



Four Leg News

Your place for online canine rehab education!!!

THIS ISSUE: OSTEOARTHRITIS UPDATES!

The Line Up of Topics!

- 2 - The CNS & OA in dogs
- 3 - Knee OA in People
- 4 - Laser and OA
- 7 - Shockwave and OA
- 8 - Manual Therapy and OA
- 9 - Acupuncture and OA
- 11 - Tramadol and OA
- 12 - Stem Cells and OA
- 12 - Laser + Stem Cells and OA
- 13 - PRP and OA

THIS ISSUE of **FOUR LEG NEWS** is a compilation of articles regarding osteoarthritis! How many cases of osteoarthritis are you seeing right now, either as the primary reason for coming or a secondary concern? I bet it's a lot! Well this issue is for you to help you be up to date on the research, to know what to do, what's working (and what maybe isn't), and give you some perspectives on how you might tweak your plan of care for the next arthritic dog or cat that comes into your practice! Enjoy the Read! Cheers! Laurie

Dogs and Osteoarthritis (OA)

"In dogs, OA is a condition affecting a large percentage of the population, with an estimated 20% to 30% of the dog population having OA and associated clinical signs. The pathophysiology of canine OA of the hip is considered to be very similar to human OA, making dogs suitable candidates to be used as spontaneous disease models. Additionally, the canine stifle joint is considered to be among the most similar to the human knee joint." (Knazovicky et al 2016)

The Central Nervous System & Canine OA

Knazovicky D, Helgeson ES, Case B, et al. Widespread somatosensory sensitivity in naturally occurring canine model of osteoarthritis. *Pain*. 2016 157(6): 1325-1332.

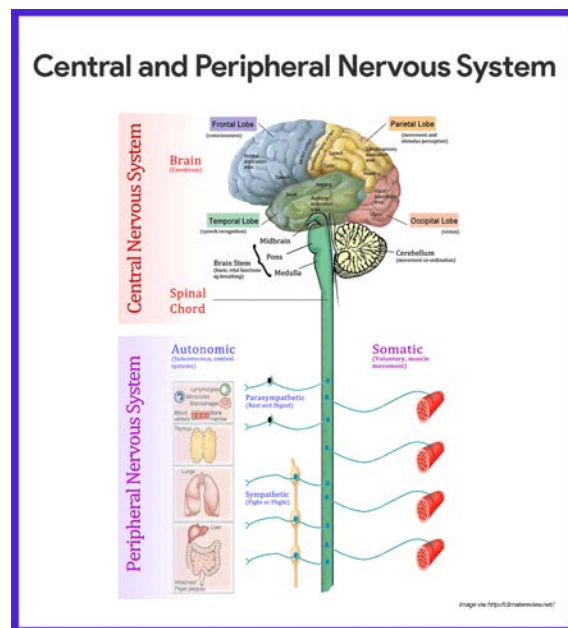
Osteoarthritis pain can be difficult to control. One reason for this may be that of central plasticity (aka central sensitization). Researchers Knazovicky et al (2016) set out to evaluate mechanical and thermal quantitative sensory testing (QST) in dogs with chronic OA-associated pain and in matched control dogs. They compared 31 dogs with hip and/or stifle OA to 23 control dogs, while testing mechanical pressure sensitivity (using an Electronic von Frey device and a Pressure algometer) and thermal sensitivity (using a thermal probe). Testing spots were located at the 'index joint', EITHER the hip (2cm craniodorsal from the greater trochanter) or the stifle joint (2cm lateral from the apex of the patella), and then also at two additional testing locations, tibial muscle (center of at the cranial tibial muscle at the dorsolateral position) and the metatarsals (dorsal surface of the metatarsus, between metatarsal bones 3 & 4).

Primary Finding:

Researchers found significantly lower mechanical and thermal thresholds at index joints (i.e. the joint with the primary OA) and at sites remote from the affected joints (tibial muscle and metatarsal) in dogs with OA as compared with control dogs without OA.

What this means:

This increased sensitivity to mechanical and thermal stimuli remote from the OA-affected joint could indicate the presence of enhanced pain processing resulting from central and, or, peripheral sensitization, with peripheral sensitization driven by circulating proinflammatory or pain-promoting substances.



Why do you care?

I'm delighted this study has come about. It sheds light on the fact that osteoarthritis, but more specifically, PAIN related to osteoarthritis, has a systemic effect. As such, we know that a multimodal approach is necessary to address it. Centralized pain cannot be combatted with medication alone. So, keep reading to see what else is helping with osteoarthritis pain (and start looking at human research as well!)

What is the Sequelae to Knee Osteoarthritis in People?

Van Tunen JAC, Dell'Isola A, Juhl C, et al. Association of malalignment, muscular dysfunction, proprioception, laxity, and abnormal loading with tibiofemoral knee osteoarthritis – a systematic review and meta-analysis. BMC Musculoskel Disord. 2018 19: 273.

A systematic review and meta-analysis of research articles pertaining to knee osteoarthritis (in people) was conducted by van Tunen et al (2018)¹. They wanted to investigate the association of specific biomechanical factors with knee osteoarthritis and knee osteoarthritis development, as well as the impact of other relevant risk factors on this association. Their literature search resulted in the identification of 6413 unique studies, of which 59 were eligible for meta-analysis.

Findings?

#1. Compared with healthy controls, patients with knee osteoarthritis have higher odds of having lower muscle strength, proprioception deficits, more medial varus-valgus laxity and less lateral varus-valgus laxity.

#2. Patients with medial knee osteoarthritis have higher odds of having a higher knee adduction moment than healthy controls

Laurie's thoughts?

What do you get when you do a literature review on Canine Osteoarthritis (+hip or +stifle) with the words clinical signs or biomechanics? You mostly get hip dysplasia articles or cruciate deficiency articles. There is a need to quantify and qualify exactly what happens with osteoarthritis (of any joint). While we are all likely able to describe what we see clinically, not much is in the literature to describe this unfortunately. Looking for a research project? There's one for you!



Let's talk LASER!

De Paula Gomes CAF, Leal-Junior, ECP, Dibai-Filho AV et al. Incorporation of photobiomodulation therapy into a therapeutic exercise program for knee osteoarthritis: A placebo-controlled, randomized, clinical trial. *Lasers Surg Med.* 2018 [Epub ahead of print].

A group of Brazilian researchers (de Paula Gomes et al 2018) investigated the clinical effects of incorporating phototherapy into a therapeutic exercise program for individuals with knee osteoarthritis (OA) and compared the results to a group that received exercise alone and to a group that received exercise and placebo phototherapy.



They took 60 men and women with unilateral knee OA and divided them into the three treatment groups (exercise along, exercise + phototherapy, or exercise + sham phototherapy). A blinded examiner evaluated the clinical outcomes before and after the 10 treatment sessions. Tests / outcome measures were: Western Ontario and McMaster University Osteoarthritis Index (WOMAC), Lower Extremity Functional Scale (LEFS), Numerical Rating Pain Scale (NRPS), pressure pain threshold (PPT) in two points of knee, muscle strength, and the Functional Reach Test (FRT).

The exercise regimen consisted of twice a week sessions of 50 minutes in length for a total of 10 sessions, and included:

- 1) Ten minutes of warm up on a treadmill with no change in grade and adopting a standardized velocity between 1.1 and 1.2 m/s [31];
- 2) Squats: the participant stood with the hips in a neutral position, the knees extended and the feet parallel and shoulder-width apart. The participant was asked to perform a squat with the leg remaining perpendicular to the ground until reaching 30° knee flexion;
- 3) Knee extension: the participant was seated in a chair at 90° knee flexion and the hip performed extension starting at 90° and finishing at 45° of knee flexion. The exercise was performed unilaterally and resistance was applied on the ventral side of the distal third of the leg with the aid of a leg weight;
- 4) Side-lying clam exercise: the participant was in lateral decubitus with the feet together, hips and knees flexed at approximately 45° and an elastic band tied around the knees. The participant was instructed to hold the feet together and lift the knee, which occurred through abduction and lateral rotation of the hip. The therapist was positioned behind the participant to avoid the trunk or pelvis from moving in the posterior direction during the exercise;
- 5) In the standing position, the participant transferred weight from one leg to the other;
- 6) In the standing position, the participant held the toes flexed.

For those who received laser, the laser was administered using a portable nine-diode cluster device (PainAway/PainCure, Multi Radiance Medical, Solon, OH), with one 905nm super-pulsed diode laser (peak power: 8.5 W; frequency: 1000 Hz; mean power of each diode: 0.9 mW), four 875nm LED (mean power of each diode: 17.5mW) and four 640nm LED (mean power of each diode: 15 mW). The portable nine-diode cluster was used overlapping three quadrants of the knee (medial, lateral and posterior) in random sequence in direct contact with the knee with the participant in the seated position. Radiance was performed for one minute in each quadrant. The energy per quadrant was 7.85 J, generating a total energy of 23.55 J delivered per session.



Result # 1: The combination of exercise and phototherapy (LLLT combined with LEDT) for patients with knee OA was effective at reducing pain as compared to the control group (exercise only) and exercise + sham laser group), as measured by the Numerical Rating Pain Scale.

Result # 2: No other significant improvements were detected using the other measurements (functional tests, strength tests or pressure algometry).

Laurie's thoughts about this paper?

1. I think they under dosed the laser. Honestly, I think they could have lasered way more and seen better results. Other research says that the optimum dose for pain is 5.9 joules (per point... not per region) – Chow et al 2009.
2. If they were hoping to see better FUNCTIONAL changes, it would have been prudent to laser BEFORE exercising, with the thought that the pain modulation from the laser therapy would allow for better muscle activation and function due to a reduction in pain-induced muscle inhibition.

Chow RT, Johnson MI, Lopes-Martins RA, Bjordal JM. Efficacy of low-level laser therapy in the management of neck pain: a systematic review and meta-analysis of randomised placebo or active-treatment controlled trials. *Lancet*. 2009 Dec 5;374(9705):1897-908.

Another study (Tomazoni et al, 2016)¹ set out to evaluate and compare the effects of a topical nonsteroidal anti-inflammatory drug (NSAID), physical activity, and photobiomodulation therapy (PBMT) applied alone and/or in combination between them in an experimental model of knee OA. So, in this study they used poor little rats and injected a nasty substance that would cause OA into their knees. At the 21-day mark, treatments began. The injected substance had

created morphological changes consistent with the disease, and the laser was most effective in reducing these changes. The laser and NSAID reduce the total number of cells in the inflammatory infiltrate, with laser being the most effective for reducing the activity of myeloperoxidase and MMP-13. The results of this study indicate that laser is the most effective therapy in stopping disease progression, and improving inflammatory conditions observed in OA.

Now, unfortunately, I wasn't able to get my hands on the original paper to tell you what dosage was used... but I just wanted to share it because of its interesting findings!

The researchers went on to test laser alone, laser with exercise, exercise alone, laser with a topical NSAID, or the topical NSAID alone using the same study parameters. Treatments were performed three times a week for eight consecutive weeks, totaling 24 therapy sessions. They evaluated a number of different inflammatory markers and found that treatment with PBMT is more effective in modulating the inflammatory process underlying OA when compared with the other therapies tested.

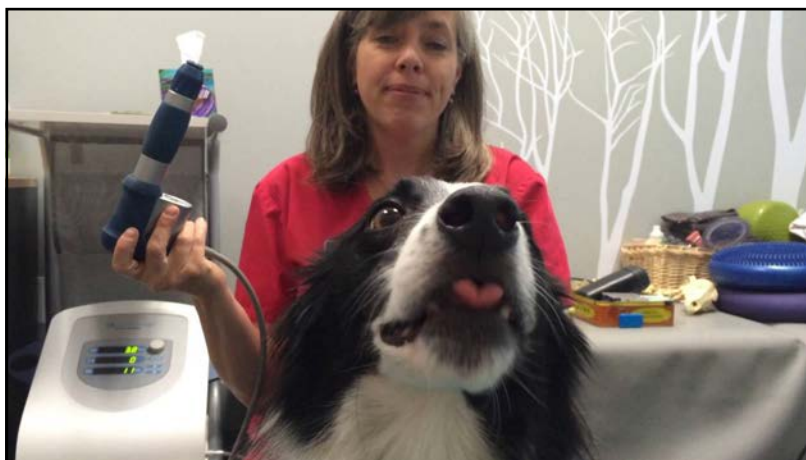
Finally, a third paper (de Oliveira et al, 2017), reported similar findings using laser therapy on induced OA in rats. They examined inflammatory mediators, pressure algometry scores, and bradykinin receptor activation. Laser was performed immediately after papain injection (to induce OA) and outcomes were measured at 6, 24, and 48 hours after 'injury'. They found that laser improved all measures evaluated. This group did report their laser parameters: 808nm wavelength, 50mW power, with 4 Joules of energy being delivered per point.

All in all, lots of potential for laser use. It's likely still good to combine laser with other therapies and with exercise. But we do know that laser can help with pain and with reducing inflammatory markers associated with osteoarthritis.

1. Tomazoni SS, Leal-Junior EC, Frigo L, Pallotta RC, Teixeira S, de Almeida P, Bjordal JM, Lopes-Martins RÁ. Isolated and combined effects of photobiomodulation therapy, topical nonsteroidal anti-inflammatory drugs, and physical activity in the treatment of osteoarthritis induced by papain. *J Biomed Opt.* 2016 Oct 1;21(10):108001.
2. Tomazoni SS, Leal-Junior EC, Pallotta RC, Teixeira S, de Almeida P, Lopes-Martins RÁ. Effects of photobiomodulation therapy, pharmacological therapy, and physical exercise as single and/or combined treatment on the inflammatory response induced by experimental osteoarthritis. *Lasers Med Sci.* 2017 Jan;32(1):101-108. doi: 10.1007/s10103-016-2091-8. Epub 2016 Oct 10.
3. de Oliveira VL, Silva JA Jr, Serra AJ, Pallotta RC, da Silva EA, de Farias Marques AC, Feliciano RD, Marcos RL, Leal-Junior EC, de Carvalho PT. Photobiomodulation therapy in the modulation of inflammatory mediators and bradykinin receptors in an experimental model of acute osteoarthritis. *Lasers Med Sci.* 2017 Jan;32(1): 87-94.



Shall we Shockwave?



Here we have original canine research!

Mueller et al (2007) studied the effects of radial shockwave on limb function. They used 24 dogs (18 were treated and 6 were controls). The shockwave was applied for 2000 shocks at 2 bar, weekly for 3 weeks. They found significant improvements in force plate measures of vertical impulse and peak vertical force at both the 4-week post treatment mark and the 3-month post-treatment mark. However, after 6-months the positive effects had ceased.

In 2016, Souza et al also studied the effects of radial shockwave on dogs with hip osteoarthritis. They used 30 dogs with bilateral hip OA as test subjects (and 30 healthy dogs), and proceeded to treat one side only using shockwave applied for 2000 pulses, at 10 Hz, and 2-3.4 bars. Three treatments were provided for 3-weeks. They then assessed the dogs at 30, 60, & 90 days following the first treatment. Mean PVF and VI values had increased in treated limbs, with no significant differences in control limbs. And quite naturally, these values were still lower than those of the healthy dogs. The visual analogue scores suggested improvement in pain and lameness in treated dogs, and owner perception data suggested improved levels of physical activity following treatment.

Thoughts:

Thus far, this modality appears to be a useful treatment modality for Osteoarthritis, and with radial shockwave, no sedation is required, and the price tag is less as well!

- Mueller M1, Bockstahler B, Skalicky M, Mlacnik E, Lorinson D. Effects of radial shockwave therapy on the limb function of dogs with hip osteoarthritis. Vet Rec. 2007 Jun 2;160(22):762-5.
- Souza AN, Ferreira MP, Hagen SC, Patrício GC, Matera JM. Radial shock wave therapy in dogs with hip osteoarthritis. Vet Comp Orthop Traumatol. 2016;29(2):108-14.

Magical Hands!

Anwer S, et al. Effects of orthopaedic manual therapy in knee osteoarthritis: a systematic review and meta-analysis. *Physiotherapy* (2017), <https://doi.org/10.1016/j.physio.2018.05.003>

In a study done by Anwer et al., they defined orthopaedic manual therapy (OMT) as “any hands-on therapy given by the physical therapist. Intervention may include moving joints in various and specific directions and at various speeds to regain movement, stretching, passive range of motion (ROM) exercise of the affected body part, or having the patient move the body part against the therapist’s resistance to improve muscle activation and timing. Selected certain soft tissue techniques may also be used to improve the mobility and function of tissue and muscle.”

The authors performed a systematic review and meta-analysis to evaluate the effects of OMT on pain, functional disability, ROM, and physical performance in patients with knee OA. They found that OMT interventions with exercise therapy compared with exercise therapy alone provide short term benefits in reducing pain, improving function, and stairs ascending-descending time in people with knee OA.



Possible mechanisms that explain pain reduction include: "joint mobilisation reduces pain by stimulating neurophysiological effects through activating type II mechanoreceptors and inhibiting type IV nociceptors. In addition, joint mobilisation enhances Golgi tendon organ activity and causes muscle relaxation via reflex inhibition. Furthermore, muscle inhibition following joint mobilisation causes reduced concentric muscle contraction and muscle tension in the peri-articular tissue, thereby reducing pain. Finally, joint mobilisation enhances pain modulation and somatosensory acuity in patients with painful knee OA."

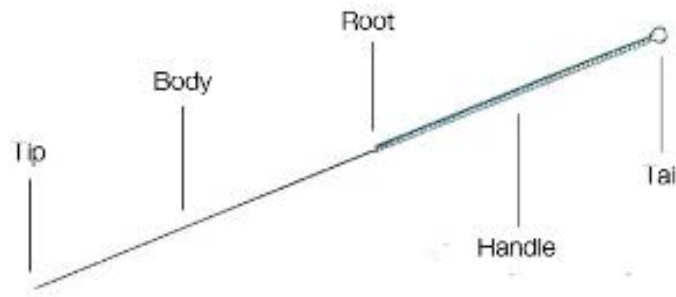
What's your 'take home'?

Add some mobilizations, massage, myofascial techniques, etc. to your therapy protocols for your canine arthritis patients! What you should note is that this study looks at a clinical benefit for a patient who can talk. What's interesting to me is that the information provided in regards to the rationale for the clinical findings and reported reduction in pain stem primarily from animal studies (lots of rats)! So, from rats to humans to dogs, it seems reasonable to use manual therapy for any mammal with osteoarthritis!!

Stick a Needle in That? Acupuncture for the treatment of Osteoarthritis (OA)

Here we open up a can of worms... but might as well read on!

Anatomy of an Acupuncture Needle



Foster et al. found that acupuncture in conjunction with advice and exercise provided no additional improvements to pain scores in studies on humans with knee OA. Also, they compared true acupuncture with non-penetrating acupuncture and saw similar results in unpleasant sensations and pain intensity in both groups, showing that these experiences are most likely not from needling effects.

Plaster et al. compared the immediate effects of electroacupuncture with manual acupuncture on pain, mobility and muscle strength in humans with knee OA and saw no significant difference after a single session; although they did notice a reduction in pain intensity. This may be due to "the release of neurotransmitters such as endorphins and monoamines which block pain messages".

Zhang et al. performed a systematic review to assess the effectiveness and safety of acupuncture to treat chronic knee pain (CKP) in humans. Only a few high-quality trials could be included in their meta-analyses but they were able to draw the conclusion that acupuncture may be effective for treating CKP at twelve weeks after treatment, and the safety of acupuncture is satisfactory.

A study that looked at gold wire implants at acupuncture points around the hip joints in dogs with hip dysplasia found significant improvement in observations of locomotion and reduction in signs of pain, despite no statistically significant differences between the treated and control groups (Hielm-Bjorkman et al 2001).

A study that looked at electro-stimulated acupuncture (ESA) in dogs with chronic elbow joint osteoarthritis secondary to elbow joint dysplasia found that ESA did not have any significant effects on severity of lameness, as determined by measurement of ground reaction forces, or severity of pain, as determined by visual analog scale pain scores (Kapatkin et al, 2006).

Despite the rise in popularity of both acupuncture and manual therapy in veterinary medicine, and the increasing number of Canadian veterinarians practicing these techniques, there is little research demonstrating their effectiveness. Lane & Hill (2016) performed a trial with 47 client-owned dogs with naturally occurring lameness. Comparison between pre- and post-treatment results demonstrated that combined acupuncture and manual therapy provides immediate short-term improvement in comfort and mobility (Lane et al, 2016).

Summarizing thoughts:

It appears that acupuncture as a stand-alone treatment for OA does not seem to yield significant improvements, however, it may have a place as a complement to other therapies. It is possible we need to assess different outcome measures in studying the effectiveness of acupuncture for treating arthritis.

Perhaps of interest, I occasionally do mini-tests on my patients. I have a patient, a Great Pyrenees x Maremma, with terrible hip arthritis. I had been doing laser, shockwave, and acupuncture to traditional hip points (GB 29, GB 30, BL 54), and he usually benefits. One day I told the owner I wanted to try something a bit different. I put 3 needles into the Deep Gluteal (i.e. GB 29 and two others near by). She reported back 2 weeks later that the dog was MUCH better with that treatment (laser and shockwave were the same) than with the traditional points. Food for thought. Maybe we can think outside of the box to get maximal benefit from traditional tools!

- Foster, Nadine et al. Acupuncture as an adjunct to exercise based physiotherapy for osteoarthritis of the knee: randomised controlled trial. *British Medical Journal*, online first. doi:10.1136/bmj.39280.509803.BE
- Plaster R, Vieira WB, Alencar FAD, et al. Immediate effects of electroacupuncture and manual acupuncture on pain, mobility and muscle strength in patients with knee osteoarthritis: a randomised controlled trial. *Acupunct Med* 2014;32:236–241. doi:10.1136/acupmed-2013-010489 237
- Zhang Q, et al. Updated systematic review and meta-analysis of acupuncture for chronic knee pain. *Acupunct Med* 2017;35:392–403. doi:10.1136/acupmed-2016-011306
- Hielm-Bjorkman A, Raekallio M, Kuusela E, Saarto E, Markkola A, Tulamo RM. Double-blind evaluation of implants of gold wire at acupuncture points in the dog as a treatment for osteoarthritis induced by hip dysplasia. *Vet Rec.* 2001 Oct 13;149(15):452-6.
- Kapatkin AS, Tomasic M, Beech J, Meadows C, Boston RC, Mayhew PD, Powers MY, Smith GK. Effects of electrostimulated acupuncture on ground reaction forces and pain scores in dogs with chronic elbow joint arthritis. *J Am Vet Med Assoc.* 2006 May 1;228(9):1350-4.
- Lane DM, Hill SA. Effectiveness of combined acupuncture and manual therapy relative to no treatment for canine musculoskeletal pain. *Can Vet J.* 2016 Apr;57(4):407-14.



“I’m addicted to acupuncture.”

Maybe 'Trama-Don't-Bother'!

The drug tramadol is getting knocked down a peg or two! A recent (Feb 2018) veterinary study showed that tramadol provides no clinical benefit for dogs with osteoarthritis of the elbow or stifle joint. The researchers (Budsberg et al)¹ from the University of Georgia studied the effectiveness of tramadol, to carprofen (Rimadyl), and placebo in a randomized, controlled study.

Each group received each treatment in a random order (with a 7-day washout period between). Testing of each substance was done for 10 days. Improvement was measured using force plate analysis and the Canine Brief Pain Inventory scoring system.

And?

Well, the results showed no improvement when tramadol was given compared to either baseline or placebo.

A good article that interviews various veterinarians on the tramadol controversy can be found at:

<https://healthypets.mercola.com/sites/healthypets/archive/2018/08/01/how-to-relieve-arthritis-pain-in-dogs.aspx>

Some of the comments are that tramadol may have a calming effect, and be useful for the emotional links that pain has on the brain. So, if you are a practitioner who has seen good results with tramadol (and I know there are some of you out there), then perhaps it would be better to think of this drug as an emotion-modifying drug as compared to a pain modifying drug. One vet warns about Serotonin syndrome.

Note: Serotonin syndrome is a potentially fatal condition in which there is excessive nerve cell activity. It is usually caused by the use of antidepressants, especially selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs). To be honest, we saw it at my clinic once in the 'early days' of tramadol prescription. The poor dog was beside himself... looked a bit like a junkie: shaking, twitching, agitated, and not at all acting like himself.

So, the bottom line is that IF you are wanting to use tramadol, then do so in knowing that it's not controlling pain. Something else will have to be 'on board' to help with that. Additionally, watch for behavioural changes in the animals to whom it is prescribed.

As a referral rehab practitioner, you may need to be the one to advocate for different pain management or to swiftly alert the referring vet of a reaction.

1. Budsberg SC, Torres BT, Kleine SA, Sandberg GS, Berjeski AK. Lack of effectiveness of tramadol hydrochloride for the treatment of pain and joint dysfunction in dogs with chronic osteoarthritis. J Am Vet Med Assoc. 2018 Feb 15;252(4):427-432.

In the Regenerative Medicine Category!

First Up... Mesenchymal Stem Cells

Shah et al. reported on the outcome of the treatment with mesenchymal stem cells (MSCs) of two hundred and three dogs diagnosed with degenerative arthritis with severe chronic pain in joints causing lameness at walk, reduced mobility, and functional disability. Post-treatment assessment data after 10 weeks revealed significant improvement of the symptoms: pain reduction, improvement of mobility, and increased daily activity as measured as quality of life score. Ninety percent of the dogs under 9 years old showed excellent improvement in pain and mobility. Sixty percent of older dogs showed good improvement. They found no change in 12% of the dogs, and one dog that had multiple joint issues experienced a worsening of the symptoms. This report provides the support for the safety and efficacies of allogeneic adipose-derived mesenchymal stem cells in a regenerative therapeutic veterinary model.

- Shah, Kiran et al. Outcome of Allogeneic Adult Stem Cell Therapy in Dogs Suffering from Osteoarthritis and Other Joint Defects. Hindawi, Stem Cells International, Volume 2018, Article ID 7309201, 7 pages. <https://doi.org/10.1155/2018/7309201>

Let's Add a Little Laser to Those Stem Cells... now what?

Stancker et al. aimed to see if photobiomodulation therapy (PBMT) could improve the bioavailability and chondroprotective benefits of mesenchymal stem cells, as well as reduce the expression of matrix metalloproteinases (MMPs) and degradation of type II collagen (COL2- 1) in the cartilage (aka 'bad signs for the joint').

The nitty gritty:

Firstly, they induced arthritis in the little rat knees. Then the 'stem cell only' group and the 'stem cell + laser' group each received an intra-articular injection of 10×10^6 ADSCs. The 'laser-only' group and the 'stem cell + laser' group also received laser (daily for 7 days) using the following parameters: wavelength: 808 nm, power: 50 mW, energy: 42 J, energy density: 71.2 J/cm², spot size: 0.028.

Findings:

#1. Laser alone and Stem Cells alone, both reduced the 'nasty joint chemicals' associated with arthritis and inflammation.

#2. Laser and Stem Cells together provided both a reduction in inflammatory chemicals within the joint AND prevented joint degeneration & degradation.

What's your take home?

Go ahead and laser the joints that have had stem cell injections!

- Stancker, Tatiana et al. Can photobiomodulation associated with implantation of mesenchymal adipose derived stem cells attenuate the expression of MMPs and decrease degradation of type II collagen in an experimental model of osteoarthritis? Lasers in Medical Science (2018) 33:1073–1084

The Other Regenerative Medicine – PRP

In canine models, it seems that PRP (platelet-rich plasma) may have beneficial effects for ACL healing, improved range of motion, decreased pain, improved limb function, improved peak vertical force, vertical impulse, & stance time, but only for about 6th months.^{1,2} In people, a systematic review demonstrated no long-term statistically significant improvement in patient validated outcomes and secondary outcomes both in patients with knee OA or following TKA for OA. However, PRP has been shown to have short to medium-term benefits in pain control after TKA and activities of daily living in patients with OA.³

So, one really needs to weigh the cost benefits of PRP to that of other therapies when selecting the best way to proceed. As well, owners need to be fully informed of the benefits and limitations of PRP therapy.

1. Cook JL, Smith PA, Bozynski CC, Kuroki K, Cook CR, Stoker AM, Pfeiffer FM. Multiple injections of leukoreduced platelet rich plasma reduce pain and functional impairment in a canine model of ACL and meniscal deficiency. *J Orthop Res.* 2016 Apr;34(4):607-15.
2. Vilar JM, Manera ME, Santana A, Spinella G, Rodriguez O, Rubio M, Carrillo JM, Sopena J, Batista M. Effect of leukocyte-reduced platelet-rich plasma on osteoarthritis caused by cranial cruciate ligament rupture: A canine gait analysis model. *PLoS One.* 2018 Mar 19;13(3):e0194752. doi: 10.1371/journal.pone.0194752. eCollection 2018.
3. Muchedzi TA, Roberts SB. A systematic review of the effects of platelet rich plasma on outcomes for patients with knee osteoarthritis and following total knee arthroplasty. *Surgeon.* 2018 Aug;16(4): 250-258



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