A Novel Regenerative Approach To Treating Canine Lumbosacral Disease:

A role for adipose-derived mesenchymal stem cells?

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ABSTRACT:

Lumbosacral disease is a common condition affecting older dogs and also younger dogs, such as Border Collies, that are involved in agility work. The disease causes a variety of symptoms from back pain, hind limb weakness, reluctance to jump and ataxia to neurological deficits causing incontinence. The condition is usually progressive and management involves drug therapy (anti-inflammatories and analgesics), exercise management, weight control and physiotherapy. Surgical options such as decompressive surgery (laminectomy) and distraction and stabilization surgeries are very invasive techniques with potential complications. A private independent veterinary practice has treated a variety of orthopaedic conditions with stem cell therapy **(SCT)** and laser therapy **(LT)**. Whilst SCT is mainly used for joint osteoarthritis cases, reports in human lumbar conditions makes this an interesting minimally invasive potential therapy for canine lumbosacral disease.

Six dogs presenting with a history of severe back pain and radiographic evidence of lumbosacral disease attending the veterinary practice have received SCT with laser therapy in this small case series. All were being treated with a non-steroidal anti-inflammatory drug and some were also receiving one or more analgesics. Subcutaneous adipose tissue was harvested from each dog under a short general anaesthetic and blood taken for cell culture. Cell Therapy Sciences Ltd isolated the adult adipose-derived mesenchymal stem cells **(ADMSCs)** from the tissue and culture-expanded them. These were then shipped in sterile vials cryogenically frozen in the dog's own serum.
The autologous stem cell treatment was given intravenously and by epidural injection at the lumbosacral junction under sedation. Immediately following implantation, the lumbosacral region was targeted with laser therapy using a class IV laser with appropriate settings for each animal. The laser treatment was repeated three times a week for two weeks and then monthly for three months. Efficacy of treatment was monitored by veterinary physical examination, pet-owner assessment using validated questionnaires (canine brief pain inventory (CBPI) and Liverpool osteoarthritis in dogs (LOAD) questionnaire) and repeat radiographs at three and six months after treatment where possible.

All treated dogs became pain free at the lumbosacral region, were able to come off all analgesics and regained full activity. The CBPI and LOAD scores were significantly reduced in all treated dogs. The author concludes that SCT combined with laser therapy is a very effective, minimally invasive, drug free treatment option for lumbosacral disease and warrants further investigation.

OBJECTIVES:

The objective of this small cases series was to determine whether intravenous and epidural administration of ADMSCs, followed by LT was an effective treatment option for dogs with LS disease.

INTRODUCTION:

Canine Lumbosacral (LS) disease is the term used for a group of diseases affecting the LS intervertebral joint and surrounding tissues. LS disease is a multifactorial degenerative disease that can affect any dog but primarily affects middle-aged-to-older large breed dogs. The condition is more common in working and agility dogs and can be acquired (degenerative) or congenital (developmental). The diagnosis of LS disease is based on history, physical examination findings, clinical signs and diagnostic imaging. Clinical signs of LS disease include lower back pain, pelvic limb lameness, sciatic pain, reluctance to jump, ataxia and weakness of the tail. Plain radiographs will also demonstrate spondylosis, osteoarthritis of the dorsal articular facets, sclerosis of the LS vertebral end plates and a collapsed L7-S1 disk space. However, imaging findings do not always correlate well with clinical findings.

Current treatment options for LS disease include conservative management and surgical management. The former involves exercise restriction, weight control, anti-inflammatory medications and analgesics. Degenerative LS stenosis (DLSS), intervertebral disk disease (IVDD) and congenital LS stenosis cause chronic nerve root compression, which tends to be progressive and medical management may not be sufficient to control the clinical signs.

Two surgical techniques have been described including dorsal laminectomy and, more recently, LS distraction-stabilisation surgery. Both of these procedures are very invasive, require careful postoperative care and are associated with potential complications and recurrence of clinical signs. However, one study demonstrated an average of 78% of dogs undergoing surgery had an excellent or good outcome.[1] Dogs with urinary or faecal incontinence show a poor response to surgery regarding resolution of the incontinence.[1]

The use of epidural steroid injections into the LS space has also been reported as a minimally invasive treatment option for LS disease.[2]

Stem cell therapy (SCT) has been used to treat a variety of orthopaedic problems including osteoarthritis in joints of dogs. Considering the LS junction is a joint, the potential for SCT to be used to treat this condition is worth exploring. A recent paper by Oehme et al, reviews 25 different studies utilising cell therapies to treat lumbar intervertebral disc disease.[3] These studies assessed the ability of different cell therapies to regenerate the intervertebral disc. Of these 25 studies four were specifically using canine models.[4,5,6,7] All four studies demonstrated positive effects on discs that were induced to degenerate prior to administration of SCT.[3]

Laser therapy (LT) has been used extensively to treat soft tissue and orthopaedic injury and pain through a process called photobiomodulation. LT has also been shown to have beneficial effects on stem cell proliferation.[8] There is little information available regarding in vivo application of LT in conjunction with MSCs.

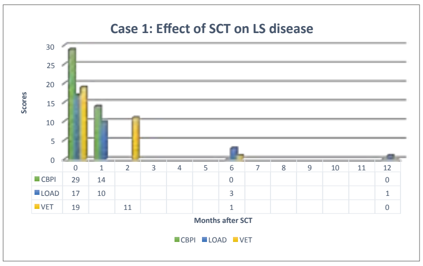
MATERIALS AND METHODS:

Six dogs presenting with clinical signs and radiographic evidence of LS disease had approximately five grams of fat harvested from the inguinal fat pad under general anaesthesia. Blood was also drawn and placed in plain blood tubes and sent chilled at 4°C with the harvested fat to Cell Therapy Sciences Ltd by overnight courier. ADMSCs were isolated from the fat and culture expanded in medium containing the dog's own serum. After completion of sterility testing the cells were cryogenically frozen in sterile vials and shipped back to the clinic in dry ice by overnight courier.

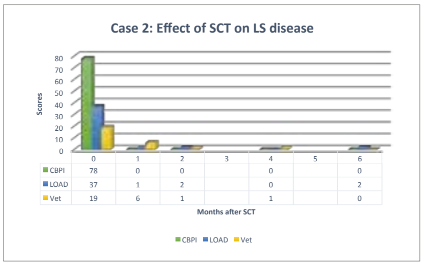
The autologous ADMSCs were defrosted, diluted in isotonic crystalloid solution (compound sodium lactate) and each dog had one million cells per kg injected by slow intravenous injection. The dogs were then sedated with medetomidine and butorphanol and the hair was clipped and skin surgically prepared in the region of the lumbosacral junction. The dogs were positioned for epidural injection with the hind limbs extended cranially in sternal recumbency. A 3.5 inch 20g spinal needle was inserted into the epidural space through the lumbosacral junction and eight million autologous ADMSCs were implanted in 0.8 ml of autologous conditioned serum. Correct needle positioning was determined using plain radiography and lack of resistance on injection. The needle was then withdrawn slightly and two million ADMSCs were implanted in the region of the dorsal articular facets.

Post implantation laser was administered using a class IV CTC Companion laser. The LT dosage was different for each patient and was dependent on body weight, body condition, hair length, hair colour and skin colour. This ensured correct penetration and appropriate levels of photons reaching the lumbosacral region. LT was applied using a Laser-contact ball to the entire lumbar region and sacrum from the dorsal and lateral approach. LT was repeated three times a week for two weeks and then monthly for two months post implantation.

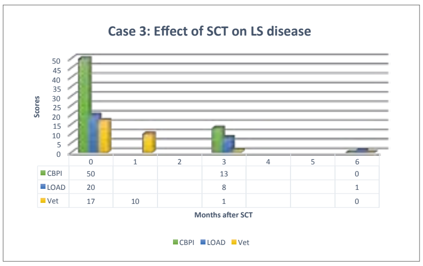
Canine brief pain inventory (CBPI) and Liverpool Osteoarthritis in Dogs (LOAD) questionnaires were filled in by each owner prior to SCT and LT and at a number of intervals following implantation to monitor response to treatment. A veterinary questionnaire was also developed to score clinical findings associated with LS disease. The vet scoring took into account the number of clinical signs evident and their severity, based on physical examination findings and gait analysis by the author. The CBPI was scored out of a 100, the LOAD out of 52 and the Vet questionnaire out of 34. The higher the score, the worse the animal was affected. Statistics were estimated using a student t-test comparison of the mean total scores for different time points following treatment.



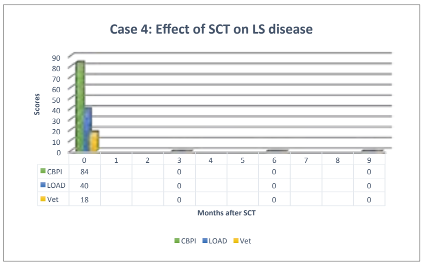
	0	1	2	3	4	5	6	7	8	9	10	11	12
CBPI	29	14					0						0
LOAD	17	10					3						1
VET	19		11				1						0



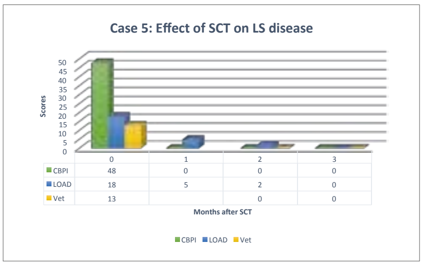
	0	1	2	3	4	5	6
CBPI	78	0	0		0		0
LOAD	37	1	2		0		2
Vet	19	6	1		1		0



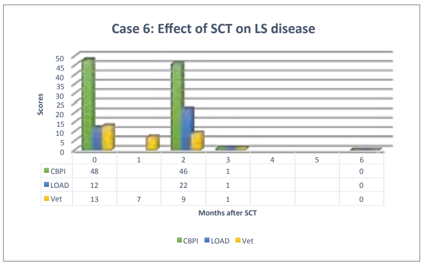
	0	1	2	3	4	5	6
CBPI	50			13			0
LOAD	20			8			1
Vet	17	10		1			0



	0	1	2	3	4	5	6	7	8	9
CBPI	84			0			0			0
LOAD	40			0			0			0
Vet	18			0			0			0



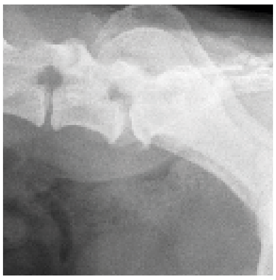
	0	1	2	3
CBPI	48	0	0	0
LOAD	18	5	2	0
Vet	13		0	0



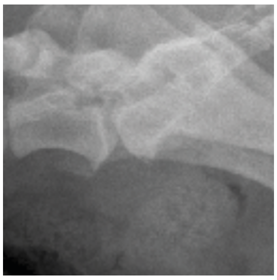
	0	1	2	3	4	5	6
CBPI	48		46	1			0
LOAD	12		22	1			0
Vet	13	7	9	1			0

Radiographs of Lumbosacral Junction Before and After SCT + LT (Case 4)

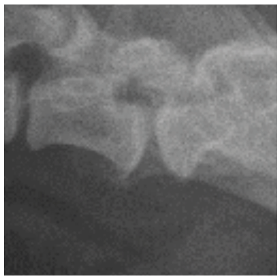
Before SCT



3 months after SCT

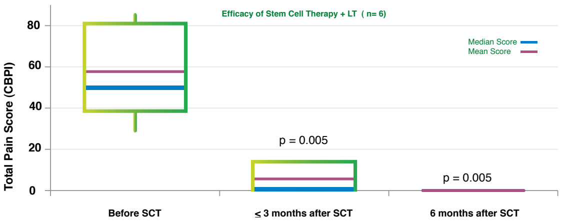


8 months after SCT



The scores from the two pet owner questionnaires and the vet clinical examinations are shown for each case in graphical representation above. One case has been followed for three months, three cases for six months, one case for nine months and one case for 12 months. The data shows a significant reduction in pain scores (CBPI p=0.005 at three and six months), LOAD (p=0.015 at three months and p=0.013 at six months) and Vet Questionnaire (p=0.0003 at three months and p < 0.0001 at six months). Improvements have been maintained up to the most recent evaluations for each case. **All six cases were able to stop their analgesics and anti-inflammatories by 12 weeks post SCT**. Radiographs are shown for Case 4 taken at diagnosis and at three and eight months post SCT. The radiographs show changes to the intervertebral disc and surrounding structures of the lumbosacral junction. Endplate sclerosis is seen to have been reduced as has ventral spondylosis arising from S1. The density of the IVD can been seen to have reduced following SCT.

RESULTS:



DISCUSSION:

The results show a significant reduction in pain and clinical signs associated with LS disease as compared with the original pre-treatment assessments. All six cases improved dramatically, to the point of showing no evidence of pain or clinical signs of LS disease. All cases were able to come off their analgesics and anti-inflammatories by 12 weeks following implantation. It should be noted that the pre-treatment scoring was done whilst the animals were receiving analgesic medications. The success rate of treatment in this case study to date is greater than reported with other treatment options currently available; however, these cases need to be followed over the rest of their lifetimes to evaluate the longevity of treatment. This is a small case series and larger numbers or a controlled clinical trial would be required to properly evaluate this treatment option. The radiographic changes seen in three of the cases over six months show no progression of the disease process but also suggest reversal of degenerative changes to the LS region. Although medical treatment can help alleviate pain and surgery can remove some of the compressive forces that cause the clinical signs, neither treatment modality can arrest or reverse the degenerative changes that occur in this disease process. This small case series shows much promise in treating LS disease, not only effectively to control pain but also to arrest and possibly also reverse the disease process. This procedure allows the possibility of repeat treatments if required and a protocol could be determined as cases are followed in the future. The author is currently collecting data on a further 30 cases of LS disease treated with stem cells and laser therapy; many of these cases also have OA in other joints that have received the same treatment protocol. Future cases will be followed with stance analysis and digital thermal imaging in addition to pet owner questionnaires and veterinary assessment.

CONCLUSIONS:

The results indicate that regenerative medicine is a very effective treatment option for LS disease.

Longer term case follow up is required to determine longevity of response but the radiographic changes seen are very encouraging. Although complete reversal of pathology may not be possible, the results indicate that the disease process could be induced into remission for an extended period of time.

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Acknowledgements

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Affiliations:
The author has no affiliations

Conflicts of interest:
The author has no potential conflicts of interest.