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The effect of electromagnetic fields on postoperative pain and locomotor recovery in dogs with acute, severe thoracolumbar intervertebral disc extrusion: a randomized placebo-controlled, prospective clinical trial.

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Running title: PEMF in canine spinal cord injury

Table of contents title: Targeted pulsed electromagnetic fields in canine spinal cord injury and wound healing.

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Abstract

Spinal cord injury (SCI) due to acute intervertebral disc extrusions (IVDE) is common in dogs and is treated by surgical decompression. Dogs with sensorimotor complete injuries have an incomplete recovery. Pulsed electromagnetic fields (PEMF) reduce postoperative pain through anti-inflammatory effects and there is growing evidence for neuroprotective effects. This randomized, controlled clinical trial evaluated the effect of PEMF on post-operative pain and neurologic recovery in dogs with surgically treated sensorimotor complete SCI due to acute IVDE.

Sixteen dogs with surgically treated complete thoracolumbar SCI were randomized to receive PEMF (15 minutes every 2 hours for 2 weeks then twice daily for 4 weeks) or placebo starting immediately after diagnosis. The primary outcome was gait score at 2 weeks. Secondary measures of gait, pain perception and proprioceptive function were evaluated at 2 and 6 weeks. Plasma GFAP concentration was measured as a SCI biomarker. Post-operative pain was quantified by measuring mechanical sensory thresholds (MST) at control and surgical sites.

There was no significant difference in demographics or GFAP concentration between the 2 groups at trial entry. There was no difference in primary outcome or in secondary measures of gait, but proprioceptive placing was significantly better at 6 weeks and GFAP concentrations were significantly lower at 2 weeks in the PEMF group. MSTs were significantly higher in the PEMF treated group.

We conclude that PEMF reduced incision-associated pain in dogs following surgery for IVDE and may reduce extent of spinal cord injury and enhance proprioceptive placing. Larger clinical trials are warranted.

Keywords: spinal cord injury; biomarker; GFAP; hemilaminectomy; pain

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Introduction

Certain breeds of dog are predisposed to early degeneration of their intervertebral discs, causing calcification of the nucleus pulposus. This in turn may result in acute extrusion of the degenerate nuclear material into the overlying vertebral canal, causing contusion and compression of the spinal cord[1]. The majority of dogs with acute, severe thoracolumbar intervertebral disc extrusions (TL-IVDE) are managed by surgical decompression, and subsequent rehabilitation[2,3]. After surgery, approximately 60% of dogs suffering the most severe grade of injury, sensorimotor complete injury, equivalent to Abbreviated Injury Scale (AIS) A, will make a successful, if incomplete recovery while the rest remain paralyzed[4-6]. The acute nature of the injury, along with the location at the thoracolumbar junction, well above the level of the lumbosacral intumescence and cauda equina in the dog, make this naturally occurring spinal cord injury (SCI) a useful model of human traumatic SCI[7]. The medical and surgical treatment of and recovery from acute TL-IVDE have remained essentially static for the last few decades and there has been a renewal in efforts to improve outcome, particularly given the translational potential of discovery in this naturally occurring model of SCI.

Recent randomized, controlled clinical trials of neuroprotective strategies have failed to show benefit of polyethylene glycol, methylprednisolone sodium succinate or N-acetylcysteine[8,9]. A trial of GM6001, a matrix metalloproteinase inhibitor showed a beneficial effect on bladder compliance and highlighted a possible response to DMSO in the most severely injured dogs that needs to be confirmed in a larger clinical trial[10,11]. Post-operative management and subacute therapies have not received much attention, and there are limited data on post-operative incisional and neuropathic pain in these dogs. Low level laser therapy and acupuncture have been assessed clinically, but most trials have not been performed in a blinded or randomized fashion[12-15]. Targeted pulsed electromagnetic fields (PEMF) have been investigated in a wide range of clinical settings in people[16]. Placebo-controlled, double blind, randomized clinical trials of targeted PEMF after breast reconstruction surgery reported a significant reduction of patient reported pain, use of narcotics and inflammatory cytokines (IL1-□)[17-19]. There is also evidence of control of osteoarthritis pain using these devices, although the clinical relevance of the benefit

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conferred is unclear[20]. More recent experimental work has investigated the effect of PEMF on traumatic brain injury (TBI)[21] and SCI[22] and other effects of PEMF on neuronal and glial health are emerging. Together these data suggest low frequency PEMF might improve neurologic outcomes following traumatic injury to the brain and spinal cord. A device has been developed to deliver PEMF to dogs by Assisi® based on human devices tested in clinical trials. The aim of this randomized, blinded, placebo-controlled trial was to investigate the effect of targeted PEMF using this veterinary device on the neurologic outcome and post-operative pain in dogs with acute, severe TL-IVDE undergoing decompressive surgery.

Material and Methods

Study Design and Animals

This study was designed according to the CONSORT guidelines[23] and was conducted in accordance with guidelines and approval of the North Carolina State University Institutional Animal Care and Use Committee (protocol number: 15-177-O). Given the lack of data on the magnitude of treatment effect of PEMF in this model, the study was designed as a pilot with a view to determining whether a larger scale study should be undertaken. A power calculation was performed with an online calculator[a] using prospectively gathered open field gait scores (OFS) from dogs with complete sensorimotor loss due to acute TL-IVDE[24]. Seven dogs were needed per group to detect a 3-point improvement in OFS (representing a clinically relevant functional improvement) 2 weeks after injury with a power of 90%. Group size was increased to 8 dogs per group to allow for case attrition. This group size also allowed detection of a 3-point difference in OFS between groups 6 weeks after injury with a power of 80%.

Inclusion criteria were: weight ≤ 20 kg; 2 to 12 years of age; acute onset of paraplegia with no pain perception in either pelvic limb or the tail; 2 days or less duration of non-ambulatory status (from the last time owner saw the dog walking) prior to presentation; neuroanatomic diagnosis of third thoracic to third lumbar (T3-L3) spinal cord segments based on assessment of spinal reflexes; diagnosis of acute TL-IVDE to be treated surgically.

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Exclusion criteria included systemic comorbidity that might affect functional recovery such as diabetes mellitus; signs of progressive myelomalacia (neuroanatomic localization more extensive than site of disc extrusion)[25]; behavior that would prevent appropriate handling and data collection. Prior treatment with steroids did not exclude patients due to lack of demonstrated effect on outcome[8]. Owners of dogs that met the inclusion criteria signed an informed consent upon presentation, and final entry into the trial occurred immediately after the diagnosis was established by cross-sectional imaging.

Randomization

Dogs were randomly assigned to either PEMF therapy or placebo in a 1:1 ratio using permuted block randomization (block size = 4). The randomization sequence was determined by Assisi® and they prepared the active and placebo kits to look identical. Each was identified by a serial number and included 4 automatic coils, 1 manual coil and usage instructions. They were stored in the NC State Veterinary Hospital pharmacy and used consecutively following their number to ensure the randomization was followed. The NC State pharmacy had the key to the randomization sequence and checked the coils were appropriately active or inactive using a field detector each time a new case was recruited. Treatment group identity was masked from the clinicians and technicians working with the cases and their owners.

Case Management

Diagnosis and treatment of IVDE

All dogs were managed according to the standard of care provided at NC State Veterinary Hospital. Dogs underwent a physical and neurological examination, as well as routine blood work (complete blood cell count, serum biochemistry panel if not already performed by the referring veterinarian) and urinalysis at time of admission. Establishing a diagnosis and undergoing surgical decompression was considered an emergency, and was pursued as soon as possible after admission. The thoracolumbar spine was imaged either with computed tomography[b] (CT) performed under sedation (using intravenous (IV) dexmedetomidine[c] and hydromorphone[d]) or MRI[e] performed under general anesthesia (premedication with IV fentanyl[f], induction with IV propofol[g] and maintenance with

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inhaled isoflurane[h] and oxygen mixture) depending on availability of imaging modality. Once the presence of a disc extrusion was confirmed, the patient was transferred for surgical preparation. For those dogs that had undergone CT, general anesthesia was induced using IV propofol and maintained with an inhaled isoflurane and oxygen mixture. All dogs had a fentanyl continuous rate infusion (CRI) during surgery. The hair on the back was shaved, the surgical site prepared and a hemilaminectomy was performed over the site of the disc extrusion and extended until all extruded material had been removed. Fenestration of the intervertebral discs at T11/12 to L2/3 was performed to reduce the risk of a recurrence[2]. The surgical incision was closed routinely and the dog recovered from anesthesia. Post-operative pain was managed in all dogs using the same protocol that included a combination of opiates, non-steroidal anti-inflammatory drugs and gabapentin (Table 1). Management of the surgical incision and rehabilitation was also standard for all dogs and included cryotherapy by application of an ice-pack[k] to the incision for 10 minutes every 12 hours for the first 48 hours after surgery. After this time, the incision was hot-packed for 10 minutes every 12 hours using a hot-pack[l] heated in the microwave for 2 minutes on high setting for the remaining 5 days of hospitalization. All dogs were housed in individual cages that were lined with 4-inch foam pads to ensure no interference from the stainless-steel cage walls. They were confined to their cage for the 7 days of hospitalization. They had passive range of motion (PROM) exercises performed on both pelvic limbs, 15 repetitions every 12 hours and they were sling walked outside every 8 hours for urination and defecation. If unable to urinate, their bladder was manually expressed, aided by treatment with oral diazepam[m] (0.5mg/kg q 8 hours) and phenoxybenzamine[n] (0.5mg/kg q12 h). If the bladder was still difficult to empty on this drug combination, prazosin[o] (0.02mg/kg q12h) was substituted for phenoxybenzamine. This was continued until voluntary urination was documented.

After 1 week, dogs were discharged to their owners with a set of written instructions on their care. All owners were instructed in how to perform PROM, sling walking and bladder expression. They were asked to keep their dogs confined to a well-padded small area, to perform PROM twice daily until the 6-week end point and to sling walk them on a non-slip surface for elimination 2 – 3 times a day. After the 2-week primary end point, they

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were asked to gradually increase the time spent outside sling walking by 2 minutes every other day, and to allow them to bear more weight on their pelvic limbs as dictated by their neurologic function. They returned for re-evaluations 2, 4 and 6 weeks after their surgery. Life-threatening adverse events that occurred at any point in the 6-week course of the trial were reported to the study safety monitor who was charged with investigating possible associations between life-threatening adverse events and treatment group.

PEMF treatment

Treatment with PEMF^{p} was initiated as soon as diagnosis of IVDE was confirmed with the first treatment administered while the dog was being prepared for surgery. The center of the loop was placed over the disc extrusion site and the loop was turned on. Treatment was delivered for 15 minutes after which the loop was removed and surgery was performed. On completion of surgery, a soft jacket was placed on the dog and the loop fixed into the correct place with Velcro tags and left in place (Figure 1). The loops were programmed to go into "stand by" mode for 2 hours and then to switch to 15 minutes of treatment with 2-hour interspaces until turned off. This treatment cycle was based on human clinical protocols aimed at the acute injury and repair phase[26] During the 15-minute treatments, two indicator lights blinked every second, and between treatments, one indicator light blinked approximately every 6 seconds, indicating the loop was in stand-by mode. Both active and inactive (placebo) loops, appeared identical. The automated loops were replaced every 4 days until the 2-week primary study endpoint to ensure that there was no battery failure. Owners were given the replacement loop they needed with instructions of when to change it out. At the 2-week time point, owners were given a manual loop and instructed to place and turn on the loop twice a day for the 15-minutes programmed treatment, during which time they were to perform the PROM exercises. The loop was then turned off automatically and removed. This manual treatment occurred for the next 4 weeks until the 6-week secondary end point, based on results of extended treatment to relieve pain in people[27]. Each owner was given a logbook and a questionnaire to record information on a daily basis.

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Data collection

Data collected from each dog included signalment (body weight, body condition score, breed, sex, and age), history including owner reported details of duration of onset (defined as time from onset of pain or paresis to paralysis and categorized as < 1 day, 1 - 3 days, 4 - 7 days, 8 – 14 days) and duration of paralysis (defined as time of onset of paralysis to presentation and categorized as < 12 h, 12 – 24 h, 24-48 h)), preoperative neurologic status, location of disc extrusion, site of hemilaminectomy, details of drugs used for pain management, and adverse events (defined as any adverse medical occurrence that developed during the course of the study).

Physical and neurologic examinations were performed daily on all dogs by the same clinician (NZ, blinded to treatment group) during the 1-week hospitalization and at the 2, 4 and 6 week revaluations. Evaluation included categorization of gait as ambulatory paraparetic (> 10 consecutive weight-bearing steps), nonambulatory paraparetic or paraplegic. Proprioceptive placing of each pelvic limb (the ability to replace the foot after the investigator knuckles it to place the dorsal surface on the ground) as well as hopping reaction, pain perception in the tail and each pelvic limb were scored as absent (0), delayed/decreased (1), or normal (2). The first day of recovery of pain perception in either limb or the tail was logged, specific to the day if in the first week, or the time period between rechecks if after discharge at the end of the first week. The patellar and withdrawal reflexes were scored as absent (0), delayed/decreased (1), normal (2), increased (3), or clonic (4). The caudal level of the cutaneous trunci reflex was recorded according to the vertebral level[28]. The number of days to independent walking (ability to take 10 consecutive weight-bearing steps) and voluntary urination was recorded. Pain assessment was performed daily while hospitalized, and on the recheck days using three different scales: Glasgow Pain Scale[29], Surgical Site Manipulation Score (Supplementary data 1), and by measurement of mechanical sensory thresholds (MSTs) using an algometer (Figure 2). Pressure algometry was performed by the same observer (NZ) in triplicate at each assessment. Measurements were first made at the level of the first to third thoracic vertebrae (control site) by applying the algometer to the paraspinal muscles and increasing manual pressure until the dog showed a behavioral response such as moving away, looking

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around or vocalizing. They were then repeated at the level of the IVDE (the hemilaminectomy site) (Figure 2). The mean MST for the control and surgical sites were calculated for each time point as well as the difference in MST between the control and surgical sites.

Dogs were videotaped walking on a non-slip surface (a carpet runner) and on a treadmill on day 1 (day after surgery), then again on days 3, 7, 14, 28 and 42 post-operatively using previously described protocols[30,31]. Dogs were only evaluated on the treadmill if able to walk independently on that surface. A video camera was placed to obtain images from the side and behind when the dog was walking on the carpet, and in a specific position to capture all four limbs when using the treadmill. On the treadmill, they were walked without support at a speed adjusted to achieve the pace that appeared most comfortable to them and at least 3 minutes of continuous walking was recorded. Videos were identified by randomized numbers and scored by a blinded observer (JF) to generate a modified OFS (Supplementary data 1) for walking on the non-slip surface[8,32], as well as a regularity index (RI) to quantify thoracic limb, pelvic limb coordination while walking on the treadmill[31,33].

Other measurements obtained included bladder volume before and after urination using ultrasound[34]. This was recorded daily in the first week, then again on days 14, 28 and 42, or until normal voiding (>80% voiding) was achieved. In addition, blood samples were drawn into EDTA on the day of presentation, as well as days 1, 2 and 14 and banked in a -80^{o}C freezer for measurement of plasma concentrations of glial fibrillary acidic protein (GFAP) to be used as a biomarker of injury severity[35]. At the end of the study, this structural biomarker was measured using an ELISA kit[q] as per the manufacturer's guidelines. Measurements were made in duplicate and mean values were calculated.

Statistical Analysis

Summary data were prepared on the demographics, clinical history, site of IVDE and hemilaminectomy as well as plasma GFAP concentrations at time of presentation and were compared between groups. Wilcoxon 2-sample tests were used to compare age, body weight, body condition score, and GFAP. Fisher's Exact Tests were used to compare breed,

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duration of signs, and time of paralysis prior to surgery.

The primary outcome measure was gait quantification by OFS at 2 weeks after injury. The secondary outcome measures included GFAP concentration at day 14, RI (as a measure of quadrupedal coordination) at day 14 and 42, as well as time to independent walking in days, proprioceptive placing score, hopping score, pain perception presence (Y or N), voluntary urination (Y or N), independent walking (Y or N) on days 14 and 42, OFS on day 42 and the measures of post-operative pain (Glasgow pain score, surgical manipulation score, and MST) on days 3, 7, 14 and 42. OFS between groups was compared using ANOVA as well as ANCOVA using GFAP at time zero as the covariate. RI was compared between groups using logistic regression (following conversion of RI to a binary product due to the large number of dogs scoring 0 at 2 weeks). The analysis was performed with and without GFAP concentrations at time zero as an effect in the model. For the 3 measures of post-operative pain that were scored on multiple days, repeated measures ordinal logistic regression model (Glasgow pain score and surgical manipulation score) and repeated measures ANOVA (MST) were fit, allowing for the effects of group and day. The remaining secondary outcome measures were evaluated by one-way ANOVA (OFS and RI at day 42), logistic regression (walking, pain, voluntary urination, yes or no on days 1, 14 and 42), ordinal logistic regression (proprioception and hopping scores on days 14 and 42) and nonparametric Wilcoxon test (GFAP concentration day 14).

Results

Seventeen dogs fit the inclusion criteria for clinical trial enrollment at time of presentation. One dog was not included due to MRI changes consistent with progressive myelomalacia. Sixteen dogs were enrolled and successfully completed their 1-week in hospital postoperative treatment and returned for the 14 and 28 day rechecks. Fifteen of 16 returned for the 42nd day recheck, 1 dog in the PEMF group was lost to follow up. This dog was paraplegic with no pain perception in either pelvic limb or tail at the day 28 recheck and the data was handled conservatively using the last observation carried forward (LOCF) convention (Figure 3).

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Group characteristics

The majority of dogs in the study were Dachshunds (9/16: 56%) dogs, 4 in the active treatment group and 5 in the placebo group. There were also 5 mixed breed dogs, 1 Beagle and 1 French bulldog. Their median age was 4 years, ranging from 2 to 11 years. Breed, age, sex, body weight, body condition score of the participating dogs did not differ significantly among treatment groups (Table 2). All dogs had sensorimotor complete injuries that localized to the T3 – L3 spinal cord segments (as required for inclusion), and there was no significant difference between groups in plasma concentrations of GFAP at the time of presentation (Table 2). The duration of clinical signs prior to presentation and duration of inability to walk did not differ significantly between treatment groups (Table 2). L2-3 was the most common site of IVDE (n = 4), followed by L1-2 (n = 3); T11-12, T13-L1 and L3-4 (n = 2 each), and T12-L1, T12-13 and L4-5 (n = 1 each).

In-patient care

All dogs were managed with the standard post-operative medication protocol with no dogs requiring additional opiates for pain control. Six dogs in the PEMF group received carprofen, and it was discontinued in 1 of these dogs on day 2 due to development of diarrhea. Of the remaining 2 dogs in PEMF group, 1 received a tapering course of prednisone and 1 did not receive an anti-inflammatory due to intermittent regurgitation from the time of admission. In the placebo group, 5 dogs received carprofen, 1 received a tapering course of prednisone and 2 did not receive any anti-inflammatory medications due to vomiting (n=1) and diarrhea (n=1). All 8 dogs in the PEMF group were administered diazepam for the 7 days of hospitalization, in combination with phenoxybenzamine for 6/8 to facilitate bladder expression. Diazepam was administered to 6/8 dogs in the placebo group, in combination with phenoxybenzamine (n=4) and prazosin (n=2). Two dogs had easily expressible bladders without medications. Two dogs in each group received trazadone^{r} (12.5 - 100mg/dog PO q8h or as needed) for anxiety while hospitalized. Eight dogs, 4 in each group, had adverse events in the first week. Five dogs developed gastrointestinal signs (diarrhea (n=3, 2 PEMF and 1 placebo group), vomiting (n=1, placebo group) and regurgitation (n=1, PEMF group). One dog (PEMF group) developed hematuria

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with a negative urine culture, 1 dog (placebo group) developed a urinary tract infection, 1 dog (placebo group) developed a superficial pyoderma, and 1 dog (placebo group) dislodged and ate its treatment coil on day 3 (a new coil was placed within 3 hours). The dog was monitored, but the pieces of coil remained in the stomach (detected on abdominal radiographs 10 days after consumption) and so on day 17 the dog was anesthetized and the coil pieces were retrieved via endoscopy. The dog never showed any clinical signs related to the coil ingestion. Two more dogs damaged their coils by chewing them in the second week once discharged to their owners, 1 dog chewed 1 coil, and another dog chewed 2 coils. Both dogs were in the placebo group and neither actually consumed their coils. Two of the 3 were replaced promptly but one dog (Dog 11) missed treatments for 3 days (days 15 – 17). All adverse events responded to treatment (Supplementary data 1).

Clinical recovery

At time of presentation, all dogs were paraplegic with no pain perception, however on the day after surgery, 4/8 dogs in the PEMF group regained pain perception (while remaining paraplegic) compared with 0/8 dogs in the placebo group, by day 14, 6/8 dogs in the PEMF and 5/8 in the placebo group had recovered pain perception and by day 42, 6 dogs in each group were able to feel their pelvic feet and tail (Table 3). Independent walking was first observed in 1/8 dogs in the PEMF group on day 7, 2/8 dogs in the PEMF group and 3/8 dogs in the placebo group were walking by 14 days and this increased to 4/8 in each group by day 42. Five/8 dogs were urinating voluntarily by day 14 in the PEMF group compared with 3/8 in the control group and this did not change by day 42 (Table 3).

Biomarker changes

Median plasma GFAP concentrations increased from day 0 to day 1 in the PEMF group and then decreased by day 14, while the median plasma GFAP concentration increased through day 2 in the placebo group before decreasing again by day 14 (Figure 4), with values in the placebo group tending to be higher than the PEMF group throughout. This was most obvious by day 14 when GFAP could not be detected in the plasma of any of the dogs in the PEMF group.

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Primary outcome

On day 14, the median OFS in the PEMF group was 2.5 (IQR: 1.25-7.25) and in the placebo group was 2.5 (IQR: 1-6). There was no significant difference between the 2 groups when comparing OFS alone and using GFAP concentration at time 0 as a covariate (P = 0.73 and 0.84 respectively).

Secondary outcome measures

The median RI on day 14 was 0 in both groups and because RI was 0 in 6 dogs in each group, RI scores were assigned a binary category with scores <10 assigned to 0 and >10 assigned to 1. Logistic regression was performed with treatment group and GFAP concentration as effects in the model. The overall model was not significant (p = 0.57) and neither group nor GFAP concentration at time 0 were significant (p = 0.48 and p = 0.67, respectively). Group did not become statistically significant upon removal of GFAP from the model (p = 0.53). Time to independent walking was analyzed with a proportional hazards regression with missing observations (i.e. dogs that had not recovered independent walking) censored at day 42. There was no significant difference between groups (p=0.96). The remaining secondary outcome measures related to functional recovery are listed in Table 3. There was no significant difference between groups in the recovery of pain perception, hopping ability, and motor or bladder function by day 42. However, when considering proprioceptive placing, by day 42, none of the dogs in the placebo group had any proprioceptive placing (score of 0) while 4 dogs in the PEMF group had positive scores (table 4). When compared using logistic regression, the difference was significant (p=0.005). Plasma GFAP concentrations were significantly higher in the placebo group 14 days after injury (p = 0.019).

Post-operative pain

Post-operative pain scores were compared between groups as they evolved over days 3, 7, 14 and 42. For the Glasgow pain scale, the vast majority of observations were 0, with only 8 of a total of 64 observations scoring more than 0 (ranging from 1 – 5 of a possible total of 24) in 6 of the 16 dogs. Fitting a repeated measures ordinal logistic regression model allowing for effect of day and group, there was no significant difference between the two

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groups (p = 0.44) or between days (p = 0.31). Likewise, the vast majority of the surgical site manipulation scores were zero with only 5 dogs scoring 1 in the first week and 1 dog scoring 2 on day 14. Fitting a repeated measures ordinal logistic regression model allowing for effect of day and group, there was no significant difference between groups (p = 0.55). However, there was a significant decrease in surgical site manipulation scores over time (p = 0.022). Mechanical thresholds at the control and surgical site are presented in Table 5. Fitting a repeated-measures ANOVA to these data, allowing for the effects of group and day (and a subject effect to take into account the within-subject correlation), neither group nor day were statistically significant at the control site (p=0.36 and p=0.08 respectively). When the MSTs at the surgical site were evaluated, there was a significant difference between groups (p=0.03), but not between days (0.06). The data was also analyzed by subtracting the MST at the surgical site from the control site in an attempt to control for individual variation in responsiveness, and again, there was a significant difference between groups (p=0.02) but not days (0.32).

Discussion

This randomized, placebo-controlled, blinded clinical trial recruited dogs with sensorimotor complete TL-SCI, causing paraplegia with loss of pain perception below the level of injury, and evaluated the effect of targeted PEMF on neurologic recovery and post-operative pain. There was no significant difference in primary outcome (gait score) between the groups at 2 weeks, or at the secondary time point, 6 weeks. Evaluation of other secondary outcomes revealed a significant difference in recovery of proprioceptive placing at 6 weeks, with half of the PEMF treated dogs recovering some proprioceptive placing compared with none of the placebo group. Evaluation of GFAP as a biomarker of injury suggested that, while clinically indistinguishable at entry into the trial, the placebo-treated group included dogs with more severe injury. Using pressure algometry to measure mechanical sensory thresholds over a 6-week period, PEMF treated dogs had significantly higher thresholds than dogs treated with placebo suggesting a significant effect on post-operative pain.

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The mechanism of action of PEMF is likely to be complex. There is *in* vitro and experimental evidence that PEMF modulates the calcium-calmodulin (CaM) nitric oxide (NO) cascade[16]. The small electrical field produced within the targeted tissues increases calcium binding by calmodulin, which binds to constitutive nitric oxide synthase (cNOS), producing NO with an immediate vasodilatory effect. Nitric oxide catalyzes guanylyl synthase, producing cyclic guanosine monophosphate (cGMP).[36] Activation of the CaM/NO/cGMP pathway downregulates IL1, limiting inflammation and reducing inducible NOS (iNOS) activity[37] as well as increasing production of FGF2 and VEGF. Indeed, several studies have demonstrated PEMF reduce iNOS and proinflammatory cytokines[38,39] and enhance angiogenesis through increased FGF2[40]. Experimentally, the effect on wound repair has been dramatic with a 60% improvement in cutaneous wound repair in rats by 3 weeks[41], and clinically this has translated to reduced IL1 levels, patient scored post-operative pain and narcotic use after breast reconstruction surgery [18,19,26] although not all trials showed the same beneficial effect[42]. As such, a reduction in post-operative pain and improved healing of the surgical incision might be anticipated. Evidence that PEMF might be neuroprotective after CNS injury is growing. Early work in a rabbit model of cerebral ischemia demonstrated a reduction in ischemic neuronal damage with PEMF[43].This observation is supported by more recent work in which PEMF delivered after traumatic brain injury in rats (via contusive and penetrating injuries) reduced CSF IL1 concentrations ten fold[21] and in a study of ischemic stroke in mice, PEMF reduced inflammatory mediators and increased activation of the BDNF/TrkB/Akt signaling pathway with a beneficial effect on outcome[44]. Application of PEMF to the normal rat brain increases cerebral microvascular perfusion and oxygenation[45]. Thus, it may be possible to limit the consequences of spinal cord injury through anti-inflammatory effects and improved perfusion. This, together with effects on neurite outgrowth[46] led us to hypothesize that PEMF may have a beneficial effect on neurological outcome of dogs with acute spinal cord injury.

This clinical trial was designed to examine the effect of PEMF on recovery of pelvic limb function, in dogs with acute, severe spinal cord injury due to acute TL-IVDE. The most severe grade of injury was chosen because recovery from this grade of injury is

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incomplete[24,47]. An early time point in the course of their recovery (2 weeks) was chosen as the primary study end point because neurologic recovery at that time, while still underway, is relatively uniform and a low number of animals would be needed to detect an effect. This strategy would allow rapid decisions on whether a larger, longer-term study should be undertaken. The primary outcome for this trial was a robust measure of walking ability, and the study was powered to detect a 3-point change because a change of this order lifts the dog from one broad category of function to the next. We were unable to detect an effect on this outcome at 2 or 6 weeks. We evaluated several different aspects of neurologic recovery as a secondary analysis, including categorical outcomes such as recovery of independent ambulation, pain perception and bladder function. Overall, 50% of dogs in each group recovered independent ambulation, comparable to historical reports of this disease[4,6]. Other more specific evaluations included ordinal scales of proprioceptive placing and hopping, as well as continuous measures of quadrupedal coordination (RI). Of these, there was a highly significant difference in proprioceptive placing, with 4 of the PEMF treated group and none of the control group showing partial or complete recovery of this function by 42 days. Proprioceptive placing is the first function lost with spinal cord compression and the last to reappear[48]. This observation, while it may reflect slightly different initial injury severity, suggests there may be a small positive effect on recovery of neurologic function and a larger clinical trial may be indicated. While the results of secondary outcomes should be considered exploratory, this finding shows that the use of multiple different assessments allows examination of different functional effects and may uncover an important treatment effect.

A unique facet of this trial was the use of plasma GFAP concentration as a biomarker of spinal cord injury severity. The dichotomization of recovery of dogs with sensorimotor complete signs into successful recovery versus permanent paralysis underscores the variability of severity of spinal cord injury in these cases that cannot be detected clinically at time of presentation. Plasma concentrations of S100□, phosphorylated neurofilament heavy chain (pNFH) and GFAP have been in investigated in dogs with SCI[35,49] and of these, plasma GFAP concentration was the most discriminating of injury severity among sensorimotor complete dogs[35]. The lack of availability of a bedside test prevented

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measurement of plasma GFAP concentration at time of trial entry for stratification prior to randomization but GFAP concentrations were incorporated as a covariate, lending strength to the analysis. While not significantly different at entry into the trial, one dog in the placebo group was an outlier with a plasma GFAP concentration of 13ng/mL and likely had a much more significant injury. The divergence between the groups increased in the first 48 hours after injury and at 14 days, GFAP concentrations were significantly higher in the placebo group. Indeed, GFAP was undetectable in the PEMF group while 5/8 of the placebo group had measureable levels. This divergence over 48 hours could reflect a more severe initial injury or a therapeutic effect.

The standard surgical treatment of TL IVDE is to perform a hemilaminectomy to decompress the spinal cord and fenestration of at risk intervertebral discs as a prophylactic measure[2]. The resulting incision spans approximately 8 vertebrae and involves extensive dissection of muscle. The post-operative pain management protocol used in this study was standard at our institution, and when dogs were evaluated using both the Glasgow Pain Scale and the SSMS their pain appeared to be well controlled. However, pressure algometry provided a more noxious stimulus and was more discriminating, clearly demonstrating a difference between the 2 treatment groups that was magnified over the course of 6 weeks with PEMF treated dogs having progressively higher thresholds compared with relatively static thresholds in the placebo group. From these data we hypothesize that PEMF improved healing of the surgical sites in the long term, with a resulting decrease in incisional pain. This finding is not unexpected given the results of human clinical trials that evaluated the use of PEMF after breast reconstructive surgery[18,26,50]. However, the studies should be compared with caution, because the human clinical trials focused on pain levels in the immediate postoperative period (48 hours), while this trial followed patients out to 6 weeks and showed a magnifying effect in the later stages of recovery. Indeed, the use of our standard analgesic protocol for the first week post-operatively may have hidden an early effect of PEMF on pain. While we could speculate on whether we are measuring incisional pain associated with wound healing or neuropathic pain associated with a severe spinal cord injury, it is difficult to separate these phenomena, and given the location of our testing, we have characterized the MSTs as a

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measure of incisional pain. However, we are investigating the possibility that there is an effect on neuropathic pain in ongoing studies.

The only complication of this clinical trial was patient interference with the device delivering the PEMF. Three dogs, all in the placebo group, damaged their coils by biting them, and one dog consumed his coil, necessitating removal via gastroscopy. Dogs wore small jackets with the coils held in place by Velcro, and could not reach them directly, but one of the dogs managed to rub off the jacket and coil on day 3 of the trial during the automated 2 hourly treatment cycle. The other 2 dogs damaged the coils outside the treatment time. Clearly, dog owners and hospital staff need to be vigilant to prevent this from happening. The significance of interference occurring only in the placebo group is unclear. The major limitation of the trial was the relatively low number of animals used. The study was specifically designed to limit the number of animals and target an early time point to allow rapid decisions to be made on the therapeutic potential. While powered to detect changes in motor function, the range of pressure algometry observations between animals was extremely narrow, allowing detection of a robust treatment effect.

Conclusions

We conclude that targeted PEMF reduce incisional pain over a 6-week period following surgical treatment of TL-IVDH. The beneficial effect on proprioceptive placing and GFAP levels in the PEMF treated group should be interpreted with caution due to the small number of animals used, but suggest a larger phase 3 clinical trial is indicated.

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Footnotes

[a] http://www.statisticalsolutions.net/pssTtest_calc.php

[b] CT, Siemens Perspective 64 slice, Cary, NC

[c] Dexmedetomidine, Orion, Espoo, Finland

[d] Hydromorphone, West Ward pharmaceutics, Eatontown, NJ

[e] MRI: 1.5T Siemens Symphony, Cary, NC

[f]Fentanyl citrate injection, West Ward pharmaceutics, Eatontown, NJ and Fentanyl transdermal, Mylan, Morgantown, WV

[g] Propofol, Sagent, Schaumburg, IL

[h] Isoflurane, Piramal Healthcare, Andhra Pradesh, India

[i] Rimadyl®, Zoetis, Lincoln, NE

[j] Gabapentin, Method, Fort Worth, TX

[k] FlexiKold®, PolyGel, Whippany, NJ

[l] Elasto-Gel™, Southwest Technologies, North Kansas City, MO

[m] Diazepam, Mylan, Rockford, IL

[n] Phenoxybenzamine, compounded by NCSU VH Pharmacy, Raleigh, NC

[o] Prazosin, Mylan, Morgantown, WV

[p] Assisi Loop, Assisi Animal Health, Northvale, NJ. Th is FDA-cleared device delivers a signal with the following characteristics: 27.12 MHz carrier, burst at 2 msec, at 2 Hz and at 0.05 Gauss.

[q] ELISA kit, GFAP, BioVendor, Asheville, NC

[r] Trazodone, TEVA, North Wales, PA

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References

1. Jeffery, N.D., Levine, J.M., Olby, N.J., Stein, V.M. (2013) Intervertebral disk degeneration in dogs: consequences, diagnosis, treatment, and future directions. J Vet Intern Med. 27, 1318-1333.

2. Brisson, B.A. Intervertebral disc disease in dogs. (2010) Vet Clin North Am Small Anim Pract. 40, 829-858.

3. Moore, S.A., Early, P.J., Hettlich, B.F. (2016) Practice patterns in the management of acute intervertebral disc herniation in dogs. J Sm Anim Pract57, 409-415.

4. Olby, N., Levine, J., Harris, T., Muñana, K., Skeen, T., Sharp, N. (2003) Long-term functional outcome of dogs with severe injuries of the thoracolumbar spinal cord: 87 cases (1996-2001). *J Am Vet Med Assoc*. 222, 762-769.

5. Aikawa, T., Shibata, M., Asano, M., Hara, Y., Tagawa, M., Orima, H. (2014) A comparison of thoracolumbar intervertebral disc extrusion in French bulldogs and dachshunds and association with congenital vertebral anomalies. Vet Surg. 43, 301-307.

6. Jeffery, N.D., Barker, A.K., Hu, H.Z., Alcott, C.J., Kraus, K.H., Scanlin, E.M., Granger, N., Levine, J.M. (2016) Factors associated with recovery from paraplegia in dogs with loss of pain perception in the pelvic limbs following intervertebral disk herniation*. J Am Vet Med Assoc.* 248, 386-394.

7. Moore, S.A., Granger, N., Olby, N., Spitzbarth, I., Jeffery, N.D., Tipold, A., Nout-Lomas, Y.S., da Costa, R.C., Stein, V.M., Noble-Haeusslein, L.J., Blight, A.R., Grossman, R.G., Basso, D.M., Levine, J.M. (2017) Targeting translational successes through CANSORT-SCI: using pet dogs to identify effective treatments for spinal cord injury. J Neurotrauma. 34, 2007-2018.

8. Olby, N.J., Muguet-Chanoit, A.C., Lim, J.H., Davidian, M., Mariani, C.L., Freeman, A.C., Platt, S.R., Humphrey, J., Kent, M., Giovanella, C., Longshore, R., Early, P.J., Muñana, K.R. (2016) A Placebo-Controlled, Prospective, Randomized Clinical Trial of

Polyethylene Glycol and Methylprednisolone Sodium Succinate in Dogs with Intervertebral Disk Herniation. J Vet Intern Med. 30, 206-214.

9. Baltzer, W.I., McMichael, M.A., Hosgood, G.L., Kerwin, S.C., Levine, J.M., Steiner, J.M., Ruaux, C.G. (2008) Randomized, blinded, placebo-controlled clinical trial of N-acetylcysteine in dogs with spinal cord trauma from acute intervertebral disc disease. Spine. 33, 1397-1402.

10. Levine, J.M., Cohen, N.D., Heller, M., Fajt, V.R., Levine, G.J., Kerwin, S.C., Trivedi, A.A., Fandel, T.M., Werb, Z., Modestino, A., Noble-Haeusslein, L.J. (2014) Efficacy of a metalloproteinase inhibitor in spinal cord injured dogs. PLoS ONE. 9(5):e96408.

11. Levine, J.M. Cohen, N.D., Fandel, T.M., Levine, G.J., Mankin, J., Griffin, J.F., Kerwin, S.C., Boudreau, C.E., Trivedi, A., Noble-Haeusslein, L.J. (2017) Early Blockade of Matrix Metalloproteinases in Spinal-Cord–Injured Dogs Results in a Long-Term Increase in Bladder Compliance. J Neurotrauma. 34, 2656-2667.

12. Bennaim, M., Porato, M., Jarleton, A., Hamon, M., Carroll, J.D., Gommeren, K., Balligand, M. (2017) Preliminary evaluation of the effects of photobiomodulation therapy and physical rehabilitation on early postoperative recovery of dogs undergoing hemilaminectomy for treatment of thoracolumbar intervertebral disk disease. Am J Vet Res. 78, 195-206.

13. Draper, W.E., Schubert, T.A., Clemmons, R.M., Miles, S.A. (2012) Low-level laser therapy reduces time to ambulation in dogs after hemilaminectomy: a preliminary study. J Sm Anim Pract. 53, 465-469.

14. Joaquim, J.G.F., Luna, S.P.L., Brondani, J.T., Torelli, S.R., Rahal, S.C., de Paula Freitas, F. (2010) Comparison of decompressive surgery, electroacupuncture, and decompressive surgery followed by electroacupuncture for the treatment of dogs with intervertebral disk disease with long-standing severe neurologic deficits. J Am Vet Med Assoc. 236, 1225-1229.

15. Hayashi, A.M., Matera, J.M., Fonseca Pinto, A.C. (2007) Evaluation of electroacupuncture treatment for thoracolumbar intervertebral disk disease in

Journal of Neurotrauma
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dogs. J Am Vet Med Assoc. 231, 913-918.

16. Pilla, A.A. (2013) Nonthermal electromagnetic fields: From first messenger to therapeutic applications. EM Bio Med. 32, 123-136.

17. Rohde, C.H., Taylor, E.M., Alonso, A., Ascherman, J.A., Hardy, K.L., Pilla, A.A. (2015) Pulsed Electromagnetic Fields Reduce Postoperative Interleukin-1β, Pain, and Inflammation. Plast Recon Surg. 135, 808e–817e.

18. Hedén, P., Pilla, A.A. (2008) Effects of Pulsed Electromagnetic Fields on Postoperative Pain: A Double-Blind Randomized Pilot Study in Breast Augmentation Patients. Aesth Plast Surg. 32, 660-666.

19. Rawe, I.M., Lowenstein, A., Barcelo, C.R., Genecov, D.G. (2011) Control of Postoperative Pain with a Wearable Continuously Operating Pulsed Radiofrequency Energy Device: A Preliminary Study. Aesth Plast Surg. 36, 458-463.

20. Li, S., Yu, B., Zhou, D., He, C., Zhuo, Q., Hulme, J.M. (1996) Electromagnetic Fields for Treating Osteoarthritis. Vol 63. (He C, ed.). Chichester, UK: John Wiley & Sons, Ltd. pps 1333-1350.

21. Rasouli, J., Lekhraj, R., White, N.M., Flamm, E.S., Pilla, A.A., Strauch, B., Casper, D. (2012) Attenuation of interleukin-1beta by pulsed electromagnetic fields after traumatic brain injury. Neurosci Lett. 519, 4-8.

22. Crowe, M.J., Sun, Z.-P., Battocletti, J.H., Macias, M.Y., Pintar, F.A., Maiman, D.J. (2003) Exposure to pulsed magnetic fields enhances motor recovery in cats after spinal cord injury. Spine. 28, 2660-2666.

23. Schulz, K.F., Altman, D.G., Moher, D., CONSORT Group. (2010) CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. PLoS Med. 7(3):e1000251.

24. Rousse, C.A., Olby, N.J., Williams, K., Harris, T.L., Griffith, E.H, Mariani, C.L., Muñana, K.R., Early, P. (2016) Recovery of stepping and coordination in dogs following acute thoracolumbar intervertebral disc herniations. Vet J. 213(C), 59-63.

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25. Castel, A., Olby, N.J., Mariani, C.L., Muñana, K.R., Early, P.J. (2017) Clinical Characteristics of Dogs with Progressive Myelomalacia Following Acute Intervertebral Disc Extrusion. J Vet Intern Med. 2017 Sep 29. doi: 10.1111/jvim.14829.

26. Rohde, C., Chiang, A., Adipoju, O., Casper, D., Pilla, A.A. (2010) Effects of Pulsed Electromagnetic Fields on Interleukin-1β and Postoperative Pain: A Double-Blind, Placebo-Controlled, Pilot Study in Breast Reduction Patients. Plast Recon Surg. 125, 1620-1629.

27. Nelson, F.R., Zvirbulis, R., Pilla, A.A. (2012) Non-invasive electromagnetic field therapy produces rapid and substantial pain reduction in early knee osteoarthritis: a randomized double-blind pilot study. Rheumatol Int. 33, 2169-2173.

28. Muguet-Chanoit, A.C., Olby, N.J., Lim, J.H., Gallagher, R., Niman, Z., Dillard, S., Campbell, J., Early, P., Mariani, C., Munana, K.R., Freeman, C., Platt, S.R., Kent, M., Giovenella, C., Longshore, R. (2012) The cutaneous trunci muscle reflex: a predictor of recovery in dogs with acute thoracolumbar myelopathies caused by intervertebral disc extrusions. Vet Surg. 41, 200-206.

29. Reid, J., Nolan, A.M., Hughes, J., Lascelles, B., Pawson, P., Scott, E.M. (2007) Development of the short-form Glasgow Composite Measure Pain Scale (CMPS-SF) and derivation of an analgesic intervention score. Anim Welf 16(S): 97-104

30. Olby, N.J., De Risio, L., Muñana, K.R., Wosar, M., Skeen, T., Sharp, N.J.H., Keene, B.W. (2001) Development of a functional scoring system in dogs with acute spinal cord injuries. Am J Vet Res. 62, 1624-1628.

31. Olby, N.J., Lim, J.H., Babb, K., Bach, K., Domaracki, C., Williams, K., Griffith, E., Harris, T., Muguet-Chanoit, A. (2014) Gait scoring in dogs with thoracolumbar spinal cord injuries when walking on a treadmill. BMC Vet Res. 10:58.

Journal of Neurotrauma
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32. Lim, J.H., Muguet-Chanoit, A.C., Smith, D.T., Laber, E., Olby, N.J. (2014) Potassium Channel Antagonists 4-Aminopyridine and the T-Butyl Carbamate Derivative of 4-Aminopyridine Improve Hind Limb Function in Chronically Non-Ambulatory Dogs; A Blinded, Placebo-Controlled Trial. PLoS ONE.;9(12):e116139.

33. Koopmans, G.C., Deumens, R., Honig, W.M.M., Hamers, F.P.T., Steinbusch, H.W.M., Joosten, E.A.J. (2005) The assessment of locomotor function in spinal cord injured rats: the importance of objective analysis of coordination. J Neurotrauma. 22, 214-225.

34. Atalan, G., Barr, F.J., Holt, P.E. (1998) Assessment of urinary bladder volume in dogs by use of linear ultrasonographic measurements. Am J Vet Res. 59, 10-15.

35. Sato, Y., Shimamura, S., Mashita, T., Kobayashi, S., Okamura, Y., Katayama, M., Kamishina, H., Sato, R., Uzuka, Y., Yasuda, J. (2013) Serum Glial Fibrillary Acidic Protein as a Diagnostic Biomarker in Dogs with Progressive Myelomalacia. J Vet Med Sci. 75, 949-953.

36. Madhusoodanan, K.S., Murad, F. (2006) NO-cGMP Signaling and Regenerative Medicine Involving Stem Cells. Neurochem Res. 32, 681-694.

37. Palmi, M., Meini, A. (2002) Role of the nitric oxide/cyclic GMP/Ca2+ signaling pathway in the pyrogenic effect of interleukin-1beta. Mol Neurobiol. 25, 133-147.

38. Reale, M., De Lutiis, M.A., Patruno, A., Speranza, L., Felaco, M., Grilli, A., Macrì, M.A., Comani, S., Conti, P., Di Luzio, S. (2006) Modulation of MCP-1 and iNOS by 50-Hz sinusoidal electromagnetic field. Nitric Oxide. 15, 50-57.

39. Vianale, G., Reale, M., Amerio, P., Stefanachi, M., Di Luzio, S., Muraro, R. (2008) Extremely low frequency electromagnetic field enhances human keratinocyte cell growth and decreases proinflammatory chemokine production. Brit J Derm. 158, 1189-1196.

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40. Tepper, O.M., Callaghan, M.J., Chang, E.I., Galiano, R.D., Bhatt, K.A., Baharestani, S., Gan, J., Simon, B., Hopper, R.A., Levine, J.P., Gurtner, G.C. (2004) Electromagnetic fields increase in vitro and in vivo angiogenesis through endothelial release of FGF-2. FASEB J. 18, 1231-1233.

41. Strauch, B., Patel, M.K., Navarro, J.A., Berdichevsky, M., Yu, H.-L., Pilla, A.A. (2007) Pulsed Magnetic Fields Accelerate Cutaneous Wound Healing in Rats. Plast Recon Surg. 120, 425-430.

42. Sværdborg, M., Momsen, O.H., Damsgaard, T.E. (2016) Pulsed Electromagnetic Fields for Postoperative Pain Treatment after Breast Augmentation: A Double-Blind, Placebo-Controlled Study. Aesthet Surg J. 36, NP199-NP201.

43. Grant, G., Cadossi, R., Steinberg, G. (1994) Protection against focal cerebral ischemia following exposure to a pulsed electromagnetic field. Bioelectromagnetics. 15, 205-216.

44. Urnukhsaikhan, E., Mishig-Ochir, T., Kim, S.-C., Park, J.-K., Seo, Y.-K. (2016) Neuroprotective Effect of Low Frequency-Pulsed Electromagnetic Fields in Ischemic Stroke. Appl Biochem Biotechnol. 181, 1360-1371.

45. Bragin, D.E., Statom, G.L., Hagberg, S., Nemoto, E.M. (2015) Increases in microvascular perfusion and tissue oxygenation via pulsed electromagnetic fields in the healthy rat brain. J Neurosurg. 122, 1239-1247.

46. Lekhraj, R., Cynamon, D.E., DeLuca, S.E., Taub, E.S., Pilla, A.A., Casper, D. (2014) Pulsed electromagnetic fields potentiate neurite outgrowth in the dopaminergic MN9D cell line. J Neurosci Res. 92, 761-771.

47. Olby, N., Harris, T., Burr, J., Muñana, K., Sharp, N., Keene, B. (2004) Recovery of pelvic limb function in dogs following acute intervertebral disc herniations. J Neurotrauma. 21, 49-59.

48. Garosi, L. (2013) Lesion localization and differential diagnosis. In BSAVA Manual of Canine and Feline Neurology 4th edition. Eds: Platt, S.R. and Olby, N.J. Ch2, BSAVA Press, Gloucester, UK, pps 25 – 35.

49. Nishida, H., Nakayama, M., Tanaka, H., Kamishina, H., Izawa, T., Hatoya, S., Sugiura, K., Suzuki, Y., Ide, C., Inaba, T. (2014). Evaluation of serum phosphorylated neurofilament subunit NF-h as a prognostic biomarker in dogs with thoracolumbar intervertebral disc herniation. Vet Surg 43, 289-293.

50. Taylor, E.M., Hardy, K.L., Alonso, A., Pilla, A.A., Rohde, C.H. (2015) Pulsed electromagnetic fields dosing impacts postoperative pain in breast reduction patients. J Surg Res. 193, 504-510.

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Tables

Table 1. Post-operative pain management protocol. * If the dog had received corticosteroids, a tapering dose of prednisone was substituted for the nonsteroidal anti-inflammatory drug and omeprazole (1mg/kg q24 hours) was administered.

	Hydromorphone	**Fentanyl**	**Carprofen*[j]**	**Gabapentin[k]**
Dose & route	0.05 – 0.1mg/kg IV	3 – 5ug/kg Cutaneous	2.2mg.kg PO	8-10mg/kg PO
Frequency	Q8h	Continuous	Q12h	Q8h
Time after surgery	First 24 hours then PRN	Days 1 - 5	Days 1 - 7	Days 1 - 7

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Table 2: Historical and clinical findings in dogs at time of clinical trial entry . MC: Male castrated; FS: Female spayed; F: Female; IQR: interquartile range; BCS: body condition score; GFAP: glial fibrillary acidic protein.

Parameter		**PEMF Group N=8**	**Placebo Group N=8**	**P value**
Breed: Dachshund; Other		4 Dachshunds 4 Other	5 Dachshunds 3 Other	1
Age (years): median (IQR)		5.5 (3.25-7.75)	4 (3 – 4.75)	0.48
Sex		3MC, 3FS, 2F	2MC, 1M, 4FS, 1F	NA
Duration of clinical signs	<1 day	1 dog	4 dogs	0.15
	1 – 3 days	4 dogs	1 dog	
	4 – 7 days	3 dogs	1 dog	
	1 – 2 weeks	0 dogs	2 dogs	
Duration of non-ambulatory status	<12h	1 dog	4 dogs	0.46
	12-24h	4 dogs	2 dogs	
	25-48h	3 dogs	2 dogs	
Imaging modality		MRI: 4; CT: 4	MRI: 3; CT: 5	NA
Body weight: median (IQR)		9.45 (6.55-14.75)	7.85 (4.16-10.23)	0.19
BCS: median (IQR)		5.5 (5-6.75)	5.0 (5-6)	0.62
GFAP (ng/ml) Time 0: median (IQR)		0 (0 – 0.26)	0.06 (0 – 0.4)	0.47

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Table 3: Secondary outcome measures. OFS: open field score; RI: regularity index; Y: yes; N: no; IQR: interquartile range; GFAP: glial fibrillary acidic protein.

Variable	PEMF Group	Placebo Group	P value
OFS Day 42: median (IQR)	5.5 (2.25-8.5)	5.5 (3-7)	0.7
RI Day 42: median (IQR)	14.55 (0-66.9)	0 (0-17.2)	0.47
Walking Y/N Day 14: number (%)	2/8 (25%)	3/8 (37.5%)	0.59
Walking Y/N Day 42: number (%)	4/8 (50%)	4/8 (50%)	1
Pain perception Y/N Day 14: number (%)	6/8 (75%)	5/8 (62.5%)	0.59
Pain perception Y/N Day 42: number (%)	6/8 (75%)	6/8 (75%)	0.61
Voluntary urination Y/N Day 14: number (%)	5/8 (62.5%)	3/8 (37.5%)	0.32
Voluntary urination Y/N Day 42: number (%)	5/8 (62.5%)	3/8 (37.5%)	0.2
Hopping score Day 14: median (IQR)	0 (0-1.5)	0 (0-0)	0.08
Hopping score Day 42: median (IQR)	1.5 (0-3.25)		0.15
GFAP (ng/ml) Day 14: median (IQR)	0 (0-0)	0.08 (0-0.27)	0.02

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Table 4: The number of dogs with specific proprioceptive placing scores on day 42. The difference between groups was significant (P=0.005).

	Proprioceptive Placing Score at Day 42				
Group	**0**	**1**	**2**	**3**	**4**
PEMF	3 dogs	0 dogs	2 dogs	1 dogs	1 dogs
Placebo	8 dogs	0 dogs	0 dogs	0 dogs	0 dogs

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Table 5: Results of assessment of post-operative pain using pressure algometry. PEMF: pulsed electromagnetic field. Values are expressed as median and interquartile range in pounds applied.

	Day 3	**Day 7**	**Day 14**	**Day 42**	**P value**
Control site: PEMF	9.95 (8.87-11)	10 (6.85-11)	11 (8.38-11)	10.6 (9-11)	0.26
Control site: placebo	10.15 (6.78-11)	8.2 (6.3-10.75)	9.8 (7.7-11)	10.5 (9.48-11)	
Surgical site: PEMF	6.3 (5.48-9.75)	7.1 (4.78-9.58)	7.8 (7.53-10.75)	9 (7.3-11)	0.03
Surgical site: placebo	5.3 (3.78-9.65)	5.3 (3.03-7.45)	6.8 (4.5-9.23)	6.6 (5.3-8.9)	
Control-surgical site: PEMF	2.25 (0.78-4.05)	2.45 (0.63-2.93)	0.85 (0-3.2)	1.3 (0-2.3)	0.026
Control-surgical site: placebo	3 (1.35-5.28)	2.5 (1.7-3.63)	2 (1.78-3.2)	2.4 (1.48-4.68)	

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Figure legends

Figure 1: A treatment loop in place in 2 dogs, Velcro straps hold the loop centered over the epicenter of the spinal cord injury.

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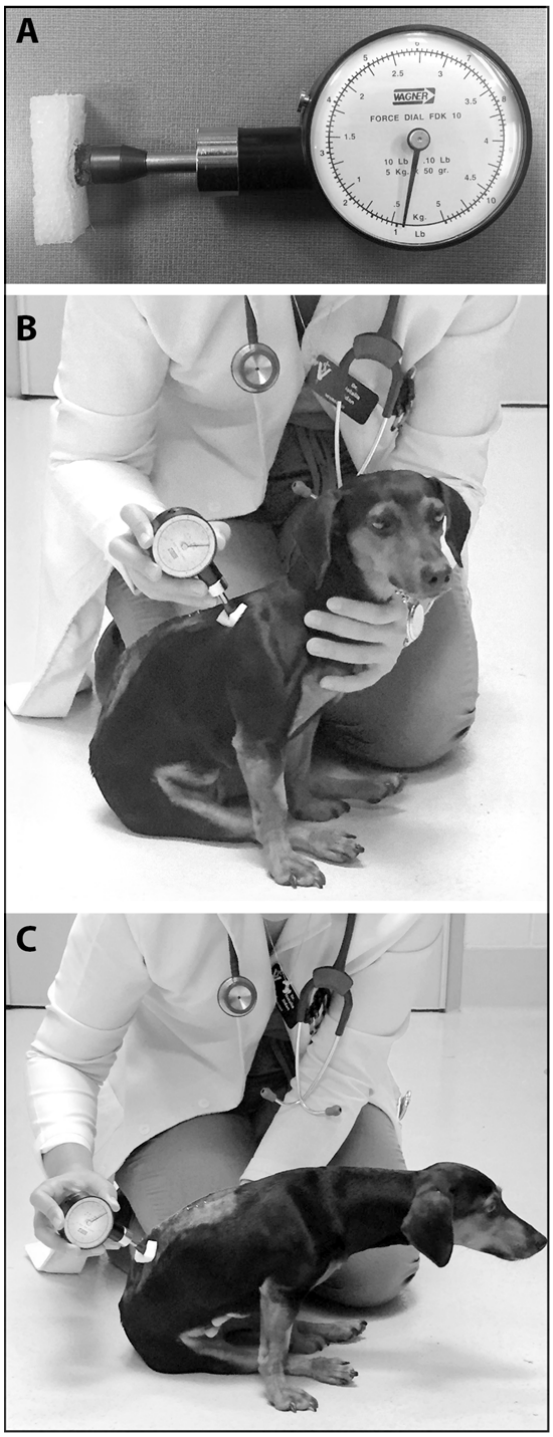

Figure 2: Mechanical sensory thresholds were measured using an algometer (a). Pressure algometry was performed at a control site between the scapulae (b) and at the level of the hemilaminectomy (c) by applying pressure to the paraspinal musculature. Measurements were performed in triplicate and the mean score calculated.

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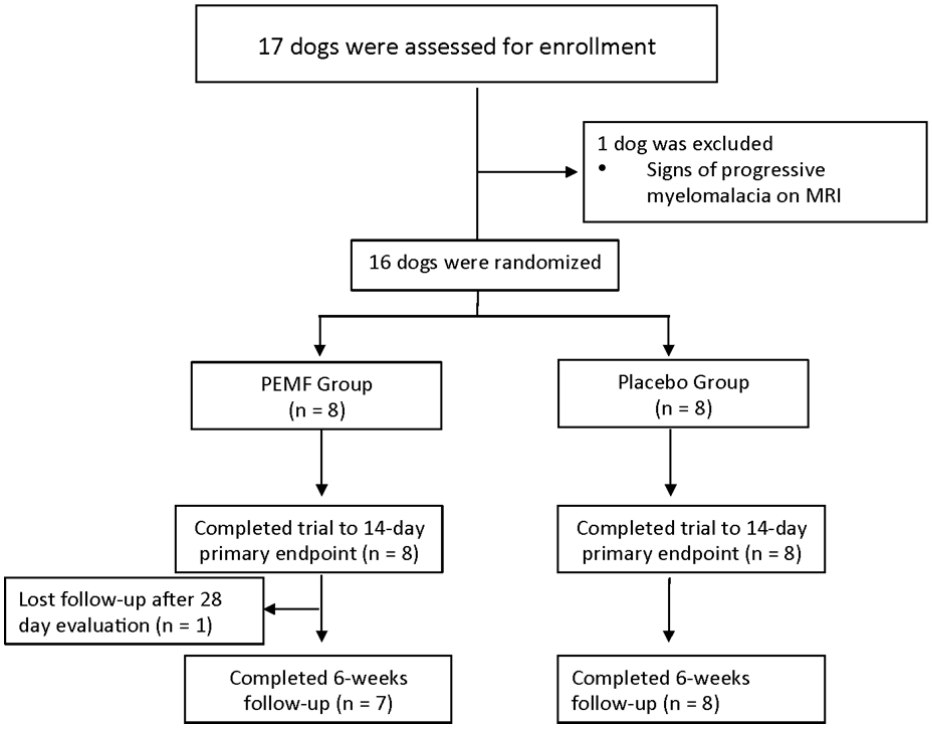

Figure 3: Consort diagram of the trial.

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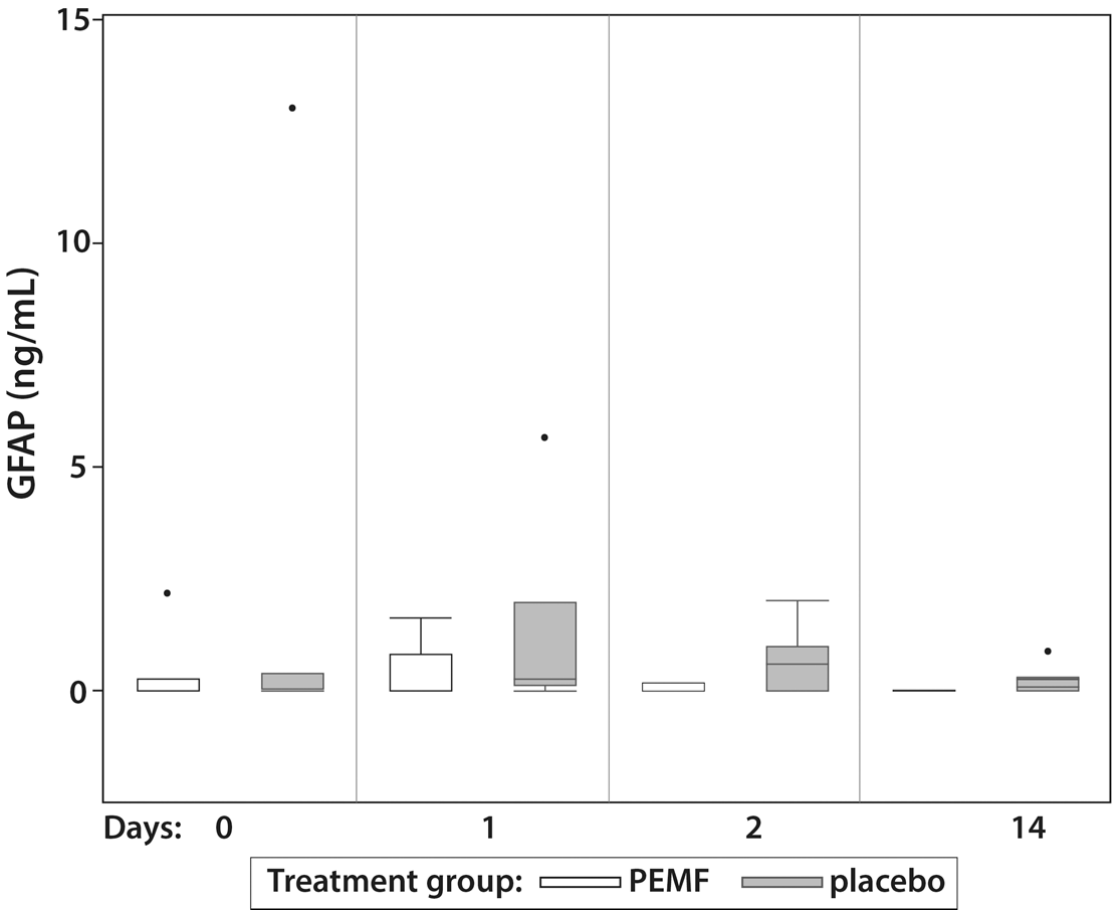

Figure 4: Box and whiskers plots of plasma GFAP concentrations days 0 (trial entry), 1, 2 and 14.

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SHORT FORM OF THE GLASGOW COMPOSITE PAIN SCALE

Dog's name _____

Hospital Number _____ **Date** / / **Time**

Surgery Yes/No (delete as appropriate)

Procedure or Condition_____

_____

In the sections below please circle the appropriate score in each list and sum these to give the total score.

A. Look at dog in Kennel

Is the dog?

(i)		(ii)	
Quiet	0	Ignoring any wound or painful area	0
Crying or whimpering	1	Looking at wound or painful area	1
Groaning	2	Licking wound or painful area	2
Screaming	3	Rubbing wound or painful area	3
		Chewing wound or painful area	4

In the case of spinal, pelvic or multiple limb fractures, or where assistance is required to aid locomotion do not carry out section **B** and proceed to **C**
Please tick if this is the case ☐ then proceed to C.

B. Put lead on dog and lead out of the kennel.

When the dog rises/walks is it?

(iii)	
Normal	0
Lame	1
Slow or reluctant	2
Stiff	3
It refuses to move	4

C. If it has a wound or painful area including abdomen, apply gentle pressure 2 inches round the site.

Does it?

(iv)	
Do nothing	0
Look round	1
Flinch	2
Growl or guard area	3
Snap	4
Cry	5

D. Overall

Is the dog? (v)		*Is the dog?* (vi)	
Happy and content or happy and bouncy	0	Comfortable	0
Quiet	1	Unsettled	1
Indifferent or non-responsive to surroundings	2	Restless	2
Nervous or anxious or fearful	3	Hunched or tense	3
Depressed or non-responsive to stimulation	4	Rigid	4

Total Score (i+ii+iii+iv+v+vi) = _____

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Surgical Site Manipulation Score:	
Score	Response upon paraspianl palpation
0	Does not notice manipulation.
1	Orients to site on manipulation, does not resist.
2	Orients to site, may lick, slight objection to manipulation
3	Withdraws from manipulation, may vocalize, excessive licking
4	Tries to escape from manipulation, or prevent manipulation, may bite or show aggression.

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Modified Open Field Score

Score	Description
0	Paraplegic
1	Minimal non-weight bearing protraction of pelvic limb (movement of 1 joint)
2	Non-weight bearing protraction of pelvic limb with > 1 joint involved < 50% of time.
3	Non-weight bearing protraction of pelvic limb with > 1 joint involved > 50% of time.
4	Weight bearing protraction of pelvic limb < 10% of time.
5	Weight bearing protraction of pelvic limb 10-50% of time.
6	Weight bearing protraction of pelvic limb > 50% of time.
7	Weight bearing protraction 100% of time with reduced strength of pelvic limb. Mistakes > 90% of time (crossing of pelvic limbs, scuffing foot on protraction, standing on dorsum of foot, falling).
8	Weight bearing protraction 100% of time with reduced strength of pelvic limb. Mistakes 50-90% of time.
9	Weight bearing protraction 100% of time with reduced strength of pelvic limb. Mistakes < 50% of time.
10	Ataxic pelvic limb gait with normal strength but mistakes > 50% of time (lack of coordination with thoracic limb, crossing of pelvic limbs, skipping steps, bunny hopping, scuffing foot on protraction, standing on dorsum of foot).
11	Ataxic pelvic limb gait with normal strength but mistakes < 50% of time.
12	Normal pelvic limb gait.

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Supplementary data 2: details of treatment of adverse events in dogs participating dogs.

Dogs with diarrhea were treated with oral metronidazole until resolution, and vomiting and regurgitation were treated with maropitant and omeprazole, again until resolution.
One dog developed hematuria and was placed on amoxicillin until urine cultures came back negative, 1 dog (placebo group) developed a urinary tract infection that was treated with marbofloxacin, 1 dog (placebo group) developed a superficial pyoderma that was treated with cephalexin.