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Review Article

Clinical Use Drugs for Joint Infiltrations of the Locomotor System

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Abstract

Within the area of Regenerative Medicine, the advances for the treatment of Osteoarthritis and Osteoarthrosis are already a reality. Grade 1, 2, 3 and 4 arthrosis receive a special treatment called joint infiltrations, which can be performed with corticosteroids and also with hyaluronic acid gel, called Visco supplementation. The most qualified professional to perform this procedure is the Physical Therapist.

Keywords: Osteoarthritis; Osteoarthrosis; Pysical Therapist; Viscosupplmentation; Infiltrations; Corticosteroids

Introduction

Since their identification in 1935, steroids have served a wide range of uses [50]. Initially, these adrenal gland isolates were thought to be useful only in patients suffering from Addison's disease. Today, many of the clinical roles of steroids are related to their potent anti-inflammatory and immunomodulatory properties. The clinically relevant side effects of steroids are common and problematic, ranging from a minor case of acne to Cushing's syndrome that can result in diabetes mellitus and potentially fatal heart disease if left untreated [7]. Side effects can occur at a wide range of doses and vary depending on the route of administration.

The term steroid applies to a wide range of molecules with varying physiological effects. More specifically, corticosteroids are a class of chemicals that encompass both laboratory synthesized and naturally produced hormones. Glucocorticoids, in general, regulate metabolism and inflammation; mineralocorticoids regulate sodium and water levels [8]. Corticosteroids fall along a spectrum from exclusively glucocorticoid effects to exclusively mineralocorticoid effects, and steroid compounds are selected based on their suitability for a particular treatment [44]. For example, while a compound may possess potent anti-inflammatory properties, it may additionally have mineralocorticoid activity that adversely affects blood pressure.

Pharmacodynamics of corticosteroids

The anti-inflammatory properties of steroids have been attributed to their inhibitory effects on the action of phospholipase A2, an enzyme critical for the production of inflammatory compounds [49].

In short, they produce their physiological effects through a multitude of biochemical pathways. Glucocorticoids interrupt the production of inflammatory mediators, such as leukotrienes and prostaglandins, and effectively stop the inflammatory cascade [9]. As their broad side effects indicate, glucocorticoids can affect many systems throughout the body. Through negative feedback regulation of the hypothalamic-pituitary-adrenal (HPA) axis, exogenous glucocorticoids can directly induce hypopituitarism in the case of continuous daily use (Addison's disease) [10]. Their actions on glucose metabolism can increase insulin resistance in tissues and increase fasting glucose levels [11]. Glucocorticoids can act directly on osteoclasts to affect bone resorption and decrease calcium absorption in the gastrointestinal tract, resulting in osteopenia and osteoporosis in cases where the patient does not receive calcium and vitamin D replacement [13].

Because of the broad effects that glucocorticoids can have on the patient's body and the HPA axis in particular, the physical therapist

should exercise caution when discontinuing their administration [17]. If steroids have been administered for less than 2 weeks, they can be discontinued without gradual reduction. For doses lasting more than 3 weeks, the gradual reduction should be based on the clinical conditions and the disease for which the drug was prescribed [43]. When the patient is on glucocorticoids for more than 4 weeks, the clinician's goal is to quickly reduce the physiologic doses and then slowly decrease the dosage while assessing adrenal function [22]. For patients who are taking doses equivalent to 30 mg of hydrocortisone daily or have established HPA axis dysfunction and are under stress (hours for 24hours, followed by gradual reduction of the previous maintenance dose by 50% daily) [25].

Mineralocorticoids, endogenously represented by aldosterone and deoxycorticosterone, cause physiological changes by altering electrolyte levels (sodium and potassium), causing volume changes. Instead of being moderated by the HPA axis like glucocorticoid production, mineralocorticoid production is regulated primarily by the renin-angiotensin-aldosterone system, although adrenocorticotrophic hormone, a product of the HPA axis, has minimal activity in stimulating aldosterone release [18].

Corticosteroids exert their anti-inflammatory and immunosuppressive effects by disrupting multiple steps in the up-regulation of the immune system20. Their suppressive activity is predominantly restricted to cellular mediation.

Corticoids are known to inhibit antigen presentation, cytokine production, and lymphocyte proliferation by binding to glucocorticoid receptors found throughout the body. In response to corticoid administration, lymphocytopenia is induced as a result of redistribution of circulating lymphocytes to other lymphoid compartments. A single corticoid dose produces lymphocytopenia within 4 hours of administration that normalizes through redistribution to the circulation away from the periphery, rather than destruction, within 24 to 48 hours [15]. Similarly, monocytes and eosinophils, which normally accumulate at the inflammatory site decrease with corticoid administration. In contrast, they induce neutrophilia through release of neutrophils from the bone marrow into the circulation, reduction in neutrophil migration out of the circulation, and demargination of neutrophils from the vascular lining [15].

The corticoid-mediated anti-inflammatory process is multimodal and begins with the synthesis of lipocortin-1, which then suppresses phospholipase A2, thereby blocking production, and further inhibiting various leukocyte inflammatory events. The end result of this process is inhibition of prostaglandin and cyclooxygenase (COX-1 and COX-2) synthesis, thus enhancing the anti-inflammatory effect [1].

Corticosteroid metabolism

Although corticosteroid metabolism is complicated by enzymatic induction, binding to proteins, molecular interconversion, and interaction with endogenous cortisol, corticosteroids are generally metabolized by the hepatic P450 system [1]. Direct application (e.g., topical, intra-articular, inhaled, or epidural) of these agents at sites of inflammation bypasses the liver and its first-pass effect, and is thus much safer and without systemic side effects.

Chronic use of oral glucocorticoids is common in patients with rheumatoid arthritis, chronic obstructive pulmonary disease, systemic lupus erythematosus, inflammatory bowel disease, and asthma [40]. Side effects of chronic use include bruising, muscle weakness, weight gain, skin changes, sleep disturbances, cataracts, and pathological fractures. Glucocorticoid administration can also have psychiatric side effects: mood disorders, anxiety, sleep disturbances, delirium, and panic disorder [24]. Psychotropic medication may be needed to treat these symptoms, but the prognosis is favorable when glucocorticoids are reduced or discontinued. Adverse effects occur in up to 90% of patients who take high doses of glucocorticoids daily for more than 60 days continuously without breaks and without dosage regulation [24].

Glucocorticoids affect bone mineralization by inhibiting calcium absorption in the gastrointestinal tract and by altering the production of signaling molecules to favor bone resorption [36]. Recommendations for preventing glucocorticoid-induced osteopenia and its subsequent complications and comorbidities include oral calcium supplementation and vitamin D 50,000 i.U. per day or orally or injectably, for glucocorticoid doses above 5 mg per day.

Because of their effects on insulin resistance, glucocorticoids are the most common cause of drug-induced diabetes mellitus. Screening guidelines using fasting glucose above 126 mg/dL or HbA1c ≥ 6.5% are adequate for the diagnosis of steroid-induced diabetes; however, according to the American Diabetes Association guidelines, the results should be confirmed by repeated testing [35]. Management is similar to that of type 2 diabetes mellitus; treatment options progress from single agent to dual agent to insulin with association of another agent, based on fasting glucose measurements and glucose control. In patients with preexisting diabetes, blood glucose should be measured more frequently than in patients without preexisting diabetes, and medications should be adjusted to maintain adequate control [24].

Mineralocorticoid activity causes the retention of sodium and free water and the excretion of potassium. Disturbances in mineralocorticoid production can manifest with abnormalities in either

of these areas. Hyponatremia, hyperkalemia, and hypotension are present to varying degrees in mineralocorticoid deficiency states (Since endogenous glucocorticoids also have activity at mineralocorticoid receptors, signs and symptoms of mineralocorticoid excess can be seen in cases of glucocorticoid overproduction (e.g., Cushing's syndrome) [24]. It is always necessary to guide patients to correct hydration.

Corticosteroid preparations

Steroid injections are associated with side effects related to dosage, duration of administration, added ingredients or contaminants, and particle size. Dexamethasone and betamethasone sodium phosphate are pure liquids, while methylprednisolone, triamcinolone, and betamethasone are solutions, and their particle size depends on the type of preparation and dosage [5]. Studies have shown that transforaminal dexamethasone is as effective in 4 mg as in 8 mg and 12 mg, and that non-particulate steroid preparations are as effective as particulate preparations in treating cervical root pain [19]. Methylprednisolone and triamcinolone are the most commonly used drugs for epidural steroid injections, and in large joints [23]. Common side effects of epidural steroid injections are paresthesia, pain at the injection site, and change in skin coloration at the application site. The most serious complications from epidural steroid injections are related to intravascular injections [26].

Topical corticosteroids (2.5% ointment, 0.1% triamcinolone ointment, and 0.05% clobetasol propionate foam) achieve more effective skin concentrations than oral prednisone. Side effects, including skin thinning, color change, and systemic effects, can be expected with topical application of corticosteroids and increase in a dose-dependent manner [29]. Inhaled corticosteroids have evolved into the mainstay of therapy for moderate to severe asthma. Efficacy and systemic bioavailability vary with each corticosteroid molecule and dosage, but in general, systemic effects are minimized with proper administration30. Common side effects of inhaled corticosteroids include gingival irritation and oral candidiasis, as well as the many systemic effects associated with corticosteroid use.

Fludrocortisone is a synthetic corticosteroid that has potent mineralocorticoid effects. It has been used clinically to achieve the mineralocorticoid effects of sodium and water retention in cases of cerebral salt loss, orthostatic hypotension, and adrenocortical insufficiency in Addison's disease [31]. Potassium loss is a common side effect of fludrocortisone administration, and electrolyte levels should be monitored while the patient is receiving fludrocortisone [32].

The potencies of corticosteroids vary widely, with synthetic compounds generally retaining greater anti-inflammatory potency and weaker salt retention properties.

Use of corticosteroids in clinical practice

Because of their multiple effects, the clinical utility is wide, but in clinical practice they are generally used for their anti-inflammatory and immunosuppressive effects [2]. Side effects of these drugs are greater with increasing duration of use and higher, supraphysiologic oral doses, so their use should be limited to specific conditions with careful evaluation of risk versus benefit [4].

The dose and duration of therapy vary based on the indication. For example, in acute conditions such as multiple sclerosis, a higher dose but shorter course of therapy may be warranted versus chronic conditions such as rheumatoid arthritis, where lower maintenance doses are advocated [48]. The application of corticosteroids in neurological diseases, although not limited to neuroimmunological diseases, range from traumatic head and spinal cord injuries to central nervous system infections [37]. The proposed benefit of corticosteroid therapy in brain and spinal cord conditions, include neuroprotection from free radicals, reduction of intracranial pressure by decreasing cerebrospinal fluid, and maintenance of normal microvasculature [37].

Methylprednisolone (MP) sodium succinate had been used in spinal trauma patients with the goal of attenuating inflammation, lipid peroxidation, and toxicity associated with acute injury [34]. At high doses, it functions as a free radical scavenger and neuroprotectant, secondary to glucocorticoid receptor-mediated inhibition of phospholipase A2 [39]. When given in high doses orally, corticosteroids impair cytokine generation and enter cell membranes. This alters the physicochemical properties as well as the activities of membrane-associated proteins [6]. These effects are deduced from the administration of corticoids in high doses to effectively treat acute exacerbations [38].

Local anesthetics

These are drugs that block nerve conduction, when applied locally to nerve tissue in appropriate concentrations. They act on any part of the nervous system and on any type of nerve fiber, and their actions are short and totally reversible [16].

Mechanism of action - They impede the production and conduction of the nerve impulse, acting on the cell membrane, blocking conduction and preventing the large transient increase in membrane permeability to sodium ions, by a rapid depolarization of the membrane, increasing the threshold of electrical excitability [21]

- They can have systemic effects on the central nervous system and cardiovascular system.
- It should never be injected into the vascular route.

- Anesthetics without vasoconstrictors (epinephrine) are used.
- High doses should not be used in soft tissues, due to the high potential for systemic absorption.
- Its effect lasts from one to several hours.
- Its use is fundamental for nerve blocks, previous cutaneous anesthesia and infiltration.

Systemic effects of local anesthesia

Central nervous system

- Central stimulation.
- Bulbar depression.
- Uneasiness, delirium, convulsions.
- Coma and respiratory arrest.

Cardiovascular system

- Stimulation.
- Depression (shock).
- Tachycardia, Hypertension, Skin rash, Bradycardia, Imperceptible pulse, Pallor, Cardiac arrest.

Viscosupplementation

To understand a little about viscosupplementation, we need to start by understanding where the Synovial Fluid comes from.

The synovial fluid

Synovial fluid is an ultrafiltrate of plasma, enriched with high molecular weight, saccharide-rich molecules, the most important of which, hyaluronate, is produced by synovial cells (fibroblast-like B synoviocytes) [27]. Hyaluronate forms a central axis of proteoglycan aggregates that are indispensable for the constitution of cartilage. It is responsible for the visco-elastic properties of synovial fluid and for the nutrition of articular cartilage [3]. The formation of synovial fluid occurs in an identical manner to that of other interstitial fluids. The flow of plasma fluid through the capillary wall is conditioned by the pressure difference in the capillary wall and the external environment according to Starling's law or colloid-osmotic pressure gradient. Small physiological molecules with a molecular mass of less than 10 KDa are in equilibrium with the plasma and the interstitium, and larger ones, such as proteins, have limited access to the latter or normal synovial fluid [41]. The protein content of synovial fluid is 13 mg/l (compared to the serum concentration of 65 to 80 mg/l), the majority being albumin, as other higher molecular weight proteins such as fibrinogen are excluded [28]. The formation of synovial fluid is balanced with its removal, via the synovial lymphatic system, which does not depend on the size of the molecule and is not affected by synovial pathology [32]. The surface of the synovium and articular cartilage are not covered by an intact, continuous layer of cells. Thus, both the cartilage matrix and synovium are in contact with synovial fluid, allowing for a homogeneous environment within the joint [42]. Because of this histological arrangement, synovial fluid is best considered a true tissue, rather than a simple body cavity fluid. It contains few cells, mainly chondrocytes and synoviocytes, transferred from the cartilage and synovium, and also some migrated leukocytes [48]. The other low weight molecules, filtered from plasma and whose concentration in synovial fluid reflects the same as that, are glucose, amino acids, uric acid, bilirubin, and some enzymes [41]. The inflammatory process may increase capillary vascular permeability and allow larger molecules such as fibrinogen to pass through, causing the synovial fluid samples obtained from the compromised joints to clot and reduce the diffusion of the smaller molecules.

Viscosupplementation properties

Viscosupplementation (VS) is an intra-articular injection (exclusively), of exogenous hyaluronic acid (HA) in the joints of the locomotor system, aimed at restoring the physiological properties of the synovial fluid, with the primary objective of being a mechanical agent, secondarily it will be analgesic, tertiarily it will be anti-inflammatory, and finally it will be a chondroprotective agent, settling in the arthritic areas, generating a protective biofilm, which will give the healthy organism the chance to try to produce its own chondroprotection, when it is not under the effect of the pathological friction [12].

AH is a high-viscosity polysaccharide naturally produced by the B-cells of the synovial membrane. from a biochemical point of view, it is classified within the glycosaminoglycan (GAG) groups [33]. It behaves, under physiological conditions, like a salt, and is therefore also called sodium hyaluronate, or hyaluronan. Its physicochemical properties are determined by its molecular weight and spatial conformation [41]. The high molecular weight molecules of HA intertwine to form a high viscosity solution, which serves as both a lubricant and shock absorber.

Mechanism of action

The osteoarthritic joint exhibits major activation of synoviocytes, which produce various disease-related cytokines and enzymes, such as interleukin (IL)-ß1, IL-6, IL-8, TNF-alpha, metalloproteinases, aggrecanases, and nitric oxide (NO) [33]. Hyaluronic acid is an important modulator, mainly through interaction with CD [44] receptors present on fibroblast-like synoviocytes [47]. Therefore, besides the mechanical effects of promoting better distribution of forces, decreasing weight-bearing pressure and recovering the physiological properties of the synovial fluid, hyaluronic acid also acts biochemically, decreasing gene expression of OA-as-

sociated cytokines and enzymes, decreasing prostaglandin production and the intra-articular concentration of metalloproteinases35. Its presence stimulates increased production of AH by the synoviocyte, has an analgesic effect by decreasing nerve impulses and sensitivity in the nociceptive nerve endings, stabilizes the cartilage matrix, stimulates chondrocyte proliferation, increases the production of type 2 collagen and aggrecan by the chondrocyte, and decreases type 2 collagen degradation [7].

Structural benefit

The beneficial structural effect of Viscosupplementation was observed through arthroscopies, performed one year after the beginning of treatment, and a better visual aspect of the joint surface was observed in comparison with the placebo group [33]. The increase in cartilage volume was also verified by imaging exams and biopsies taken before and after Viscosupplementation and showed that after six months there was a reconstitution of the superficial layer, better quality of the matrix and a greater density of chondrocytes, with a greater number of organelles inside them [33]. A reduction in joint space loss was observed one year after the procedure by Magnetic Resonance Imaging, also in comparison with the placebo group. From the economic point of view, there is an increasing number of studies showing that, if incorporated into the treatment of knee osteoarthritis, viscosupplementation may present a good cost-effectiveness ratio, and may even delay the need for total knee replacement [41].

Synthesis

Exogenous Hyaluronic Acid is produced by

- Avian origin: from animal raw material (rooster crest). It has allergenic potential due to avian antigens. Products of avian origin in the domestic market: Polireumin® and Synvisc®.
- **Non-avian origin or fermented:** by bacteria (Streptococcus zooepidemicus) through biofermentation. Lower allergenic potential. Products of non-avian origin in the domestic market: Synolis VA®, Suplasyn®, Fermathron®, Orthovisc®, Suprahyal®, Osteonil® and Viscoseal®.

Regarding their synthesis, hyaluronic acids can be classified into two types.

- **Hyaluronans:** long molecule chains, extracted from the cock's crest or by biofermentation, with molecular weight between 0.5 and 1.8 x 106Da (Polireumin®, Suplasyn® , Fermathron®, Orthovisc®, Suprahyal®, Osteonil® and Viscoseal®);
- **Hilano:** hyaluronan molecule chemically modified through cross-linking, with a liquid phase of higher molecular weight (around 6x106Da) by joining long hyaluronan ribbons by cross-links, and a solid portion (infinite molecular weight) formed by an even greater presence of bridges (Synolis VA®, Synvisc®).

Molecular weight

Regarding molecular weight, although all hyaluronic acids used in orthopedics and rheumatology are considered high molecular weight, we can classify current products into

- "Low molecular weight", between 0.5 and 1 x 106Da, among them: Suplasyn®, Polireumin®, Fermathron® and Suprahyal®.
- "Intermediate molecular weight", between 1 and 1.8 x 106Da: Osteonil®, Orthovisc® and Viscoseal®.
- "High molecular weight", with 6x106 Da: Synolis VA®, Synvisc®.

The molecular weight, concentration and the presence of cross-links have a positive influence on the results of viscosupplementation, both *in vivo* and *in vitro*, results show that the higher the molecular density, the greater the analgesia, and conversely, the lower the molecular weight, the greater the chondroprotection [41].

In clinical practice, what is most observed is that those of intermediate weight, despite having a slightly shorter duration (between 3-4 months), are good cost/benefit for patients, and present both chondroprotection and analgesia [7].

But it's worth remembering that the greater the damage to the cartilage, we should always start the treatment with high molecular weight products, with monthly applications for 6 months, and then start with medium molecular weight products every 3 months for a year. And maintenance with the low molecular weight every 4 months [33].

There are still several other ways to use viscosupplementation, and other protocols that clinically the physiotherapist can be performing.

The treatments should always be accompanied by imaging exams, so that we can select the best treatment for our patients. Always request imaging examinations during treatment every 6 months [33]. You physiotherapists should always remember that you are clinicians, just as much as orthopedists, and imaging examinations should be part of your clinical routine.

Indications

Viscosupplementation is indicated in the treatment of osteoarthritis, for the recovery of the physiological properties of synovial fluid, analgesia, improvement of function and regeneration of articular cartilage, as well as after arthroscopy [7].

Virtually any osteoarthritic joint can be infiltrated [46]. The vast majority of work concerns the knees, but intra-articular injection (IA) of Hyaluronic Acid also shows good results in the hips, shoulders, ankles, sacroiliacs, elbows, hands, and feet (however, the physiotherapist must be up to date with his infiltration skills, since the product is completely different from corticoids) [46]. Viscosupplementation is performed on an outpatient basis, and the application regimen is well established only for the knees and is still subject to discussion for the other joints, where the amount to be applied and the frequency of applications will depend on the characteristics of the product and the experience of the practitioner.

In knees, hylan G-F 20 is the only drug that allows a single application of 6ml (three ampoules of Synvisc Classic® or one ampoule of Synolis VA® or Synvisc One®). Hyaluronanes, on the other hand, should have one ampoule applied weekly for three to five weeks, with the best results found in the literature referring to studies that used a regimen of one application weekly for five weeks33. Sodium hyaluronate has an intra-articular half-life of 13 hours, while the half-life of hylan G-F 20 is 1.5 days (liquid phase) and 8.8 days (solid phase), probably due to the presence of cross-links, which may explain the good results obtained with only one application. There is a study applying three doses of a hyaluronate with 1.3 x 106 Da (15mg/ml - 2ml per ampoule - Orthovisc®) immediately post-arthroscopy, showing the improvement of arthroscopy results by IA injection of HA. However, besides hylan G-F 20, we also have Suprahyal®, which is highly recommended as it is low cost for the physiotherapist and has a wide monograph of action for the treatment of osteoarthritis of the knees, rhizarthrosis and shoulder pain. Weekly applications of this product can be made in the patients' joints, thus being a cost/benefit alternative of great commercial viability, and potentially of good financial return for the physiotherapist and of excellent quality results for the patients [45].

On the other hand, hyaluronic acid infiltration of two million Daltons diluted in 10 ml (Viscoseal®) immediately after arthroscopy showed that the functional and analgesic results obtained by arthroscopy were maintained even after two years of arthroscopy much more in the injected group than in the operated-on group. Arthroscopy washes away the hyaluronic acid film that coats and protects the surface layer of articular cartilage, and a few days are required for the synovium to produce this coating/protective hyaluronic acid again. Post-artroscopy viscosupplementation has the function of replacing this film, besides its analgesic and anti-inflammatory properties, reducing the inflammatory pain caused by the surgical aggression.

The protein chains are agglomerated and juxtaposed, much more so when there is a load of weight after the applications, and the patient should not rest. On the contrary, after viscosupplementation, rehabilitation work should be intensified, as well as the performance of activities of daily living, so that the protein webs become stronger, thereby increasing the quality of the viscosupplement used, and thus increasing the half life of this drug within the joint [41].

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