4/10) and discomfort until their full recovery.

We used the commercially available Thesit® gel 50g (Gepepharm GmbH, Hennef Germany) with the standard concentration of 8% for topical application. Patients were instructed to apply an amount as large as a cherry pit of Thesit® gel 3 times a day, topically for the first 2 weeks. There were no reported side effects.

At the first appointment patients were taught how to perform static stretching exercises at home. They were instructed to perform the same at least once (up to 3 times) per day and to hold the position for 30 seconds. Additionally, they received a document presenting these exercises. For Achilles and patella tendon both groups stretched statically hip flexors/extensors, knee flexors/extensors and the plantar flexors (M. triceps surae) in 5 different exercises. For wrist extensor TP patients stretched the extensors carpi radialis and the flexor carpi ulnaris in 2 different exercises. At the second visit we reviewed the correct performance of stretching and evaluated stretching compliance by asking, how many times per day or week exercises have been performed. Stretching was continued during the whole study. We chose static stretching over eccentric exercises (EE), since static stretching is easier to apply without having to use additional devices such as decline boards or rubber bars. In addition, there are studies showing no benefits of EE over static exercises in AT or wrist extensor TP, e.g. Frizziero et al. reported a²⁷⁻²⁹ superiority of EE in only 2/9 studies in wrist extensor TP. For a better comparison we used static stretching for all the 3 different types of TP in our study.

Clinical evaluation by VISA-A/P and DASH

For pain evaluation (0/1/6 month) the validated Victorian Institute of Sports Assessment (VISA) questionnaires in German for Achilles (VISA-A) and patella TP (VISA-P) had been chosen^{30,31}. Each consists of 10 differently weighted questions with a total of 0 (highest pain) to 100 points (no pain at all). For evaluation of wrist extensor TP we chose the German version of the Disability Arm Shoulder Hand (DASH) Score³² which consists of 30 equally weighted questions with a total of 100 (highest pain) to 0 points (without pain). Questionnaires were filled in 0,1 and 6 months. Relevant improvement or worsening was decided by a minimum change of +10/-10 score points. Scores over 90 (VISA) or 10 (DASH) were considered as excellent outcome³³.

Sonographic evaluation

Sonographic evaluation was done by B-mode ultrasound (US), power-Doppler sonography (PD) and Shear Wave Elastography (SWE) with a high-resolution linear 15 MHz transducer (Aixplorer™, Super-Linear™ SL 15-4, SupersonicImagine, Aix-en-Provence France) with a band-width of 4-15 MHz. In

every participant a gel cushion delay block (Sonogel, Sonokit Proxon, length 100 x 100 mm, delay distance 20 mm) was used for better docking. Two experienced radiologists with at least 5 years of experience in musculoskeletal sonographic imaging performed all sonographic examinations. For comparison both tendon sides were evaluated without knowledge of the affected side. Tendons were examined in relaxed stance: the examination of Achilles tendon was done in prone position, the patient's foot project beyond the examination table and in neutral subtalar position. The examination of patellar tendon was done with the patient in dorsal position, the leg in relaxed extended position. Wrist extensor tendons got examined in a sitting position with the forearm lying on the thigh in a slightly flexed position. The acquired SWE-information was evaluated quantitatively in Kilopascal (kPa) up to a maximum tissue rigidity of 300 kPa at three representative locations in the proximal, mid and distal part of the tendon. Mean (SWE mean) and maximum (SWE max) tissue rigidity was quantitatively evaluated by ROI-based analysis in the most rigid area in every image. Standardized diameter of the ROI was 3 mm. NeoV was graduated by the Öhberg score (0-4)¹⁸. Morphological changes (B-Mode) in the tendons were classified by 0=none, to degree 4=major change.

Statistical analyses

For all analyses, SPSS 22.0 was used to assess statistical significance, which was defined as $p < 0.05$. The T-Test with connected variables compares the groups before and after treatment. Furthermore, a one-way ANOVA with repeated measures (Greenhouse-Geisser correction) were made for each tendon localisation to examine significant changes over time. Post hoc tests used the Bonferoni correction. Spearman's correlation coefficient analyses correlation between the VISA-A/P; DASH score and the sonographic parameters as B-Mode, Öhberg Score and SWE. By this we compared the difference between the first and the last score after 6 months with the difference in the sonographic parameters during this time.

Results

General results

In summary, 22 patients improved, 11 patients did not feel a relevant improvement, while 1 patient worsened. 9 patients reached scores over 90 points (VISA-A/P) or less than 10 points (DASH). Furthermore, 6 patients reached points over 80 points (VISA-A/P) / under 20 points (DASH), showing encouraging results in nearly half of the patients. All patients used the total 50g Thesit® gel tube during the 6 months. As Thesit® is free for sale, 5 of the 11 patients without improvement after one month informed us about using additional 50g, but still they did not improve more than 10 points in total. Compliance for stretching exercises and gel application was good. In the

first month, all participants were performing the exercises at least once per day, while in the following period of 5 months monitoring of compliance was difficult, but participants were able to state a performance of at least 4 times per week. There were no reported side effects of therapy. No correlation of outcome relating to type of loading-activity, gender, higher or lower initial score could be found.

Achilles tendon

For Achilles TP (n=14) the mean initial VISA-A score was 56 (range 26-68, SD 15) and increased to 65 (range 35-85, SD 13) after 1 month and to 75 (range 10-97, SD 25) after 6 months (Diagram I). Initial scores on average rose about 19 points (range -16 to 53, SD 21) during 6 months and increased significantly from the beginning ($p < 0,01$). The repeated ANOVA with a Greenhouse-Geisser correction determined that mean VISA-A differed statistically significantly between the measure points [$F(1,1155;12,700) = 7,859, p < 0,013$]. Post hoc tests using the Bonferoni correction revealed that there were significant changes between the beginning and after the 1. month ($p = 0,005$) as well as after 6 months ($p = 0,02$), while after the 1. until the 6. month there was no significant change ($p = 0,229$). During therapy 1 patient worsened, 3 patients showed no improvement and 8 patients improved. Half of these 8 patients (n=4,

mean initial score: 57) reached a mean final score of 95. Symptom improvement during 6 month correlated moderately with SWE mean ($r = 0,46; p = 0,16$) and max ($r = 0,48; p = 0,14$) values, while B-Mode ($r = 0$) and PD ($r = 0,13$) did not correlate at all.

Patella tendon

Initial mean VISA-P score for patella TP (n=11) was 59 (range 43-78; SD ± 11), increased to 67 points (range 46-87; SD ± 13) after 1 month and rose up to 72 (range 53-98; SD ± 15) at 6 months (Diagram II). Initial scores on average rose about 13 points (-3 to 43; SD ± 14) during 6 months and increased significantly from the beginning ($p < 0,01$). ANOVA yield that there is a significantly change between time points [$F(1,954;19,536) = 5,596, p < 0,012$] with a significant score difference between the beginning and after 6 months ($p = 0,025$) in the post hoc tests. Between the beginning and the 1. month ($p = 0,175$) and the 1. month until the 6. months ($p = 0,686$) there were no significant changes. During therapy no patient worsened, 5 patients maintained the level of pain, while 6 improved with 1 reaching a score of 98. SWE mean ($r = 0,6; p = 0,05$) and SWE max ($r = 0,42; p = 0,20$) changes correlated moderately with symptom-alteration during the 6 month follow-up, in contrast to B-Mode ($r = 0$) and PD ($r = -0,5$), which did not correlate at all.

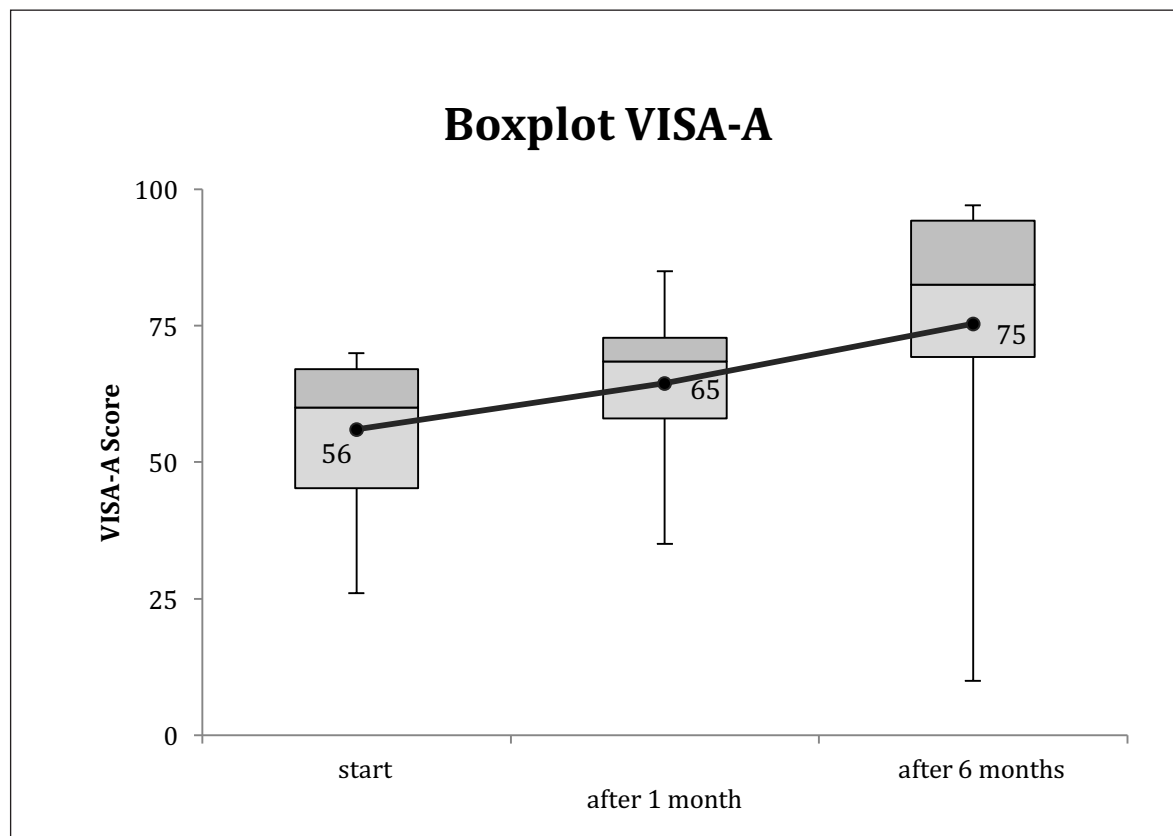


Diagram I. Progression in Achilles tendinopathy.

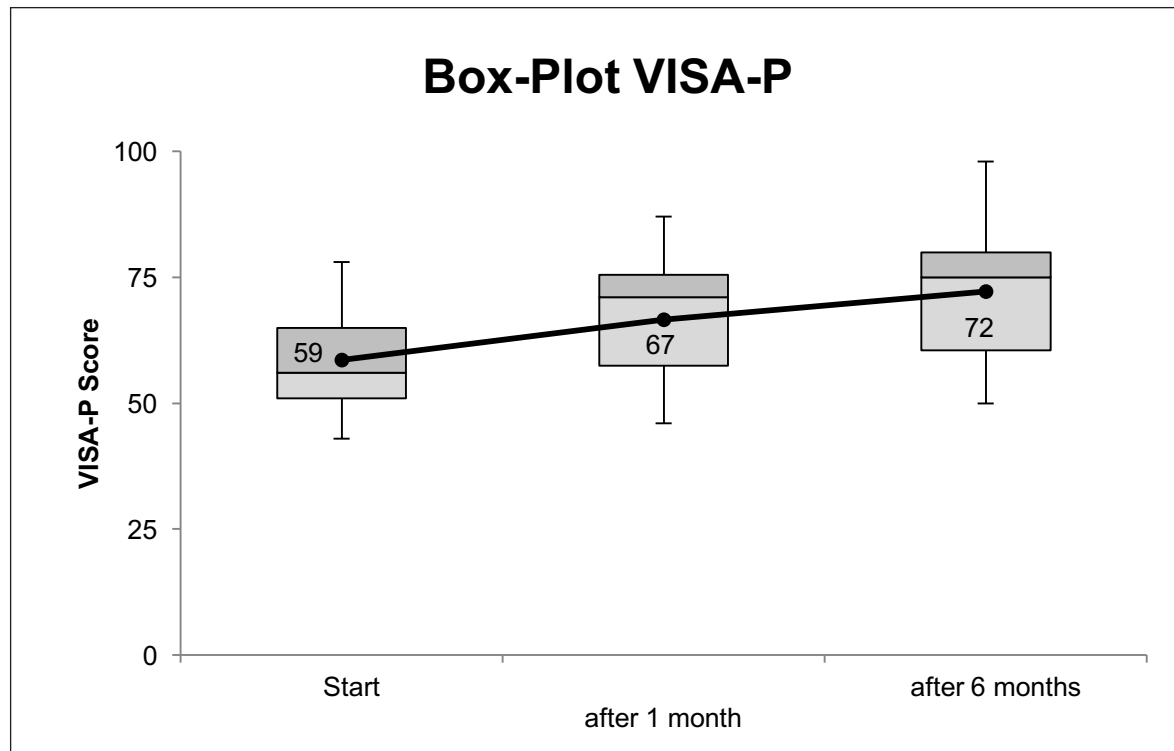


Diagram II. Progression in patella tendinopathy.

Wrist extensor

DASH- Score for wrist extensor TP (n=11) decreased from initially 40 points (range 49-25; SD \pm 7) to 28 (range 56-5; SD \pm 15) after 1 month and reached 20 points (range 50-2; SD \pm 15) at the end of 6 months (Diagram III). Initial scores decreased 20 points (range -38 - 6, SD \pm 14) in total during 6 months and differ significantly from the beginning ($p < 0,01$). ANOVA showed a statistically significant difference between the measure points [$F(1,934;19,337)=13,098$, $p < 0,0005$]. There are significant changes in the post hoc tests between the beginning and after the 1. month ($p=0,038$) and 6 month ($p=0,02$) respectively, while after the 1. until the 6 month ($p=0,164$) DASH increase was not significant. During therapy no patient worsened significantly, 3 patients stayed nearly at the same level, while 8 improved with 4 healed patients reaching scores under 7,5. During the whole period of follow-up, SWE mean ($r=0,54$; $p=0,09$) and SWE max ($r=0,47$; $p=0,14$) changes correlate moderately with symptom-alteration, in contrast to B-Mode ($r=0$) and to PD ($r=-0,5$), which remained nearly constant.

Discussion

This pilot study investigates the topical application of polidocanol combined with static stretching exercises in three different types of chronic TPs (patella,

Achilles, wrist extensors) showing good to excellent clinical results in nearly half of the patients. There is no correlation with previous activity loading, symptom duration or gender, making it suitable for all kinds of patients suffering from TPs. In Achilles tendons and wrist extensors the outcome was similar (+19/20 points), while in patella TP the average improvement was 13 points. First, it is difficult to compare different scores despite the same range, as a specific change in one score is not valid the same change in the others. Secondly, neoV in patella tendons coming from the deep infra-patellar fat pad might be insufficiently reachable by topical application³⁴. Although, neoV in the Achilles tendon seems to come from the ventral side of the tendon as well, it might be better reachable through lateral application¹⁸.

Making general statements about the natural course of healing is difficult and patients differ a lot e.g. in risk factors or loading. Symptoms of patella TP in amateur athletes last in average 18 months³⁵. In Achilles TP 29% fail conservative treatment³⁶. Wrist extensor TP seems to be self-limiting during the first 8-13 months³⁷. To sum up, normal healing process during 6 months could only play a minor role in explaining our results.

Comparison to other therapeutic modalities is difficult due to different scoring systems, different activity loadings and symptom intensity. In our study on average patients' VISA-A increased about 19 points during 6 months. In a randomized controlled clinical

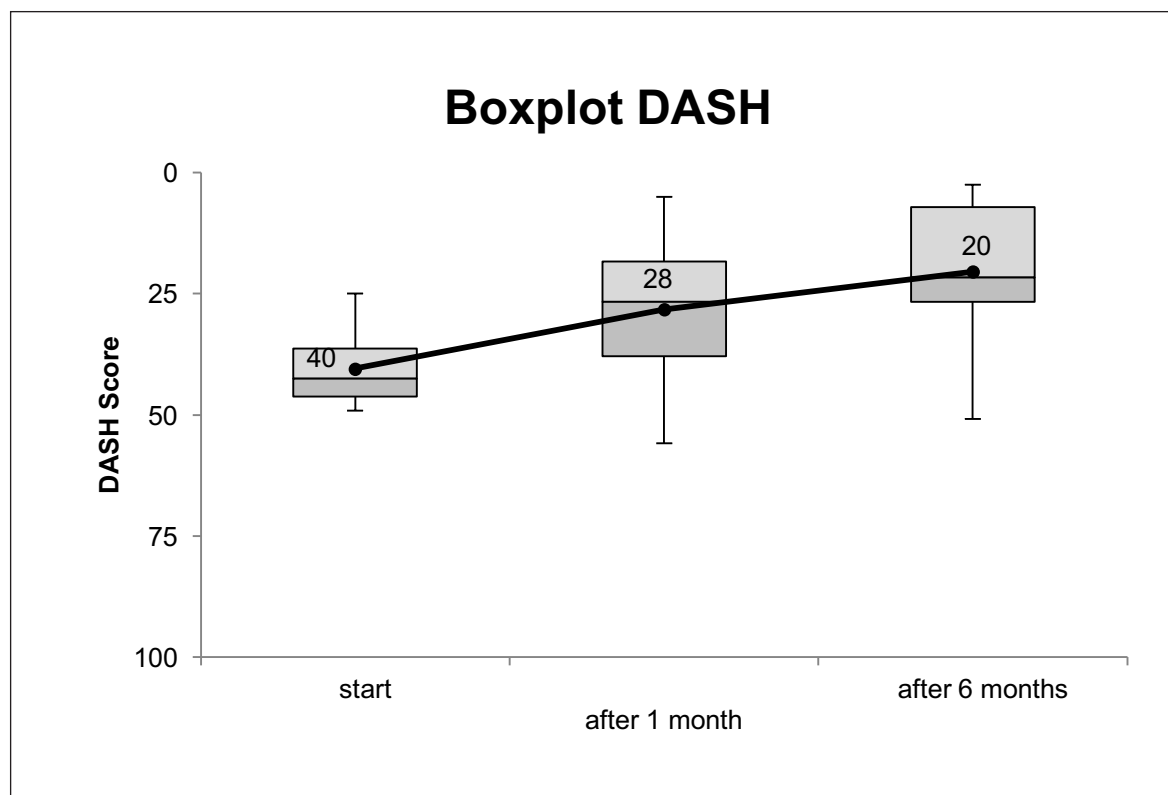


Diagram III. Progression in wrist extensor tendinopathy.

trail glyceroltrinitrat showed good results: twenty-eight (78%) of thirty-six Achilles tendons in the glyceryl trinitrate group were asymptomatic with activities of daily living at 6 months, but some patients had reversible side effects like headache and rash³⁸. VISA-Score was just used in one study about polidocanol injection therapy. In it, VISA-P points increased about 26 after one year²⁰, while we reached 13 points with the topical application after half a year.

A drawback of our study is that it is unclear, if polidocanol reached the area of interest after penetrating the skin due to a lag of pharmacokinetic and dynamic datas regarding topically applied polidocanol. However, at least 2% of cutaneous applied polidocanol or related substances are absorbed through the human skin^{15,25}. Using a 50g tube polidocanol gel (50.000 mg) with a concentration of 8% and a minimal absorption rate of 2%, theoretically at least 80 mg (50.000mg*0,08*0,02) should penetrate the skin and might reach the area of interest. This would be equal to 16 ml of injected polidocanol (standard dosage 5 mg/ml) or 8 intravasal injections (2 ml per injection)¹⁷. Furthermore, evaluation of the polidocanol's effect can be solely made by clinical improvement, as neoV remained mainly constant and did not correlate with symptom improvement. Nonetheless, if a total sclerosis is necessary for symptom improvement is questionable. Directly after polidocanol injections no blood flow is noticeable, followed by a higher blood flow af-

ter 1-3 weeks³⁹. It seems that neoV in some cases is not pain related and not adequate for evaluating the therapeutic effect for injected and topical polidocanol. Referring to the pathogenesis model mentioned in the introduction polidocanol is able to address neoV and its accompanying nerves, but not the posttraumatic inflammatory response of leukocytes or the effects of MMPs induced by VEGF. Additionally, Willberg assumed ischemic effects on nerve fibers accompanying neoV in TP (17), which might explain the long-term symptom improvement despite the recurrent neoV. Besides the sclerosing effect of polidocanol, an additional anesthetic effect is often quoted, but nowadays discussed controversially regarding topical application. Mainly older studies state an anesthetic potential by injective treatment, while topically applied polidocanol was not showing any anesthetic potential in thermal sensory analysis and pinpricking^{40,41}. The exact effect of injected and topical applied polidocanol concerning TP is still unexplored, nevertheless in 2005 a RCT study reported a positive effect of polidocanol on symptom improvement in TP⁴². Moreover, in a special formula with a lipophilic base polidocanol concentration can be increased up to 9% and potentially even more of the agent could reach the area of interest. In contrast, in injection therapy there is no significant evidence that higher dosage (5 mg/ml up to 10mg/ml) improves the outcome¹⁷. It would be of interest in future studies to examine higher dose cutaneous application in a RCT trial.

Static exercises could have an influence on the final outcome, but studies alone using VISA-A/-P or DASH scores were not found on pubmed or PEDro. Stasinopoulos reported excellent results after one month of a combination of static stretching and eccentric exercises (+42 VISA-P) in patients with patella TP while eccentric exercises alone reached +28 points. In contrast to Stasinopoulos' patients, ours had a higher grade of severity, more therapeutical approaches (3,75 compared to 1) and longer mean symptom duration (12 months compared to 6)⁴³. Nevertheless, eccentric home based exercises can also lead to an unsatisfactory increase of 11 VISA-A after 6 months⁴⁴.

To sum up, in this conservative approach both the physical exercises and the polidocanol application can be responsible for symptom improvement without knowing the exact influence of each part. ANOVA revealed in wrist extensors and Achilles TP a significant change in the first month, where polidocanol was used daily in the first 2 weeks. In the period where mainly stretching exercises were used, there was no significant score difference, giving a hint that daily usage of Thesit® has a further effect than stretching exercises alone.

SWE seems to display tendon healing better than US or PD and might be a useful tool for follow-up of tendinopathies under therapy. Conventional ultrasound provides "findings on imaging creating a confusing clinical picture" with a questionable possibility of monitoring⁴⁵. However in this study correlation of SWE with clinical scores and symptom alteration was better than standard sonographic B-Mode or Power Doppler showing that SWE might be a powerful tool for monitoring. Further studies investigating the correlation between score changes and imaging changes of different treatment options need to evaluate the potential of SWE. Even though SWE is a relatively new tool in tendon diagnostics, it is already known that asymptomatic tendons are harder than symptomatic ones⁴⁶. In conclusion, increased tendon rigidity during the 6 month follow-up of our study, refutes a single placebo effect of the combined polidocanol and stretching therapy.

In summary, 45% of the patients suffering from chronic TP reached good or excellent clinical results. Further blinded randomized prospective studies need to evaluate the efficiency of polidocanol in comparison to currently used treatment options.

Conflict of interest

The Author has no financial or personal relationships with other people or organizations that could inappropriately influence their work.

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