Consensus on the use of infiltration in sport. Document of Consensus of the Spanish Society of Sports Medicine

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Summary

Infiltration is a therapeutic option used for the treatment of various diseases, which comprises injected administration into precise locations of different substances. They may have an analgesic and / or anti-inflammatory and healing effect.
Its use is common in the treatment of many soft tissue injuries such as bursitis, synovitis, plantar fasciitis, sprains, muscle injuries, tendinopathies and chondral injuries and must be preceded by the appropriate diagnosis.
Almost all local infiltrations have mild side effects and, sometimes, these may be systemic and may have some specific contraindications depending on the administered substance. Most of the adverse effects are caused by improper use of the drug.
The most used active substances are: *local anesthetics* that produce immediate pain relief, such as lidocaine and bupivacaine. They can be used alone or in combination with corticosteroids producing an immediate analgesic combined effect on local pain and a therapeutic effect of longer duration. *Corticosteroids,* whose main property is a very powerful anti-inflammatory action. The most used are betamethasone, methylprednisolone and triamcinolone. *Hyaluronic acid,* used in the treatment of joint diseases, particularly knee osteoarthritis and chondromalacias/chondropathias . It lubricates joints and appears to have direct effects on the function of synovial cells and synovial fluid. *Sclerotherapy,* which is the introduction of a chemical substance in the light of the blood vessels, causing obliteration and secondary fibrosis. It is indicated mainly in tendinopathies with vascular proliferation. *Biorregulators:* They stimulate healing when modulate or activate various involved substances. *Platelet-rich plasma:* autologous plasma containing more platelet concentration that normal blood, secreting a large amount of growth factors. *Prolotherapy,* it consists in substances infiltration that stimulate regeneration and tissue repair. *Other:* Nonsteroidal anti-inflammatory drugs, growth factors, stem cells and related therapies.

Key words:
Consensus. Injection. Infiltration. Soft tissues. Injury. Sport.

Consenso sobre utilización de las infiltraciones en el deporte. Documento de Consenso de la Sociedad Española de Medicina del Deporte

Resumen

La infiltración es una opción terapéutica, utilizada para el tratamiento de diversas patologías, que consiste en la administración inyectada en localizaciones precisas de diferentes sustancias. Pueden tener un efecto analgésico y/o antiinflamatorio y curativo.
Su uso es frecuente en el tratamiento de muchas lesiones de tejidos blandos como bursitis, sinovitis, fascitis plantar, esguinces, lesiones musculares, tendinopatías y lesiones condrales y deben de ir precedido del correspondiente diagnóstico.
Casi todas las infiltraciones tienen efectos secundarios locales, leves y, en algunas ocasiones, sistémicos y pueden presentar algunas contraindicaciones específicas que dependen de la sustancia administrada. La mayor parte de los efectos adversos son debidos a uso inapropiado del medicamento.
Los principios activos más utilizados son: *Anestésicos locales* que producen un alivio inmediato del dolor, como lidocaína y bupivacaína. Se pueden usar solos o en combinación con corticosteroides ejerciendo un efecto combinado analgésico inmediato del dolor local y un efecto terapéutico de mayor duración. *Corticoides* cuya propiedad fundamental es una acción antiinflamatoria muy potente. Los más utilizados son betametasona, metilprednisolona y triamcinolona. *Ácido hialurónico,* utilizado en el tratamiento de patologías articulares, especialmente la artrosis de rodilla y las condromalacias. Lubrifica las articulaciones y parece tener efectos directos sobre la función de las células sinoviales y el líquido sinovial. *Escleroterapia,* que es la introducción de una sustancia química en la luz de los vasos sanguíneos, provocando una obliteración y fibrosis secundaria. Está indicada fundamentalmente en las tendinopatías con proliferación vascular. *Biorreguladores:* Estimulan la curación al modular o activar diversas sustancias implicadas. *Plasma rico en plaquetas:* plasma autólogo que contiene más concentración de plaquetas que la sangre normal que segregan una gran cantidad de factores de crecimiento. *Proloterapia,* que consiste en la infiltración de sustancias que estimulan la regeneración y reparación de los tejidos. *Otros:* Antiinflamatorios no esteroideos, factores de crecimiento, células madre y terapias relacionadas.

Palabras clave:
Consenso. Inyección. Infiltración. Tejidos blandos. Lesión. Deporte.

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Introduction: evidence and utility

Infiltrations consist in local drug administration either by puncture or injection into soft tissue and joints. These therapeutic techniques are frequently used in a number of pathologies of the musculoskeletal system, for the purpose of achieving analgesic and anti-inflammatory effects and for healing injuries. Although some injectable drugs have proven efficacy in the treatment of sports injuries, the benefits of many others remain questionable[1]. In most cases, infiltrations are not considered to be a first choice treatment and are generally administered when the more conservative therapies have failed. They offer patients a therapeutic alternative to other routes of administration and, on occasions, their use leads to a faster return to training and competition.

As well as Sports Medicine specialists, infiltrations are also often used by anaesthetists, traumatologists, rehabilitation doctors, rheumatologists and general practitioners as a therapeutic option. Although they are almost always used for their analgesic, anti-inflammatory and / or tissue regeneration effect, on occasions they may also be used for diagnostic purposes[2].

Although a number of studies have been published on the effects of the infiltrations of different substances, the poor quality and methodological uniformity in many of these studies, as well as contradictory results, forces us to be cautious when evaluating their effectiveness[3]. Amongst the many sources of controversy, we could cite the following:

- the lack of knowledge, in many cases, of the etiopathogenesis of the problem being addressed;
- the choice of drug, dose level, the moment at which the infiltration is performed, the number of sessions and frequency;
- the administration technique used;
- care and rehabilitation following the process;
- the result is due to the substance, placebo effect, the puncture itself and/or the dose level administered.

Therefore, on many occasions, the guidelines are more based on personal experience than scientific evidence. Even so, their use is recommended in a number of therapeutic use guides[4].

In any case, although this is a simple technique, it does require a thorough knowledge of musculoskeletal disorders, the anatomical site where the infiltration is to be made and the substances to be administered. Moreover, it is essential to make a proper patient selection and to perfuse the minimum effective quantity of the correct drug, at the precise site and at the right time. Many of the problems that may arise with infiltrations are related to a poor choice of drug, incorrect dose level, the injection at an incorrect site or tissue, excessive frequency, or forgetting the cause or origin of the injury in addition to the subsequent care and rehabilitation[5,6].

Indications

Independently of the use of infiltrations of a number of substances in patients with autoimmune diseases (rheumatoid arthritis, juvenile chronic arthritis, systemic lupus erythematosus, etc.), spondyloarthropathies, gout, degenerative osteoarthritis, etc., as far as sport is concerned, soft tissue and joint infiltrations have been made for decades for analgesic and anti-inflammatory treatment in order to regain functional limitations or joint stiffness, to speed up the healing of certain injuries and to reduce or eliminate the need for more aggressive treatments. On occasions, the administration of a substance is preceded by the aspiration of intra-articular fluid (synovial fluid, haemarthrosis) intra-muscular fluid, etc. The last few years have witnessed an upswing in its application in regenerative therapy. Local anaesthetics are also frequently used to confirm a presumptive diagnosis by alleviating the symptomatology.

The injection of substances or drugs is very common in the treatment of a large number of pathologies or soft tissue injuries (muscles, tendons, ligaments, fascia, bursae, etc.): inflammatory problems such as bursitis (subacromial, goosefoot, pre-patellar, trochanteric, isquiatic, olecranon) or plantar fascitis; tendinopathies (patellar, achilles, supraspinatus, bicipital, epicondylitis, medial epicondylitis, De Quervain's tenosynovitis, etc.); sprains; muscle injuries; calcaneal spur; nerve entrapments (carpal tunnel syndrome, Morton's neuroma) and trigger points. In joint pathology, they are used in the treatment of synovitis and chondral and ligament injuries of traumatic or unknown origin[7].

The application of drugs through this route of administration must be justified by the expected benefits for each particular patient and type of injury. In order to perform an infiltration, there must be a clear diagnosis of the injury and rationale for treatment. Furthermore, there is a need to know the dose level, the application technique, any undesirable effects of the drug and contraindications.

Almost all infiltration of substances to treat pain, inflammation or tissue degeneration, have side effects, which are sometimes serious, and must be taken into account. Moreover, they could have undesirable effects, with particular mention of:

- Transitory pain after injecting the drug.
- Local haematoma.
- Infection.

With regard to the dose level for the majority of substances used, there are no specific criteria or consensus, neither are there a recommended number of infiltrations or the time interval between one infiltration and another.

Contraindications

There are circumstances in which infiltrations must never be performed and others in which there is a relative contraindication and the infiltration may be performed if the risk can be assumed. When in doubt, it is preferable not to perform the infiltration.

Absolute contraindications

- Hypersensitivity or allergy to any of the drugs used (risk of an anaphylactic reaction).
- Local or systemic infections.

- Risk of tendon rupture. Intra-tendon injections should be avoided, as they weaken the tendon and increase the risk of rupture (corticosteroids in particular).
- A recent fracture site, as it can delay the formation of the callus of the fracture.
- For joint prosthesis, due to the risk of infection.
- Minors under 18, with the exception of some chronic diseases.
- Medical - legal aspects such as the lack of informed consent or patient reticence.

Relative contraindications

- Risk of bleeding. For patients on anticoagulant treatment, with no clear evidence of the risk of bleeding, then infiltrations can be permitted.
- Diabetes Mellitus. There is a greater risk of sepsis.
- Secondary immunosuppression to disease or drug therapy.
- Pregnancy.
- Psychogenic pain, given the fact that an increase in the perception of pain may occur.
- Lack of positive results.

Conditions

The use or prescription of parenterally administered substances for diagnostic and/or therapeutic purposes to professional athletes requires knowledge of, and compliance with, the national and international anti-doping legislation, up-dated on an annual basis (www.aea.gob.es, www. wada-ama.org).

Before performing any infiltration, the patient must receive written and verbal information on the type of procedure in addition to the associated risks and benefits, and must sign an infiltration consent form.

In order to reduce the risk of infection, strict sterile conditions must be maintained, particular with regard to an intra-articular injection.

Provided that the skin is intact and in order to alleviate the pain produced by the injection, it may be useful to use ice, cooling sprays and topical anaesthetics (cream or patches with lidocaine, alone or in combination with other anaesthetics).

From a technical point of view, professionals performing infiltrations are required to have considerable anatomical knowledge of the site and, in this respect, an ultrasound scan leads to increased accuracy, thereby reducing the risk of complications[8,9]. An ultrasound scan is primarily used in small joints and soft tissue, for radiation-free, real-time viewing of the tissues and needle, thereby avoiding contact with vessels, nerves and fascia, as well as tendons, unless these are the target of the procedure (neo-vessel sclerosis in tendinitis). Fluoroscopy, CT and magnetic resonance are primarily used for large joints, the spine and sacroiliac joints, although the ultrasound scan is becoming increasingly more decisive in this field[5,9].

Imaging techniques may be of particular help and are reserved for the following circumstances and sites[6,10]:

- When the injection or aspiration has failed.
- When the objective is fundamentally for diagnostic purposes.
- For obese patients.
- Spinal infiltrations.
- To verify a site in research studies.
- To monitor the effects of the infiltration.

Types of infiltrations

Based on the application site, infiltrations can be classed into intra-articular and extra-articular or soft tissues. The route for extra-articular infiltrations can be either intradermal, subcutaneous, intramuscular or intravenous, whilst a number of therapeutic techniques can be used (biopuncture, mesotherapy, etc.).

Active ingredients and substances used

Local anaesthetics

Local anaesthetics either reversibly reduce or block the nerve conduction through the blockade of Na^+ channels, causing the temporary loss of the autonomic, motor and/or sensory functions. They act by reducing the membrane depolarisation rate, thereby increasing the electrical excitability threshold. The blocking affects all the nerve fibres: Autonomic NS, sensitive NS and motor NS, sensations are gradually lost in the following order: pain, temperature, touch, proprioception and muscle tone[11].

This is extremely useful with regard to therapeutics (analgesia), diagnosis (to confirm the source of pain), as a medium to dilute other substances (corticosteroids, ...) etc. From a therapeutic point of view, the local injection of anaesthetics provides immediate pain relief.

Local anaesthetics are classed into esters and amides, depending on the type of link contained (Table 1). The clinical use of esters is limited to local anaesthetics, due to their instability and to the fact that they frequently cause allergic reactions.

Table 1. Types of local anaesthetics.

Esters	Amides
Benzocaine	Articaine
Cocaine	Bupivacaine
Novocaine	Cinchocaine
Oxybuprocaine	Etidocaine
Procaine	Lidocaine
Tetracaine	Levobupivacaine
	Mepivacaine
	Prilocaine
	Ropivacaine

Amides are more frequently used for local infiltrations and particularly 1% or 2% lidocaine and 0.25% and 0.5% bupivacaine (especially for nerve blocks). Lidocaine and mepivacaine (1 or 2%) are characterised by a rapid onset of action (1-2 minutes and even shorter for mepivacaine) and shorter duration (1 hour and slightly more for mepivacaine which produces less vasodilation), whilst bupivacaine has a slow onset of action (30 minutes) and a greater duration (8 hours) (Table 2).

Amides are safer than esters, and should be used without a vasoconstrictor given the fact that, although vasoconstrictors serve to increase the duration of the anaesthetic effect, reducing bleeding and the adverse systemic effects, their use can produce tissue necrosis and delay the healing of surgical wounds[12].

Indications for the infiltration of anaesthetics

In sporting terms, local anaesthetics are used to alleviate pain in joint, tendon, ligament, skeletal, bursa injuries, etc. for an earlier return to sports activity, thereby reducing the number of injured athletes. In competitions, in the event of pain, anaesthetics are frequently used to block pain and achieve maximum performance; within the therapeutic arsenal available, this is a medical procedure that offers risks and benefits. Provided that the benefits are greater than the risks, then this procedure can be justified[13].

Logically, the anaesthetic effect will block all kinds of sensations at a local level. Therefore there will be a loss of proprioception with all its consequences. As a result, amongst some professional groups, its use as a therapeutic method to block pain is considered to be unethical, and is prohibited in some organisations, whilst others support its administration[12-14].

Local anaesthetics can be used alone or in combination with corticosteroids, exerting a combined effect to provide immediate relief of local pain and a longer-lasting therapeutic effect provided by the corticosteroid[15]. The combination also increases the area of distribution, avoiding high concentrations of corticosteroids in a small site. Manufacturers advise against mixing corticosteroids with lidocaine, due to the risk of flocculation and the precipitation of steroid crystals.

At the moment, there are no specific guidelines for prescribing anaesthetic infiltrations, which makes it even more difficult for Sports Medicine professionals to make a decision of this nature[13].

Table 2. Properties of anaesthetics.

	Short	**Medium**	**Long**
Latency	Chloroprocain Mepivacaine Etidocaine Lidocaine	Bupivacaine Levobupivacaine Ropivacaine	Procaine Tetracaine
	Low	**Medium**	**High**
Potency and of effect	Chloroprocaine Procaine	Prilocaine Mepivacaine Lidocaine	Bupivacaine Levobupivacaine Ropivacaine Tetracaine

Side effects

Although rare, local anaesthetics can provoke local reactions or systemic effects, whilst most adverse effects are due to improper drug use[16,17].

Amongst the local side effects, particular mention should be made of the following:

- Erythema, itching, tingling, bruising, pain at the infiltration site, infections, vascular or nerve injuries due to mechanical damage.
- Muscle injuries due to the direct infiltration on the muscle, particularly affecting small muscles, with the possibility of causing tissue necrosis (myotoxicity).
- Nerve tissue injuries due to direct injection or through prolonged exposure to the anaesthetic agent (neurotoxicity).
- Infiltrations in an injured muscle, tendon or ligament could create a greater risk of rupture or a deterioration of the injury.
- Although systemic reactions are uncommon, if they do occur, they could be fatal. They are generally due either to an overdose or to intra-vascular infiltrations[17,18].
- Although highly uncommon, some of the most serious adverse effects include allergic reactions when using esters. This is due to the fact that it has PABA as an intermediate metabolite, which stimulates allergic reactions in pre-sensitised patients.
- Vasovagal reactions with hyperventilation, paresthesias or vagal symptoms.
- On rare occasions, cardiovascular manifestations may occur, related to the plasma concentration and to the anaesthetic agent used; these are more frequent with bupivacaine[13].
- Infiltrations with high dose levels of prilocaine, articaine and benzocaine can cause methaemoglobinemia.

Corticosteroids

Corticosteroids were first used in local intra-articular injection in the middle of the last century[19] and, from then onwards, they have been widely used in the sports sector. The most commonly used agents for infiltration are synthetic analogues of the endogenous cortisol (hydrocortisone) segregated in the adrenal cortex.

Once administered they combine with certain intracellular receptors that control the gene transcription, modifying the synthesis of certain proteins. They act on the carbohydrate metabolism, the lipids and proteins at a locomotor system level, on the cardiovascular system, the central nervous system and on other hormones.

Their use in the treatment of sports injuries is primarily due to their extremely potent anti-inflammatory effect. They inhibit all the inflammation stages, early and late (fibroblastic proliferation, healing and cell proliferation) without acting on the underlying causes.

The anti-inflammatory effect is produced by inhibiting the A2 phospholipase protein, blocking the production of different pro-inflammatory mediators (leukotrienes, porstaglandins, thromboxanes and prostacyclin), stabilising the lysosomal membrane of the inflammatory cells, reducing the local vascular permeability and modifying the chemotaxis and the functioning of the neutrophils[20,21]. Furthermore, they inhibit the release of eosinophils and reduce the activity of the B and T lymphocytes.

Table 3. Type of corticosteroids according to the duration and potency of their effects.

Long duration (36-54 h) High potency	Betamethasone Dexamethason
Intermediate duration (18-36 h) Medium potency	Deflazacort Methylprednisolone Prednisone Prednisolone Triamcinolone
Short duration (8-12 h) Low potency	Hydrocortisone (Cortisol)

On the other hand, with regard to their side effects, account should be taken of the fact that, as well as the anti-inflammatory effect, they also stimulate gluconeogenesis and increase the catabolic activity in the muscles, skin, connective tissue, adipose and lymphatic tissue.

Although all corticosteroids can be used in local infiltrations (Table 3) the most popular are those with delayed effects or with the chemical characteristics of fat-soluble esters (acetate or acetonide), because absorption is slower and the therapeutic effect is therefore of longer duration. The most used are betamethasone, methylprednisolone and triamcinolone[20,21].

The duration of effect is inversely proportional to the solubility of the agent. The most soluble (dexamethasone and betamethasone) have greater systemic effects; triamcinolone and methylprednisolone are of an intermediate solubility and duration and are most used in soft tissues; the least hydro-soluble corticosteroids (acetonide and triamcinolone hexacetonide) are most used for intra-articular infiltrations and their use is not recommended in soft tissue due to the increased risk of tissue atrophy[7,22,23].

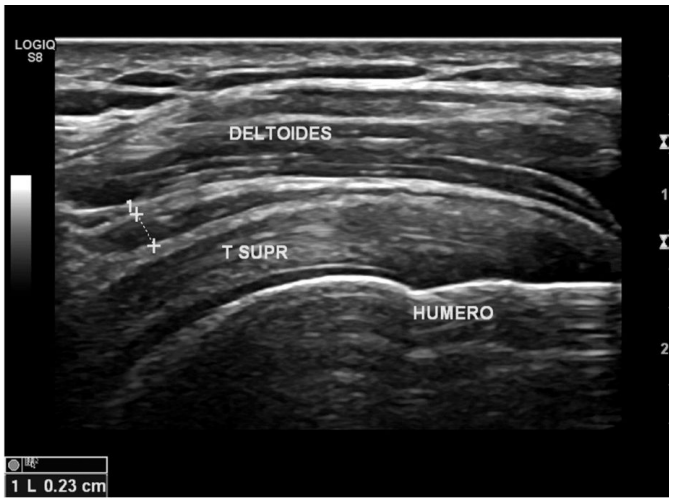
Indications

There is considerable disagreement with regard to the clinical use of local infiltrations with corticosteroids (alone or combined). Whilst some professionals support their use for the treatment of some tendinopathies[24], tenosynovitis[25], bursitis[26,27], sprains or simply as painkillers[2], others can find no benefit. In any case, with corticosteroids, there is always the need to observe the principle of using the smallest possible dose for the shortest possible time.

Local infiltrations are only recommended when conservative treatment has failed (rest, exercise, physiotherapy, orally administered anti-inflammatory medication) and when the anatomical site that is the source of the symptom can be located (Figure 1). No more than three injections should be applied, spaced several weeks apart, and with repeat injections given only if previous ones have proved to be successful. Following corticosteroid infiltration, patients are normally recommended to rest for 3 to 7 days.

There are few clinical indications for the use of intra-articular corticosteroids, amongst other reasons because they can inhibit the

Figure 1. Subacromial bursitis. A long axis examination of the supraspinatus tendon shows that, above it, the bursa has a thickness of more than 2 mm.



formation and repair of the articular cartilage, particularly when used at high dose levels. The primary objective of most articular infiltrations is to remove the pain, thereby improving the joint function.

For load-bearing joints, some authors advise considerable caution due to potential chondral damage caused by corticosteroids in the long term[28]. For others, there are few cases of steroid arthropathy described in the literature and always following a high number of injections[29]. The recommendation to infiltrate with intervals of at least three months is mostly based on consensus than on true scientific evidence. However, at least for the knee, with this frequency and for two years, it appears safe[30]. In any case, the use of corticosteroids shall only be considered if other conservative treatments have failed.

The simultaneous infiltration of a number of large joints should be avoided, as this increases the risk of suppression of the hypothalamic–pituitary–adrenal axis.

Evidence that tendinopathies are not associated with the presence of inflammatory cells is one of the reasons why corticosteroids are no longer used in this type of pathology[31,32]. Compared to other conservative treatments and even to placebo, the local injection of corticosteroids in epicondylitis demonstrated an improvement in the short term, yet in the medium term (after 6 weeks) and long term, the evolution was worse[3,33,34]. A systematic review by Koester *et al.*[35] could find no evident improvements with infiltrations in the treatment of rotator cuff disease. Therefore, for chronic non-inflammatory tendinopathies, steroids should be used in moderation[36].

Another reason for questioning the treatment of tendinopathies with corticosteroids is the fact that data are available indicating that they cause non-beneficial cell and extracellular matrix tissue disorders[37].

Despite the fact that a significant improvement is found, the results of the studies made on bursitis (anserine and trochanteric) must be questioned given the fact that they are mainly observational in nature and lack a control group[26,27,38].

Nowadays, the local infiltration of corticosteroids in muscle injuries is not recommended despite the fact that some studies[39] found a shorter recovery time, however this is questionable due to the poor methodological design of the studies.

In general, although application is extremely widespread in the world of sports medicine, its benefits have not been validated in those pathologies in which inflammation is only a secondary reaction[40]. On the other hand, it has been confirmed that corticosteroids behave differently according to the type of injury and the damaged tissue. Infiltrations of corticosteroids are never recommended immediately after the injury, before a competition or in the event of concomitant infection.

The dose level depends on the type of tissue and the size and seriousness of the injury. For joints, the quantity of hydrocortisone to be infiltrated ranges from 10 to 25 mg for small joints and soft tissue and 50 mg for large joints. The dose level of methylprednisolone ranges from 2 to 10 mg for small joints and soft tissue and 10-80 mg for large joints. The dose level of dexamethasone ranges from 0.5 to 3 mg for small joints and soft tissue and 2-4 mg for large joints. Betamethasone should be applied in dose levels from 1 to -3 mg for small joints and soft tissue and 2-6 mg for large joints.

Infiltrations with betamethasone are more effective than with methylprednisolone and triamcinolone as pain relievers[41].

They are frequently used in combination with a local anaesthetic, basically due to their almost immediate analgesic effect, which also helps to confirm the correct location of the needle. However, the combination with an anaesthetic may slightly increase the risk of infection and provoke the precipitation of crystals and a reduction in the bioavailability of the corticosteroid[5,6].

Side effects

Adverse effects are rare and, when they do occur, they are generally minor and temporary in nature[3]. At a local level, they may be associated with the infiltration at an inadequate site or with an excessive dose. The most common side effects are: pain, which generally appears 24-36 hours following injection, sometimes due to cortisone crystallisation, bruises, local erythema, infections at the infiltration site (cellulite, abscesses, bursitis, arthritis…), cutaneous atrophy, subcutaneous fat atrophy and skin depigmentation or hypopigmentation, occurring between 6 and 12 weeks after injection.

Infiltrations in tendons, fascia and ligaments increase the fragility and the risk of rupture[42,43]. With regard to this latter effect, studies on tenocyte cultures with dexamethasone have demonstrated a dose-dependent decrease in tenocyte proliferation, collagen production and tendon progenitor cell recruitment[44]. It appears that peritendinous infiltrations may also affect the mechanical properties of the tendon, similar to the negative effects of the intra-tendinous infiltrations, increasing the risk of rupture[40,42,43,45].

Systemic effects (in general these are rarely found with local infiltrations, although the risk is slightly greater when injected in soft tissue):

- Post-infiltration vasovagal reaction.
- Decreased cellular and humoral immunity, with increased susceptibility to infections.
- Dyslipidemia, HBP, thrombosis, vasculitis.
- Hyperglycaemia - glucose intolerance due to increased gluconeogenesis and insulin resistance.
- Menstrual alterations, due to alterations in gonadotropin secretion.
- Cushing's syndrome.
- Facial flushing.
- Gastritis, peptic ulcer, gastrointestinal bleeding, pancreatitis.
- Osteoporosis-osteonecrosis due to increase protein catabolism.

Contraindications

Corticosteroid infiltrations are contraindicated when there is hypersensitivity to the drugs or when there is a record of adverse reactions, in the event of fractures, when there is a risk of tendinous rupture or in the presence of concomitant infections. Neither are they recommended when there is no precise diagnosis, if the injury is very recent, during competitions or in the absence of informed consent.

Moreover, care should be taken when the patient has uncontrolled diabetes or HBP, osteoporosis, a history of avascular necrosis, coagulation disorder, thrombocytopenia, or joint replacements at the infiltration site.

Hyaluronic acid (HA)

Hyaluronic acid is a glycosaminoglycan lubricant specifically used in the treatment of joint pathologies. It is most frequently used in the treatment of large joint pathologies, specifically arthrosis of the knee joint and Chondromalacia.

Many studies are in favour of its use in cartilaginous injuries given the fact that there is at least a clinical improvement for an extended period of time in a high percentage of cases. It appears to cause the normalisation of the synovial fluid viscoelasticity and to stimulate the regeneration of the chondral tissues.

It lubricates the joints and appears to directly affect the function of the synovial cells and synovial fluid[46,47]. The articular cartilage and synovial fluid are known to have different concentrations of HA depending on their physiological state, whilst osteoarthritic joints have a lower concentration of HA than healthy joints.

According to some studies, exogenous HA may increase the endogenous synthesis of chondrocytes and proteoglycans, prevent the degradation of the cartilage and promote its regeneration. On the other hand, it may reduce the production of pro-inflammatory mediators and matrix metalloproteinases and reduce the nervous impulses and sensitivity of the nerves associated with joint pain[48].

Therefore, the intra-articular infiltration of HA (Viscosupplementation) will improve the quality of the synovial fluid and its viscoelasticity.

The treatment of osteoarthritis with hyaluronic acid is yet another alternative, particularly for those patients with a poor response to non-drug therapy or to analgesics and orally-administered NSAIDs[49].

It has also been seen that, for some tendinopathies (epicondylitis) it has better effects than the placebo[3,50], although the response is not satisfactory in all cases.

There are a number of types of hyaluronic acid which can generally be divided into those which are of short duration, requiring injections

once a week, and those of long duration which remain for a longer period of time in the joint, making it possible to give a single injection which will last for a longer period of time, ranging from 6 to 12 months.

Side effects

The infiltration of HA is a safe technique if performed correctly and if carried out aseptically. However, it may cause slight, local side effects in 1-2% of cases, with particular mention of: skin redness, bruising, localised itching or local inflammation at the injection site which disappear in 1-3 days[51]. A few cases of pseudogout and chondrocalcinosis have also been described following administration of HA.

Contraindications

HA has the contraindications characteristic of intra-articular infiltration and for those patients that are hypersensitive to this substance. It is not recommended for patients with coagulation disorders and must be administered with caution in patients with severe lymphatic or venous insufficiency. Neither is it recommended for pregnant women or when breastfeeding.

Scelerosing agents

Sclerotherapy is a medical procedure consisting in introducing a chemical substance into the blood vessel lumen, causing vessel thrombosis and obliteration and secondary fibrosis. The most common scelerosing agents include polidocanol used for the sclerosis of neovessels formed in tendinosis[52-54], although others are also available (sodium tetradecyl sulfate, chromic glycerine, etc.) used in the sclerosis of other pathologies.

Indications

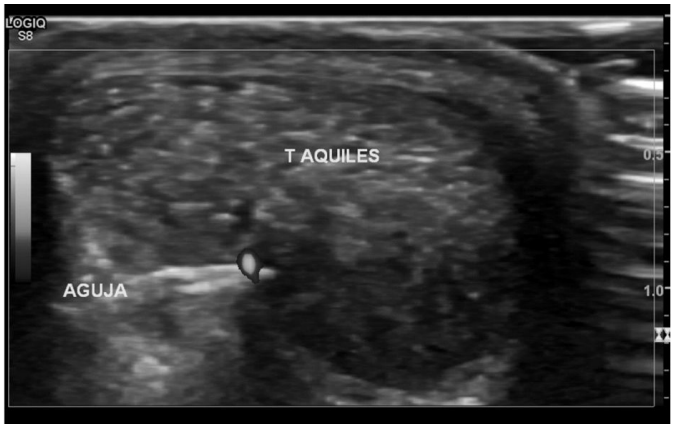
Sclerotherapy has many different applications, including the area of Sports Medicine, especially different types of tendinopathies. The use of sclerotherapy in tendinopathy is based on the demonstration that some tendinous injuries lead to the proliferation of small blood vessels in the areas of the tendons affected and the sensitive nervous fibres also proliferate around these neoformed blood vessels, being the cause of the pain (Figure 2). In theory, the injection of a scelerosing agent in the neovascularised areas provokes vascular sclerosis and, moreover, can eradicate the pain sensors[53-55].

At present, the results of sclerotherapy for Achilles tendinitis, epicondylitis, etc. are contradictory[3].

Adverse reactions

This drug rarely has any adverse effects. Sclerotherapy is a safe, well tolerated procedure. The undesirable effects at a local level include haematoma formation at the injection site, oedemas, temporary irritation (of the endothelial wall of the injected vein), slight pain at the injection site, hypopigmentation (in 10 to 30% of cases). Allergies appear only on rare occasions[54].

Figure 2. Sclelerotherapy technique for Achilles tendinitis. In this cross-section of the Achilles tendon, the point of the needle can be seen to reach the vessel to be scelerosed. Note that the needle chamfer is oriented towards the tendon.



Superficial thrombophlebitis or nodular fibrosis are not generally observed in operations of this type on small vessels, although there is the risk of thrombosis due to the incorrect administration of intravaricose injections.

Contraindicationss

By acting on small vessels, contraindications are almost limited to cases of known allergy to the scelerosing agent, although it is advisable to proceed with caution for patients with severe, acute disorders, a recent history of thrombosis or immobilised patients..

Bioregulators

Bioregulator drugs comprise active ingredients that are basically plant and mineral sourced, acting by stimulating the natural recovery mechanisms of the damaged tissue[56]. Compared to inflammation blocker drugs, bioregulators (Traumeel, Zeel, Spascupreel, etc.) are directed at modulating the inflammation. These bioregulators have been shown to inhibit the production and release of some pro-inflammatory cytokines[57-59].

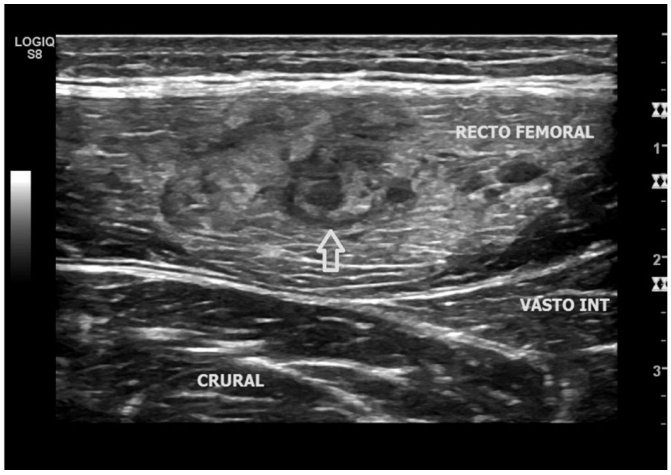
Indications

Clinical and experimental studies have shown their beneficial effects in different sports injuries in relation to soft tissue (Figure 3) and chondral damage[60-62]. These injectable therapies can either be administered alone, concomitantly, or together with other drugs or techniques (physiotherapy, thermotherapy, RICE, etc).

Side effects

These substances have practically no side effects, with very good tolerability, although, in rare cases, there may be hypersensitivity or allergic reactions.

Figure 3. Fractured fibula of the straight femoral muscle. An examination of the short axis of this muscle shows a heteroechoic image (arrow) that blots out the intra-muscular wall, characteristic of a muscle tear with septum rupture.



Contraindications

In the event of allergy or hypersensitivity to these products or to any of their components, and for pregnant and breastfeeding women. As a precaution, it is advisable not to use these therapies for some systemic diseases (leukaemia, tuberculosis or autoimmune diseases), which require a different type of treatment.

Platelet-rich plasma

The last few years have witnessed the extended use of platelet-rich plasma (PRP) or the growth factors to accelerate the healing of many types of injuries. PRP is an autologous plasma that contains a greater concentration of platelets than normal blood. It was first used in the treatment of pathologies related to dentistry and maxillofacial surgery and this is the area with most experience.

Platelets transport substances in their granules and these influence the tissue repair processes. Following activation, they secrete a large quantity of growth factors (they can hold as many as 1100 active proteins) including the platelet derived growth factor (PDGF), beta 1 transforming growth factor (TGF-β1), platelet factor 4 (FP-4), vascular endothelial growth factor (VEGF), insulin-like growth factor 1 (IGF-1), epidermal growth factor (EGF), fibroblast growth factor (FGF), nerve growth factor (NGF), hepatocyte growth factor (HGF), etc. whilst an increase in the systemic levels of some of these factors such as IGF-1, FGF, and VEGF[63] have been observed. Many of these growth factors (GF) are active in the healing of different pathologies[32,64].

More than 30 different platelet concentration systems are available on the market, achieving different densities depending on the extraction, centrifugation, filtration methods, etc. However, at present, the platelet concentration offering the most beneficial effects has yet to be determined, neither is it known whether or not the presence of leukocytes in PRP is beneficial.

The greatest problem with this technique is that there are no clear criteria on how to prepare PRP, right from the blood collection up to the administration of the preparation. There is no consensus on the centrifugation speed and time, the activation of the PRP, which can be made either before or after administration to the tissue, on the volume of PRP to be applied, the frequency of application or the number of applications[65,66]. And, most importantly, the PRP content: the growth factors contained and those factors that are useful for the treatment of the injury and those that could be harmful.

Indications

There is an increasing number of articles on the role played by PRP in the treatment of chronic tendon injuries[3,67-70], articular cartilage injuries[71], ligament injuries[72], meniscus injuries[73], muscle injuries[74-77], etc.

In addition to the potential beneficial effects on soft tissue injuries, there are the bactericidal effects of the antibacterial and fungicidal proteins stored in the platelets (opsonophagocytosis), which may help to prevent infection[78]. In the future, it could be used in the prophylaxis of infections and, in particular, for surgical wounds. Furthermore, HGF is a potent antifibrotic agent and its secretion may help to reduce tissue scar formation.

The results on the effectiveness of this technique are extremely varied from one author to another. Some investigations show PRP to be effective and to accelerate the healing of certain injuries, whilst others show no benefit at all. This disparity of criteria may be due to the technique employed, the tissue treated, the type of injury[79-81], etc.

However, in most cases, with regard to sports injuries, there is little scientific evidence, and the evidence available is of poor quality.

Given the fact that, at present, the clinical results of infiltrations with PRP are extremely dubious[66,82] due to the poor methodological quality of most of the investigations published, and a lack of consensus, despite the fact that a consensus document was recently published[65], it would be necessary to conduct randomised clinical trials (RCT) on the use of PRP in the treatment of different sports injuries, and which include clear, specific protocols.

Side effects

There are no clear scientific reports to suggest possible side effects following the administration of PRP. At a local level, temporary inflammatory reactions may appear at the puncture site. Bearing in mind the fact that it is an autologous substance, in theory it ought not to provoke allergic or immunogenic responses or other harmful effects, and ought to be a safe and secure product[83,84]. However, if it contains bovine thrombin, then this could be a problem, and the latest techniques endeavour to avoid this substance.

PRP can improve the proliferation of mesenchymal stem cells and migration, yet it can also limit stem cell differentiation, although, for the time being, there are no references for side effects in this area[83].

Contraindications

PRP infiltrations are contraindicated in those cases with septicema or local infection at the infiltration site, neither should this treatment

be applied to patients with platelet dysfunction syndrome or thrombocytopenia.

As relative contraindications, we could cite patients either with cancer, a low platelet count or with a fever at the time of infiltration.

Prolotherapy

Prolotherapy, proliferation therapy or regenerative injection therapy (RIT) consists in the infiltration of substances that stimulate tissue regeneration and repair. The treatment is based on the infiltration of irritating chemical solutions with local anaesthetics around the injured structures, to allow for the increased resistance of the tissue and, secondarily, to reduce pain and disability[85].

Prolotherapy uses three types of substances: irritants, chemotactic agents and osmotic agents; Although the mechanism of action has not been clearly established, irritants (phenol, guaiac and tannic acid) produce direct cell damage, chemotactic agents (morrhuate sodium) generate an inflammatory response whilst osmotic agents (concentrated solutions of dextrose, glucose, glycerine or zinc sulphate) provoke the osmotic rupture of cells and an inflammatory response, releasing cytokines and growth factors that promote healing, improving the joint function and tissue recovery[86-88]. Hypertonic dextrose is the most commonly applied solution, because it is non-toxic, amongst other reasons.

Prolotherapy technique involves the administration of a small quantity of a specific solution at typical trigger points (ligaments, tendons, etc.). The solution is generally administered at 3 to 6 week intervals, with a total of four to eight sessions[89].

Indications

According to some investigations, it could be an alternative treatment in chronic pathologies of the locomotive system, such as back pain, sprains, tendinopathies, joint instability, ligament laxity, fibromyalgia, plantar fasciitis, sciatica, Osgood-Schlatter and osteoarthritis amongst others[32,87,88,90-92], although more studies are required in order to openly recommend this therapy[93].

Prolotherapy lessens pain according to some studies that have used the VAS (visual analogue scale)[94] and it also reduces locomotive disability.

Tendinopathy and myofacial pain syndrome improve clinically and functionally with prolotherapy[93,9-98].

Prolotherapy (dextrose) considerably reduces pain levels, thereby speeding up the resumption of sports activities in pathologies such as Osgood Schlatter[99,100].

Benefits have also been observed for meniscal degeneration[98].

For oastoarthritis and other degenerative joint pathologies, prolotherapy with dextrose produces a significant improvement in pain[101,102].

Side effects

Normally, there is a post-injection pain flare that can last from a few minutes to several days, but the discomfort is bearable. Headaches and dizziness have also been described, due to phenol, a potentially toxic substance. Therefore, treatment with dextrose alone is preferable[89,103]. When dextrose is used, significant adverse affects do not generally appear[87], and allergic reactions are uncommon.

Contraindications

Allergies to some of the infiltrated products, local infection at the treatment site, significant local inflammation, septic arthritis and significant coagulation disorders.

Other substances used

Autologous blood infiltrations. This is based on the same principles as PRP, given the fact that blood contains substances, including growth factors, which can modify cell activity. The technique is very simple, consisting in drawing some 2-3 cc of venous blood from the patient, with subsequent local infiltration at the pathological site. Anything from one to three autologous blood infiltrations can be applied, with an interval period of 1-2 months.

It is basically used in the treatment of tendinopathies, although the results are contradictory[104-108].

Non-steroidal anti-Inflammatory drugs. NSAIDs are the most commonly used drugs in the treatment of most sports injuries and, although the oral route is the one that is most frequently used, they are also administered by the injectable route. For tendon injuries with no inflammatory component, these drugs are merely pain relievers and, as such, their administration is the subject of much discussion[36,109,110]; this is also the case for muscle injuries. For acute sprains, they have an analgesic and anti-inflammatory effect, whilst they are also prescribed for this same reason following surgical operations[111,112].

Stem Cells, Growth Factors and Related Therapies. Although they are now part of the present, stem cells and related therapies will form part of the therapeutic arsenal for sports injuries and other locomotor system disorders.

Until now, most growth factors have been studied in vitro and on test animals, yet this is a therapy with a great future given the fact that the specific growth factors of the tissue to be treated would be introduced into the damaged site.

For their part, stem cells provide very important immunomodulating activity with regard to tissue repair and, in particular, for tendon, chondral, muscle and ligament pathologies, they have great therapeutic potential[32,113,114].

Botulinum Toxin. Type A botulinum toxin is a neurotoxin that inhibits the release of the neurotransmitter acetylcholine at the neuromuscular junction, provoking the temporary paralysis of the skeletal muscle and, secondarily, a reduction in pain. Some trials have been conducted on its application in some injuries such as epicondylitis and, in general, it can be said that improvement is questionable[3,115,116], and could be used as a final treatment option, although more robust studies are required to demonstrate its effectiveness[32].

References

1. Rifat SF, Moeller JL. Basics of joint injection. General techniques and tips for safe, effective use. *Postgrad Med.* 2001;109:157-60.

2. Bhagra A, Syed H, Reed DA, Poterucha TH, Cha SS, Baumgartner TJ, *et al*. Efficacy of musculoskeletal injections by primary care providers in the office: a retrospective cohort study. *Int J Gen Med.* 2013;6:237-43.
3. Krogh TP, Bartels EM, Ellingsen T, Stengaard-Pedersen K, Buchbinder R, Fredberg U, *et al.* Comparative effectiveness of injection therapies in lateral epicondylitis. A systematic review and network meta-analysis of randomized controlled trials. *Am J Sports Med.* 2013;41:1435-46.
4. National Collaborating Centre for Chronic Conditions (UK). *Osteoarthritis: national clinical guideline for care and management in adults.* London: Royal College of Physicians; 2008.
5. De Muynck M, Parlevliet T, De Cock K, Vanden Bossche L, Vanderstraeten G, Özçakar L. Musculoskeletal ultrasound for interventional physiatry. *Eur J Phys Rehabil Med.* 2012; 48:675-87.
6. Saunders S, Longworth S. Injection therapy – The evidence. In: Saunders S, Longworth S, Eds. *Injection techniques in musculoskeletal medicine. A practical manual for clinicians in primary and secondary care*, 4th Edition. Elsevier 2012; pp. 5-71.
7. Cardone DA, Tallia AF. Joint and soft tissue injection. *Am Fam Physician*. 2002;66:283-8.
8. Malfair D. Therapeutic and diagnostic joint injections. *Radiol Clin North Am*. 2008;46: 439-53.
9. Daley EL, Bajaj S, Bisson LJ, Cole BJ. Improving injection accuracy of the elbow, knee, and shoulder: does injection site and imaging make a difference? A systematic review. *Am J Sports Med.* 2011;39:656-62.
10. Hall S, Buchbinder R. Do imaging methods that guide needle placement improve outcome? *Ann Rheum Dis.* 2004;63:1007-8.
11. Yagiela JA. Local anesthetics. *Anesth Prog.* 1991;38:128-41.
12. Orchard JW1, Steet E, Massey A, Dan S, Gardiner B, Ibrahim A. Long-term safety of using local anesthetic injections in professional rugby league. *Am J Sports Med.* 2010; 38:2259-66.
13. Orchard J. The use of local anaesthetic injections in professional football. *Br J Sports Med.* 2001;35:212-3.
14. Down S, Waddington G, Adams R, Thomson M. Movement discrimination after intra-articular local anaesthetic of the ankle joint. *Br J Sports Med*. 2007;41:501-5.
15. Jacobs JW. How to perform local soft-tissue glucocorticoid injections. *Best Pract Res Clin Rheumatol.* 2009;23:193-219.
16. Mather LE, Copeland SE, Ladd LA. Acute toxicity of local anesthetics: underlying pharmacokinetic and pharmacodynamic concepts. *Reg Anesth Pain Med.* 2005;30:553-66.
17. Neal JM, Bernards CM, Butterworth JF, DiGregorio G, Drasner K, Hejtmanek MR, *et al.* ASRA Practice advisory on local anesthetic systemic toxicity. *Regional Anesthesia and Pain Medicine.* 2010;35:152-61.
18. Tetzlaff JE. The pharmacology of local anesthetics. *Anesthesiol Clin North Am*. 2000;18: 217-33.
19. Hollander JL, Brown EM, Jessar RA, Brown CY. Hydrocortisone and cortisone injected into arthritic joints; comparative effects of and use of hydrocortisone as a local anti-arthritic agent. *JAMA.* 1951;147:1629-35.
20. Baxter JD, Forsham PH. Tissue effects of glucocorticoids. *Am J Med.* 1972;53:573-89.
21. Creamer P. Intra-articular corticosteroid injections in osteoarthritis: do they work, and if so how? *Ann Rheum Dis.* 1997;56:634-6.
22. Stephens MB, Beutler AI, O'Connor FG. Musculoskeletal injections: a review of the evidence. *Am Fam Physician.* 2008;78:971-6.
23. Nepple JJ, Matava MJ. Soft Tissue Injections in the Athlete. *Sports Health: A Multidisciplinary Approach.* 2009;1:396-404.
24. Smidt N, Assendelt WJ, van der Windt DA, Bouter LM. Corticosteroid injections for lateral epicondylitis: a systematic review. *Pain*. 2002;96:23-40.
25. Richie CA, Briner WW. Corticosteroid injection for the treatment of de Quervain's tenosynovitis: a pooled quantitative literature evaluation. *J Am Board Fam Pract.* 2003;16:102-6.
26. Calvo-Alén J, Rua-Figueroa I, Erausquin C. Anserine bursitis treatment: local corticosteroid injection against NSAID: a prospective study. *Rev Esp Reumatol.* 1993;20:13-5.
27. Lustenberger DP, Ng VY, Best TM, Ellis TJ. Efficacy of Treatment of Trochanteric Bursitis: A Systematic Review. *Clin J Sport Med.* 2011;21:447-53.
28. Granter R. Treatments used for musculoskeletal conditions: more choices and more evidence. En: Bruckner P, Kahn K, Eds. *Clinical Sports Medicine,* 4th Edition. McGraw-Hill Australia 2012; pp. 164-209.
29. Cameron G. Steroid arthropathy: myth or reality? *Journal of Orthopaedic Medicine*. 1995; 17:51-5.
30. Raynauld J, Buckland-Wright C, Ward R, *et al*. Safety and efficacy of long term intraarticular steroid injections in osteoarthritis of the knee. *Arthritis Rheum.* 2003;48:370-4.
31. Coombes BK, Bisset L, Vicenzino B. Efficacy and safety of corticosteroid injections and other injections for management of tendinopathy: a systematic review of randomised controlled trials. *Lancet*. 2010;376:1751-67.
32. Kahlenberg CA, Knesek M, Terry MA. New Developments in the Use of Biologics and Other Modalities in the Management of Lateral Epicondylitis. *Biomed Res Int.* 2015; 2015:439309.
33. Scott A, Khan KM. Corticosteroids: short-term gain for long-term pain? *Lancet.* 2010; 376:1714-5.
34. Hart L. Corticosteroid and other injections in the management of tendinopathies: a review. *Clin J Sport Med*. 2011;21:540-1.
35. Koester MC, Dunn WR, Kuhn JE, Spindler KP. The efficacy of subacromial corticosteroid injection in the treatment of rotator cuff disease: A systematic review. *J Am Acad Orthop Surg.* 2007;15:3-11.
36. Childress MA, Beutler A. Management of chronic tendon injuries. *Am Fam Physician.* 2013;87:486-90.
37. Zhang J, Keenan C, Wang JH. The effects of dexamethasone on human patellar tendon stem cells: implications for dexamethasone treatment of tendon injury. *J Orthop Res.* 2013;31:105-10.
38. Shbeeb MI, O'Duffy JD, Michet CJ, Matteson EL. Evaluation of glucocorticoid injection for the treatment of trochanteric bursitis. *J Rheumatol.* 1996;23:2104-6.
39. Levine WN, Bergfeld JA, Tessendorf W, *et al.* Intramuscular corticosteroid injection for hamstring injuries. *Am J Sports Med*. 2000;28:297-300.
40. Dvorak J, Feddermann N, Grimm K. Glucocorticosteroids in football: use and misuse. *Br J Sports Med.* 2006;40 (Suppl 1):i48-i54.
41. Godwin M, Dawes M: Intra-articular steroid injections for painful knees: Systematic review with meta-analysis. *Can Fam Physician*. 2004;50:241-8.
42. Nichols AW. Complications associated with the use of corticosteroids in the treatment of athletic injuries. *Clin J Sport Med.* 2005;15:370-5.
43. Brinks A, Koes BW, Volkers ACW, Verhaar JAN, Bierma-Zeinstra SMA. Adverse effects of extra-articular corticosteroid injections: a systematic review. *BMC Musculoskeletal Disorders.* 2010;11:206.
44. Scutt N, Rolf CG, Scutt A. Glucocorticoids inhibit tenocyte proliferation and Tendon progenitor cell recruitment. *J Orthop Res.* 2006;24:173-82.
45. Chen SK, Lu CC, Chou PH, Guo LY, Wu WL. Patellar tendon ruptures in weight lifters after local steroid injections. *Arch Orthop Trauma Surg*. 2009;129:369-72.
46. Altman R, Akermark C, Beaulieu A, Schnitzer T; Durolane International Study Group. Efficacy and safety of a single intra-articular injection of non-animal stabilized hyaluronic acid (NASHA) in patients with osteoarthritis of the knee. *Osteoarthritis Cartilage*. 2004;12:642-9.
47. Petrella RJ. Hyaluronic acid for the treatment of knee osteoarthritis: long-term out comes from a naturalistic primary care experience. *Am J Phys Med Rehabil.* 2005;84: 278-83.
48. Moreland LW. Intra-articular hyaluronan (hyaluronic acid) and hylans for the treatment of osteoarthritis: mechanisms of action. *Arthritis Res Ther.* 2003;5:54-67.
49. Wang CT, Lin J, Chang CJ, Lin YT, Hou SM. Therapeutic effects of hyaluronic acid on osteoarthritis of the knee. A meta-analysis of randomized controlled trials. *J Bone Joint Surg Am.* 2004;86:438-45
50. Petrella RJ, Cogliano A, Decaria J, Mohamed N, Lee R. Management of Tennis Elbow with sodium hyaluronate periarticular injections. *Sports Med Arthrosc Rehabil Ther Technol.* 2010;2:4.
51. Salk RS, Chang TJ, D'Costa WF, Soomekh DJ, Grogan KA. Sodium Hyaluronate in the treatment of Osteoarthritis of the Ankle: A Controlled, Randomized, Double-Blind Pilot Study. *J Bone Joint Surg Am*. 2006;88:295-302.
52. Ohberg L, Alfredson H, Khan K. Ultrasound guided sclerosis of neovessels in painful chronic Achilles tendinosis: pilot study of a new treatment. *Br J Sports Med.* 2002;36: 173-7.
53. Lind B, Ohberg L, Alfredson H. Sclerosing polidocanol injections in mid-portion Achilles tendinosis: remaining good clinical results and decreased tendon thickness at 2-year follow-up. *Knee Surg Sports Traumatol Arthrosc.* 2006;14:1327-32.
54. Alfredson H, Cook J. A treatment algorithm for managing Achilles tendinopathy: new treatment options. *Br J Sports Med.* 2007;41:211-6.
55. Andres BM, Murrell GA. Treatment of tendinopathy: what works, what does not, and what is on the horizon. *Clin Orthop Relat Res.* 2008;466:1539-54.
56. Smit A. Multitarget Regulation in Modern Bioregulatory Medicines. *Alternative therapies.* 2011;17(2 suppl):2.
57. Nathan C. Points of control in inflammation. *Nature.* 2002;420:846-52.
58. Hotamisligil GS. Inflammation and metabolic disorders. *Nature.* 2006;444:860-7.

59. Porozov S, Cahalon L, Weiser M, Branski D, Lider O, Oberbaum M. Inhibition of IL-1beta and TNF-alpha secretion from resting and activated human immunocytes by the homeopathic medication Traumeel S. *Clin Dev Immunol.* 2004;2:143-9.
60. Birnesser H, Oberbaum M, Klein P, Weiser M. The homeopathic preparation Traumeel S compared with NSAID s for symptomatic treatment of epicondylitis. Traumeel S in epicondylitis. *J Musculoskel Res*. 2004; 8:119-28.
61. Schneider C, Klein P, Stolt P, Oberbaum M. A homeopathic ointment preparation compared with 1% diclofenac gel for acute symptomatic treatment of tendinopathy. *Explore.* 2005;1:446-52.
62. Schneider C. Traumeel - an emerging option to nonsteroidal anti-infl ammatory drugs in the management of acute musculoskeletal injuries. *Int J Gen Med.* 2011;4:225-34.
63. Wasterlain AS, Braun HJ, Harris AH, Kim HJ, Dragoo JL. The systemic effects of platelet-rich plasma injection. *Am J Sports Med.* 2013;41:186-93.
64. Bachl N, Derman W, Engebretsen L, Goldspink G, Kinzlbauer M, Tschan H, *et al.* Therapeutic use of growth factors in the musculoskeletal system in sports-related injuries. *J Sports Med Phys Fitness*. 2009;49:346-57.
65. Engebretsen L, Steffen K, Alsousou J, Anitua E, Bachl N, Devilee R, *et al*. IOC consensus paper on the use of platelet-rich plasma in sports medicine. *Br J Sports Med*. 2010; 44:1072-81.
66. Franklyn-Miller A, Etherington J, McCrory P. Sports and exercise medicine--specialists or snake oil salesmen? *Br J Sports Med.* 2011;45:83-4.
67. Mishra A, Pavelko T. Treatment of chronic elbow tendinosis with buffered platelet-rich plasma. *Am J Sports Med.* 2006;34:1774-78.
68. De Vos RJ, Weir A, van Schie HT, Bierma-Zeinstra SM, Verhaar JA, Weinans H, *et al.* Platelet-rich plasma injection for chronic Achilles tendinopathy: a randomized controlled trial. *JAMA*. 2010;303:144-9.
69. Peerbooms JC, Sluimer J, Bruijn DJ, Gosens T. Positive effect of an autologous platelet concentrate in lateral epicondylitis in a double-blind randomized controlled trial: platelet-rich plasma versus corticosteroid injection with a 1-year follow-up. *Am J Sports Med.* 2010;38:255-62.
70. Gosens T, Peerbooms JC, Van Laar W, Den Oudsten BL. Ongoing positive effect of platelet-rich plasma versus corticosteroid injection in lateral epicondylitis: a double-blind randomized controlled trial with 2-year follow-up. *Am J Sports Med.* 2011;39:1200-8.
71. Milano G, Sanna Passino E, Deriu L, Careddu G, Manunta L, Manunta A, *et al*. The effect of platelet rich plasma combined with microfractures on the treatment of chondral defects: an experimental study in a sheep model. *Osteoarthr Cartil.* 2010;18:971-80.
72. Eirale C, Mauri E, Hamilton B. Use of platelet rich plasma in an isolated complete medial collateral ligament lesion in a professional football (soccer) player: a case report. *Asian J Sports Med.* 2013;4:158-62.
73. Ishida K, Kuroda R, Miwa M, Tabata Y, Hokugo A, Kawamoto T, *et al.* The regenerative effects of platelet-rich plasma on meniscal cells in vitro and its in vivo application with biodegradable gelatin hydrogel. *Tissue Eng*. 2007;13:1103-12.
74. Orchard JW, Best TM, Mueller-Wohlfahrt HW, Hunter G, Hamilton BH, Webborn N, *et al.* The early management of muscle strains in the elite athlete: best practice in a world with a limited evidence basis. *Br J Sports Med.* 2008;42:158-9.
75. A Hamid MS, Mohamed Ali MR, Yusof A, George J, Lee LP. Platelet-rich plasma injections for the treatment of hamstring injuries: a randomized controlled trial. *Am J Sports Med.* 2014;42:2410-8.
76. Bubnov R, Yevseenko V, Semeniv I. Ultrasound guided injections of platelets rich plasma for muscle injury in professional athletes. Comparative study. *Med Ultrason*. 2013;15:101-5.
77. Sánchez M, Anitua E, Delgado D, Sánchez P, Orive G, Padilla S. Muscle repair: platelet-rich plasma derivates as a bridge from spontaneity to intervention. *Injury.* 2014;45 Suppl 4:S7-14.
78. Hammer JH, Mynster T, Rosendahl S, Reimert CM, Brünner N, Skov F, *et al.* Bacterial antigen-induced release of white cell- and platelet-derived bioactive substances in vitro. *Int J Gastrointest Cancer.* 2002;31:165-79.
79. Sánchez M. El plasma rico en plaquetas: ¿una moda o una realidad? *Arch Med Deporte.* 2010;138:252-4.
80. Kon E, Filardo G, Marcacci M. Platelet-rich plasma (PRP) to treat sports injuries: evidence to support its use. *Knee Surg Sports Traumatol Arthrosc.* 2011;19:516-27.
81. Lee KS, Wilson JJ, Rabago DP, Baer GS, Jacobson JA, Borrero CG. Musculoskeletal applications of platelet-rich plasma: fad or future? *AJR Am J Roentgenol.* 2011;196:628-36.
82. Randelli P, Arrigoni P, Ragone V, *et al*. Platelet Rich Plasma (PRP) in arthroscopic rotator cuff repair. A prospective RCT study, 2 years follow-up. *J Shoulder Elbow Surg*. 2011; 20:518-28.
83. Wang-Saegusa A, Cugat R, Ares O, Seijas R, Cuscó X, Garcia-Balletbó M. Infiltration of plasma rich in growth factors for osteoarthritis of the knee short-term effects on function and quality of life. *Arch Orthop Trauma Surg.* 2011;131:311-7.
84. De La Mata J. Platelet rich plasma. A new treatment tool for the rheumatologist? *Reumatol Clin*. 2013; 9:166-71.
85. Paoloni JA, Orchard JW. The use of therapeutic medications for soft-tissue injuries in sports medicine. *Med J Aust.* 2005;183:384-8.
86. Jensen K, Rabago D, Best T, Patterson J. Response of knee ligaments to prolotherapy in a rat injury model. *Am J Sports Med* 2008;36:1347-57.
87. Rabago D, Slattengren A, Zgierska A. Prolotherapy in primary care practice. *Prim Care.* 2010; 37:65-80.
88. Rabago D, Zgierska A, Fortney L, Kijowski R, Mundt M, Ryan M, *et al.* Hypertonic dextrose injections (prolotherapy) for knee osteoarthritis: results of a single-arm uncontrolled study with 1-year follow-up. *J Altern Complement Med*. 2012;18:408-14.
89. Hauser RA, Hauser MA, Baird NM. Evidence-based use of dextrose prolotherapy for musculoskeletal pain: A scientific literature review. *Journal of Prolotherapy.* 2011; 3:765-89.
90. Sanderson LM, Bryant A. Effectiveness and safety of prolotherapy injections for management of lower limb tendinopathy and fasciopathy: a systematic review. *J Foot Ankle Res*. 2015;8:57.
91. Bertrand H, Reeves KD, Bennett CJ, Bicknell S, Cheng AL. Dextrose prolotherapy versus control injections in painful rotator cuff tendinopathy. *Arch Phys Med Rehabil.* 2016; 97:17-25.
92. Lee DH, Kwack KS, Rah UW, Yoon SH. Prolotherapy for refractory rotator cuff disease: Retrospective case-control study of 1-year follow-up. *Arch Phys Med Rehabil.* 2015; 96:2027-32.
93. Dong W, Goost H, Lin XB, Burger C, Paul C, Wang ZL, *et al.* Injection therapies for lateral epicondylalgia: a systematic review and Bayesian network meta-analysis. *Br J Sports Med.* 2015. pii: bjsports-2014-094387.
94. Emshoff R, Emshoff I, Bertram S. Estimation of clinically important change for visual analog scales measuring chronic temporomandibular disorder pain. *Journal of Orofacial Pain*. 2010; 24:262-9.
95. Kang SH, Seo KM, Kim DK, Shin JY, Song IS. Ultrasonographic findings of chronic lateral epicondylitis with partial tear before and after Prolotherapy. *J Korean Acad Rehabil Med.* 2004;28:88-93.
96. Lyftogt J. Subcutaneous Prolotherapy for Achilles tendinopathy: the best solution? *Australasian Musculoskeletal Medicine Journal.* 2007;12:107-9.
97. Ryan M, Wong A, Taunton J. Favorable outcomes after sonographically guided intratendinous injection of hyperosmolar dextrose for chronic insertional and midportion achilles tendinosis. *AJR Am J Roentgenol.* 2010;194:1047-53.
98. Hauser RA, Phillips HJ, Maddela HS. The case for utilizing Prolotherapy as first-line treatment of meniscal pathology: a retrospective study shows Prolotherapy is effective in the treatment of MRI-documented meniscal tears and degeneration. *Journal of Prolotherapy*. 2010;2:416-37.
99. Topol G, Podesta LA, Reeves KD, Raya MF, Fullerton BD, Yeh HW. Hyperosmolar dextrose injection for recalcitrant Osgood-Schlatter disease. *Pediatrics.* 2011;128:e1121-8.
100. Reeves KD. Prolotherapy: Basic Science, Clinical Studies, and Technique. In: Lennard TA (ED). *Pain Procedures in Clinical Practice*. (Second Edition). Philadelphia, PA: Hanleey and Belfus; 2000:172-90.
101. Reeves KD, Hassanein K. Randomized prospective double-blind placebocontrolled study of dextrose Prolotherapy for knee osteoarthritis with or without ACL laxity. *Altern Ther Health Med.* 2000; 6:68-74, 77-80.
102. Reeves KD, Fullerton BD, Topol GA. Evidence-based regenerative injection therapy (prolotherapy) in sports medicine. In: Seidenberg PH, Beutler PI, Eds. *The Sports Medicine Resource Manual.* Philadelphia: Saunders/Elsevier 2008; pp. 611-19.
103. Dagenais S, Ogunseitan O, Haldeman S, Wooley JR, Newcomb RL. Side effects and adverse events related to intraligamentous injection of sclerosing solutions (prolotherapy) for back and neck pain: A survey of practitioners. *Arch Phys Med Rehabil.* 2006;87:909-13.
104. Ozturan KE, Yucel I, Cakici H, Guven M, Sungur I. Autologous Blood and Corticosteroid Injection and Extracoporeal Shock Wave Therapy in the Treatment of Lateral Epicondylitis. *Orthopedics*. 2010;33:84-91.
105. Moriatis J, Ozer K, Scott F, Gordon M, Williams A. Comparison of Autologous Blood, Corticosteroid, and Saline Injection in the Treatment of Lateral Epicondylitis: A Prospective, Randomized, Controlled Multicenter Study. *J Hand Surg*. 2011;36:1269-72.
106. Bell KJ, Fulcher ML, Rowlands DS, Kerse N. Republished research: Impact of autologous blood injections in treatment of mid-portion Achilles tendinopathy: double blind randomised controlled trial. *Br J Sports Med*. 2014;48:1334.
107. Sánchez M, Anitua E, Lopez-Vidriero E, Andía I. The future: optimizing the healing environment in anterior cruciate ligament reconstruction. *Sports Med Arthrosc*. 2010; 18:48-53.

108. Resteghini P, Khanbhai TA, Mughal S, Sivardeen Z. Double-blind randomized controlled trial: injection of autologous blood in the treatment of chronic patella tendinopathy-a pilot study. *Clin J Sport Med*. 2016;26:17-23.

109. Pattanittum P, Turner T, Green S, Buchbinder R. Non-steroidal anti-inflammatory drugs (NSAIDs) for treating lateral elbow pain in adults. *Cochrane Database Syst Rev*. 2013; 5:CD003686.

110. Stovitz SD, Johnson RJ. NSAIDs and musculoskeletal treatment: what is the clinical evidence? *Phys Sportsmed*. 2003;31:35–52.

111. Rømsing J, Møiniche S, Ostergaard D, Dahl JB. Local infiltration with NSAIDs for postoperative analgesia: evidence for a peripheral analgesic action. *Acta Anaesthesiol Scand.* 2000;44:672-83.

112. Kehlet H, Andersen LØ. Local infiltration analgesia in joint replacement: the evidence and recommendations for clinical practice. *Acta Anaesthesiol Scand.* 2011;55:778-84.

113. Pruna R, Artell R. Cambios conceptuales en la medicina deportiva actual. *Arch Med Deporte.* 2014;31:297-8.

114. Bashir J, Sherman A, Lee H, Kaplan L, Hare JM. Mesenchymal Stem Cell Therapies in the Treatment of Musculoskeletal Diseases. *PM&R.* 2014;6:61-9.

115. Keizer SB, Rutten HP, Pilot P, Morré HH, v Os JJ, Verburg AD. Botulinum toxin injection versus surgical treatment for tennis elbow: a randomized pilot study. *Clin Orthop Relat Res*. 2002;401:125-31.

116. Placzek R, Drescher W, Deuretzbacher G, Hempfing A, Meiss AL. Treatment of chronic radial epicondylitis with botulinum toxin A. A double-blind, placebo-controlled, randomized multicenter study. *J Bone Joint Surg Am*. 2007;89:255-60.

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