

PAPER

Low-level laser therapy reduces time to ambulation in dogs after hemilaminectomy: a preliminary study

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OBJECTIVES: A prospective study to determine if low-level laser therapy and surgery for intervertebral disk herniation encourage ambulation faster than surgery alone.

METHODS: Thirty-six dogs with acute paraparesis/paraplegia due to acute intervertebral disk herniation were evaluated and given a modified Frankel score. Dogs with scores 0 to 3 were included in the study. Dogs were assigned to the control group (1) or the laser treatment group (2) based on alternating order of presentation. All dogs underwent surgery for their herniated disk. Dogs in group 2 were treated postoperatively with low-level laser therapy daily for five days, or until they achieved a modified Frankel score of 4. A 5×200-mW 810-nm cluster array was used to deliver 25 W/cm² to the skin. All dogs were scored daily by the investigators using the modified Frankel scoring system.

RESULTS: The time to achieve a modified Frankel score of 4 was significantly lower ($P=0.0016$) in the low-level laser therapy group (median 3.5 days) than the control group (median 14 days).

CLINICAL SIGNIFICANCE: Low-level laser therapy in combination with surgery decreases the time to ambulation in dogs with T3-L3 myelopathy secondary to intervertebral disk herniation.

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INTRODUCTION

Intervertebral disk disease is the most common cause of endogenous acute spinal cord injury in dogs and typically results from mechanical failure of a degenerated intervertebral disk (Hoerlein 1987, Davis and Brown 2002). The thoracolumbar region is the most common region for intervertebral disk herniation (Griffin and others 2009). Dogs that are non-ambulatory as a result of disk herniation are commonly treated by surgical decompression, and 83 to 95% of these dogs will regain voluntary ambulation after decompression if they had entire pedal deep pain sensation before surgery (Gambardella 1980, Muir and others 1995, Duval and others 1996), while 58 to 69% of dogs will regain voluntary ambulation after decompression if they lacked pedal deep pain sensation (Duval and others 1996, Scott and McKee 1999, Olby and others 2003, Ito and others 2005, Ruddle and others 2006). A previous study showed that dogs with absent deep pain sensation before surgery were 1.7 times less likely to regain voluntary ambulation than dogs with entire deep pain sensation (Ruddle and others 2006). The mean time to ambulation after surgery

can vary. On the basis of two studies, small breed dogs with entire deep pain sensation before surgery have a mean time to recover voluntary ambulation in 10 or 13 days (Davis and Brown 2002, Ferreira and others 2002). Large breed dogs had a mean recovery time to ambulation of seven weeks, though the majority recovered in four weeks, and the time to ambulation increased with increasing weight and age (Cudia and Duval 1997).

Low-level laser therapy (LLLT) has been used to treat injuries of various portions of the body in human medicine. The theory behind this is called photobiomodulation. This is the application of a particular wavelength of light at a certain energy density to a cell (or cells) in the body. These cells will react to that light in a predetermined fashion depending on the absorption spectrum of the cells. It has been shown that energy density between 0.2 and 10 J/cm² applied directly to central nervous system (CNS) tissue enhances neuronal cell metabolism (Rochkind and Ouaknine 1992, Byrnes and others 2005), while 632- or 780-nm-wavelength light at an energy density of 60 J/cm² projected directly on fibroblast cells decreases cell mitoses (Rochkind and Ouaknine 1992). There are a multitude of studies, ranging from in vitro cell culture experiments to clinical trials, indicating that

LLLT reduces glial scarring (Rochkind and Ouaknine 1992), the immune/inflammatory response and secondary damage (Byrnes and others 2005), increases migration and neurite sprouting of cultured embryonic nerve cells as well as cultured adult brain microexplants (Wollman and others 1996, Wollman and Rochkind 1998) and promotes axonal sprouting and regeneration after spinal cord injury (Byrnes and others 2005, Rochkind and others 2006). Sprouting and fibre outgrowth occur in primates and rodents during recovery of neurological function following cerebrocortical injury or stroke, and are accompanied by new synapse formation in regions adjacent to the focus (Jones and Schallert 1994, Stroemer and others 1995). Additionally, transcutaneous laser irradiation of the spinal cord improves recovery of the corresponding injured peripheral nerve (Rochkind and others 2001, Shamir and others 2001) and speeds recovery from severe spinal cord injury when laser therapy is combined with sciatic nerve graft in the spinal cord (Rochkind and Ouaknine 1992). Specifically, 810 nm light improves axonal regrowth, locomotor function and alters the immune response in a damaged rat spinal cord model (both hemisection and contusion models) (Byrnes and others 2005, Wu and others 2009). These studies indicate that the low-level laser will penetrate through tissue to allow an effective energy density to be applied to the spinal cord.

On the molecular level, the mechanism of LLLT has been attributed to several processes. One mechanism is the reduction of activity of nuclear factor kappa-light-chain enhancer of activated B cells (NF- κ B) (Rizzi and others 2006). Activated astrocytes play a role in propagating secondary spinal cord injury through the activity of NF- κ B. Inhibition of NF- κ B correlates with reduced expression of pro-inflammatory mediators and increased white matter preservation (Brambilla and others 2005), potentially leading to increased axonal sparing and sprouting following spinal cord injury (Brambilla and others 2009). LLLT also alters mitochondrial oxidative metabolism by stimulation of cytochrome oxidase (Eells and others 2003). This is possibly due to the absorption of the light by the cytochromes of the respiratory chain in the mitochondria. Cytochrome oxidase has absorption bands in the 780 and 830 nm range (Rochkind and Ouaknine 1992). Cytochrome oxidase is an important energy-generating enzyme that is critical for function in almost all cells, especially in highly oxidative organs such as the CNS (Wong-Riley 1989). Nitric oxide (NO) produced in the mitochondria can inhibit respiration by binding to cytochrome oxidase and displacing oxygen, especially in stressed or hypoxic cells (Brown 2001). It is proposed that LLLT may displace the NO from the cytochrome oxidase, allow binding of oxygen, and thus restart the mitochondrial respiration pathway (Lane 2006). Reactive oxygen species (ROS) are possible mediators of the biological effects of light therapy (Grossman and others 1998, Karu 1999). While ROS are usually thought of as detrimental to cells, it has been suggested that in small amounts they may be a significant biostimulant, ultimately promoting mitosis (Williams 1985, Kanofsky 1989, Rochkind and Ouaknine 1992).

The purpose of this prospective study was to evaluate LLLT as an adjunctive treatment for non-ambulatory paraparesis or paraplegia due to thoracolumbar intervertebral disk disease (IVDD),

specifically to see if LLLT expedites the ability of the affected dog to ambulate voluntarily. It was hypothesised that LLLT therapy would decrease time to ambulation. To the authors' knowledge, there have been no clinical studies in the dog using LLLT as an adjunctive treatment for spontaneous spinal cord disease.

MATERIALS AND METHODS

From December 2009 to December 2010, dogs presenting to the University of Florida College of Veterinary Medicine with signs consistent with thoracolumbar disk herniation were evaluated and each animal was assigned a modified Frankel score (MFS) to describe neurological dysfunction. This scale was used because it accounts for more than one examiner and has been used in previous studies (Frankel and others 1969, Levine and others 2006, 2009). The MFS is defined as spinal hyperaesthesia only (grade 5), ambulatory with paraparesis and/or ataxia (grade 4), non-ambulatory paraparesis (grade 3), paraplegia with entire superficial nociception in the pelvic limbs (grade 2), paraplegia with entire deep nociception in the pelvic limbs (grade 1) and paraplegia with absent nociception in pelvic limbs (grade 0). Superficial nociception was tested using mosquito haemostats to pinch a small section of skin over the dorsal pes. Deep nociception was tested using mosquito haemostats to compress the periosteum of P2 of one of the digits on the rear limb. Positive nociception was recorded if a conscious response was noted by the patient (i.e. vocalisation, turning to look at the point of stimulus, sudden increase in heart rate that was subsequently reduced after cessation of the stimulus). Animals were considered ambulatory if they could rise from a sitting position and take three steps of their own volition (e.g. left, right, left) without falling and without physical manipulation by the examiner (i.e. pulling on the leash, "tail walking", pushing from behind). Assessment of ambulation in all dogs was done on a non-slick rubber mat running the length of a hallway. A dog was considered to have non-ambulatory paraparesis (MFS 3) if voluntary motor function in the pelvic limbs was noted during the examination, but the dog was not able to rise and take three steps of their own volition. To be included in the study the dogs had to meet the following criteria: clinical signs for less than five days, neurological exam findings consistent with a T3-L3 myelopathy, an MFS of 0 to 3 and a complete diagnostic regimen with appropriate treatment approved by the owner. Dogs were assigned to one of two groups by alternating order of presentation to obviate selection bias. The 18 dogs in group 1 were diagnosed and treated in a way consistent with current standards of care including (but not limited to) complete blood count, serum biochemistry, advanced imaging (MRI or CT) to diagnose intervertebral disk herniation and surgical decompression via hemilaminectomy±pediculectomy. The 17 dogs in group 2 were diagnosed and treated in a way consistent with current standards of care combined with LLLT postoperatively. LLLT was performed using a laser array with five 200-mW 810-nm-wavelength lasers [LX2 Control Unit+Laser Cluster Probe, wavelength=810 nm, power=1 W (5×200 mW), THOR Photomedicine Ltd, London, UK]. Postoperatively the

laser was applied transcutaneously over the spinal segment associated with the hemilaminectomy and the two adjacent ones (one cranial and one caudal). The laser array was applied to each area for 1 minute, delivering 25,000 mW/cm² to the overlying skin (private communication of unpublished experimental data from James Carroll of THOR Photomedicine) per day for five days. As light in the infrared spectrum is not absorbed by haemoglobin and can penetrate deep into living tissue, this delivered an appropriate energy density (2 to 8 J/cm²) to the spinal cord (private communication of unpublished experimental data from James Carroll of THOR Photomedicine) (Oshiro and others 1996, Vladimirov and others 2004). While they were hospitalised, all dogs were evaluated on a daily basis via physical and neurological examinations by the primary investigator. All dogs were given an MFS daily. Each dog was considered to have successfully completed the study when they achieved an MFS of 4. If the dogs left the hospital before achieving an MFS of 4, the owners were instructed to contact the attending clinician when they confirmed that the dog was able to rise and walk three steps on its own. This confirmation was corroborated via video footage of the dog sent to the attending clinician, phone discussion between the attending clinician and another veterinarian that had confirmed the ambulatory status, or by requesting that the owner bring the dog back to the University of Florida Neurology Service for evaluation by the attending clinician. Basic physical rehabilitation exercises (passive range of motion, supported standing and toe-pinch withdrawal) were discussed with the owners and recommended for at-home use for all of the patients in this study.

This study was reviewed, and approved, by the Institutional Animal Care and Use Committee (IACUC) and the Clinical Research Review Committee (CRRC) at the University of Florida.

Age, sex, breed, weight, number of non-ambulatory days before presentation, MFS on admission, number of days required to achieve MFS grade 4, and whether or not glucocorticoids were used at any time were recorded for all study dogs.

Differences in time to reach an MFS of 4 between the two groups were determined by survival analyses using the Kaplan-Meier (KM) method. Significant differences in time to reach an MFS of 4 were determined by the log-rank P values derived from the KM method. Multivariate Cox proportional hazard models were constructed to identify factors independently associated with time to reach an MFS of 4. Age, weight, duration of clinical signs at presentation, MFS at presentation, and group were the independent factors inserted into the models. Analysis was performed and all data were retained in the models. Hazard ratios (HRs) for time to MFS of 4 and 95% confidence intervals (CIs) were calculated for each variable. A P value of less than 0.05 was considered significant in all analyses. MediCalc software (version 12) was used to analyse the data and provided the descriptive statistics for the groups.

RESULTS

Group 1 (control group) consisted of 18 dogs (3 entire males, 5 castrated males, 1 entire female and 9 spayed females) that

included 13 dachshunds, 3 mixed-breed dogs, 1 bulldog and 1 shih-tzu. The mean age was 5.4 years, with a mean weight of 9.1 kg and duration of clinical signs before entering the study of 1.32 days. The median MFS on initial presentation was 1. Six dogs had an MFS of 3, two had MFS of 2, nine had MFS of 1 and one had MFS of 0 at presentation. Six of these dogs were treated with glucocorticoids.

Group 2 (LLLT group) consisted of 17 dogs (1 entire male, 6 castrated males and 10 spayed females) that included 13 dachshunds, 2 cocker spaniels, 1 Jack Russell terrier and 1 mixed-breed dog. The mean age was 5.2 years with a mean weight of 7.5 kg and duration of clinical signs before entering the study of 1.15 days. The median MFS on initial presentation was 1. One dog had an MFS of 3, 4 had MFS of 2, 10 had MFS of 1 and 2 had MFS of 0 at presentation. Eight of these dogs were treated with glucocorticoids.

Of the dogs enrolled in the study, 34 of 35 achieved an MFS of 4. While all of the dogs in the laser treatment group were ambulatory at the end of the study, one dog in the non-laser control group had not attained an MFS of 4 at the conclusion of the study. This dog had an MFS of 2 on presentation. This dog was not included in the statistical analysis. There were 10 dogs in group 1 (55%) and 6 dogs in group 2 (35%) that were discharged without attaining an MFS of 4. These dogs were followed up as noted in the previous section to determine the day they attained an MFS of 4.

According to the KM survival analysis the shape of the survival curves was different between the LLLT group and the control group. This univariate analysis showed that there was a significant difference [log-rank P=0.0016, $X^2=9.978$, df=1, HR 2.5425 (95% CI 1.2049 to 5.3652)] in the median time to MFS of 4 of 3.5 days in the LLLT group compared to 14 days in the control group (see Fig 1 and Table 1 for expanded comparison). In the multivariate Cox proportional hazards models, group was the only factor independently associated with achieving an MFS of 4 [P=0.0036, $X^2=17.86$, df=5, HR 3.08 (95% CI 1.4466 to 6.5577)]. Age, weight, duration of clinical signs at presentation,

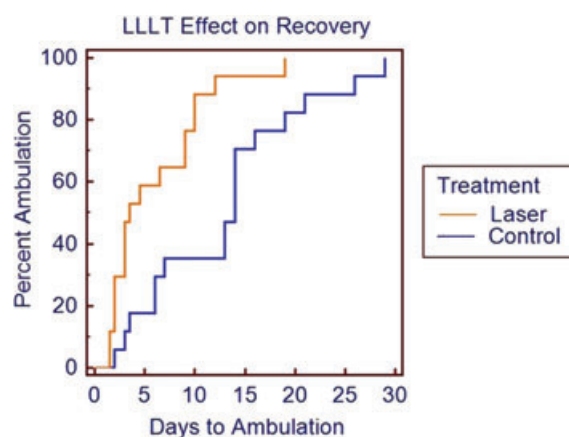


FIG 1. Kaplan-Meier curve demonstrating a significant difference between the low-level laser therapy (LLLT) and control groups in time to a modified Frankel score of 4 (P=0.0016)

Table 1. Kaplan-Meier analysis indicating days needed to reach a modified Frankel score of 4 between the control and LLLT groups

Group	Range	Lower quartile	Median	Upper quartile	Interquartile range
Control	2.0 to 29.0	6.0	14.0	16.0	10.0
LLLT	2.0 to 19.0	2.0	3.5	9.0	7.0

LLLT Low-level laser therapy

Table 2. Data from Cox proportional hazards models

Variable	HR	95% CI low	95% CI high	P value
Group (LLLT or control)	3.08	1.4466	6.5577	0.0036
Age (years)	0.8102	0.6410	1.0242	0.0799
Weight (kg)	0.9815	0.8891	1.0836	0.7130
MFS at admission	1.1072	0.7770	1.5779	0.5749
Duration of clinical signs before surgery (days)	1.2253	0.8581	1.7496	0.2660

Confidence interval, LLLT Low-level laser therapy, MFS Modified Frankel score

and MFS at presentation were not independently associated with achieving an MFS of 4 (Table 2). This analysis indicates that the only variable that was associated with a shorter time to MFS 4 was LLLT.

DISCUSSION

The results of this study support the original hypothesis that LLLT, in conjunction with decompressive surgery, decreases time to ambulation in dogs that are non-ambulatory because of thoracolumbar IVDD. The presented data indicate that LLLT may play an important role in the treatment of acute spinal cord injury secondary to intervertebral disk herniation. There was a statistically significant difference in the median time to ambulation between the two groups that was independent of age, weight, MFS on presentation, or duration of clinical signs on presentation. The mean time to ambulation after decompressive surgery in previous publications [10.8 days (Ferreira and others 2002) and 12.9 days (Davis and Brown 2002)] was similar to the mean and median times to ambulation in the non-laser control group of this study (12.9 and 14 days, respectively). This relationship indicates that the population of dogs in the present study is similar to the populations previously reported in the literature.

Time to ambulation was chosen as it is an objective measurement that can be evaluated by the MFS. For this study, it was considered a reliable manifestation of the efficacy of the treatment as it provides a measurable outcome for assessment. Ambulation is also an important part of the healing process for the dog as well as the owner. Ambulatory dogs have a lower incidence of urinary tract infections, pneumonia, disuse muscle atrophy and decubital ulcers. At this stage of neurological recovery, they are also able to urinate on their own. This signifies an important step in the owner's ability to care for the dog at home as they do not have to concern themselves with advanced care directives such as bladder expression.

It is recognised that there are several weaknesses in this study that could contribute to a type I statistical error (incorrectly rejecting a true null hypothesis). In retrospect, some of these could have been controlled for. Among them are the low number of dogs in each group, lack of blinding of the evaluating clinician and true randomisation of the groups, and failure to sham-treat the control dogs. Some that would be more difficult to control are medications or treatments that are given before referral. All of the dogs in this study received polyethylene glycol 30% (PEG) treatment (2.2 mL/kg iv postoperatively and again the next morning), as this is standard therapy in the authors' hospital. There were dogs in both treatment and control groups that received glucocorticoids, mostly before the patients arrived at the hospital. This is not seen as a confounding variable as there are studies indicating that glucocorticoids do not affect the outcome in dogs with IVDD (Boag and others 2001, Levine and others 2008).

While the exact reason why LLLT may have worked in this scenario is not known, it would follow that addressing the secondary injury to the spinal cord via mechanisms previously discussed was the difference in the two groups. This finding may indicate that more studies are warranted to find the actual beneficial mechanism. On the basis of the data from this study, LLLT provides a treatment option that reduces the time to ambulation in dogs that undergo decompressive surgery for thoracolumbar intervertebral disk herniation.

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Conflict of interest

None of the authors of this article has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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