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Management of Osteoarthritis in Small Animals Mini Series

Session Two: Management of OA in small animals: it is not only drugs. New horizons with regenerative medicine

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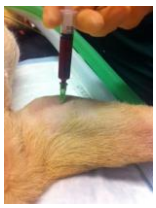


1. Management

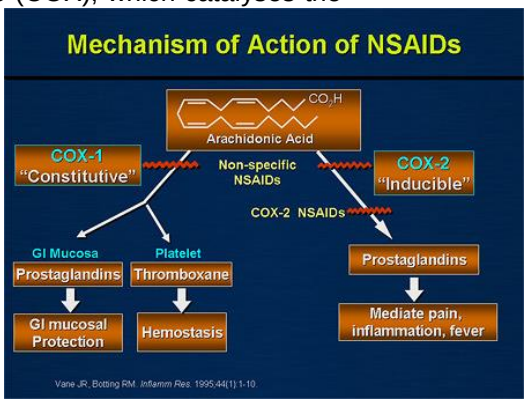
Chronic pain induced by OA cause some physical and behavioural changes in the patient, and this may perpetuate the painful feeling. It is therefore crucial to start a treatment plan early to try to avoid hypersensitivity and allodynia. Management of OA is multimodal:

- **Weight management:** Obesity contributes to the development of OA, not only for its mechanical effect over the joints, but also due to the proinflammatory effect that fat tissue possesses.

- **Analgesics:** The analgesic drugs that can be used during management of OA include:

    - **Non-steroidal antiinflamatories (NSAIDs):**

      They inhibit the Cyclooxigenase enzyme (COX), which catalyses the production of prostaglandins and thromboxane from arachidonic acid. While COX1 coenzyme presents a more physiological function (regulating normal physiological processes), COX2 coenzyme is related more to inflammatory processes in the organism. Prescription of COX2 selective drugs is recommended to allow physiological function of COX1. There are a variety of NSAID families:

        - *Acetic acid derivatives* (diclofenac, etodolac)
        - *Coxib* (firocoxib, deracoxib, mavacoxib, robenacoxib)
        - *Fenamic acid derivatives* (tolfenamic acid)
        - *Oxicam derivatives (enolic acid)* (meloxicam)
        - *Propionic acid derivatives* (ibuprofen, ketoprofen)
        - *Salicilates*

      Other antinflammatory drugs, such as grapiprant block the inflammatory cascade much lower, by targeting the EP4 receptor and therefore not acting on COX enzymes.

    - **Opioids:** Opioids can be very helpful in patients with chronic pain, such as fentanyl and buprenorphine patches, or opioid derivatives like tramadol (some recent research questions the efficacy of tramadol in dogs).

    - **Other:** Clinicians can find some commercial drugs that were initially destined to treat other conditions, but they have been reported to

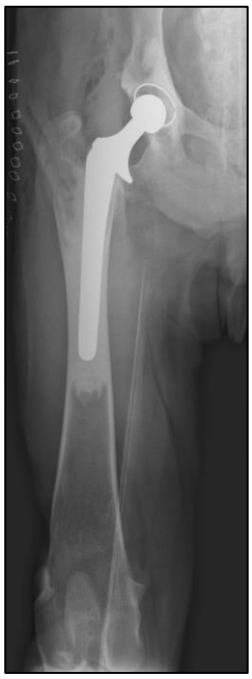
provide an analgesic effect. These can be very useful in animals with chronic pain that don't respond, or respond only partially, to other pharmacological therapies.

- Gabapentin- anticonvulsant, GABA receptor analogue.
- Amantadine- NMDA receptor antagonist.
- Amitriptyline- serotonin-norepinephrine reuptake inhibitor.

- **Disease modifying osteoarthritic drugs (DMOADs):** These substances could potentially stimulate the production of proteoglycans and hyaluronic acid, inhibit catabolic enzymes and COX2, favour the normalization of the synovial fluid and cartilaginous matrix, and generally reduce inflammation, providing an improvement in clinical signs. There are many products in the market:
    - Glucosamine: 90% is absorbed after oral administration and it is distributed to the articular cartilage. It stimulates the synthesis of proteoglycans and it has a slight anti-inflammatory effect.
    - Chondroitin sulphate: Thus is a long-chain glycosaminoglycan with variable absorption (5%). It inhibits the degrading enzymes, reducing the clinical signs of the patient. It has a synergic effect with glucosamine.
    - Polysulfated Glycosaminoglycan (adequan): It has been observed that this substance can modify the progression of OA by maintaining the chondrocyte viability, stimulating their division and reducing the degradation of the extracellular matrix. The recommended dose is 4mg/Kg IM twice per week for 4 weeks (8 doses).
    - Pentosan Polysulphate Sodium (cartrophen): It is a semisynthetic GAG with similar structure to heparin and therefore, it has some anticoagulant effects. It seems to be able to delay the degradation of cartilage and it stimulates the production of hyaluronic acid.
    - Green lipped mussel: It contains high levels of omega-3 fatty acids and it has some anti-inflammatory effects. It has been observed that animals with OA receiving this product would improve their clinics signs of pain and lameness.
    - Omega-3 fatty acids: This is a group of polyunsaturated fatty acids, being the most important the linoleic acid and alfa-linolenic acid. Higher levels of omega-3 fatty acids over omega-6 fatty acids seem to have therapeutic and anti-inflammatory effects on osteoarthritic animals. Lameness improvement by means of force plate analysis has been reported with this therapy.
    - Other: Avocado Soybean Unsaponifiables, antioxidants, Boswellia serrate, turmeric acid, milk protein concentrate, Zeel, etc.

- **Intraarticular injections:** Generally these therapies are reserved to animals with more advanced OA that fail to respond to less invasive treatments. It is critical the injections are performed under aseptic conditions and with the patient under heavy sedation or general anaesthesia.
    - Intraarticular (IA) injection of hyaluronic acid: This injection provides viscosity to the synovial fluid, reduces articular inflammation and increases the synthesis of GAG. It has been observed that 70% of patients receiving this therapy showed a positive response with improvement in function and pain.
    - Steroid IA injection: This therapy inhibits the intraarticular formation of prostaglandins and proinflammatory cytokines, reducing inflammation. However, steroids also have a negative effect on the articular cartilage and they may be associated with complications, such as pain, systemic absorption or joint infection.

- **Surgery.**



Generally more than 75% of animals with hip OA respond positively to non-surgical management, with only a low % of animals requiring surgical treatment. Those animals that don't respond to an adequate multimodal conservative treatment are candidates for surgical management of OA. Nowadays the surgical procedures available can be classified in 3 groups:

    - Joint prosthesis, in which part or the totality of the joint is substituted by implants, maintaining the mechanical function of the joint. There are many prosthetic systems for the different joints, with a variable difficulty and prognosis depending on the system and the joint involved.
    - Arthrodesis or fusion of the joint in a physiological angle. This procedure eliminates the joint mobility, erradicating pain but affecting the normal mechanical function of the limb. The difficulty and prognosis for this procedure varies depending on the joint involved.
    - Excisional arthroplasty, where part of the joint is removed leading to pseudoarthrosis. This procedure eliminates rubbing of the degenerated articular surfaces that caused pain, allowing a pain free joint motion. However, a completely normal function (range of motion and loading) is not obtained
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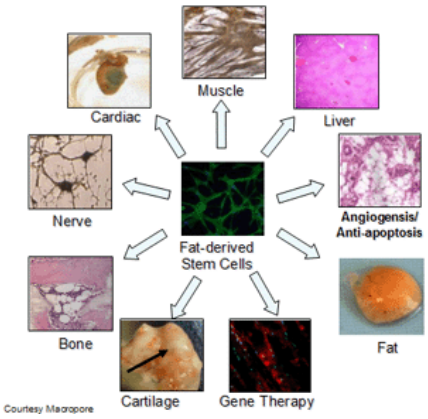
Regenerative medicine

Regenerative medicine includes innovative therapies that allow the body repair, replace and regenerate the injured or diseased tissues. This therapy does not rely on just one mechanism of action, but it involves several systems by means of secreting cytokines and growth factors. Additionally, it promotes differentiation of pluripotent cells into cells of a variety of cell lines. Regenerative therapy includes stem cell therapy and platelet rich plasma.

1. STEM CELL THERAPY

This therapy involves the use of undifferentiated and pluripotent cells, which can differentiate into cells of different lines. (i.e. cardiac, muscular, cartilaginous cells, etc). Pluripotent cells originated in mesodermic derived tissues are called mesenchymal stem cells (MSC), which are the most studied and used stem cells. These cells have the characteristics of self-renewal (cell division and creation of more MSC) and differentiation into cells of mesenchymal lines. The differentiation into different lines will depend on the environment and information received from the surrounding tissues by means of cell signalling mechanisms (autocrine, paracrine and endocrine). Part of this signalling mechanism is undertaken by cytokines, which bind with their specific receptor in the MSC and stimulate their proliferation and differentiation.



MSC can be obtained from a variety of tissues, being adipose tissue and bone marrow the most common. A greater number of MSC has been reported to be obtained from adipose tissue and, as this technique is easier than obtaining cells from the bone marrow, adipose tissue is a frequent origin of MSC (specifically from the falciform ligament and inguinal subcutaneous fat). Once obtained under aseptic conditions, the fat sample is placed in a special kit and it is sent to the lab. Stem cells will then be isolated, cultured and expanded in very specific conditions (animal growth media, antibiotics and adequate temperature/humidity: 37º, 5% CO_2) until appropriate numbers are obtained.

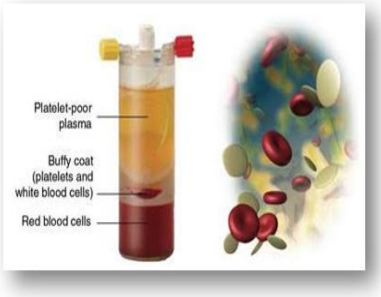
MSC therapy has multiple applications:

- Dermatology: Wound healing secondary to their paracrine action and pro-angiogenic properties, burns, diabetic ulcers, systemic sclerosis, etc.
- Cardiology: Cardioprotection against heart infarcts.
- Orthopaedics: Reduced joint degeneration during OA, functional recovery of injured tendons and decreased risk of reinjury, etc.
- Other: neurology, ophthalmology, etc

Although further studies are needed to determine the most adequate treatment protocols with MSC, there is evidence that MSC have positive effects in soft tissues. Tissue healing and clinical improvement have been observed in animals with tendinopathies and OA when stem cell therapy has been applied. A 3-month long clinical improvement has also been reported following intraarticular injection of MSC, although the positive effect seems to last for up to 6 months when MSC are injected in combination with PRP. However it is important to be cautions about these results as treatments and study conditions are usually quite variable.

2. PLATELET RICH PLASMA

Alfa-granules in platelets contain a number of growth factors, such as IGF-1, VEGF, PDGF, among others. These growth factors enhance tissue healing and they have been reported to have a synergistic effect with MSC to recruit pluripotent cells, and stimulate migration, proliferation and differentiation of cells of different lines.



Platelet Rich Plasma consists of the blood fraction that contains at least twice the platelet concentration as blood. PRP can be obtained by blood centrifugation (most common) or by filtration and concentration of platelets. There are many systems and centrifugation protocols in the market to obtain PRP, such as IRAP-ACS, Arthrex-ACP, CRT Pure PRP, ProTec PRP, or SmartPReP. The filtration method is commercialised as V-PET. There are many studies reporting the beneficial effects of growth factors in multiple tissues and organs, especially in articular cartilage. Here it has been observed an increased cell viability and proliferation, as well as an enhanced synthesis of proteoglycans, GAG and type 2-collagen. PRP seems to inhibit the catabolic effect of proinflammatory cytokines, and it may have an immunemodulatory effect that reduces joint inflammation and it recruits MSC. Clinically, it has also been observed an improved level of pain and lameness, both subjective and objectively, for a duration of at least 3 months following intraarticular injection. PRP has also been used in the treatment of tendinopathies, such as supraspinatus tendinopathy, where collagen fibres became more normalised and the hypoechogenic foci observed with ultrasound were also reduced. However, these positive results improve even further when PRP is combined with MSC.

It is still unknown which characteristics of PRP are most adequate to obtain an optimal tissue effect, in regards to platelet concentration, WBC presence or not, or RBC concentration. Due to the great variability in obtaining PRP, comparing results among studies proves quite challenging. A recent study compared the characteristics of PRP being obtained by means of different techniques. It proved the great variability in platelet concentration, WBC or RBC presence, etc among the different systems.