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Review Article

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TREATMENT ALTERNATIVES FOR REFRACTORY SUPRASPINATUS TENDINOPATHY

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ABSTRACT

Supraspinatus tendinopathy is the most frecquent pathological finding under the rotator cuff pathology. Pain and disability represent the main complains. In the acute phase, standard therapies include anti-inflammatory drugs, rest, physical modalities and therapeutic exercise. Failure of symptoms resolution after a number of therapy sessions represents a challenge for the practising clinician. New methods aim at reducing pain and disability, in the meantime focusing on tendon structural alteration. Physical exercise remains an important tool to obtain proper functioning. It requires medical supervision, consistency and an important number of sessions, that may reduce the patient compliance. Combining physical exercise with new therapies promises better and faster results. Studies are available on extracorporeal shockwave therapy, dry needling, prolotherapy, hyaluronic acid and topical application of nitric oxide. Some results are encouraging, other need more validation. The availability of ultrasound imaging helps the documentation of structural changes and the correlation with clinical course.

KEYWORDS: Supraspinatus tendinopathy, extracorporeal shock wave therapy, prolotherapy, hyaluronic acid, nitric oxide.

INTRODUCTION

Rotator cuff consists in supraspinatus, infraspinatus, teres minor and subscapularis tendon. Its function is to compress the humeral head into the glenoid fossa. Dysfunction of the rotator cuff produces pain over the shoulder. The most affected tendon is reported to be supraspinatus.

Anatomic structure of supraspinatus tendon insertion comprises four distinct zones visible at optical microscope, with a soft transition between them: tendon, fibrocartilage, mineralized fibrocartilage and bone.[1] The extracellular matrix of the first zone, the proper tendon, consists in type I collagen and a small amount of decorin. The fibrocartilage zone consists in types II and III collagen, with a small participation of types I, IX and X collagen. The mineralized fibrocartilage contains types II and X collagen and aggracan. The fourth zone is formes by type I collagen, forming the bone-tendon attachment.[2,3]

The tendon structural alteration is known under the name of tendinopathy. Older nominations, as tendinitis or tendinosis are to be avoid, as the model of anatomopathologic changes evolved over time. The inflammatory process present in first stage subsides and the degenerative changes dominate the structure. The underlying mechanism seems to be an excessive stress that surpasses the healing capacity of the tendon cells. The loads are maximum at the articular zone of the anterior insertion of the tendon on the greater tubercle.[4] At this level, an increase of collagen turnover predispose to tendon tear.[5]

Intrinsec factors modify tendon morphology and performance. They include age, vascular local particularities, altered tendon matrix, mechanical particularities of the tendon, sex and genetic factors.[6,7,8]

Extrinsec factors lead to narrowing the subacromial space, compressing the bursal surface of the tendon and defining the impingement syndrome. Narrowing of the subacromial space may be due to anatomical variations of acromion or to altered shoulder biomechanics.

Acute phase therapy

Therapeutic modalities are classified as passive (medication, ultrasound, laser, shock wave therapy, heat/cold, bracing) and active: physical exercise to remodel and strenghten the degenerated tendon.[9]

The acute phase requests conservatory treatment.

Anti-inflammatory drugs are prescribed in short course, either orally (non-steroidal) or locally (corticosteroids).

The role on non-steroidal anti-inflammatory drugs (NSAIDs) is controversial, as inflammation may play a role only in the acute phase of tendinopathies. As researchers did not agree on the presence or absence of inflammatory cells in the degenerated tendon, the main goal of the these drugs seems to be analgesia. However, analgesia may have detrimental effects, masking the pain, preventing the rest and postponing tendon healing, especially when overuse is the main cause.[10]

NSAID are administered either orally or locally, as patches (ketoprofen).[11] Acute phase means under 4 – 7 - 15 days of onset. The short course of NSAID means 10 to 14 days.[12,13] Researchers believe that, in the absence of inflammation, in the chronic stage of tendinopathy, the use of NSAIDS is inappropiate.[10]

Corticosteroid drugs have antiinflammatory and may have antinociceptive properties. For a number of patients, they are an important tool to control shoulder pain, especially when refractory to conservative methods. Subacromial administration of corticosteroid, into the subacromial bursa, mai lead to temporary weakening of the supraspinatos tendon. Long-acting corticosteroids and the lowest doses are recommended.[14] After this procedure, patients are asked to refrain from rotator cuff strengthening exercises for 3 weeks and are allowed only flexibility exercises. Experts recommend to reduce the number of corticosteroid infiltration to two.

Rest as complete immobilization is to be avoided, as it has catabolic activity and reduces protein synthesis. In the form of limitation of overexertion and of triggering activity rest may lead to healing.[15]

Physical therapy modalities include therapeutical ultrasound, low level laser therapy, iontophoresis (ionizing current to deliver medicine topically), phonophoresis (ultrasound to deliver medicine topically), deep transverse friction massage, microwave deep hyperthermia. Medicines for topical use of modalities are NSAIDs and corticosteroids.

Local hyperthermia increases local blood flow and oxygen supply, favouring healing.[16] A study compared microwaves hyperthermia, therapeutic ultrasound and no intervention for athletes with supraspinatus tendinopathy on sonographic exam. All of them were followed by physical exercise. On short term (4 to 6 weeks), the hypertermia group produced the higher reductions of pain (VAS scale) and the higher proportion of activity returns, followed by ultrasound group.[17]

Physical exercise is prescribed as a program including stretching, isometric, concentric and especially eccentric strengthening, manual therapy and has beneficial effects on the tendon structure and healing.[18] Majority of reaserch includes physical exercise in the study of shoulder pathology.

Corticosteroids injections benefit shortly, mainly on pain, their effect lasts under 6 weeks. They do not influence the recurrence rate. Risks include tendon rupture, either spontaneously or when performing strengthening exercises.

When does the conservative treatment fail?

As a rule, the conservative treatment fails when the symptoms persist despite a period of application. This period of time may vary according to different studies from 3 months to 4 months and to 6 months.[19,20]

Other studies consider failure of the conservative treatment after a certain number of physical therapy session (usually 10), a number of subacromial injections of steroids (usually 2) and intake of NSAID (usually 10 – 14 days).

After aknowledging the primary treatment failure, the physician may consider other therapeutic alterantives.

It is important to mention that all these treatment alternatives are associated with physical exercise; their ultimate aim is to reduce pain, to shorten the recovery phase and to promote proper functioning of the shoulder. Another point deserves consideration: physical exercise needs medical supervision, consistency and adherence from the patient and requires some time to achieve the results. These factors may reduce the compliance of the patient; he may not attend or complete the rehabilitation program, even in the situation of a home-based program, with remote medical surveillance. All efforts are to be done in order to achieve painless shoulder in a shorter period of time and to improve mobility and strenght.

1. Extracorporeal shock wave therapy (ESWT)

Application of a mechanical stimulus on the tissue leads to a biochemical response which influences fundamental cell functions as migration, proliferation, differentiation and apoptosis. This process is called mechanotransduction. Tenocytes seem to be very sensitive to mechanical stimulus, responding to the optimal doses with healing and regeneration through different pathways: reducing expression of several metalloproteinases and interleukins, increasing cells proliferation and migration, increasing collagen synthesis and lubrycin expression.[21]

ESWT is classified according to energy levels as low-energy (enegy flux density EFD up to 0,08 mJ/mm^2), medium-energy (0,08 – 0,28 mJ/mm^2) and high-energy (EFD 0,28 – 0,60 mJ/mm^2).[22] Information on positive effects of high-energy level ESWT is available for calcific suprapsinatus tendinopathy.[23]

For non-calcific supraspinatus tendinopathy evidence is scarse and controversial. Studies on 3 weekly sessions of moderate-energy ESWT (0,11 and 0,12 mJ/mm^2) showed no difference versus control at 6 and 12 weeks.[24,25,26] In the meantime, another study on 2 weekly application of low-energy ESWT versus placebo offered better results on pain and shoulder function at 6 and 12 weeks.[27] Three weekly application of low-energy versus high-energy ESWT produced the same effect on shoulder pain and function at 12 weeks and 1 year follow-up.[28]

2. Dry needling

Clasically, dry needling is a therapeutic approach of trigger points. The technique implies introduction of a needle into the structure (trigger point, tendon), producing small lesions.

The fenestration disrupts the tendinotic tissue, causing bleeding, which drives growth factors to stimulate healing. The healing cascade is mediated by transforming growth factor-beta and basic fibroblastic growth factor.[29,30] The two factors promote cellular proliferation and matrix synthesis.[31] The result of this cascade is remodeling of the tendon and restauration of mechanical properties.[32]

A patient with mild supraspinatus tendinopathy and 4 monts′ history of symptoms, after one session of dry needling followed by physical exercise, reported a mild pain exarcerbation in the first two days after the intervention and symptoms clearance at 10 days. The technique consisted in tendon fenestration under ultrasound guidance (15 penetration without touching the cartilage surface), into the exact area of structural modification, with an optimal exposure in the Crass modified position.[33]

3. Prolotherapy with polydeoxyribonucleotide PDRN

Prolotherapy is an injection-base complementary and alternative medical therapy for chronic musculoskeletal pain, which aims at stimulating a natural local healing response.[34] It uses different irritant agents injected in the tendon or ligament, near the bone insertion site and initiates an inflammatory cascade with fibroblast proliferation and collagen synthesis. As inflammation is involved in the process, there is strong recommendation to avoid anti-inflammatory drugs after the procedure in order not to compromise its success.

PDRN is a mixture of deoxiribonucleotide polymers, with lenghts of chains between 50 and 2000 base pairs, extracted from the sperm of salmon or trout. PDRN is supposed to act via multiple ways. Being a sourse of pyrimidines and purines PDRN stimulates nucleic acid synthesis through salvage way.[35] It increases vascular endotelial growth factor VEGF synthesis and thus induces angiogenesis and collagen production.[36,37] VDRN has also an anti-inflammatory activity, increasing the anti-inflammatory cytokine interleukine 10 (IL-10) and reducing pro-inflammatory cytokines (interleukin-6 and tumor necrosis factor alpha). All these mechanisms sustain the regenerative and wound healing properties.

Research was published on a regimen of three weekly ultrasound guided injections, either in the subacromial bursa only or in the subacromial bursa and in the exact area of structural tendon defect. Compared to control, the results showed improvement of subjective complains at 3 months (pain and disability) with no difference in functional parameters (isometric strength of shoulder abductor, active range of motion and maximal tear size of the tendon).[38]

Another regiment, of maximum 5 weekly injections, in the same structures, noted reduction of pain and disability at 1 week after treatment completion; result were mentained at 1 and 3 months.[39]

4. Prolotherapy with hypertonic dextrose injection

The hypertonic glucose induces DNA-encoded growth factors in human cells and the healing cascade. Dextrose may also have a pain modulation effect through a sensorineural mechanism. The neuropathic pain afferent fibers have the transient receptor potential vanilloid-sensitive receptor-1 (TRPV1) cation channel (previously considered a capsaicin-sensitive receptor). It seems that topical application of manitol, a hyperosmotic agent, produces analgesic effect mediated through TRPV1 receptor.[40]

Research on one single injection into the tendon insertion site (5 ml dextrose 20%) offered temporary pain relief at 2 weeks but not at 6 weeks, with no mobility difference and no structural sonographic alterationcompared to placebo.[41]

Another study reported that increasing the number of injections may lead to improvement of both subjective and objective parameters. For chronic refractory supraspinatus tendinopathy, 10 ml of 16,5% dextrose injection on 8 – 12 points, repetead at intervals, to a maximum 8 treatment session, according to pain level. After one year, with an average of 4,8 treatment session, there was improvement in both subjective parameters (pain, disability) and objective shoulder function.[42]

5. Prolotherapy with other sclerosant agents (sclerotherapy)

The rationale behind use of sclerosant agents is the fact that neovessels and sensory nervous travel together from the soft tissue outside the tendon into the area with structural changes; this particularity is responsible for the pain.[43] Injecting small amount (1 – 2 ml) of polidocanol, in successive ”shots” in the areas of hipervascularization from the bursa wall and supraspinatus tendon was followed by immediate reduction of pain, supposedly from local analgesic effect. The injection was repeted after 4 – 8 weeks if pain and

hypervascularity were still present. On a medium term, 4 – 6 months, the results were resolution of pain and functional limitation.[44]

6. Prolotherapy with platelet rich plasma (PRP)

Platelet rich plasma PRP is an autologous blood product obtained through centrifugation. There are different methods to prepare PRP, leading to different volumes and platelets concentrations. Among the PRP growth factors, some researchers suggest that TGF-β1 and IL-1β in certain amounts were associated with supraspinatus tendon healing (as proved by sonographic imaging).[45] The cellularity of PRP may also differ. According to the preparation method, the concentration of leucocytes may vary. Leucocytes produce cytokines with catabolic and inflammatory activity, perpetuating inflammation and delaying tissue healing.[46]

The ultimate aim is to enhance the healing process through growth factors, promoting matryx synthesis and atracting circulatory cells to the tendon. With a number of studies in rotator cuff injuries in dogs and rats.

Methodology of PRP injections differ through literature: the subacromial bursa, the precise area of hypoechogenicity in focal tendinopathy, a combination of the precise area of hypoechogenicity and around it (for instance in four adiacent points into the tendon), a combination of precise area of tendon hypoechogenicity and the subacromial space (bursa), the intraarticular gleno-humeral space.[47]

Injecting the focal area of hypoechogenicity under sonographic guidance, one single administration through peppering technique, produced after 24 weeks a decrease of supraspinatus tendon thickness. It is documented that tendon thickness increases in degenerative tendinopathies, being a diagnostic criteria and it decreases as the tendon heals. Discussion arises on the number of PRP administration. After one single administration, the clinical course improved in 12 weeks and afterwards reached a plateau or a slight decrease. This may be an argument for repeating the procedure.

Other reasearchers found that one single PRP injection under sonographic guidance, into the focal area of hypoechogenicity of the supraspinatus tendon and in 4 points around it was not superior to saline injection at one year follow up. The outcomes were clinical and functional parameters. There was no sonographic evaluation of the tendon after completion of the study.[48]

Administration of two PRP injections at one month interval in the hypoechogenicity area and in the subacromial bursa offered the same pain reduction as therapeutical exercise alone at 6 months, but inferior results in shoulder mobility and function.[49]

Intraarticular glenohumeral PRP injection, 3 weekly administration, for patients with chronic supraspinatus tear followed by physical modalities offered similar results as physical modalities alone at 12 months; disability score improved better in PRP group.[50]

One costicosteroid infiltration provided more pain reduction and the same functional improvement at 6 weeks and 6 months versus single PRP in a blind subacromial administration.[51] While corticosteroids provide antiinflammatory and analgesic effect, PRP promotes also the healing process.[52] It is important to take into account the adverse effects of corticosteroids.

7. Topic application of nitric oxide (NO)

Nitric oxide a free radical, a gas produced by nitric oxide synthases (NOSs). It is toxic in large doses and it acts like a messenger molecule in small, physiological doses. There are three isoforms of the NO synthases: eNOS (in endothelial cells), bNOS (in brain and neuronal tissue), iNOS (part of host defense mechanisms).[53] After a tendon lesion, the NOS expression in augmented, in the secquence of iNOS – eNOS – bNOS. NO synthesis increases local blood flow, collagen synthesis and host defence. NO stimulates transcription and translation of extracellular matrix genes which, in turn, increase production of different types of collagen and other structural proteins. NO also modifies cellular adhesion in tenocytes.[54]

These observations are the base of clinical use of glyceryl trinitrate (GTN) patches which deliver locally NO.[55] Patches containing 5mg/24 h were cut into four and one quarter was applied daily on the most painfull area over the shoulder, usually right under the anterolateral edge of the acromion. Patches were applied until disappearance of symptoms or end of the study (6 months). Pain, active and passive range of motion and force in the supraspinatus improved at 2 weeks and were mentained at 24 weeks. The most important side effect was headache, in 58% of the study group, mainly in the first 2 weeks; the headache disappeared with continuation of therapy. A limitation for the GTN patch is the concomitant ischemic heart disease which requires referral to a cardiac physician.

8. Hyaluronic acid (HA) infiltration

Hyaluronic acid is a polysaccharide macromolecule, a glycosaminoglycan of high molecular weight. It is composed of repetitions of disaccharides of glucuronic acid and N-acetylglucosamine. The synovial liquid contains HA produced by chondrocytes and synoviocytes.[56]

Viscosupplimentation uses HA products classified as low-molecular weight (0,5 – 1,5 $x10^6$ Dalton) and high-molecular weight (6 – $7x10^6$ Dalton). HA products may differ also as cross-linkage and derivation sourse (avian or bacterial fermentation). Studies suggest that high-molecular weight (HMG) HA and those biological fermentation-derived provide better eficacy and safety.[57]

HA in supraspinatus tendinopathy was administered repeatedly, either peritendinously, intrabursal (subacromial bursa) or in both sites, under sonographic guidance, to target the precise area of delivery.

Hyaluronic acid in a peritendinous administration can reduce tendon adhesion, increase the vascular endothelial growth factor and type IV collagen, thus accelerating tendon healing.[58] Two injections at 2 weeks distance, in the form of sodium hyaluronate, in the subacromial space, under sonographic guidance, produced better results on pain and shoulder function than physiotherapy at 12 weeks and the gap between the results of the two treatments decreased at 24 weeks. The sonographic guidance is important to target the superior limitant of the supraspinatus tendon, where the thinner crescent fibers are located within the critical hypovascular zone, where the risk of degeneration and tearing exists.[59]

Another study used 5 weekly injections of hyaluronic acid under ultrasound guidance in the superior limitant of the tendon followed by physical therapy and reported better results than control for pain and symptom resolution at 3, 6 and 12 months. There were no differences in the tendon structure on ultrasound examination between the groups and the moments of treatment.[60]

Hyaluronic acid administered into the subacromial bursa, in 2 weekly injections followed by physical therapy provided significant pain reduction and functional recovery, with an earlier return to work as compared to physical therapy at 3 months′ evaluation.[61]

In the subacromial bursa, 3 weekly injections for subacromial impingement provided better pain relief and the same functional improvement than one single corticosteroid injection. The lack of adverse effects and of the potential risks of corticosteroids underlines the usefulness of hyaluronic acid.[62]

CONCLUSIONS

Supraspinous tendinopathy is the main responsible for shoulder pain and disability. Treatment in the acute phase includes medication, rest, physical modalities and therapeutic exercise. When symptoms fails to resolve and degenerative changes are documented, the clinician may resort to other conservatory therapies. The literature is rich in studies focusing on different approaches, everyone promising tendon healing, pain and disability reduction and functional restoring. The debate between extracorporeal shock wave therapy, dry needling, prolotherapy, hyaluronic acid, topical application of glyceryl trinitrate opens the field for new research and offers the practising physician many alternatives. Scientific papers are needed to develop a clear protocol for the refractory cases of supraspinatus tendinopathy.

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