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Comparison of Preoperative Quantitative Magnetic Resonance Imaging and Clinical Assessment of Deep Pain Perception as Prognostic Tools for Early Recovery of Motor Function in Paraplegic Dogs with Intervertebral Disk Herniations

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Background: Prognostic tools to predict early postoperative motor function recovery (MFR) after thoracolumbar intervertebral disk herniation (IVDH) in paraplegic dogs represent an opportunity to timely implement novel therapies that could shorten recovery times and diminish permanent neurological dysfunctions.

Hypothesis: Fractional anisotropy (FA) values obtained using diffusion tensor imaging have a higher prognostic value than a lesion extension ratio in T2-weighted images (T2W-LER) and clinical assessment of deep pain perception (DPP) for MFR.

Animals: Thirty-five paraplegic dogs with diagnosis of acute or subacute thoracolumbar IVDH.

Methods: Prospective, descriptive observational study. At admission, absence or presence of DPP, T2W-LER, and FA values was evaluated. MFR was assessed within 4 weeks after decompressive surgery. Values of T2W-LER and FA of dogs with and without MFR were compared using *t*-tests. All 3 methods were evaluated for their sensitivity and specificity as a prognostic factor.

Results: No differences were found between groups regarding T2W-LER. FA values differed statistically when measured caudally of lesion epicenter being higher in dogs without MFR compared to dogs with MFR ($P = .023$). Logistic regression analysis revealed significance in FA values measured caudally of the lesion epicenter ($P = .033$, area under the curve = 0.72). Using a cutoff value of FA = 0.660, the technique had a sensitivity of 80% and a specificity of 55%. Evaluation of DPP had a sensitivity of 73.3% and specificity of 75% ($P = .007$).

Conclusions and Clinical Importance: Evaluation of DPP showed a similar sensitivity and a better specificity predicting early MFR than quantitative magnetic resonance imaging.

Key words: Canine; Diffusion tensor imaging; Paraplegia; Spinal cord injury.

Acute thoracolumbar intervertebral disk herniation (IVDH) is a common neurological disease in dogs that may lead to permanent sensorimotor and visceral function impairments.[1–3] Thoracolumbar IVDH occurs predominantly in chondrodystrophic dogs due to early degeneration of intervertebral disks and exerts a mixture of contusive and compressive forces to the spinal cord.[4–6]

Current treatment for paraplegic dogs with IVDH is focused on eliminating the source of primary mechanical damage and consists of surgical decompression of the spinal cord.[7–10] However, shortly after the primary injury, a complex and dynamic cascade of cellular processes including inflammation, edema, ischemia, reactive species liberation, excitotoxicity, and microglial and astrocytic activation occur.[11–14] This spectrum of responses is known as the "secondary injury," and it occurs seconds to weeks after the primary injury.[12,15]

Research on novel therapies is performed and aims to neutralize or diminish the effects of the early secondary

Abbreviations:

AUC	area under the curve
DPP	deep pain perception
FA	fractional anisotropy
IVDH	intervertebral disk herniation
MRI	magnetic resonance imaging
ROC	receiver-operating characteristics
ROI	region of interest
SCI	spinal cord injury
SD	standard deviation
T2W-LER	T2-weighted—lesion extension ratio
T2W	T2-weighted

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wave of damage.[16,17] Early motor function recovery (MFR) has been rarely explored as an outcome measurement, but represents an opportunity for timelier implementation of novel therapies that could shorten recovery times and contribute to diminish permanent neurological dysfunctions.

Assessment of deep pain perception (DPP) during neurological examination, composition of cell populations and biomarkers present in the cerebrospinal fluid (CSF) and quantitative magnetic resonance imaging (MRI) have been formerly evaluated as prognostic factors for long-term functional recovery in dogs with thoracolumbar IVDH.[2,3,18–25] Evaluation of DPP and length of intramedullary hyperintense signal in sagittal T2-weighted MRI were proven to be useful predictive tools for long-term MFR.[2,18,21,23]

Diffusion tensor imaging (DTI) is a state-of-the-art modality of MRI that allows in vivo microstructural evaluation of white matter tracts by quantifying water molecule diffusion.[26] DTI of the spinal cord has been increasingly applied for numerous diseases including SCI in different animal models and humans.[27–30] Fractional anisotropy (FA) is a unitless value that ranges from 0 to 1. An FA equal to zero represents unrestricted directional diffusion of water molecules, and FA equal to one represents a completely restricted diffusion in only one possible direction.[26,31] Therefore, highly organized tissues such as white matter tracts provide a homogeneous anisotropic environment for water molecule diffusion.[27,32] Recently, feasibility of DTI of the canine healthy spinal cord has been reported and the tissue was characterized.[33–35] As a correlation between parenchymal damage of the spinal cord and severity of neurological deficits was found by Henke and colleagues,[36] the introduction of DTI as an objective clinical tool for assessment of structural integrity of the spinal cord may be valuable for preoperative determination of prognosis.

Therefore, the aim of this study was to evaluate the potential preoperative prognostic value for early MFR in a population of dogs with thoracolumbar IVDH using 3 techniques: measurement of the extension of spinal cord compression and hyperintensity in sagittal T2W sequences at the level of SCI, FA values obtained from DTI sequences, and clinical assessment of DPP. We hypothesize that DTI parameters will show a higher sensitivity and specificity than a lesion extension ratio in T2W images (T2W-LER) and assessment of DPP predicting postoperative MFR.

Materials and Methods

Animals

For this study, dogs admitted to the Department of Small Animal Medicine and Surgery of the University of Veterinary Medicine Hannover between June 2013 and April 2015 were prospectively recruited. The dogs had to fulfill the following inclusion criteria: acute paraplegia (0–7 days since observed onset of clinical signs) or subacute paraplegia (8–28 days since onset of clinical signs),[23,37,38] SCI confined to the T3-L3 spinal cord segments and a body weight <20 kg. Onset of clinical signs was defined and recorded as the time point when owners noticed a nonambulatory state of their dog. Time elapsed between nonambulatory state of the dog and admission to the clinic was used for classification of acute and subacute paraplegia.[25] At admission, each dog underwent a physical and neurological evaluation, plain radiographic imaging of the thoracic and lumbar vertebral column and MRI of the thoracolumbar spinal cord to diagnose IVDH. Furthermore, complete blood workup, serum biochemistry, and CSF analysis were performed to exclude differential diagnoses. IVDH was confirmed during surgery, all dogs were treated with decompressive surgery of the spinal cord, and appearance of MFR was documented within 4 weeks thereafter. Dogs were excluded from the study, if a compression caudal to the L4 vertebral body or neurological deficits compatible with a lower motor neuron lesion were present. Postoperative MFR was noted, when dogs regained voluntary movement of the hindlimbs together with presence of DPP within 4 weeks after decompressive surgery and was recorded as a dichotomous outcome (yes or no). This study was performed after the approval of the German Animal Welfare instances (Number: 33.9-42502-04-11/0661) and the written owners' consent for each examination.

Assessment of Deep Pain Perception

Dogs were tested for presence or absence of DPP during clinical evaluation. Presence of DPP was defined as an obvious and reproducible behavioral response that could be interpreted as pain toward a noxious stimulus (ie, whining, sudden turning the head, and/or biting attempts toward the source of stimulus). For the test, digits of both hindlimbs were clamped using forceps.[2,25,39]

Magnetic Resonance Imaging

Magnetic resonance imaging scans were performed under general anesthesia using a 3 tesla scanner[a] and protocols consisted of sagittal and transversal T2W and transversal DTI sequences as previously reported.[33,34] T2-weighted images sequences were assessed by board certified neurologists (AT, VS, or both) to determine localization of SCI for subsequent surgical procedures. Lesion extension ratio in T2W images (T2W-LER) was defined as lengths of spinal cord compression and intramedullary hyperintense signal expressed as a ratio in relation to length of vertebral body of L2.[21] T2-weighted—lesion extension ratio was evaluated in sagittal planes using commercially available software.[b]

Moreover, T2W images were used as templates for placement of regions of interest (ROIs) in transversal DTI sequences using a DTI software tool.[c] Regions of interest were placed in signals deriving from the spinal cord in FA maps directly dorsally of intervertebral disk spaces at the epicenter of the lesion and one vertebral body cranial and caudal to the epicenter. Epicenters were defined as spinal cord segments with compression evidenced in T2W sequences. As a clear differentiation between gray and white matter can be challenging in the lesioned spinal cord even evaluating conventional T2W sequences, ROIs were positioned in the whole spinal cord parenchyma, as reported previously.[33,34,40] Regions of interest were placed using individual voxels, sized $1.65 \times 1.65 \times 2$ mm, to avoid measuring diffusion metrics deriving from CSF or epidural fat. Afterward, voxels were fused and values of FA were obtained from each ROI.

Statistical Analysis

Dogs were divided into 2 groups: dogs with and without postoperative MFR. Age and body weight between groups were compared via *t*-tests. Variance analyses for FA values at each independent localization were performed. Significances in logistic

regression analyses were calculated and receiver-operating characteristics (ROC) curves were plotted to assess and describe validity of FA and T2W-LER measurements and Youden indices were applied for significances found in order to set a cutoff point. Sensitivity and specificity of DPP was calculated as a dichotomous model using Fisher's exact test. False positives were defined as dogs presenting intact DPP or quantitative MRI values below the cutoff point and showing no MFR. Furthermore, false negatives were defined as dogs presenting absent DPP or quantitative MRI values above the cutoff point and showing early MFR. Continuous variables were depicted descriptively as mean (±standard deviation; SD) for normally distributed variables. Significance level was considered as $P < .05$. Power and sample size calculation, analysis of data, and graphic generation were performed using statistical software.[d,e,f]

Results

Animals

Thirty-five dogs, 19 males and 16 females, fulfilled the inclusion criteria. Thirty-three dogs presented an acute and 2 dogs a subacute SCI due to IVDH. The mean time between onset of nonambulatory status and preoperative clinical examination was 2.2 days (median 1 day, range 0–22 days). Most dogs were Dachshunds with 17 individuals and 7 mixed-breed dogs. Furthermore, 3 French bulldogs, 2 Jack Russell Terrier, 2 Shih-Tzu and 1 dog of each of the following breeds were included: Chihuahua, small Munsterlander pointer, and Lhasa Apso. Twenty dogs showed early MFR within 4 weeks after surgical decompression of the spinal cord, whereas 15 dogs did not improve. No differences in age, weight, or time since onset of clinical signs were found between groups (Table 1). Most common localizations for IVDH were Th12/13 and Th13/L1 with 10 cases each.

T2W—Lesion Extension Ratio

Mean T2W-LER measured from dogs without postoperative MFR was 4.46 ± 1.73 and with postoperative MFR 3.33 ± 1.96. Variance analysis revealed no significant differences between dogs with and without MFR after decompressive surgery ($P = .085$). Logistic regression analysis displayed no significant differences for prediction of early MFR between groups ($P = .097$). ROC curves displayed an area under the curve (AUC) = 0.73 (Fig 1).

Table 1. Comparison of age, body weight, and time between onset of nonambulatory status and clinical examination between groups.

	MFR (n = 20)	No MFR (n = 15)	*P*
Age (years; mean ± SD)	5.5 ± 2.8	6.8 ± 3.5	.22
Body weight (kg; mean ± SD)	9.8 ± 4.2	9.2 ± 3.1	.70
Time between onset of nonambulatory status and clinical examination (days; mean ± SD)	2.9 ± 5.2	1.3 ± 2.0	.28

MFR, motor function recovery; SD, standard deviation.

Fractional Anisotropy

Mean values of FA obtained at the level of epicenters were 0.764 ± 0.067 and 0.775 ± 0.073 for dogs with

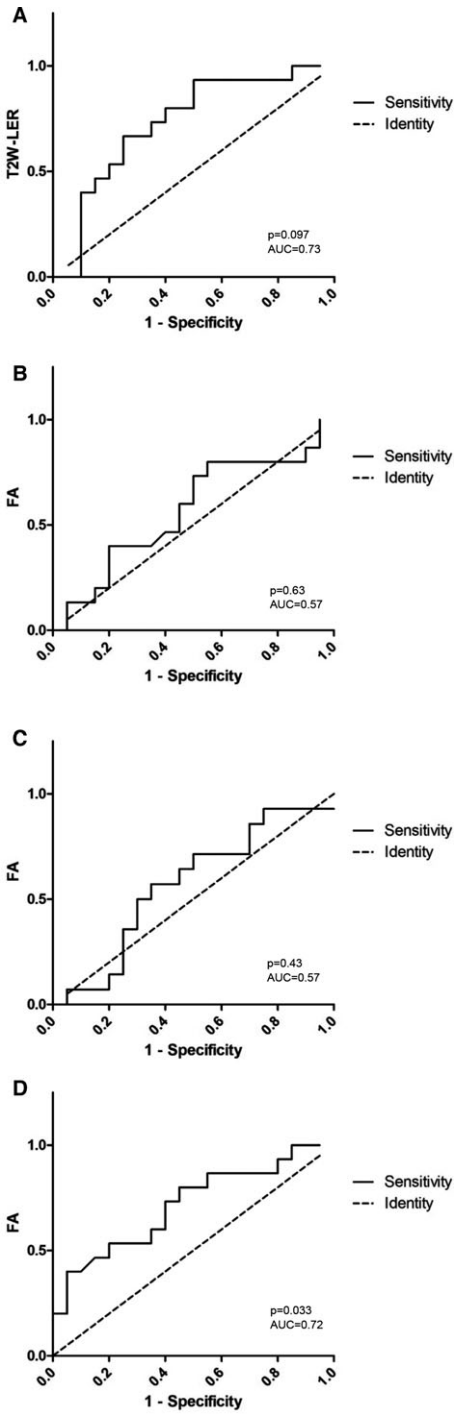

Fig 1. Receiver-operating characteristics (ROC) curves to predict early motor function recovery (MFR). ROC curve for (**A**) values of T2-weighted-lesion extension ratio (T2W-LER) and (**B–D**) fractional anisotropy (FA) values obtained from the spinal cord of 35 paraplegic dogs at the (B) epicenter, (C) one vertebral body cranially, and (D) one vertebral body caudally. *P* value derived from linear predictors calculated through logistic regression analysis at each localization. Abbreviations: AUC, area under the curve.

Table 2. Temporal distribution of dogs at admission time point, motor function recovery (MFR), and presence or absence of deep pain perception (DPP).

	MFR (n = 20)			No MFR (n = 15)			
Time between onset of nonambulatory status and clinical examination	0–1 day	2–3 days	>3 days	0–1 day	2–3 days	>3 days	Total
Presence of DPP	11 (58%)	0 (0%)	4 (21%)	3 (16%)	0 (0%)	1 (5%)	19 (100%)
Absence of DPP	2 (13%)	2 (13%)	1 (6%)	8 (50%)	1 (6%)	2 (13%)	16 (100%)

MFR, motor function recovery; DPP, deep pain perception.

postoperative MFR and without postoperative MFR, respectively. One vertebral body cranially, mean FA value from dogs with MFR was 0.714 ± 0.104, whereas in dogs without MFR values of 0.741 ± 0.093 were determined. Furthermore, measurements of FA one vertebral body caudally to epicenters had a mean of 0.658 ± 0.093 for dogs with MFR and 0.735 ± 0.094 for dogs without MFR. Variance analysis showed no significant differences between groups at lesion epicenters ($P = .95$) and one vertebral body cranial to the epicenter ($P = .44$); however, significant differences in FA were evidenced in the spinal cord one vertebral body caudal to the epicenters ($P = .023$).

Similarly, logistic regression analysis of FA values to predict postoperative MFR revealed no significant differences between groups at the level of epicenters ($P = .63$, ROC curve AUC = 0.57) and one vertebral body cranially ($P = .43$, ROC curve AUC = 0.57). Nonetheless, a significant difference was found caudal to the epicenter ($P = .033$, ROC curve AUC = 0.72; Fig 1). Youden index calculations applied to FA values caudal to the lesion epicenter revealed a sensitivity of 80% (CI 95%, 51.9–95.7%) and a specificity of 55% (CI 95%, 31.5–76.9%) for prediction of negative outcome using a cutoff value of FA >0.660.

Deep Pain Perception

Evaluation of DPP before decompressive surgery revealed a positive response in 19 dogs and a negative response in 16 dogs. About 79% of dogs with intact DPP (15/19) and 31% of dogs with absent DPP (5/16) developed postoperative MFR within 4 weeks after decompressive surgery. Table 2 describes the distribution of paraplegic dogs according to presence or absence of DPP, early MFR, and elapsed time between onset of clinical signs and admission to the clinic.

Fisher's exact test for evaluation of DPP as a prognostic tool for lack of early functional recovery displayed a significance of $P = .007$, sensitivity of 73.3% (CI 95%, 50.9–95.7%), and specificity of 75% (CI 95%, 56–94%).

Discussion

This study prospectively evaluates preoperative measurements of spinal cord lesion extension in conventional T2W MRI sequences, DTI parameters, and clinical assessment of DPP as prognostic factors for early MFR in a population of paraplegic dogs with acute and subacute SCI. Dogs were tested for presence or absence of DPP, length of SCI was measured in sagittal T2W sequences, and values of FA were obtained from epicenter of the lesion and one vertebral body cranially and caudally. After decompressive surgery, neurological examinations were repeated and data from dogs with and without postoperative MFR within 4 weeks were compared.

Evaluation of prognostic tools for early MFR in paraplegic dogs with SCI has been uncommonly reported.[20,41] Establishment of clinical tools that could provide a prognostic value in the time window of early MFR may have an impact on timely selection of patients with unfavorable prognosis for early implementation of novel therapies.

In the population of affected dogs, Dachshund was the breed presented the most and Th12/13 and Th13/L1 occurred most frequently as localization of thoracolumbar IVDH, in ten and eleven cases, respectively, as previously reported.[8,23,42,43] Chondrodystrophic breeds such as Dachshunds are frequently affected by early degeneration of intervertebral disks and presence of intercapital ligaments may partially prevent intervertebral disks to herniate in cranial segments of the thoracic vertebral column.[2–5,23,42,44,45]

Assessment of DPP remains an accepted and commonly applied test for prognosis of recovery in paraplegic dogs with IVDH,[25] although its performance and interpretation have been considered as controversial.[46,47] For long-term functional recovery, presence of DPP in nonambulatory dogs with thoracolumbar IVDH is associated with positive outcomes in nearly 100% of the cases;[2,39,48] however, absence of DPP has been correlated with a recovery rate of approximately 50%.[2,6,25,39] A clear difference is detected in the current study with lower accuracy of DPP to predict early MFR in comparison with formerly reported prediction of long-term MFR. Late-onset recovery of ambulation in paraplegic dogs with IVDH after surgical decompression can appear up to 6 months thereafter and ranges from 13.4% to 31.8% of which some dogs regain ambulation without regaining DPP.[2] However, for early application of novel treatment strategies in dogs which would fail standard therapy, prediction of early MFR becomes useful and necessary allowing selection of target populations.

Values of T2W-LER displayed no significant differences between dogs with and without early MFR. This finding contrasts previous studies, where longer

intramedullary hyperintensities in sagittal T2W sequences were predictive for unfavorable long-term outcome using 0.3 and 1 tesla magnetic fields.[18,21,23] Use of high-field MRI leads to increase in signal-to-noise ratio and consequently to a change in image resolution;[49] therefore, mild intramedullary hyperintensities in sagittal T2W sequences may be more frequently evident using 3 tesla magnetic fields. Presence of intramedullary T2W hyperintensities during acute and subacute stages of SCI is assumed to be a consequence of edema, hemorrhage, and necrosis.[6,50] This study intended not only to quantify hyperintense signal in sagittal T2W sequences but the complete extension of the SCI, including length of intramedullary intensity changes as well as extramedullary spinal cord compressions. However, preoperative T2W-LERs seem not to be of prognostic value for early MFR using high-field MRI. Based on the previous literature evaluating early MFR,[41,51] a sample size of 44 paraplegic dogs, 22 per group, was calculated to detect differences between groups with an alpha level of 0.05 and power of 0.80 using DPP as gold standard technique. Although the initial calculated sample size could not be reached, achieved statistical power for DPP and FA was 0.81 and 0.79, respectively. However, the achieved power for T2W-LER within the population evaluated reached only 0.60, and therefore, a type II statistical error could influence the data concerning T2W-LER.

To the author's knowledge, this study is the first report to evaluate DTI parameters as prognostic tool for MFR in paraplegic dogs with IVDH. Increased preoperative FA values were found one vertebral body caudal to the lesion epicenter in dogs without MFR compared to dogs that showed MFR suggesting the occurrence of cytotoxic edema and axonal swelling.[52–54] Although a difference was found, the ability of DTI parameters to predict early MFR was lower than evaluating DPP preoperatively, displaying a similar sensitivity but a remarkably lower specificity. Therefore, the assessment of preoperative DTI parameters did not offer benefits over DPP assessment.

Differentiation between gray and white matter in the compressed and lesioned spinal cord is challenging, even in conventional MRI sequences. Attempts to independently measure DTI metrics from white and gray matter using clinically applicable protocols could lead to partial volume effects;[55] therefore, ROIs were placed in both, gray and white matter, and were positioned equally in all patients. Albeit no intramedullary signal voidance was noticed in T2* sequences, foci of intramedullary hemorrhage may have an impact in diffusion metrics.[56]

In conclusion, ability to predict early postoperative MFR was evaluated for clinical assessment of DPP, sagittal T2W sequences, and DTI parameters of the spinal cord of paraplegic dogs with acute and subacute IVDH. The hypothesis could not be proven that DTI shows a higher sensitivity and specificity than a lesion extension ratio in T2W images (T2W-LER) and assessment of DPP predicting postoperative MFR. In fact, presence of intact DPP had a similar sensitivity and a better specificity in predicting early functional recovery than quantitative MRI, herewith still emphasizing the importance of clinical examination.

Footnotes

[a] Philips Achieva, Phillips Medical Systems, Eindhoven, The Netherlands
[b] EasyVET, Version 8.0.0.03/R3, Isernhagen, Germany
[c] Extended MR workspace, Version 2.6.3.4, Philips Medical Systems, The Netherlands
[d] G*Power, version 3.1.9.2, University of Duesseldorf, Germany
[e] SAS software, version 9.2, SAS Institute, Cary, NC
[f] GraphPad Prism, version 5, GraphPad Software, CA

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Conflict of Interest Declaration: Andrea Tipold serves as Associate Editor for the Journal of Veterinary Internal Medicine. She was not involved in review of this manuscript.

Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

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