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A randomized, blinded, prospective clinical trial of postoperative rehabilitation in dogs after surgical decompression of acute thoracolumbar intervertebral disc herniation

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Background: Experimental evidence shows benefit of rehabilitation after spinal cord injury (SCI) but there are limited objective data on the effect of rehabilitation on recovery of dogs after surgery for acute thoracolumbar intervertebral disc herniations (TL-IVDH).

Objective: Compare the effect of basic and intensive post-operative rehabilitation programs on recovery of locomotion in dogs with acute TL-IVDH in a randomized, blinded, prospective clinical trial.

Animals: Thirty non-ambulatory paraparetic or paraplegic (with pain perception) dogs after decompressive surgery for TL-IVDH.

Methods: Blinded, prospective clinical trial. Dogs were randomized (1:1) to a basic or intensive 14-day in-house rehabilitation protocol. Fourteen-day open field gait score (OFS) and coordination (regulatory index, RI) were primary outcomes. Secondary measures of gait, post-operative pain, and weight were compared at 14 and 42 days.

Results: Of 50 dogs assessed, 32 met inclusion criteria and 30 completed the protocol. There were no adverse events associated with rehabilitation. Median time to walking was 7.5 (2 – 37) days. Mean change in OFS by day 14 was 6.13 (confidence intervals: 4.88, 7.39, basic) versus 5.73 (4.94, 6.53, intensive) representing a treatment effect of −0.4 (−1.82, 1.02) which was not significant, $P = .57$. RI on day 14 was 55.13 (36.88, 73.38, basic) versus 51.65 (30.98, 72.33, intensive), a non-significant treatment effect of −3.47 (−29.81, 22.87), $P = .79$. There were no differences in secondary outcomes between groups.

Conclusions: Early postoperative rehabilitation after surgery for TL-IVDH is safe but doesn't improve rate or level of recovery in dogs with incomplete SCI.

KEYWORDS
ataxia, gait training, locomotion, plasticity, spinal cord injury

1 | INTRODUCTION

Acute thoracolumbar intervertebral disc herniation (TL-IVDH) is a common cause of spinal cord injury (SCI) in dogs and the standard treatment for non-ambulatory dogs is surgical decompression.[1,2] With surgical management, over 90% of dogs that suffer an incomplete injury (nonambulatory paraparetic or paraplegic with pain perception) recover independent ambulation and continence.[3,4] Dogs with functionally complete injuries (paraplegic without pain perception) are less certain of a good outcome with nearly 60% of dogs ultimately recovering.[5–7] However, while recovery of ambulation is a major accomplishment, many of these dogs are left with deficits in strength and quadrupedal coordination.[4]

Much has been published on the surgical techniques and recovery rates of dogs with TL-IVDH, but the effect of postoperative management on recovery has received less attention. Standard post-operative care includes pain management, bladder evacuation, skin care, and cage rest.[1,8] Low level laser treatment has become popular and a controlled clinical trial evaluating this modality reported an increased speed of recovery of ambulation.[9] Recommendations on postoperative rehabilitation range from advising against it, to implementing multimodal rehabilitation programs.[1] Objective evidence for the role of rehabilitation in dogs after surgical treatment of TL-IVDH is sparse, and evidence available is somewhat contradictory with retrospective studies suggesting benefit[10–13] and a recent, randomized, controlled (RCT) clinical trial failing to demonstrate an effect.[14]

Experimental studies in rodents and cats have shown that gait training soon after SCI enhances recovery of locomotion, but have also shown disadvantages such as reduced ability to walk without a treadmill and highlight the importance of task specific training.[15] Numerous RCT in people have concluded that locomotor training in patients with incomplete injuries enhances walking ability with an emphasis on the benefit of duration of training.[16–18] Overall, an intensive multimodal inpatient rehabilitation program increases the likelihood of patients returning home.[17,19]

Dogs with complete SCI might benefit the most from rehabilitation.[13] However, only 25% of dogs with acute TL-IVDH suffer complete injuries and recovery is extremely variable, necessitating large group sizes in clinical trials.[20–23] In contrast, recovery of nonambulatory dogs with incomplete injuries is more uniform and they account for 70% of all cases, making a timely, high powered study viable. While these less severely injured dogs recover independent ambulation, their quadrupedal coordination is not normal and recovery rate could be improved.[4] We hypothesized that, in this group of dogs, early implementation of a multimodal rehabilitation protocol after decompressive surgery would be safe and would increase the speed of recovery and improve quadrupedal coordination when compared with basic postoperative care.

This RCT evaluated non-ambulatory paraparetic or paraplegic (with pain perception) dogs that underwent decompressive surgery and fenestration for TL-IVDH. A postoperative management program typical of one instituted at home ("basic program") was compared with a professionally managed staged rehabilitation program ("intensive program") over a 14-day period starting at 24-hours after surgery. The study aims were to determine the safety and feasibility of different exercises and to compare the effect of these programs on rate and level of recovery of ambulation 14 and 42 days after surgery.

2 | MATERIAL AND METHODS

2.1 | Study design and animals

This randomized, blinded, prospective clinical trial in dogs with surgically decompressed acute TL-IVDH was conducted and reported according to the CONSORT guidelines[24] with the approval of the North Carolina State University Institutional Animal Care and Use Committee (protocol number: 15–173-O). The study population was restricted to dogs presenting with non-ambulatory paraparesis or paraplegia with pain perception. The potential treatment effect was estimated from a pilot study in 12 dogs with surgically treated acute TL-IVDH that compared a 14-day rehabilitation protocol with cage restriction. Three dogs were paraplegic with no pain perception, and the remaining dogs were paraplegic or nonambulatory paraparetic. Mean time to appearance of pelvic limb motor function was reduced from 8.4 days (restricted group) to 4.5 days (treated group), supporting designing this clinical trial to detect a 20% improvement in outcome.[25] In a separate study, we prospectively evaluated the postoperative recovery of dogs with TL-IVDH using a validated open field score (OFS, an ordinal gait score ranging from 0 to 12, Supporting Information Data 1) and treadmill-based quadrupedal coordination (regulatory index: RI, ranging from 0% to 100%) score.[4] Together, these outcome measures quantify gait walking on a non-slip surface (OFS) and quadrupedal coordination walking on a treadmill (RI). This study population included 44 dogs that were nonambulatory paraparetic (n = 23) or paraplegic with pain perception (n = 21) at presentation and all received rehabilitation comparable to the basic arm of this trial. Using the data from the pilot trial of rehabilitation to support our estimate of benefit, and our baseline data on walking and coordination at 14 days, we performed a power analysis (https://www.statisticalsolutions.net/pssZtest_calc.php) to determine that a group size of 15 dogs would confer 80% power to detect a 2-point increase in OFS and 83% power to detect an increase in coordination (RI) from 60% to 80% at the 14-day time point.

Inclusion criteria for the trial were as follows: weight ≤ 20 kg; 2 to 12 years of age; neurologic status of paraplegia with pain perception or nonambulatory paraparesis at presentation and at time of entry into the trial (to eliminate the dogs that show a dramatic improvement or a deterioration immediately after surgery); a maximum of 3 days duration of non-ambulatory status before admission (from the last time owner saw the dog walking); diagnosis of acute TL-IVDH by magnetic resonance imaging (MRI) or computed tomography (CT) and surgical decompression of the spinal cord. Exclusion criteria included comorbidity that might affect recovery of neurological function, multidrug resistant bacteriuria (as defined by hospital infectious disease control standards), and intolerance of daily handling. Prior treatment with

TABLE 1 Drugs used postoperatively for pain and anxiety control and to facilitate bladder expression

Drug	Dose/route	Frequency	Duration	Reason
Hydromorphone[a]	0.05-0.1 mg/kg IV	Q8h	24 hours	Pain control
Carprofen[b,c]	2.2 mg/kg PO	Q12h	7 days	Pain control
Meloxicam[c,d]	0.1 mg/kg PO	Q24h	7 days	Pain control
Fentanyl[e]	3–5 μg/kg/h Transdermal	Continuous release	5 days	Pain control
Gabapentin[f]	10 mg/kg PO	Q8h	10 days	Pain control
Phenoxybenzamine[g,h]	0.5 mg/kg PO	Q12h	As needed	Bladder expression
Prazosin[g,i]	1–2 mg/dog PO	Q8–12h	As needed	Bladder expression
Diazepam[j]	0.5 mg/kg PO	Q8h 20 min before bladder expression	As needed	Bladder expression
Trazodone[k]	2–8 mg/kg PO	Q8–12h	As needed	Anxiety

Abbreviations: d, day; h, hour; IV, intravenous; min: minutes; PO, per os.

[a] Hydromorphone: West Ward Pharmaceutics, Eatontown, New Jersey

[b] Carprofen: Rimadyl, Zoetis, Lincoln, Nebraska

[c] The nonsteroidal anti-inflammatory drug (NSAID) choice was influenced by which NSAID had been administered before referral. If dogs were receiving corticosteroids before admission, omeprazole[h] (1 mg/kg, PO, q24h) and prednisone[i] in a tapering course were substituted for the NSAID.

[d] Meloxicam: Metacam, Boehringer Ingelheim, St Joseph, Missouri

[e] Fentanyl transdermal patch, Mylan, Morgantown, West Virginia

[f] Gabapentin: Method, Fort Worth, Texas

[g] Dogs were placed on phenoxybenzamine if they were unable to urinate. If their bladder could not be expressed readily after 48 hours on this drug prazosin was substituted.

[h] Phenoxybenzamine: compounded by NCSU VH Pharmacy, Raleigh, North Carolina

[i] Prazosin: Mylan, Morgantown, West Virginia

[j] Diazepam: Mylan, Rockford, Illinois

[k] Trazodone: TEVA, North Wales, Pennsylvania

corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs) did not exclude dogs.

Owners of dogs that potentially met the inclusion criteria were informed of the clinical trial at time of admission and provided with the trial details. All dogs underwent a diagnostic evaluation and decompressive surgery within 24 hours of presentation. This consisted of general anesthesia, cross sectional imaging with either CT (CT: Siemens Perspective 64 slice, Cary, NC) or MRI (MRI: 1.5T Siemens Symphony, Cary, North Carolina) to establish the site of disc herniation, followed by hemilaminectomy to remove herniated disc material and fenestration of discs between T11/12 and L2/3. A standard postoperative pain management protocol was instituted on recovery from anesthesia (Table 1) and the incision was treated with cryotherapy to ensure all potential trial participants were treated in the same way. Entry into the trial occurred the day after surgery if the dog was still nonambulatory paraparetic or paraplegic with pain perception. Because of the different times of day dogs underwent surgery, if surgery was completed between midnight and midday, day 1 of the trial was the following calendar day. If surgery was completed between midday and midnight, day 1 of the trial was 2 calendar days postoperatively. Owners signed an informed consent at this time. Dogs were randomized by the North Carolina State Pharmacy to each treatment group in a 1 : 1 ratio in blocks of 4. Randomization was stratified by status at trial entry so that equal numbers of nonambulatory paraparetic versus paraplegic dogs were randomized to each treatment group given the effect of injury severity on recovery of coordination.[4]

2.2 | Postoperative care

Dogs were housed in well-padded cages with access to water at all times. Pain was assessed daily and any need for additional analgesic drugs was noted. Inability to urinate was managed by manual bladder expression in addition to alpha-adrenergic antagonism and diazepam (Table 1). Dogs that appeared anxious (panting, crying, and whining whereas resting in the cage with low pain scores) were treated with trazodone (Table 1). All dogs were taken outside (using a sling to provide support if necessary) and had their bladder palpated and expressed every 8 hours as needed. All dogs had passive range of motion (PROM) exercises performed every 12 hours. Two investigators masked to the intervention performed morning evaluations (physical and neurological examination, and pain assessments) and treatments (administration of medications, sling walking, bladder expression, cryotherapy [for the first 48 hours postoperatively] or heat treatment, PROM exercises, and feeding) daily. On each weekday, all dogs were moved to the rehabilitation center after morning care. Supportive care during the day was provided by the rehabilitation service in addition to rehabilitation treatments. Dogs were delivered back to the wards in the afternoon and evening feeding, supportive care, and cryotherapy or heat treatment were provided by the hospital ward technicians. During the weekend, trained staff performed rehabilitation treatments after morning treatments were complete and the investigators had left the wards. The rehabilitation staff were the only people who knew the treatment group assignment.
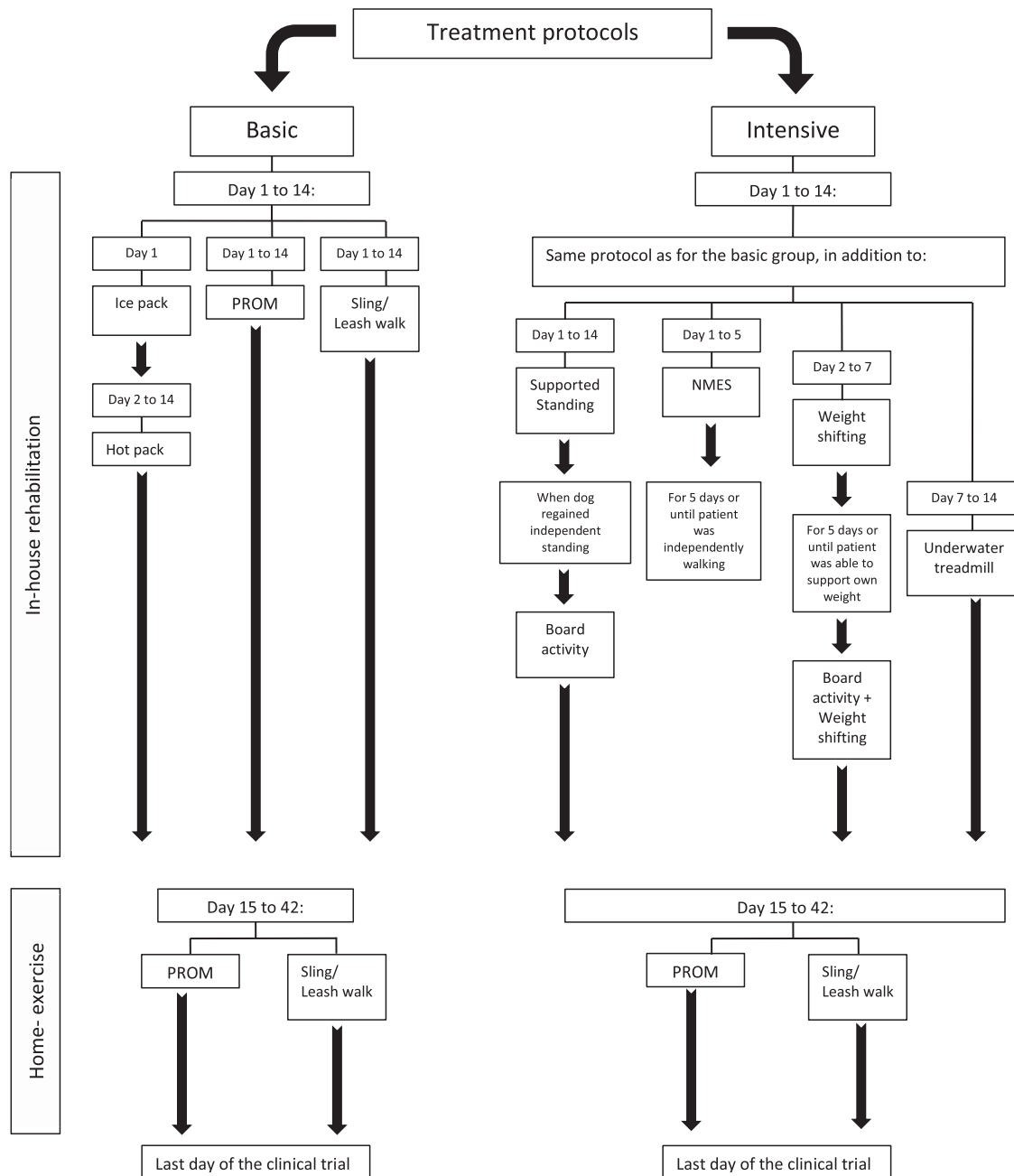
FIGURE 1 Diagram depicting the rehabilitation protocols and how they evolved over time. Day 1 is day of entry into the trial. PROM, passive range of motion; NMES, neuromuscular electrical stimulation

Dogs in the basic rehabilitation group received the care detailed above. Dogs in the intensive rehabilitation group received the same treatment as well as a staged progression through supported standing, neuromuscular electrical stimulation (NMES), weight shifting and balance board exercises and underwater treadmill (UWT) work (Figure 1 and Supporting Information Data 2). In order to evaluate the feasibility of each rehabilitation exercise in this early postoperative period, the rehabilitation staff recorded a feasibility score at each treatment (Supporting Information Data 2).

After the 14-day treatment period, dogs were discharged to their owners. All owners were shown how to perform PROM exercises and sling walking, and were given written instructions for home care along with a treatment log for daily recording of exercises. There was no difference in management between the 2 groups of dogs from time of discharge until their final evaluation at 42 days postoperatively. Owners were contacted once a week by telephone to ensure adherence to protocol. Dogs were rechecked at 28 days to ensure owners were fully compliant with care at home and that dogs were not developing any complications and 42 days to determine whether any effect of rehabilitation treatment detected at 14 days was maintained beyond the treatment period.

2.3 | Data collection

Data collected for each dog included signalment (body weight, body condition score [BCS], breed, sex, and age), history including owner reported details of duration of clinical signs (defined as time from onset of clinical signs including back pain to presentation) and duration of inability to walk (defined as time of loss of the ability to walk observed by the owner, to surgery), preoperative neurologic status, site of TL-IVDH and surgical details (hemilaminectomy sites). Physical and neurologic examinations were performed daily on all dogs while hospitalized and at the 28 and 42-day re-evaluation by the same investigator (NZ). Body weight and thigh circumference were recorded on day 1, 3, 7, 14, 28, and 42. Thigh circumference measurements were performed by the same person (NZ) using standard techniques.[26] An observation sheet that captured walking ability (paraplegic, nonambulatory paraparetic, ambulatory paraparetic, ataxic, and normal), proprioceptive placing, hopping, segmental spinal reflexes and pain perception (each parameter was allocated an ordinal score for each pelvic limb as follows: 0: absent, 1: reduced, 2: normal) was completed at each evaluation and the number of days to independent walking (ability to take 10 consecutive weight bearing steps) was recorded.

2.3.1 | Gait

Dogs were videotaped walking on a flat nonslip surface to generate an OFS (ranging from 0 to 12) and on a treadmill to generate unsupported RI using standard procedures developed in the investigator's laboratory.[21,27–29] Dogs were only placed on the treadmill if they could walk without support (OFS ≥ 5). If dogs could not walk without support, their unsupported RI was 0. Videotaping was performed on day 1 of the trial, then again on days 3, 7, 14, and 42 postoperatively. Videotapes were identified by randomized numbers and scored by a blinded observer working at a different institution (JF).[21,27]

2.3.2 | Pain

Postoperative level of pain assessment was performed daily for 14 days of hospitalization and on days 28 and 42 using a short form Glasgow Composite Pain Scale (GCPS)[30] (Supporting Information Data 3).

Adverse events were defined as any untoward medical occurrence that developed during the course of the study whether or not considered related to rehabilitation and were noted. Deterioration in neurologic status (decreased motor function or increased pain) were considered serious adverse events to be reported to the study safety monitor who was charged with investigating associations between neurologic deterioration and treatment group.

2.4 | Statistical analysis

Summary data were generated on the demographics and clinical history including age, sex, breed (dachshund or other), BCS, duration of inability to walk before surgery, gait category (paraplegic, nonambulatory paraparetic) at admission and day 1 of trial, and number of hemilaminectomy sites and were compared between groups. Continuous data were compared using either the Student's t test for normally distributed data or the Wilcoxon Rank sum test for non-normally distributed

data. Categorical data were compared by construction of contingency tables and application of a Chi square test or Fishers exact test as appropriate.

The primary outcome measures were the change in the OFS and RI at 14 days postoperatively. The OFS from day 1 to day 14 was tested in 2 different ways. Firstly, the change in OFS from day 1 to day 14 (calculated as day 14's value minus day 1's value), was analyzed using a one-way ANOVA with treatment group as the fixed effect. Secondly, it was analyzed by ANCOVA in a model that included OFS day 14 as the response and OFS day 1 as a covariate with treatment group as the fixed effect. The RI value at day 14 was tested by ANOVA in a model that included RI as the response and both groups as treatment factor. For both OFS and RI, gait category (nonambulatory paraparetic versus paraplegic) on day 1 of the trial was included as a covariate in additional analyses. Residual and other model fit diagnostics were checked for model fit and violations of assumptions.

Pain scores; time to independent walking in days; change in OFS and RI at 42 days; proprioceptive placing scores (both pelvic limbs combined) at 14 and 42 days; changes in body weight and thigh circumference measured on days 1, 14, and 42; and incidence of adverse events during the 14-day rehabilitation program were examined as secondary outcome measures. Short form GCPS scores from each dog were analyzed at day 1, 3, 7, 14, and 42 of the trial. Because all variables were non-normally distributed, a nonparametric Wilcoxon rank sum test was used to evaluate each response variable. A significance level of $P < .05$ was established for all analyses and all analyses were performed without knowledge of which treatment each group received. Treatment group identity was revealed once the final analysis was complete.

3 | RESULTS

Fifty dogs met the inclusion criteria at time of presentation but 18 were excluded after surgery (Figure 2). Of the 14 dogs excluded because of changes in neurologic status, 12 improved to an OFS > 4 immediately postoperatively and 2 deteriorated to lose pain perception. The remaining 32 dogs met the inclusion criteria and were enrolled in the study. Two dogs were withdrawn because they developed antibiotic resistant bacteriuria, leaving 30 dogs available for analysis. There were 17 Dachshunds, 5 mixed breeds, 2 Havanese, 2 American Cocker Spaniels, and 1 each of Bichon Frise, Chihuahua, Corgi and Shih Tzu. Breed, age, sex, and body weight of the participating dogs did not differ significantly between treatment groups; however, BCS was significantly higher in the basic rehabilitation group (Table 2). There was no significant difference in duration of inability to walk, or number of hemilaminectomy sites (Table 2). T13-L1 was the most frequently affected IVD site (n = 11), followed by T12–13 (n = 7), T11–12 (n = 6), L2–3 (n = 3), L3–4 (n = 2), and T10–11 (n = 1) (Figure 3). Four dogs in the basic group and 3 in the intensive group had previous episodes of paresis from which they made a full recovery after decompressive surgery (1 in each group) or medical management.

There were 19 nonambulatory paraparetic dogs and 11 paraplegic dogs at time of presentation and on the day after surgery (at time of
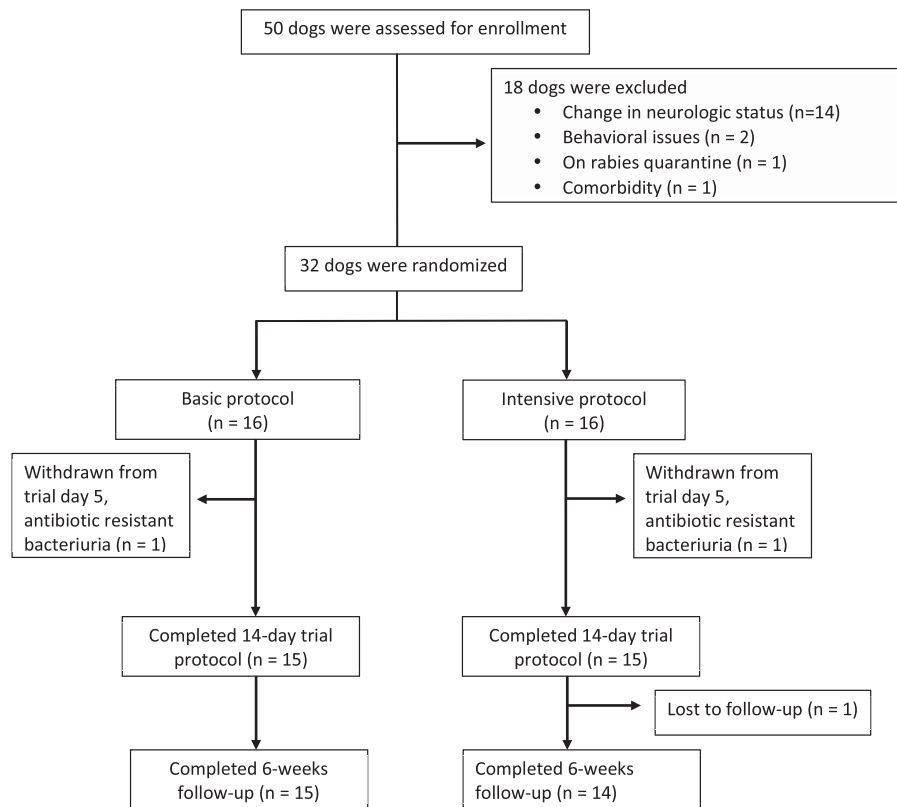
FIGURE 2 CONSORT flow diagram of the clinical trial. Of the 14 dogs with a change in neurologic status, 2 dogs deteriorated and lost pain perception in their pelvic limbs and 12 dogs improved to take some weight bearing steps

enrollment into the trial) both treatment groups had 9 nonambulatory paraparetic and 6 paraplegic dogs (Table 2). All 30 dogs successfully completed their 14-day postoperative treatment and 28-day recheck, and 14 of 15 returned for the 42-day recheck. One dog that did not attend the final 42-day appointment was ambulatory with an OFS 7 at time of discharge (day 14 in the clinical trial). All but 1 dog were independently ambulatory by the end of the 14-day trial period with an overall median time to walking of 7.5 days (range: 2–37).

TABLE 2 Comparison of demographics and clinical history, and findings at trial entry

Variable		Basic protocol	Intensive protocol	P value
Breed: Dachshund; Other		10 Dachshunds	7 Dachshunds	$P = .88$
		5 Other	8 Other	
Age (years) Mean (SD)		6 (2.25)	5.4 (2.5)	$P = .22$
Sex		9 M, 5 FS, 1 F	2 M, 7 MC, 6 FS	
BCS, median (range)		6 (4–8)	5 (2–6)	$P = .036$
Body weight, median (range)		7.4 (4.3–13.9)	7.6 (2.8–14.5)	$P = .58$
Duration of nonambulatory status (dogs)	<12 hours	1	1	$P = .94$
	12–24 hours	7	5	
	24–48 hours	4	6	
	48–72 hours	3	3	
Neurologic status preoperative/Day 1 of trial	Nonambulatory paraparetic	8/9	11/9	$P = .45$/NA
	Paraplegic	7/6	4/6	
Imaging modality		MRI: 8; CT: 7	MRI:11; CT:4	NA
Number of hemilaminectomy sites, median (range)		1 (1–4)	1 (1–3)	$P = .32$

Other breeds included American Cocker Spaniel, mixed breed, Chihuahua, Corgi, Havanese, and Shih Tzu.
Abbreviations: BCS, body condition score; CT, computed tomography; F, female; FS, female spayed; M, male; MC, male castrated; MRI, magnetic resonance imaging; OFS, open field score.
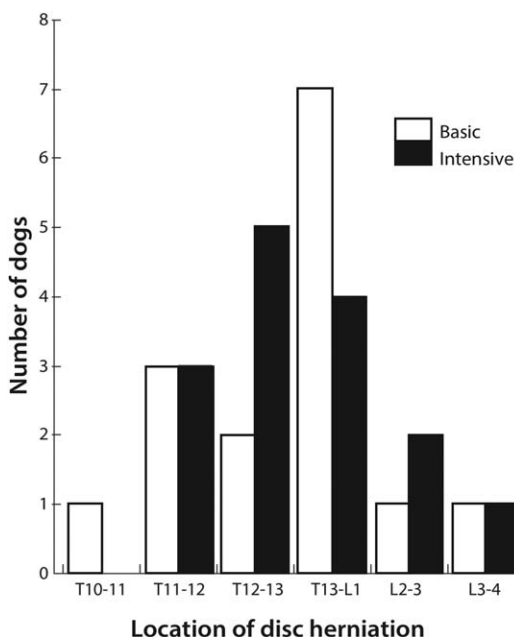
FIGURE 3 The number of dogs with intervertebral disc herniations at different locations in each group. T: thoracic; L: lumbar

Postoperative pain was managed well with the standard protocol with no dogs requiring administration of additional opiates. One dog in each group received prednisone instead of an NSAID and 1 dog in the intensive group was not treated with an anti-inflammatory drug because of gastrointestinal signs (diarrhea) before surgery. Diazepam was administered to 3 dogs in each group to facilitate bladder expression, phenoxybenzamine was administered to 1 dog in each group. This was substituted for prazosin in 1 dog in the intensive group. Seven dogs in each group received trazodone while hospitalized. Three dogs in each group received antibiotics PO for different reasons including bacteriuria (3), pyoderma (1), fever (1), and diarrhea (1).

Dogs tolerated intensive rehabilitation well. Feasibility scores for assisted standing were 0 for all dogs. The weight shift exercises were tolerated with feasibility scores of 0 by all but 1 dog. The most challenging treatment was NMES. In 10 dogs, the feasibility score was 0 throughout, but in 5 dogs, tolerance decreased with treatment number and the last 2 treatments could not be completed in 3 of these 5 dogs. UWT was tolerated well in 14 dogs (feasibility scores of 0) but 1 dog refused to walk on the treadmill and the exercise could not be completed.

TABLE 4 GCPS score in dogs at each time point in each treatment group

Time points	Basic protocol Median (range)	Intensive protocol Median (range)	P-value
Day 1	4 (0–9)	2 (0–8)	.14
Day 3	2 (0–7)	1 (0–5)	.46
Day 7	1 (0–4)	0 (0–6)	.49
Day 14	0.56 (0–1)	0 (0–4)	.60
Day 28	0 (0–2)	0 (0–1)	.22
Day 42	0 (0–1)	0 (0–1)	.26

3.1 | Primary outcome

The mean OFS and RI values with 95% confidence intervals (CI) for each group are provided in Table 3. The treatment effect of the intensive rehabilitation protocol as measured by the difference in OFS changes from days 1 - 14 was −0.400 (95% CI: −1.82, 1.02), which is not statistically significant when evaluated using both statistical techniques described in the methods ($P = .57$ for ANOVA analysis; $P = .66$ for ANCOVA analysis). The value of OFS at Day 1 did significantly influence the final OFS across both groups ($P = .0045$). In contrast, grading as paraplegic versus nonambulatory paraparetic (broader categories than the OFS) on the first day of the study did not predict changes in OFS between day 1 and day 14 ($P = .82$).

The treatment effect of the intensive protocol on recovery of quadrupedal coordination as quantified by the difference in RI at day 14 was −3.47 (−29.81, 22.87), which is not statistically significant. ($P = .79$). There was highly significant difference on RI value at day 14 in dogs graded on day 1 of the trial as nonambulatory paraparetic versus paraplegic ($P = .0002$), but treatment group remained not significant because of equal distribution of these grades between groups ($P = .73$).

3.2 | Secondary outcomes

Dogs had their highest GCPS on the first day of the trial but the maximum score on that day was only 9/24. The scores rapidly decreased and there was no significant difference between the 2 treatment groups (Table 4). The remaining secondary outcomes variables are summarized in Table 5, and there was no significant difference in these outcomes between basic and intensive groups. Twenty-four of 30 dogs

TABLE 3 Primary outcome measures

Group		OFS mean (SE)	95% CI	RI mean (SE)	95% CI
Basic (n = 15)	Day 1	1.73 (0.48)	0.70-2.77	0 (0)	NA
	Day 14	7.87 (0.61)	6.56-9.17	55.13 (8.51)	36.88-73.38
	Change	6.13 (0.58)	4.88-7.39	NA	NA
Intensive (n = 15)	Day 1	2 (0.47)	1.0–3.0	0 (0)	NA
	Day 14	7.73 (0.4)	6.88-8.58	51.65 (9.64)	30.98-72.33
	Change	5.73 (0.37)	4.94-6.53	NA	NA

Abbreviations: CI, confidence interval; OFS, open field score; RI, regulatory index; SE, standard error.

TABLE 5 Secondary outcome measures

Variable		Basic protocol		Intensive protocol		P value
		N	Median (range)	N	Median (range)	
Time to walking (D)		15	5 (2–37)	15	8 (3–15)	.46
OFS change D42-D1		15	8 (3–11)	14	7 (5–10)	.69
RI D42		15	80.95 (23.1–100)	14	82 (25.4–98)	.84
PP D14		15	1 (0–4)	15	1 (0–4)	.98
PP D42		15	3 (0–4)	14	3 (0–4)	.98
L thigh circ change	D1–14	15	0.1 (−0.2-0.7)	15	0.3 (−0.7-1)	.24
	D14–42	15	−0.1 (−1.8-1.2)	14	−0.15 (−1.5-0.4)	.45
	D1–42	15	0 (−1.8-1.7)	14	0 (−1.4-1.4)	.91
R thigh circ change	D1–14	15	0.2 (−0.4-0.8)	15	0.2 (−0.7-1.1)	.35
	D14–42	15	−0.1 (−1.8-1.2)	14	−0.15 (−1.5-0.4)	.73
	D1–42	15	−0.1 (−1.1-1.6)	14	−0.05 (−1.1-1.5)	.73
Weight change	D1–14	15	0.5 (−0.6-1.2)	15	0.4 (−1-1)	.50
	D14–42	15	−0.3 (−1.7-1.1)	14	0 (−0.5-0.8)	.25
	D1–42	15	0.3 (−0.6-0.9)	14	0.45 (−0.4-1.4)	.63

Abbreviations: circ, circumference; D, day; L, left; OFS, open field score; PP, proprioceptive placing; R, right; RI, regularity index.

lost weight during their 14-day hospitalization although 1 dog with a BCS of 2 gained 1 kg (13.4–14.4.kg). Most dogs regained weight after discharge. Changes in thigh circumference mirrored this weight loss pattern with most losing circumference over the first 14-days and then regaining it over the subsequent month.

Details of adverse events are recorded in Table 6. There were no adverse events that caused neurologic deterioration (motor or sensory function or pain level) in any dog. There were comparable numbers of adverse events in each group and all were resolved with appropriate treatment.

4 | DISCUSSION

This randomized, blinded, prospective clinical trial examined the effect of intensive versus basic postoperative rehabilitation protocols in dogs with incomplete SCI because of TL-IVDH. We demonstrated that early initiation of intensive postoperative rehabilitation is safe and well toler-ated in dogs after hemilaminectomy and fenestration. However, there was no detectable difference in the level or speed of recovery of ambu-lation (quantified with the OFS gait scale) and quadrupedal coordina-tion (quantified with the RI) between the 2 treatment groups. In addition, we documented weight loss and decreased thigh circumfer-ence in the first 14 days after injury but found no significant difference in the change in these parameters between the 2 groups.

The importance of physical rehabilitation on recovery from neuro-logic injury has been demonstrated experimentally and in people in many different types of injury including SCI. In rodent and feline exper-imental models of SCI, a wide range of different training protocols have been shown to improve motor recovery, reduce muscle atrophy, and enhance coordination after incomplete injury.[31] The optimal timing of initiation of rehabilitation is unclear, but there is evidence that early ini-tiation is beneficial[32] and it is clear that the type of rehabilitation

undertaken (so-called task-specific rehabilitation) is important because enhancement of one function can occur at the cost of another.[33–35] Interpreting the effect of rehabilitation in humans with SCI is more complicated, and the term rehabilitation is more holistic, including physical, speech, occupational, and psychosocial treatment amongst others. Among these, locomotion treatment is the most relevant to the clinical trial we report here.[36] Large analyses conclude that patient and injury driven factors (eg, injury severity and patient resilience) are over-whelmingly important in determining outcome.[37,38] However, once patient groups with more homogeneous injury severity are evaluated, generating groups more analogous to the homogenous population of

TABLE 6 Summary of the adverse events recorded in both groups

Adverse event	Basic protocol	Intensive protocol
Bacteriuria	*Pseudomonas* (n = 1) At admission	*E. coli* (n = 1) at admission
	E. coli (n = 1) Week 2	
GI signs	Transient vomiting (n = 2) Week 1	Regurgitation Week 1 (n = 2)
		Diarrhea Week 1 (n = 1) Inappetant days 1–5 (n = 1)
Superficial pyoderma	At presentation (n = 1)	
Hematuria		Week 1 (n = 1). Sterile urine culture
Fever		Week 1, unknown origin (n = 1)
Seroma	Week 2–4 (n = 1)	

Abbreviation: GI: gastrointestinal.
Adverse events in all dogs were resolved with appropriate treatment.

dogs examined in our trial, the effects of type and duration of locomotor training during physical treatment become apparent with longer duration and overground walking both highlighted as important for locomotor function.[39–42] Here, we evaluated dogs with incomplete injuries and hypothesized that early initiation of a staged physical rehabilitation program focused on strength and coordination would improve the rate and level of their recovery.

This study evaluated dogs that were nonambulatory paraparetic or paraplegic with pain perception based on the frequency of dogs presenting in this gait category, their incomplete recovery of coordination, and their uniform recovery curve, all of which allowed an efficient and yet powerful study to be designed. Dogs were considered for inclusion when they first presented to the hospital, but were only included the day after surgery if they still met the inclusion criteria. As noted in Figure 2, 14 of 50 (28%) dogs that fit the inclusion criteria at time of presentation were excluded after surgery, 12 (12/50: 24%) of which showed an improvement in motor function and scored >4 on the OFS scale. This decision was made because of our prior (unpublished) observations that these dogs would be walking independently the following day, reducing the opportunity for any postoperative intervention to play a significant role in their recovery of ambulation. This is an important piece of data to consider when evaluating postoperative therapies and highlights the need for randomization at time of starting a postoperative treatment, not at time of presentation to the hospital.

Two rehabilitation protocols were evaluated starting the day after surgery and continuing for 14 days. This period was targeted because of evidence of benefit from early onset of training[32,43] and because the majority of the dogs with serious but incomplete spinal cord injuries are walking within 14 days. The basic protocol focused on PROM exercises and limited (sling) walking. The intensive protocol was designed to maintain muscle mass, increase motor strength, and improve coordination through staged exercises and was based on experimental evidence in rodents with incomplete SCI that treadmill training, cycling, and swimming all improve motor recovery.[44–46] The outcome parameters used were selected for their ability to discern both quality of gait and quadrupedal coordination, and to document parameters such as hind limb muscle and weight loss. Throughout the 14-day period, the dogs were confined to cages and provided with cryotherapy and heat treatment. The lack of significant difference in outcome between these protocols could simply reflect the fact that the speed of spontaneous recovery in this group of animals is such that the impact of interventions is limited. However, in light of the finding in people and in experimental models of SCI that increased duration of training improves outcome, it is possible that modification of the exercises, for example by increasing the time spent walking on the UWT would be beneficial and should be considered given the lack of adverse consequences of these exercises in this population.

The results of our study are in agreement with results from a recent randomized, blinded clinical trial on the efficacy of immediate postoperative laser treatment and rehabilitation in dogs after surgery for TL-IVDH.[14] This trial included paraplegic, pain perception negative dogs as well as the dogs included in our trial, but like ours, did not find any difference in recovery time and outcome among dogs in the different treatment groups. In contrast, 2 different retrospective studies on postoperative rehabilitation that combined a wide range of different exercises as well as use of the cold laser, suggested a benefit.[11,12] One of the studies concluded that from among a cohort of dogs receiving rehabilitation, dogs that had more UWT sessions and longer duration of rehabilitation improved more than those that did not. Notably, mean time to walking (defined as 3 consecutive steps) was 16 days, longer than the dogs reported here (with a more stringent definition of 10 consecutive steps) and in other studies,[3,22,47–49] and it is likely that dogs with worse recoveries were selected for rehabilitation. In addition, it included a heterogeneous population with no limit on body size and a wide variety of presenting neurologic severities, both of which alter outcome.[5,50] The other retrospective study compared outcomes between dogs that did and did not receive in-house and owner-delivered rehabilitation and suggested that postoperative rehabilitation was associated with a higher chance of complete functional recovery.[11] Rehabilitation was started at 14 days and again, time to walking was longer than our study or other reported studies,[3,22,47–49] suggesting dogs with poor recovery were targeted for rehabilitation. A more recent retrospective study in paraplegic pain perception negative dogs, focusing on those dogs that did not recover pain perception over a protracted period, also reported a benefit of an intensive multimodality rehabilitation protocol.[13] These studies together highlight the possibility that rehabilitation might benefit dogs making a slow or incomplete recovery.

One outcome variable that could be compared with the majority of the retrospective literature on canine SCI because of IVDH was time to ambulation. While there are inconsistencies in defining ambulation, in this study, the median time to ambulation did not differ between groups and across the whole cohort was 7.5 days. When data on dogs with the same grade of initial injury severity is extracted from large case cohort publications, a time to ambulation of 10 days is reported.[3,49] Typically these dogs are sent home to their owners in 4–7 days after surgery. Bearing in mind, these previously published data do not exclude dogs with a rapid postoperative recovery as occurred in our trial, the overall time to ambulation of 7.5 days compares very favorably with these previous studies. This raises the question of whether meticulous and standardized postoperative care for 14-days improves the rate of recovery. Indeed, while many studies examine preoperative and perioperative predictors of recovery,[3,5,6,47,49,51] the effect of duration of hospitalization has not been examined. Such an observation should be made with caution given the different populations of animals examined, but suggests the role of in-house versus at-home care deserves examination.

The mean and median group values for muscle and weight loss suggest there was no change over the total 42-day study period. However, these values were somewhat obscured by outliers that were either extremely thin (and gained weight) or overweight (and lost weight). Indeed, 80% of dogs lost weight and thigh circumference over the 14-day period postoperatively and then regained it after 28 days. While the weight loss and atrophy can result from loss of different tissue types, these data suggest that even short-lived partial loss of motor strength results in muscle atrophy. These findings are in line with experimental studies that report both a decrease in body weight and muscle atrophy in rodents during the first week after a SCI, followed

by a slow recovery.[44–46] Similarly, both weight loss and muscle atrophy are reported in people with SCI.[52] The reasons underlying this initial weight loss are not completely understood, however it has been proposed that the stress increases the metabolic rate,[44,46] and this, coupled with loss of mobility, produce muscle atrophy and accentuate weight loss. Although the majority of dogs in this trial lost weight during their 14-day hospitalization, we found no significant difference in the change in thigh circumference measurement and body weight between the 2 groups and so the interventions employed in the intensive group were not enough to prevent muscle loss and a more intensive protocol might be indicated. This is in contrast with experimental rodent studies in which treadmill training, cycling, and swimming all preserved muscle mass and enhanced recovery.[44,53]

Postoperative pain was assessed daily and combinations of opiate, nonsteroidal anti-inflammatory and muscle relaxant drugs were used in all animals. No animal needed additional analgesic drugs beyond the standardized protocol and there was no instance of deterioration in pain score that could be related to performing rehabilitation exercises. While there were several adverse events during the trial relating to the gastrointestinal and urinary tracts, these were readily resolved with appropriate treatment, and were not related to treatment group.

We conclude that early initiation of intensive postoperative rehabilitation is safe and well tolerated in dogs after hemilaminectomy and fenestration for TL-IVDH. However, we found no significant improvement in outcome of dogs receiving early intensive postoperative rehabilitation compared with a less intensive postoperative treatment in these dogs with incomplete spinal cord injuries. Important observations included the weight loss and decrease in thigh circumference that occurred in the first 14-days after injury, and the rapid recovery to walking in this cohort of dogs under expert management in hospital for 14-days after decompressive surgery. Investigation of the effect of intensive rehabilitation in dogs with complete spinal cord injuries, and/or delayed recovery of function because of other factors, is warranted.

CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Approved by North Carolina State University IACUC (protocol number: 15–173-O).

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

Supplementary Data 1

Supplementary Data 2: Rehabilitation protocol details, and feasibility scoring Basic rehabilitation protocol

Supplementary Data 3