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A Placebo-Controlled, Prospective, Randomized Clinical Trial of Polyethylene Glycol and Methylprednisolone Sodium Succinate in Dogs with Intervertebral Disk Herniation

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Background: Acute intervertebral disk herniation (IVDH) is a common cause of spinal cord injury in dogs and currently there is no proven medical treatment to counter secondary injury effects. Use of methylprednisolone sodium succinate (MPSS) or polyethylene glycol (PEG) as neuroprotectants is advocated but controversial because neither treatment has been tested in placebo-controlled, randomized, blinded trials in dogs.

Hypothesis: Polyethylene glycol will improve the outcome of severe spinal cord injury caused by IVDH compared to MPSS or placebo.

Animals: Client-owned dogs with acute onset of thoracolumbar IVDH causing paralysis and loss of nociception for <24 hours.

Methods: Dogs were randomized to receive MPSS, PEG, or placebo; drugs appeared identical and group allocation was masked. Drug administration was initiated once the diagnosis of IVDH was confirmed and all dogs underwent hemilaminectomy. Neurologic function was assessed 2, 4, 8, and 12 weeks postoperatively using an open field gait score (OFS) as the primary outcome measure. Outcomes were compared by the Wilcoxon rank sum test.

Results: Sixty-three dogs were recruited and 47.6% recovered ambulation. 17.5% developed progressive myelomalacia but there was no association with group. There was no difference in OFS among groups. Although full study power was not reached, conditional power analyses indicated the futility of continued case recruitment.

Conclusions: This clinical trial did not show a benefit of either MPSS or PEG in the treatment of acute, severe thoracolumbar IVDH when used as adjunctive medical treatment administered to dogs presenting within 24 hours of onset of paralysis.

Key words: Neuroprotection; Paraplegia; Secondary injury; Spinal cord injury.

From the College of Veterinary Medicine, NCSU, Raleigh, NC (Olby, Muguet Chanoit, Lim, Mariani, Humphrey, Early, Muñana); the Center of Comparative Medicine and Translational Research, NCSU, Raleigh, NC (Olby, Lim, Mariani, Muñana); the Department of Statistics, NCSU, Raleigh, NC (Davidian); the College of Veterinary Medicine, UGA, Athens Georgia (Freeman, Platt, Kent); and the Gulf Coast Veterinary Specialists, Houston, TX (Giovanella, Longshore) This clinical trial was coordinated from North Carolina State University College of Veterinary Medicine. Cases were recruited at the Colleges of Veterinary Medicine at North Carolina State University, University of Georgia, Cornell University and University of Minnesota; Gulf Coast Veterinary Specialists; Animal Neurology and MRI Center; Animal Specialty Center; Bush Veterinary Neurology Services; Carolina Veterinary Specialists; Center for Veterinary Specialty Care; Miami Veterinary Specialists; Valley Central Veterinary Referral Center; and, VCA South Shore Animal Hospital. Trial coordination, outcome scoring and data analysis were performed at North Carolina State University.

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Abbreviations:

CT	computed tomography
CRI	continuous rate infusion
F	female
FS	female spayed
LOCF	last observation carried forward
M	male
MN	male neutered
MPSS	methylprednisolone sodium succinate
MRI	magnetic resonance imaging
Mgm	myelogram
NASCIS	National Acute Spinal Cord Injury Studies
OFS	open field score
PEG	polyethylene glycol
PMM	progressive myelomalacia
TL IVDH	thoracolumbar intervertebral disk herniation

Acute (Hansen type 1) intervertebral disk herniation (IVDH) is a common cause of spinal cord injury in certain breeds of dog.[1] The resulting injury to the spinal cord is caused by a combination of compression and contusion.[2] Compression of the spinal cord can be treated effectively by surgical decompression, but optimal medical management of the contusive injury remains unclear. Contusion causes primary mechanical damage and precipitates a cascade of secondary biochemical events that result in the progressive expansion of tissue damage over the hours after the injury.[3] Events such as free radical formation and excitotoxicity are central to

this pathologic event. Many different drug therapies that target this secondary injury cascade improved outcome experimentally, but few have shown significant clinical benefit.[4,5] Methylprednisolone sodium succinate (MPSS) has been evaluated in a series of clinical trials in humans (the National Acute Spinal Cord Injury Studies [NASCIS] trials) for its ability to decrease free radical production when used at high dosages, thus limiting secondary injury. It produced a small benefit if treatment was initiated within 8 hours of injury.[6] However, the results of these trials are controversial, and MPSS has not been adopted as a standard of care in human medicine.[7,8] Polyethyelene glycol has received attention for its ability to fuse membranes and has improved outcome in experimental models of spinal cord injury.[9] It also has been evaluated in a clinical trial in dogs with the most severe grade of injury caused by IVDH.[10] The outcome of dogs in this trial was favorable when compared with historical controls, but was comparable to outcomes reported with surgery alone in retrospective studies.[11–13]

We hypothesized that polyethylene glycol (PEG) but not MPSS would improve the outcome of acute spinal cord injury in dogs with acute thoracolumbar intervertebral disk herniation (TL-IVDH). The aims of this placebo-controlled, randomized, blinded clinical trial were to evaluate the safety and efficacy of MPSS and PEG when used as an adjunct to decompressive surgery in dogs with severe spinal cord injuries caused by acute IVDH.

Materials and Methods

Study Design and Animals

This randomized, blinded, placebo-controlled, 3-arm clinical trial compared the effect of MPSS,[a] PEG,[b] and saline on the outcome of surgically treated dogs with acute TL-IVDH (Fig 1). The study was designed according to the guidelines for the conduct of spinal cord injury trials.[14] Because of the rapid and high recovery rate of dogs with acute TL-IVDH causing incomplete injury (paraparesis or paraplegia with intact nociception),[15–17] the trial was limited to dogs that were paralyzed with no nociception (clinically complete injuries). The number of animals needed per group was determined by power analysis using previously published prospectively gathered data on the recovery of ambulatory function quantified by the open field score (OFS) in dogs with acute TL-IVDH.[16] The group size needed to detect a 3-point improvement in function (representing a clinically relevant functional improvement) at 12 weeks after surgery in a 3-arm clinical trial with 90% power at a significance level of 5% (adjusting for multiplicity) was calculated using simulation.[18] The recovery data from the preliminary work on surgically treated dogs were used as a basis for generating hypothetical study data. The power for detecting a 3-point difference was based on computing the Wilcoxon test on each of a million such hypothetical simulated datasets. It was determined that 45 dogs would be needed per group for a total of 135 dogs.

Centers were recruited for the trial through the ACVIM neurology specialty e-mail list server. Inclusion criteria for the trial were dogs weighing <20 kg, aged between 2 and 10 years with acute onset of paralysis of ≤24 hours duration (from the last time the owner saw the dog walk); absent nociception in both hind limbs and the tail; no prior treatment with corticosteroids and treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) limited to 2 or fewer doses; no clinically relevant systemic comorbidity; and diagnosis of acute TL-IVDH that was treated surgically. Owners of dogs that met the initial criteria with a high suspicion of an acute TL-IVDH signed an informed consent form. Final entry into the trial occurred once the diagnosis was established by cross-sectional imaging. Each institution managed the dogs as emergent cases, performing baseline laboratory work, cross-sectional imaging, and surgical decompression by hemilaminectomy as soon as possible after hospital admission. Anesthesia protocol and postoperative care varied by institution but all institutions included an opioid for pain management. All dogs were placed on famotidine PO while hospitalized because of the possibility of receiving MPSS.

Randomization, Drug Preparation and Administration

Dogs at each center were randomized to 1 of 3 treatment groups by the NC State Veterinary Hospital pharmacy using block randomization to ensure even distribution of treatment arms at each center. Drug kits designed to mask drug identity were prepared by the same pharmacy and sent to each center with instructions on reconstitution (Data S1). Each drug kit was identified by its study number (3 letters identifying the center and consecutive numbers) and was accompanied by a set of study forms, also identified by the appropriate study number (Data S2). Each center used consecutively numbered drug kits, thus ensuring the randomization schedule was followed. Because drugs theoretically could be identified by their preparation steps, preparation was completed by a pharmacist or technician who concealed drug identity and was not involved in data collection or outcome assessment. Drugs were reconstituted once the diagnosis had been confirmed by imaging, and delivered to the clinician as 2 bolus doses and a continuous rate infusion (CRI; Table 1). Treatment was initiated as soon as drug preparation was complete. All dogs received drug boluses at a volumetric dosage rate of 2 mL/kg given over 15 minutes at initiation of treatment and at 4 hours, with a CRI at a rate of 0.22 mL/kg for 24 hours, starting 1 hour after initiation of treatment, with saline substituted where appropriate. Drug administration forms were completed by clinicians to confirm that appropriate protocol was followed (Data S2).

Patient Data and Neurologic Assessments

Patient signalment, history including owner reported details of duration of onset (defined as time from walking normally to paralysis) and duration of paralysis (defined as time of onset of paralysis to presentation), preoperative neurologic status, cross-sectional imaging findings, surgical details, details of drugs used for anesthesia and pain management, and postoperative care were recorded. The initial and re-evaluation neurologic examinations were recorded on forms (Data S2) and videotaped. This evaluation included categorization of gait as ambulatory paraparetic, nonambulatory paraparetic or paraplegic. Proprioceptive placing of each hind limb was scored as absent (0), delayed/decreased (1), or normal (2), and nociception of the tail and each hind limb was scored using the same scale, as were the patellar and withdrawal reflexes. The caudal border of the cutaneous trunci reflex was recorded according to its vertebral level. Adverse events, defined as any untoward medical occurrence that developed during the course of the study whether or not considered drug-related, also were recorded. Life-threatening adverse events were reported to the study safety monitor (CLM) who was charged with investigating possible associations between life-threatening adverse events and treatment group.

Dogs were evaluated by neurologic examination (recorded in study forms) and videotaping of gait 24 hours postoperatively, at

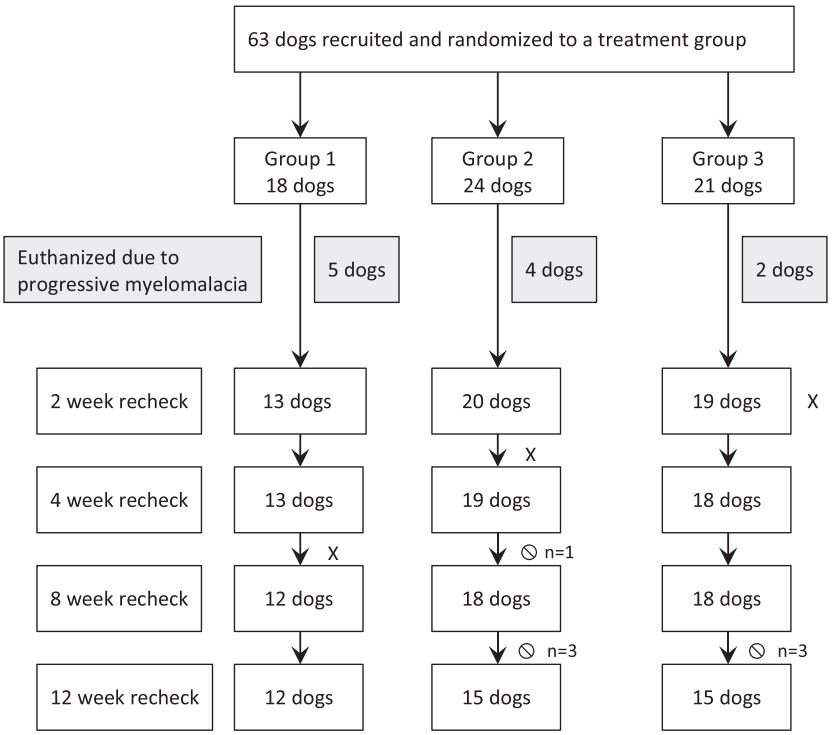

Fig 1. Flowchart documenting the numbers of dogs recruited to each treatment group, and following their progress through the trial. X, Owner opted for euthanasia; ⊘, Dog failed to attend recheck. n, number.

Table 1. Drug regimens for each group taken from published drug protocols[6,10].

Group	Bolus 1	CRI	Bolus 2
1: Saline	0.9% saline 2 mL/kg	0.9% saline	0.9% saline 2 mL/kg
2: PEG	PEG 2 mL/kg	0.9% Saline	PEG 2 mL/kg
3: MPSS	MPSS 30 mg/kg	MPSS 5.4 mg/kg/h	0.9% saline 2 mL/kg

CRI, continuous rate infusion; MPSS, methylprednisolone sodium succinate; PEG, polyethylene glycol.

time of discharge and then at 2, 4, 8, and 12 weeks. Assessment of nociception and proprioceptive placing recorded on study forms was confirmed by 2 independent, blinded observers who reviewed the videotapes. Gait was scored using the OFS[19] modified to remove nociception (because it was scored separately) and voluntary tail wag because this response was not reliably recorded when in hospital (Data S3). The mean of the OFS scores between the 2 observers was calculated, but if the scores differed by ≥2 points, a consensus was reached by review of the videotapes. The presence of nociception and independent walking also were categorized as "yes" or "no" at each time point. All protocols were reviewed and approved by the NCSU Institutional Animal Care and Use Committee (protocol numbers: 07-074-O; 10-066-O).

Statistical Analysis

The descriptive data of dogs in each group were compared using the Kruskal-Wallis test for continuous data and by constructing contingency tables and performing a chi-square test for categorical data; Fisher's exact tests were performed when there were <5 observations in contingency table cells. The OFS, proprioceptive placing, and nociception scores were calculated for each group at each time point and expressed as the mean and SD. The numbers of dogs walking independently and recovering nociception also were recorded for each group at each time point. The primary outcome measures were the OFS and the ability to walk ("yes" or "no") at 12 weeks. The proprioceptive placing scores, nociception presence, and score at each time point, and the OFS and ability to walk at 2, 4, and 8 weeks were examined as secondary outcome measures. Categorical outcomes were compared across groups with a chi-square or Fisher's exact test. Pairwise tests of treatment differences also were conducted by chi-square tests. Ordinal outcomes were evaluated across the groups using the Kruskal-Wallis test with pairwise comparisons among groups performed using Wilcoxon rank sum tests. Evaluation of other factors (age, sex, speed of onset of signs, duration of paralysis, number of sites decompressed) that might influence outcome (walking "yes" or "no"; OFS at 12 weeks) was undertaken using chi-square and Fisher's exact tests for dichotomous outcomes and Kruskal-Wallis and Wilcoxon rank sum tests for ordinal data. When data were missing, analysis was performed both without the data, and using the last observation carried forward (LOCF) convention. This represented a conservative approach to the data given that some animals were improving, and none deteriorated. P values of <.05 were taken as significant.

An interim analysis was performed when approximately half of the dogs had been recruited to ensure there was no early detectable treatment effect (positive or negative) and to perform condi-

tional power calculations if indicated. These calculations give an estimate of the probability of observing a statistically significant result for the specified pairwise comparison when all of the intended information has been collected, given the data observed in the study thus far.[20,21] Interim and final analyses were performed without knowledge of which treatment each group received. Drug identity was revealed once the final analysis was complete.

Results

Patient Population

Sixty-four cases were recruited by 13 different centers; 1 case withdrew from the trial shortly after entry leaving data from 63 dogs available for analysis (Fig 1). Individual centers (n) recruited 21 (n = 1), 16 (n = 1), 8 (n = 1), 5 (n = 1), 2 (n = 4), and 1 (n = 5) cases. Recruitment was ended based on the results of conditional power calculations performed with interim data (see Statistical Analysis) despite failure to recruit all 135 dogs. The breed, age, sex and weight of the participating dogs are summarized in Table 2 and did not differ significantly among treatment groups.

Clinical Histories

Duration of onset of paralysis, established from owner observations, ranged from <1 to 24 hours and was categorized as <1, <6, <12, 12–24 hours (Table 2). Because there were periods when dogs were unobserved, dogs could have had a more rapid onset than their category implied and there were 13 dogs for which the data could not be reliably established from the owners. Time from owner observed onset of paralysis to study entry ranged from 1 to 24 hours with 21 dogs presenting within 6 hours, 20 within 12 hours, and 22 between 12 and 24 hours. For this variable, the time dogs went unobserved was included and therefore duration could have been shorter than reported. There were no significant differences among groups for either of these variables (Table 2). The majority of diagnoses were made by computed tomography (CT; Table 2) and hemilaminectomies were performed at a single site in 33 dogs, 2 sites in 21 dogs, 3 sites in 5 dogs, 4 sites in 3 dogs, and 6 sites in 1 dog.

Data Attrition and Adverse Events

Eleven dogs (17.5%) developed signs of progressive myelomalacia (PMM; cranial migration of cutaneous trunci reflex, loss of hind limb reflexes taking into account the possible reduction, or loss of the withdrawal reflex caused by spinal shock,[22] tetraparesis) and were euthanized within the first week (Fig 1 and Data S4). There was no significant difference in incidence of PMM between groups ($P = .32$). Pairwise tests between groups also failed to show a significant difference (group 1 versus 2: $P = .38$; group 1 versus 3: $P = .14$; group 2 versus 3, $P = .48$). Outcome data from the dogs with PMM was handled according to data type. For dichotomous outcomes on recovery of independent

Table 2. Signalment, onset, and duration of paralysis and imaging of dogs enrolled in the study.

	Group 1 (Saline)	Group 2 (PEG)	Group 3 (MPSS)
Breeds	14 Dachshunds	19 Dachshunds	15 Dachshunds
	2 Cocker spaniels	1 Miniature poodle	1 Cocker spaniel
	1 Corgi	1 Beagle	1 ShihTzu
	1 Mix breed	1 Pekingese	3 Pekingese
		1 Bichon Frise	1 Lhasa Apso
		1 Chihuahua	
Mean age (years) (SD)	4.17 (0.86)	4.42 (1.35)	4.86 (1.11)
Sex	10 FS; 2 F	13 FS; 1 F;	9 FS; 1F;
	4 MN; 2 M	8 MN; 2 M	9 MN; 2 M
Mean weight (kg) (SD)	7.98 (3.25)	7.12 (1.71)	7.4 (2.41)
Speed of onset (n = 50)			
<1 hour	1	6	2
<6 hour	5	5	3
<12 hour	9	5	6
12–24 hour	1	3	4
Paralysis to enrollment			
<6 hour	8	8	5
<12 hour	4	9	7
12–24 hour	6	7	9
Imaging modality			
CT	11	14	9
MRI	3	5	6
Mgm	1	0	2
CT mgm	3	5	4

F, female; FS, female spayed; M, male; MN, male neutered; CT, computed tomography; MRI, magnetic resonance imaging; Mgm, myelogram.

There was no significant differences in these characteristics between groups: age: $P = .2$; sex: $P = .86$; weight: $P = .83$; speed of onset: $P = .25$; paralysis to enrollment: $P = .54$.

walking and nociception they were categorized as "no", but for ordinal scales, they were excluded from further analysis because it can be argued that they did not generate a score.

Three dogs were euthanized before the end of the study, 1 each at 2, 4, and 8 weeks, because of owner dissatisfaction with level of recovery (Fig 1). None of these dogs had recovered nociception, but 1 had recovered some motor function at the time of euthanasia. Eight dogs were not presented for every re-evaluation (Fig 1). Data from these incomplete records were examined both as missing data, and using the LOCF. Because the results from both approaches were qualitatively the same and had the same statistical conclusions, data presented in tables include missing data replaced by LOCF for incomplete records and dichotomous data for PMM dogs.

No life-threatening adverse events occurred other than development of PMM. Six dogs developed urinary tract infections, 2 in group 1, 1 in group 2, and 3 in group 3. Three of these infections developed in the first week, 2 at 4 weeks, and 1 at 8 weeks. Seven dogs developed soft feces or diarrhea, 2 each in groups 1 and 2, and 3 in group 3. Six of these dogs developed signs in the first week after surgery, and 1 at 4 weeks. One dog in group 1 developed melena on the day of presentation and 2 dogs, 1 each in groups 2 and 3, developed vomiting on the day after surgery, signs resolved within 48 hours in both of these dogs. Three dogs in group 2 were reported to have decreased appetite while hospitalized. Three dogs developed fever of >103°F, 2 in group 2, and 1 in group 3; 1 of these dogs also had a urinary tract infection. Fever resolved in all dogs after 24 hours with no treatment in 1 dog and treatment with PO antibiotics in the other 2 dogs. One dog in group 3 developed aspiration pneumonia the same day that it was euthanized for PMM, 3 days postoperatively. Individual dogs, both in group 3, were reported to have an anal gland abscess 2 weeks postoperatively and pododermatitis 4 weeks postoperatively. Excluding PMM, there were not enough adverse events to make a meaningful statistical comparison among groups.

Outcomes

An interim analysis was performed when 58 dogs had completed the protocol, 17 in group 1, 23 in group 2 and 18 in group 3; and, because the results are qualitatively the same as those presented, they are not included. Conditional power calculations were performed using the interim data. The probabilities of detecting a significant difference between any 2 groups at the end of the study were <0.56 (Table 3) indicating the futility of continuing case recruitment. Case recruitment therefore was terminated, and cases active in the trial were completed and included in the final analysis of 63 dogs.

By the 12-week study endpoint, 30 of 63 dogs (47.6%) recovered independent walking with a mean OFS of 5.7 (SD, 3.6; median, 5.75; range 0–11.5) and 32 dogs recovered nociception. Three of the 30 walking dogs did not regain nociception, and 5 of the 32 dogs that regained nociception did not regain independent walking by 12 weeks but did have motor function. Of the 32 dogs that regained nociception, 29 regained it by the 2-week re-evaluation, 2 by the 4-week re-evaluation, and 1 by the 8-week re-evaluation. The outcome scores for each group at each evaluation are provided in Table 4. There was no significant difference in primary or secondary outcomes at 12 weeks among the groups (Table 5). Similarly, comparisons of all outcome measures at each evaluation did not identify significant differences (Data S5).

Table 3. Results of conditional power calculations using data from the first 58 dogs.

Groups being Compared	Conditional Power
1–2 positive	0.46
2–1 positive	0.31
1–3 positive	0.36
3–1 positive	0.56
2–3 positive	0.47
3–2 positive	0.15

No association was identified between outcome (walking "yes" or "no"; OFS at 12 weeks) and age, sex, speed of onset of signs, duration of paralysis, or number of sites decompressed. The influence of these factors on development of PMM also was examined, and no significant association was found.

Discussion

This blinded, placebo-controlled, randomized, prospective clinical trial in surgically treated acute, severe TL-IVDH failed to detect a treatment effect of PEG or MPSS when compared to saline. All dogs presented with the most severe grade of thoracolumbar spinal cord injury within 24 hours of onset of paralysis and all were treated with prompt surgical removal of the herniated disk material, with 47.6% recovering ability to walk by the 12-week study endpoint. A high rate of PMM was encountered, with 17.5% of dogs being euthanized for this problem, but an association of this complication with a particular treatment was not identified. Neither of the treatments was associated with clinically relevant adverse events. The study was terminated before recruitment of the full number of cases required to reach the planned study power based on results of a conditional power analysis performed with interim data.

The biggest challenge of this trial was case recruitment despite participation of multiple centers. The majority of dogs meeting the inclusion criteria that were presented to these centers were enrolled with prior administration of corticosteroids being the most common exclusion that occurred. In addition, there were potential participants the owners of which could not afford the cost of diagnosis and surgical treatment. Defraying these costs could have attracted additional cases, but would have markedly increased the cost of the clinical trial, making it challenging to fund. It is standard to perform an interim analysis during a trial

Table 4. Outcomes in each group at each evaluation.

Outcome Measure	Group 1 Saline n = 18	Group 2 PEG n = 24	Group 3 MPSS n = 21	Combined Groups
2-week				
Gait score	0 (0–6)	0 (0–7)	0 (0–8)	0 (0–8)
No. dogs walking	1 (5.9)	2 (8.3)	2 (9.5)	5 (7.9)
Nociception score	0 (0–6)	0 (0–6)	3 (0–6)	2 (0–6)
No. dogs + nociception	7 (39)	11 (45.8)	12 (57.1)	30 (47.6)
Proprioception score	0 (0–0)	0 (0–1)	0 (0–0)	0 (0–1)
4-week				
Gait score	2.5 (0–9.5)	2.5 (0–8)	1 (0–9.5)	3 (0–9.5)
No. dogs walking	6 (33.3)	6 (25)	7 (33.3)	19 (30.2)
Nociception score	0 (0–6)	0 (0–6)	5 (0–6)	4.5 (0–6)
No. dogs + nociception	8 (44.4)	10 (41.7)	12 (57.1)	30 (47.6)
Proprioception score	0 (0–3)	0 (0–2)	0 (0–3)	0 (0–3)
8-week				
Gait score	4.5 (1–10.5)	5.5 (0–8.5)	5 (0–10.5)	5.25 (0–10.5)
No. dogs walking	7 (38.9)	12 (50)	11 (52.4)	30 (47.6)
Nociception score	6 (0–6)	3 (0–6)	6 (0–6)	5.5 (0–6)
No. dogs + nociception	8 (44.4)	11 (45.8)	12 (57.1)	31 (49.2)
Proprioception score	0 (0–4)	0 (0–4)	1 (0–3)	0(0–4)
12-week				
Gait score	**7.5 (1–11.5)**	**5.75 (0–9.5)**	**5 (0–11.5)**	**5.75 (0–11.5)**
No. dogs walking	**7 (38.9)**	**12 (50)**	**11 (52.4)**	**30 (47.6)**
Nociception score	4 (0–6)	3 (0–6)	6 (0–6)	4.5 (0–6)
No. dogs + nociception	8 (44.4)	12 (50)	12 (57.1)	32 (50.8)
Proprioception score	2 (0–4)	0.5 (0–4)	0 (0–4)	0.5 (0–4)

Primary outcomes are bolded. Data are presented as median (range) for scores and number (percentage) of dogs with nociception and independent walking for dichotomous outcomes. Data include LOCF for missing data and dichotomous data on PMM dogs, but excludes ordinal scores of PMM dogs.

Table 5. *P* values for each 12-week outcome measure.

	Walking Y/N	OFS	Nociception Y/N	Nociception Score	Proprioception Score
Across groups	**0.67**	**0.64**	0.73	0.72	0.84
Group 1 versus 2	**0.7**	**0.32**	0.94	0.81	0.58
Group 1 versus 3	**0.39**	**0.56**	0.44	0.65	1
Group 2 versus 3	**0.58**	**0.81**	0.35	0.43	0.66

Primary outcome measures are bolded. The *P* values given are for the Chi statistic. When performed, the Fisher's exact test did not qualitatively alter results.

to ensure that there is no negative treatment trend, to allow early termination of the trial if a benefit already has been shown, and to assist in decisions on trial continuation.[14] If there is no trend for benefit in the interim analysis, a conditional analysis (defined as the conditional probability that the final result will exceed a critical value given the data observed and the study design assumptions) can be performed.[20,21] The lack of trends led to us to perform the conditional power calculations that showed that there was at best a 56% chance of detecting a 3-point change in OFS if all cases were recruited. The decision to halt recruitment therefore was based on the already prolonged nature of case accrual (5 years) and the low likelihood of either of the treatments producing a significant change in outcome. Despite this, decreased case enrollment resulted in a study that was underpowered based on the study design.

The power of the study was further impacted by the high rate of PMM. This progressive, fatal complication occurred in 17.5% of cases, higher than previously reported rates of 9–11.6% for similar case cohorts.[11–13] Early literature on acute TL-IVDH can be difficult to compare to current literature, because of differences in reporting of neurologic findings, but there is a suggestion that 20% of dogs that did not receive decompressive surgery developed PMM[23] and a recent study on French bulldogs reported a rate of 33%.[13] The current study highlights the importance of this complication of acute TL-IVDH in paraplegic dogs with no nociception. When comparing the incidence of PMM in dogs in each group, the presence of only 2 cases in the group receiv-

ing MPSS versus 5 in the saline group may indicate a possible treatment advantage for MPSS. However, there is insufficient data to draw this conclusion.

Both PEG and MPSS were well tolerated in this trial. A number of adverse events such as urinary tract infections developed, but they were rare, were not considered serious, and were distributed across all the groups. The main concern was the potential for severe gastrointestinal ulceration or perforation because of high doses of MPSS.[24,25] Animals that had already received corticosteroids or >2 doses of NSAID were excluded because of the increased risk of gastrointestinal complications when these 2 classes of drug are combined,[26] and gastrointestinal protection was provided with famotidine. With these precautions, only 3 dogs in each group suffered gastrointestinal signs in the first week after surgery, with 3 additional dogs in Group 2 (PEG) showing inappetence in the same period. This compares favorably with other reports of higher rates of gastrointestinal signs occurring in dogs receiving high doses of MPSS.[25,27] In these retrospective clinical reports, however, dogs frequently received a combination of corticosteroids and NSAIDs.

Methylprednisolone has free radical scavenging properties when used at high dosages, limiting lipid peroxidation, preserving spinal cord blood flow, and decreasing excitotoxicity among other effects, and much hope was placed on targeting this injury mechanism as a critical component of secondary injury.[28] Although numerous studies report the beneficial effect of MPSS in experimental models of spinal cord injury, a critical evaluation of the literature reported that 58% of experimental studies were unable to show benefit, as compared to 34% that did.[29] Comparing studies is extremely difficult because of the use of different injury models, species, treatment protocols and outcome measures, and the challenges in translating such results into clinical use are well recognized.[30] The NASCIS II and III trials were the first clinical trials in humans to demonstrate a benefit with MPSS treatment in patients with acute spinal cord injury[31,32] and their results have been replicated by some[33] and not by others,[34] leading to ongoing controversy over their study design, the impact of adverse effects, and the long-term benefits.[7,8,35]

Given this controversy in human medicine, it is not surprising that similar confusion exists in veterinary medicine. Of 3 placebo-controlled experimental studies in dogs that investigated MPSS, 1 failed to show benefit[36] and 2 showed benefit.[37,38] Of the 2 that showed benefit, 1 used a very different glucocorticoid dosing regimen that combined dexamethasone and low dose MPSS[37] and the other initiated MPSS treatment (30 mg/kg q6h for 6 doses) 48 hours after injury.[38] However, there were no data presented on study power, and blinding and randomization were not consistently performed. Given the experimental evidence that there may be benefit in dogs, testing MPSS rigorously in clinical cases was indicated. During trial design, determining the treatment window was a compromise. Logically, if the intent of treatment is to limit secondary injury, the sooner it is administered after injury, the more potential for benefit. Indeed, in the majority of experimental studies, it is given before, at the time of, or within a few hours of injury. The NASCIS trials identified a benefit if treatment was initiated within 8 hours, that was not present if treatment was initiated >8 hours after injury.[31,32] However, concerns have been raised over the possibility of false discovery by retrospective subanalysis of the outcome data.[7,8,39] In particular, injury severity may not have been comparable between control and treated patients in the group seen within 8 hours.[7] In acute TL-IVDH, defining when the initial injury event occurs is problematic because dogs may become paralyzed within an hour or have mild ataxia for several days before deteriorating. In the current trial, the decision was made to allow a 24-hour window from owner observation of onset of paralysis considering the positive finding using a 48-hour window in an experimental canine model of spinal cord injury[38], uncertainty about the statistical validity of the findings in the NASCIS trials,[7] inability to define the precise time when a dog starts to show subtle signs, and concern that the ability to recruit cases would be seriously compromised with shorter time restrictions. Indeed, in this 5-year recruitment period, only 21 dogs presented within 6 hours of onset of paralysis, although with the inclusion of time when dogs were unobserved, some of the dogs allocated to the 12- to 24-hour duration of paralysis group might in reality have presented within the first few hours of onset. The question of whether MPSS would have efficacy in dogs with TL-IVDH if administered at time of onset of paralysis has not been answered in this trial, and will be difficult to address given the time that typically elapses from a dog becoming paralyzed and being presented to a clinical trial study site. Even more difficult to answer is the question of the effect of MPSS if administered at first appearance of paraparesis because the majority of dogs do not progress to paraplegia with no nociception.

Polyethylene glycol also has generated considerable interest for its neuroprotective potential in spinal cord injury. It is a surfactant used in cell culture for its ability to fuse cell membranes.[40] After acute spinal cord injury, membrane permeability is disrupted with devastating results,[41] and this membrane disruption as well as damaged intracellular organelles present a therapeutic target for PEG.[9,42,43] Experimental work in an ex vivo spinal cord preparation demonstrated restoration of conduction across crushed spinal cord.[42,44] In vivo experimental studies also showed functional improvement with topical and systemic administration[45–47] of PEG and a clinical study performed in a similar population of dogs demonstrated its safety.[10] The lack of efficacy shown in this trial is disappointing but does mirror a lack of efficacy shown in 1 experimental study.[48] However, given the safety of this compound and the possibility of enhancing efficacy by better delivery to the injury site, further investigation of its utility is indicated.

We conclude that adjunctive medical treatment of surgically decompressed acute TL-IVDH with either PEG or MPSS is safe when using the protocols outlined

here, but neither drug produced an improvement in outcome in this trial. The power of the trial was limited, but conditional power analyses suggested that additional case recruitment would have been futile. The challenges of recruiting a large number of dogs within a short period of time after severe spinal cord injury are emphasized by this trial.

Footnotes

[a] Solumedrol, Pharmacia and Upjohn Company LLC, Kalamazoo, MI

[b] #P2906: 30% w/w in sterile saline; ~3,500 Da, Sigma Chemical Company, St. Louis, MO

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Supporting Information

Additional Supporting Information may be found online in Supporting Information:

Data S1. Instructions on drug reconstitution.
Data S2. Study paperwork provided to each center.
Data S3. Open field gait score modified from Ref.[19]
Data S4. Signs of PMM in 11 dogs that were euthanized for this problem.
Data S5. *P* values from comparisons of primary and secondary outcome measures between each group at each time point.