



## Canine Research

# Clinical findings in degenerative lumbosacral stenosis in ten dogs—A pilot study on the analgesic activity of tramadol and gabapentin



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## ABSTRACT

Degenerative lumbosacral stenosis is a relatively common multifactorial disease that affects mainly large breed or working dogs. It can cause neuropathic pain, and advanced imaging techniques are essential to achieve a final diagnosis. For improving the quality of life, when surgery is not possible, a conservative treatment is necessary. The management of pain requires early intervention and evaluation of response on an individual-patient basis. The aim of the study was to evaluate the use of tramadol for the treatment of lumbosacral pain in dogs affected by degenerative lumbosacral stenosis diagnosed by radiographs, computed tomography, and computed tomography myelography, considering gabapentin as an alternative treatment in case of unresponsiveness. Ten dogs were enrolled, and clinical findings and their severity scores were recorded; the short form of the Glasgow composite pain scale was used to assess pain scores before ( $8.6 \pm 1.5$ ; 7–11/20) and during treatment (after 1, 2, and 4 weeks) with oral tramadol (3 mg/Kg every 8 hours) and prednisolone (0.5 mg/Kg/die) for 4 weeks. After the first week of therapy, only half of the dogs (5/10, T-group) showed a significant improvement of Glasgow composite pain scale score; in the remaining five dogs (G-group), tramadol was changed with oral gabapentin (10 mg/Kg every 8 hours for 3 weeks), with an improvement in pain score in one week. At the end of treatment, all the dogs showed low pain scores (T-group:  $2.8 \pm 0.8$ ; G-group:  $1.6 \pm 0.9$ ), below the intervention level (4/20). Given the supported evidence, oral tramadol should not be relied on as a sole or, perhaps, first-line analgesic in dogs, and gabapentin might be a valid alternative option in an outpatient setting. As controlled clinical trials are still lacking in animals, further studies should be carried out to confirm the analgesic activity of gabapentin in veterinary painful conditions and to rule out eventual adverse effects related to a prolonged administration.

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## Introduction

The International Association for the Study of Pain defines nociception as “the neural processes of encoding and processing noxious stimuli.” The International Association for the Study of Pain now clearly distinguishes between nociceptive and neuropathic pain.

Nociceptive pain is a pain caused by tissue injury that is stimulus-evoked and mediated by normally quiescent C polymodal nociceptors through dorsal root ganglion and spinal neurons; it is associated with increased neuronal activity through wide dynamic range neurons in the spinal cord, and it can be managed by opioids (Shubayev et al., 2010).

Neuropathic pain is a “pain initiated or caused by a primary lesion or dysfunction in the nervous system” (Merskey and Bogduk, 1994). To clarify the unspecific term of “dysfunction,” another definition described neuropathic pain as a “pain arising as a direct result of a lesion or disease affecting the somatosensory system” (Treede et al., 2008). Such pain does not provide any benefit to the organism and can be considered as a disease in itself (Epstein et al.,

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2015). Neuropathic pain is often refractory to traditional analgesic medications (Shubayev et al., 2010). Neuropathic pain has been reported in 8% of dogs and 7% of cats (Muir et al., 2004).

If the diagnosis of nociceptive physiological pain is difficult in nonverbal veterinary patients, the diagnosis of neuropathic pain can be extremely difficult, unless a predisposing lesion or injury is identified. Some conditions are well known to cause neuropathic pain in dogs and cats and can be associated with surgery, neuropathies, congenital abnormalities, and vasculitis.

A common source of neuropathic pain in dogs is degenerative lumbosacral stenosis (DLSS), caused by several alterations of the bone and soft tissues surrounding the *cauda equina* (L7-S1 segment), resulting in the compression of the terminal part of the medulla (Meij and Bergknut, 2010). This compression causes the demyelization and inflammation of nerve roots with the release of various proinflammatory cytokine (tumor necrosis factor, interleukin-6, and interleukin-1 $\beta$ ) and growth factors, and the activation of astrocytes and microglia that in turn will release cytokines (neuropathic cascades). Cytokines regulate changes in neuronal ion channels, also influencing endocytosis of  $\gamma$ -aminobutyric acid (GABA) receptor and glutamate uptake by glial transporters (Shubayev et al., 2010).

The complex of clinical signs commonly reported in dogs with DLSS is known as *cauda equina* syndrome, consisting in caudal lumbar or lumbosacral pain, pelvic limb lameness, hyperesthesia or self-mutilation of the lumbosacral area or pelvic limbs, difficulty with rising, sitting, or lying down, reluctance to jump or climb, dragging of toes, a low carriage of the tail, and urinary and fecal incontinence (Meij and Bergknut, 2010). Clinical signs can be acute or chronic, continuous, or intermittent.

The syndrome occurs mainly in large breed dogs, especially German Shepherd and working dogs, with a prevalence rate increasing with age (mean age at presentation 7 years) and with male dogs more affected than female (De Risio et al., 2001; Suwankong et al., 2008). Dogs undergoing intensive work or physical activity and overweight are at a higher risk (De Decker et al., 2014; Suwankong et al., 2006, 2008).

Diagnosis is initially based on history and neurological examination. Although plain radiographs can help to exclude bone neoplasia and traumatic luxation, they are not enough to rule out a suspicion of DLSS. To confirm the diagnosis, more advanced techniques, such as computed tomography (CT), magnetic resonance imaging, and CT myelography (myelo-CT) are required (Steffen et al., 2007; Suwankong et al., 2006).

Dorsal laminectomy is the main surgical treatment performed in dogs with DLSS (Suwankong et al., 2008), with the aim of decompressing the *cauda equina* and free the entrapped nerve roots (Meij and Bergknut, 2010). The success rate reported after surgery ranged between 70% and 93% (De Risio et al., 2001; Suwankong et al., 2008). Although the prognosis for dogs surgically treated for DLSS is generally good, return to normal function is more likely in the least affected dogs, whereas severely affected dogs often show persisting neurologic deficits. Moreover, recurrence of clinical signs may occur after surgery.

Medical conservative treatment of DLSS aims at controlling pain and does not solve the underlying problem. Medical treatment usually consists of the administration of nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroids, together with the reduction of body weight and physical activity (Meij and Bergknut, 2010). Physiotherapy, regular walks, and underwater treadmill may help recovery and improving muscle tone. Lumbosacral injections of methylprednisolone have been shown to be an effective treatment in dogs without proprioceptive deficits and urinary and/or fecal incontinence, showing an improvement in 79% of the animals (Janssens et al., 2009). Only one retrospective study exists on conservative treatment in dogs with DLSS. Based on clinical signs and

owner's opinions, 55% of the animals had a successful outcome (De Decker et al., 2014).

In human medicine, given the tendency to respond less to traditional treatments, several drugs have been used to treat neuropathic pain and lumbosacral stenosis, such as tramadol and gabapentin (Parker et al., 2014; Pribudak et al., 2015; Yaksi et al., 2007).

Tramadol is a synthetic codeine analog, which provides pain relief through different levels of action, especially the inhibition of norepinephrine and serotonin uptake. Its primary metabolite, O-desmethyltramadol, which is not produced by dogs, shows an affinity with  $\mu$ -receptors 20 to 200 times higher than tramadol itself (KuKanich and Papich, 2004; Kukanich, 2013). The inhibition of the reuptake of norepinephrine and serotonin is thought to contribute significantly to the drug's analgesic activity, possibly representing an advantage in humans and animals with neuropathic pain. Compared with other opioids, it appears to cause less respiratory depression and problems of tolerance and abuse. In humans, it has a half-life of about 4–6 hours, and the onset of the analgesic effect is achieved after 10–20 minutes. Administered orally and parenterally in humans and animals, it seems to have a good analgesic activity on different types of pain (Perez-Jimenez et al., 2016). Undesirable effects include dysphoria and sedation, especially in cats, and reduced seizure threshold in humans. Tramadol is often used in dogs for postoperative pain control because of its nonaddictive effect and relatively low cost. In the United States, tramadol is classified as a narcotic drug, requiring a narcotic type prescription; however, in other countries, it is still considered a non-narcotic drug, representing a good compound for short-term treatment at home. Although some studies have evaluated the analgesic effects of tramadol in dogs undergoing surgical procedures (Giudice et al., 2017), there are few studies assessing the effects of tramadol administration to canine patients in controlled clinical trials, and there is a lack of report on neuropathic pain. The last Cochrane report (Duehmke et al., 2017) on the use of tramadol for neuropathic pain in humans assessed that larger trials are needed to know if tramadol is really useful for the management of neuropathic pain. There are few sufficiently powered studies in dogs or cats to allow determination of effect size (KuKanich, 2013).

Gabapentin [1-(aminomethyl) cyclohexanecarboxylic acid] is an antiepileptic drug, which is a structural analogous of GABA, but it does not bind to GABA-A or GABA-B receptors, it is not metabolically converted into GABA or a GABA agonist, and it is not a reuptake inhibitor of GABA (Cheng and Chiou, 2006). Several studies have shown that gabapentin blocks the channels of Ca<sup>2+</sup> and Na<sup>+</sup>, by binding  $\alpha 2\text{-}\delta$  subunit of the voltage-gated calcium channels, and opens K<sup>+</sup> channels, acting presynaptically by decreasing the glutamate and glutaminergic synaptic transmission and substance P release (Taylor, 2009). Moreover, it has been described that gabapentin interacts with N-methyl-D-aspartate receptors involved in the development of central sensitization (Pozzi et al., 2006) and activates the descending noradrenergic system and induces spinal norepinephrine release (Takeuchi et al., 2007).

More recently, gabapentin has been found to be effective for the management of chronic and neuropathic pain in humans (Lewis et al., 2016; Yaksi et al., 2007). In lumbar spinal stenosis, the drug has been reported to provide a longer walking distance, lower pain score, and better recovery of sensory deficit compared with standard treatment with NSAIDs and physiotherapy (Yaksi et al., 2007).

Along with published clinical case reports in animals, the data suggest a strong rationale for using gabapentin in dogs and cats with similar conditions (Epstein et al., 2015). Gabapentin analgesic mechanism is still not completely understood, but it showed anti-hyperalgesic and antiallodynic effects in a rat model of induced neuropathic pain (Mangaiarkkarasi et al., 2015). In the veterinary

literature, gabapentin has been used to treat pain both in dogs and cats (Epstein et al., 2015; Plessas et al., 2015). Gabapentin has also been used in dogs for postoperative treatment after intervertebral disc surgery (Aghighi et al., 2012), forelimb amputation (Wagner et al., 2010), and mastectomy (Crocioli et al., 2015), with no effects. However, inappropriately low dosages (5–10 mg/kg every 12 hours) were used, meaningful conclusions could not be drawn from these studies (KuKanich, 2013). Although no significant adverse effects except somnolence have been reported both in human and animal studies after treatments with gabapentin (Epstein et al., 2015), sedation, and ataxia are possible when administered at higher dosages or when combined with other drugs that produce similar adverse effects (KuKanich, 2013).

The aim of this study was to evaluate the use of tramadol as medical conservative treatment for lumbosacral pain in dogs affected by DLSS, considering gabapentin as an alternative treatment in case of unresponsiveness.

## Material and methods

This prospective study was carried out in a high-standard veterinary referral clinic specialized in neurosurgery, in accordance with good clinical practice (Federation of Veterinarians of Europe, FVE, Code of Good Veterinary Practice, 2003). Protocols of animal husbandry and experimentation were reviewed in accordance with the Directive 2010/63/EU for animal experiments and approved by the Ethics Committee of the Department of Veterinary Sciences of the University of Messina.

All dogs diagnosed with DLSS that underwent a conservative medical treatment were enrolled in the study, after the informed consent was provided by the owners. Animals that, based on the history and clinical examination, were affected by concomitant painful diseases were excluded from the study.

On first clinical evaluation, anamnesis regarding type and onset of clinical signs was recorded. The dogs underwent a neurological examination, to determine the localization of the lesion by assessing postural reactions and spinal reflexes of the hind legs. The hemistand, hemiwalk, hopping, conscious proprioception, and wheelbarrow thoracic limbs tests were performed to assess the conscious perception of body position in the space and to emphasize the possible weakness in the forelegs. The normality of these tests allowed the exclusion of spinal injuries located at an upper level than the lumbosacral area. The evaluation of the spinal reflexes of the hind limbs, the patellar, cranial tibial muscle, sciatic nerve, and withdrawal reflexes was performed to evaluate the L4–S2 spinal tract. Abnormalities of the hind leg spinal reflexes, together with normal postural reactions, provided a clinical diagnosis of a lumbosacral lesion and a suspect of DLSS.

All the dogs suspected of DLSS were selected for CT examination, undergoing a preanesthesia screening. Two spine radiographs in laterolateral and ventro-dorsal projections were performed and a CT spiral scan (Toshiba, “Asteion VR”) examination of the L4–S1 spinal tract was started, with the anesthetized patient in dorsal recumbency. When it was not possible to find an obvious hypodense or hyperdense lesion of the spinal tissue on the CT examination, a myelo-CT of the same spinal segment was performed, to achieve a definitive diagnosis. An organic tri-iodinated nonionic contrast medium (Iohexol, Omnipaque® 300 mg I/mL, GE Healthcare; 0.1 mL/Kg) was injected in L5–L6 subarachnoid space, to highlight any intradural or extradural compression. All the imaging studies were reviewed by the same veterinarian.

After the diagnosis of DLSS was performed, in dogs where the surgical treatment was rejected because of the animal clinical conditions or financial constraints, a conservative medical treatment was suggested.

Each dog underwent neurological examinations before the medical treatment was started (T0) and after one (T1), two (T2), and four (T4) weeks of treatment. Evaluations of muscle tone, conscious proprioception, and withdrawal and patellar reflexes were recorded at each time point, assigning a verbal rating with a corresponding numerical score, as follows:

- Muscle tone: normal (0), decreased (1), and muscle atrophy (2);
- Proprioception: normal (0), decreased (1), absent (2), and exaggerated (3);
- Withdrawal reflex: normal (0), decreased (1), absent (2), and exaggerated (3);
- Patellar reflex: normal (0), decreased (1), absent (2), and exaggerated (3).

To evaluate the degree of lumbosacral pain, the short form of the Glasgow composite pain scale (GCPS-SF) (Reid et al., 2007; Figure 1) was used, and the scores obtained at T0, T1, T2, and T4 were recorded. Pain evaluation was performed by the same veterinarian, to avoid a possible interobserver variability. The owners were specially trained to use GCPS-SF and their feelings about the behavioral changes and degree of pain of their animals were also recorded on each day of the treatment (Figure 1).

The dogs were treated with prednisolone (Vetsolone® 5 mg, Bayer Spa, Div. Sanità Animale, Milan, Italy; 0.5 mg/Kg/die) orally for three weeks and then on alternate days during the fourth week. At the same time, the dogs were treated with tramadol (Altadol®, Farmavet, Urbisaglia, MC, Italy; 3 mg/Kg PO every 8 hours) for 4 weeks (T-group). A weight loss diet was suggested to reduce the postural stress related to overweight, when indicated.

On the third day, when the dog did not show any significant improvement of lumbosacral pain (based on the evaluation of the owner, questioned by phone), tramadol was increased to 4 mg/Kg. On the seventh day, during the first control visit (T1), when the dog did not improve in the GCPS-SF score, it was considered unresponsive. Tramadol was then changed with gabapentin (Gabapentin®, Teva Italia, Milan, Italy; 10 mg/Kg PO every 8 hours) and treatment continued for 3 weeks (G-group).

## Statistical analysis

Descriptive statistic was applied for age and body weight, evaluating mean  $\pm$  standard deviation and range (minimum–maximum). Data were analyzed for normal distribution with the Shapiro-Wilk normality test and were not normally distributed ( $P > 0.05$ ).

The Mann-Whitney U Test and Wilcoxon signed rank test were used to evaluate the effect of the treatment and time on the evaluated parameters (muscle tone, conscious proprioception, withdrawal and patellar reflexes, and GCPS-SF scores) between and within groups of dogs (T-group: tramadol; G-group: gabapentin) at each time point (T0, T1, T2, and T4). Statistically significance was set at  $P < 0.05$ . All data collected during the trial were entered into a spreadsheet (Microsoft Excel); the statistical tests were performed using the STATISTICA 7 software (Stat Soft, Inc, Tulsa, OK; 2003).

## Results

Ten dogs of different breeds (2 Labrador retriever; 2 mongrel dogs; 1 boxer; 1 collie; 1 Kurzhaar; 1 Samoyed; 1 Siberian husky; 1 Newfoundland), sex (5 males and 5 females), age ( $6.9 \pm 3.5$ ; 2.5–11.5 years), and body weight ( $32.4 \pm 8.7$ ; 22–52 Kg) met the inclusion criteria and were enrolled in the study. Seven of ten dogs (70%) were companion animals, whereas three (30%) were working

SHORT FORM OF THE GLASGOW COMPOSITE PAIN SCALE

Dog's name \_\_\_\_\_  
 Hospital Number \_\_\_\_\_ Date / / Time \_\_\_\_\_  
 Surgery Yes/No (delete as appropriate) \_\_\_\_\_  
 Procedure or Condition \_\_\_\_\_

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

**A. Look at dog in kennel**

Is the dog?

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

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

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

When the dog rises/walks is it?

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

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

Does it?

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

**D. Overall**

Is the dog?

(v)	
Happy and content or happy and bouncy	0
Quiet	1
Indifferent or non-responsive to surroundings	2
Nervous or anxious or fearful	3
Depressed or non-responsive to stimulation	4

Is the dog?

(vi)	
Comfortable	0
Unsettled	1
Restless	2
Hunched or tense	3
Depressed or non-responsive to stimulation	4

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

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Short Form of the Glasgow Composite Pain Scale (SF-GCPS) with assessment record sheet, to be used by dog owners

If Total Score is greater than 5 (4 when not carrying out section B) give analgesics

Date:

Time:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
A1																								
A2																								
B1																								
C1																								
D1																								
D2																								
Total																								

Notes:

Figure 1. The short form of Glasgow composite pain scale (GCPS-SF) with the record sheet (Reid et al., 2007).

dogs. All the dogs were slightly to moderately overweight (body condition score: 6.1 ± 0.9; 4.5-7/9).

The most common clinical signs reported by owners were weakness, back pain, monolateral or bilateral hind leg lameness and reluctance to jump, climb the stairs, and sit down. According to the owners, clinical signs started from 3 days to 2 months before (19.7 ± 17 days). None of the dogs showed urinary or fecal incontinence, and postural tests did not show any proprioceptive deficit, allowing the exclusion of spinal injuries above the lumbosacral tract.

On the first clinical evaluation, evoked pain on palpation of the L7-S1 spinal tract and mild to severe monoparesis or paraparesis of hind limbs were found in all the dogs (10/10). A decreased muscle tone, a patellar pseudohyperreflexia, and a marked slowing in the hind limb withdrawal reflexes occurred in 70% (7/10), 50% (5/10), and 70% (7/10) of dogs, respectively (Table 1). All these changes were indicative of a lesion involving the L4-S1 spinal segment.

Standard survey radiographs were indicative of lumbosacral disease only in 30% (3/10) of dogs. In particular, the laterolateral

**Table 1**

Major neurological signs at enrollment and pain scales GCPS-SF per dog at the different time points during 4-week treatment (T-Group: tramadol; G-Group: gabapentin) in canine degenerative lumbosacral stenosis

Group	Case	Neurological signs	GCPS-SF score			
			T0	T1	T2	T4
T-Group	1	Evoked lumbosacral pain, mild hind limb paraparesis	7	6	5	2
	2	Evoked lumbosacral pain, mild left hind limb paresis	8	5	4	2
	3	Evoked lumbosacral pain, mild hind limb paraparesis with muscular hypotrophy, and marked slowing in the withdrawal reflexes and patellar pseudohyperreflexia	9	6	5	3
	5	Evoked lumbosacral pain, severe hind limb paraparesis with muscular hypotrophy, and marked slowing in the withdrawal reflexes and patellar pseudohyperreflexia	10	6	5	4
	7	Evoked lumbosacral pain, severe right hind limb paresis with muscular hypotrophy, and marked slowing in the withdrawal reflex and patellar pseudohyperreflexia	9	7	6	3
	Mean ± SD		8.4 ± 1.1	6.0 ± 0.7	5.0 ± 0.7	2.8 ± 0.8
G-Group	4	Evoked lumbosacral pain, mild hind limb paraparesis with muscular hypotrophy, and marked slowing in the withdrawal reflexes	9	9	5	2
	6	Evoked lumbosacral pain, severe hind limb paraparesis and muscular hypotrophy, marked slowing in the hind limb withdrawal reflexes, patellar pseudohyperreflexia	11	10	7	3
	8	Evoked lumbosacral pain, mild hind limb paraparesis	6	8	5	1
	9	Evoked lumbosacral pain, mild hind limb paraparesis with muscular hypotrophy, and marked slowing in the withdrawal reflexes	8	8	6	1
	10	Evoked lumbosacral pain, severe hind limb paraparesis and muscular hypotrophy, marked slowing in the hind limb withdrawal reflexes, patellar pseudohyperreflexia	9	9	6	1
	Mean ± SD		8.6 ± 1.8	8.8 ± 0.8	5.8 ± 0.8	1.6 ± 0.8

GCPS-SF, short form of the Glasgow composite pain scale.

projection showed subchondral sclerosis of the L7-S1 endplates (case 10), increased radiopacity of the L7-S1 intervertebral space (case 7), and S1 caudal displacement (case 2), respectively.

The CT examination allowed definitive diagnosis of DLSS in 50% of the dogs, whereas in the remaining 50% (cases 3, 4, 6, 7, and 9), it was necessary to perform myelo-CT (Figure 2A). Slight L7-S1 disc bulging and disc protrusion (Figure 3A) was found, respectively, in 40% (cases 5, 6, 7 and 9) and in 30% of dogs (cases 3, 4 and 10) with reduction of the vertebral foramen and dorsal deviation of the dural sac and *cauda equina*; S1 showed mild caudal displacement (Figure 2B) in 30% (cases 2, 4, and 7); mild to moderate intervertebral foraminal stenosis was seen (Figure 3B), with the presence of hyperdense material in the foraminal space, in 60% (cases 2, 3, 5, 6, 7, and 8), monolateral only in one dog (case 2); L7-S1 showed endplates irregularity in 50% (cases 1, 6, 7, 8, and 10) due to severe sclerosis (hyperdensity; cases 6 and 10), lysis (hypodensity, consistent with discospondylitis; cases 1 and 8) or deformity (consistent with spondylarthritis; case 7) (Table 2).

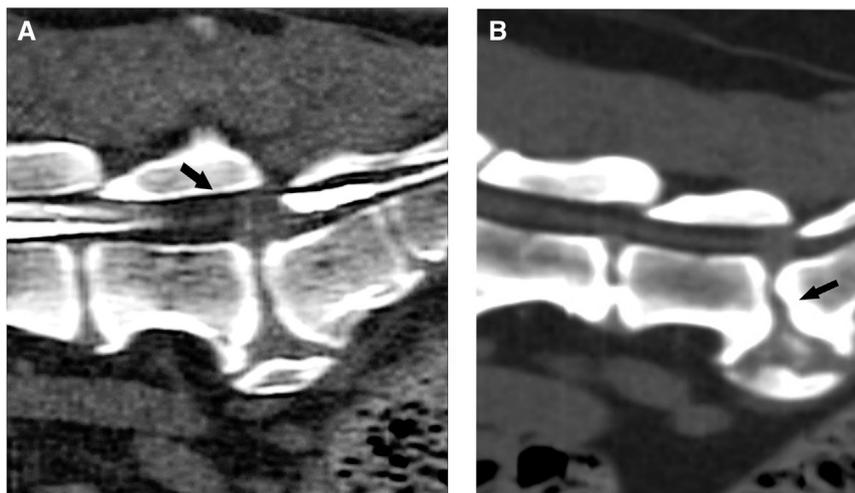
After one week of treatment (T1), 50% (5/10) of dogs showed only a slight improvement of clinical and neurological conditions, without any significant decrease of lumbosacral pain (Table 1), thus tramadol was changed with gabapentin (G-group).

In the responding dogs (5/10; T-group), based on the owner's assessment record sheet, time lag before improvement was  $50 \pm 10$  hours. Owners reported relevant improvement in general condition: the dogs were quiet but more responsive to surroundings, moved more easily, and improved in mood.

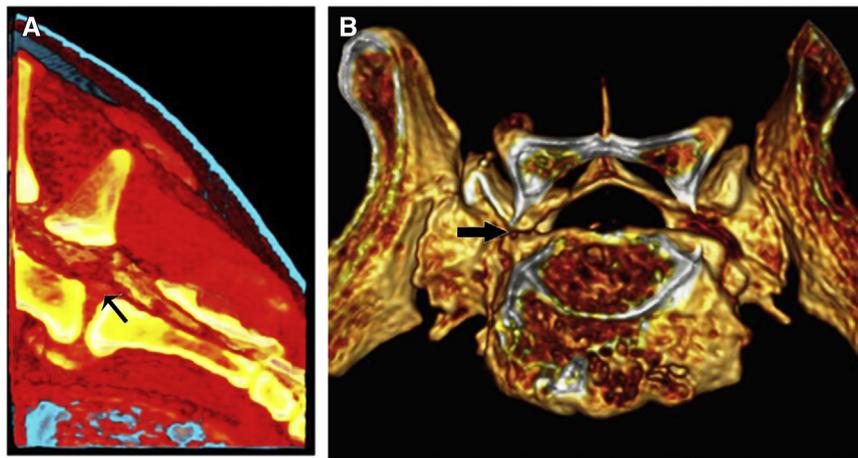
Conscious proprioception remained normal (score 0) in all the dogs at each time points.

Statistical analysis showed a significant effect of time on muscle tone and lumbosacral pain but not on withdrawal and patellar reflexes. In particular, there was a significant effect of treatment on increasing muscle tone only in the G-group at T4 ( $P < 0.05$ ) but not at T2 or in the T-group at all time points (Figure 4).

Regarding lumbosacral pain assessment, section B (mobility) of GCPS-SF was not carried out because all the animal showed



**Figure 2.** (A) Disappearance of the contrast lines on computed tomography myelography (myelo-CT) due to a severe compression of the L7-S1 dural sac (case 3); (B) CT image of S1 caudally displacement (case 2).



**Figure 3.** (A) 3D Reconstruction (soft tissues algorithm) of a computed tomography (CT) image of L7-S1 disc protrusion (case 3); (B) 3D reconstruction (bone tissue algorithm) of a CT image in transverse section of moderate foraminal stenosis (case 2).

different degrees of paresis of the hind legs, so that the total score was of 20 rather than 24 (Figure 1).

At the first clinical evaluation (T0), the GCPS-SF mean score was  $8.6 \pm 1.5$  (range: 6–11), above the intervention level (4 out of 20), attesting a moderate degree of pain. No statistically significant difference ( $P > 0.05$ ) between the two groups was recorded, showing homogeneity of the sample (T-group:  $8.6 \pm 1.1$ , 7–10; G-group:  $8.6 \pm 1.8$ , 6–11). In the T-group, a lower ( $P < 0.001$ ) GCPS-SF score was found at T1 ( $6.0 \pm 0.7$ ) when compared with T0 and to G-group ( $8.8 \pm 0.8$ ). In the G-group, GCPS-SF score did not change ( $P > 0.05$ ) after one week of treatment with tramadol (T1), attesting that these animals were nonresponders. However, after the analgesic treatment has been switched to gabapentin, a significant decrease ( $P < 0.001$ ) in pain score occurred in all the five dogs; no statistical differences ( $P > 0.05$ ) were found between the two groups both at T2 and T4, and a statistical effect of time ( $P < 0.001$ ) was found within both groups in all the time points. In particular, after the second week of treatment (T2), GCPS-SF scores were considerably lower in both groups (T-group:  $5.0 \pm 0.7$ , 4–6; G-group:  $5.8 \pm 0.8$ , 5–7), but still around the possible intervention level. After four weeks of treatment (T4), all the dogs showed a further reduction in GCPS score (T-group:  $2.8 \pm 0.8$ , 2–4; G-group:  $1.6 \pm 0.9$ , 1–3), below the intervention level (Table 1 and Figure 5).

## Discussion

The results of this study are in accordance with the epidemiology of DLSS in dogs. All the animals were of middle sized to large breed, with a mean age of 7 years, as it was already described in

previous studies (De Risio et al., 2001; Suwankong et al., 2008), and most of them were in an overweight condition.

Clinical signs, and the time of onset before the first clinical evaluation, were comparable to previous studies (Suwankong et al., 2008), with lameness, back pain, and difficulty to jump and sit down the most commonly reported.

Advanced diagnostics had been essential for the diagnosis of DLSS. Only in three cases, conventional radiology provided a suspect of disease, whereas in half of the patients, it was necessary to perform a myelo-CT to confirm the diagnosis. As already described (Suwankong et al., 2006), the most common abnormalities detected on CT scan were L7-S1 disc bulging or protrusion; mild to moderate foraminal stenosis, more often bilateral, severe sclerosis or lysis of the endplates.

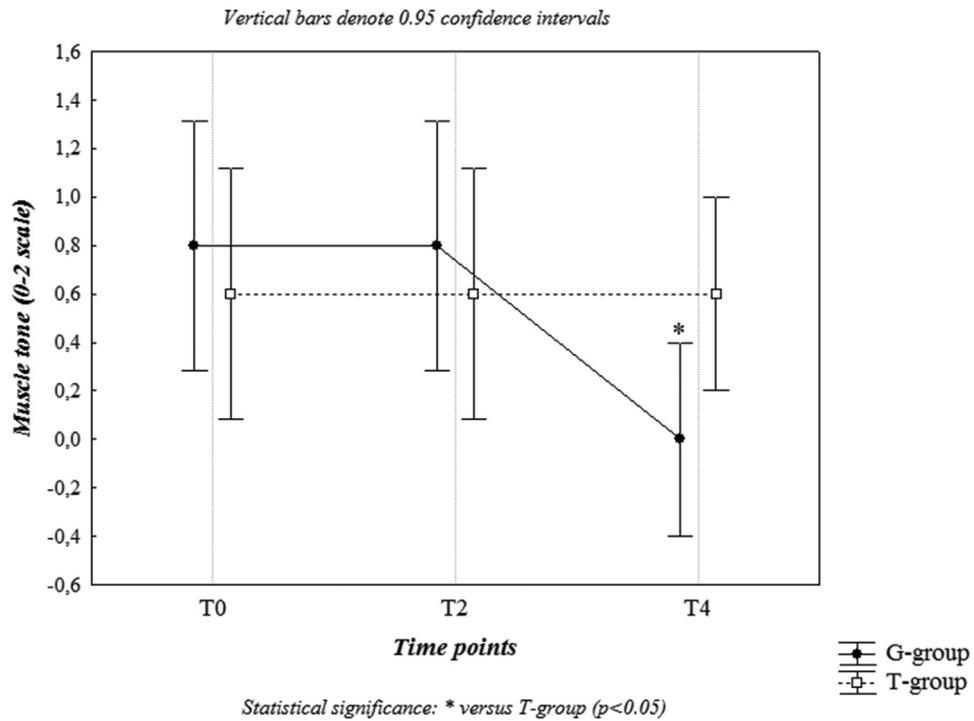
It is widely recognized that disc and spine pathological conditions and surgeries are characterized by moderate to severe degree of pain, as confirmed by the pain scores recorded during the first evaluations of our sample. The control of pain is part of a veterinarian's duty of care to ensure animal welfare. Painful sensations determine alterations of various body systems, including cardiovascular, respiratory, gastroenteric, and immune systems, and slow down the tissue healing process. Pain is also known to provoke behavioral changes potentially dangerous for humans. Behavioral changes are currently the principal indicator of pain and its course of improvement or progression, and the basis for recently validated pain scores (Epstein et al., 2015). The GCPS is a validated behavior-based composite scale, developed using psychometric methodology, to assess acute pain in dogs (Morton et al., 2005). A short form of GCPS-SF was developed for routine clinical use, where the emphasis is on speed, ease of use, and guidance for analgesia provision (Reid et al., 2007).

Although the importance of analgesia in veterinary medicine has increased significantly over the past two decades, several surveys suggested that analgesic drug use in small animal veterinary practice is still suboptimal (Reid et al., 2007). The growing awareness has been accompanied by a proliferation of pain control options, including new drugs labeled for veterinary use and several compounds routinely used off-label, such as tramadol and gabapentin, respectively.

Although tramadol has become very popular in veterinary medicine, significant and ongoing debate about its clinical efficacy in dogs still exists (Epstein et al., 2015; KuKanich, 2013). Although it appears to have a wide margin of safety and minimal adverse effects, a large amount of both preclinical and clinical research

**Table 2**  
Distribution of cases within the different class of findings detected on computed tomography examination in 10 dogs affected by degenerative lumbosacral stenosis

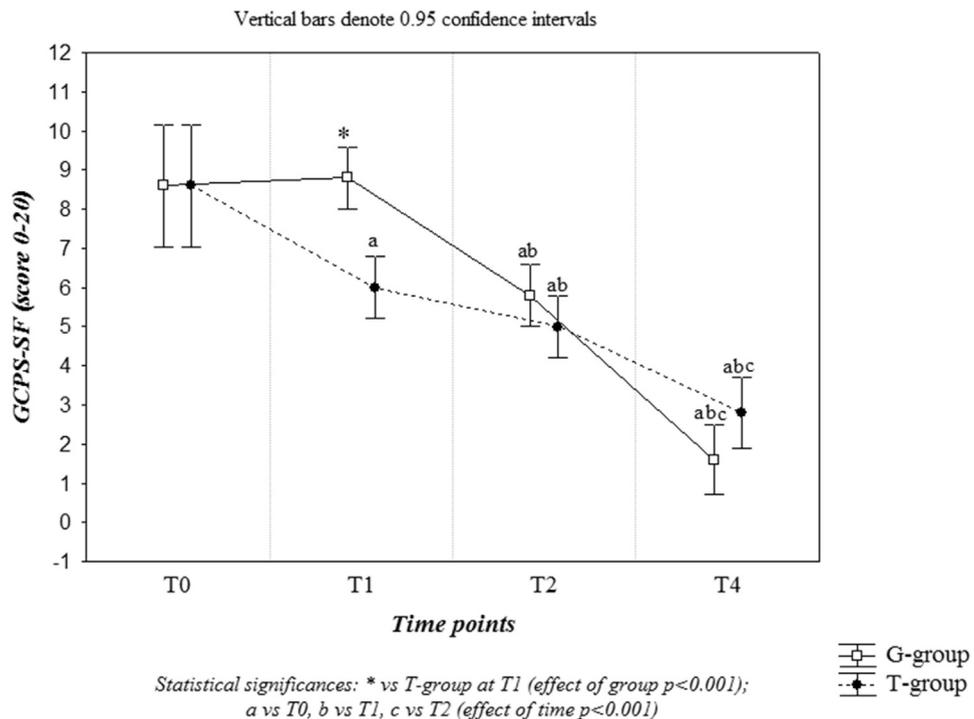
Imaging findings	Case	%
L7-S1 endplates irregularity:		50
Sclerosis (hyperdensity)	6, 10	
Lysis (hypodensity)	1, 8	
Deformity	7	
L7-S1 intervertebral foraminal stenosis:		50
Monolateral	2	
Bilateral	3, 5, 7, 10	
L7-S1 disc bulging	5, 6, 7, 9	40
L7-S1 disc protrusion	3, 4, 10	30
S1 caudal displacement	2, 4, 7	30



**Figure 4.** Muscle tone score (0-2 scale) evaluated in G-group (gabapentin) and T-group (tramadol) after the first clinical evaluation (T0) and after 2 (T2) and 4 (T4) weeks of treatment with the respective significance between the groups.

suggests unclear benefits. Unlike in humans and cats, tramadol in dogs has a very short half-life (1.7 hr) and negligible amounts of the opioid O-desmethyltramadol metabolite are produced (Epstein et al., 2015; Giorgi et al., 2009). In contrast with parenteral tramadol, convincing evidence for a pain-modifying effect of oral

tramadol remains elusive, and already low plasma levels quickly diminish with sequential administration. One small study of oral tramadol did report a significant increase of mechanical threshold levels in dogs but only at the 5- and 6-hour time points (Epstein et al., 2015).



**Figure 5.** The short form of Glasgow composite pain scale (GCPS-SF) scores (intervention level 4/20) evaluated in G-group (gabapentin) and T-group (tramadol) after the first clinical evaluation (T0) and after 1 (T1), 2 (T2), and 4 (T4) weeks of treatment, with the respective significance found within and between the groups.

In both groups of dogs enrolled in the present study, no adverse effects were observed. However, half of the dogs showed no significant reduction of GCPS-SF lumbosacral pain score after one week of treatment with oral tramadol. The decision to start extra-label gabapentin treatment for pain management in these dogs was due to ethical reasons related to the moderate degree of pain experienced and a decreased quality of life, as reported by the owners.

It was not possible, due to the restriction of prescription, to start a treatment with an opioid, considering the outpatient setting. Because of concomitant corticosteroid therapy and the risk of enhancing side effects, especially on the gastrointestinal tract, NSAIDs were not considered a suitable option.

The use of gabapentin is widely recognized in humans as a treatment for neuropathic pain and lumbosacral stenosis in particular (Yaksi et al., 2007). Although not registered for use in companion animals, several reports on its use in animal models of neuropathic (Mangaiarkarasi et al., 2015) and postoperative pain (Aghighi et al., 2012; Crociolli et al., 2015; Wagner et al., 2010) exist. Gabapentin exhibits less than proportional increases in plasma concentrations with increasing doses after oral administration because of saturation of active transporters in the gastrointestinal tract. It is primarily eliminated as an unchanged drug in most species except dogs, in which metabolism to N-methyl-gabapentin accounts for up to 40% of drug disposition (KuKanich, 2013). A pharmacokinetic study (KuKanich and Cohen, 2011) performed in Greyhounds treated with gabapentin (10–20 mg/Kg) showed a terminal half-life of about 3 hours, with plasma concentrations that exceeded 2 µg/mL (minimum targeted concentration associated with efficacy in humans) within the first 8 hours after administration but not after 12 hours; hence, our choice on the drug's dosage (10 mg/Kg every 8 hours). A lower frequency of administration, for example, every 12 hours, may not guarantee adequate pain control, as observed in some reports of postoperative use in dogs (Aghighi et al., 2012; Crociolli et al., 2015; Wagner et al., 2010).

On first examination, all the animals did not have any proprioceptive deficit or urinary and/or fecal incontinence, that have been reported to be related with a worse outcome in other studies (Suwankong et al., 2008).

The results of this study seem to suggest that both tramadol and gabapentin could be effective treatments in reducing lumbosacral pain in dogs with DLSS. However, some dogs can be nonresponders to tramadol, even if given at the higher dose and more frequently than suggested by the manufacturer (2–4 mg/Kg every 12–24 hours). Clinical effectiveness of tramadol is actually questioned in species such as dogs that mainly metabolize this molecule to inactive metabolites, especially after oral administration, suggesting 6 daily drug administrations to maintain the analgesic effect. This dosing pattern would suggest that this drug is not suitable for pain treatment as in humans (Giorgi et al., 2009). Just after one week of treatment with gabapentin, nonresponder dogs showed a significant decrease in pain score, like the responder ones. This seems to suggest a rapid onset of gabapentin analgesic activity, also supported by the resumption of normal behaviors and physical activity reported by owners. Moreover, the improvement of muscle tone in the gabapentin-treated dogs at the end of 3-week therapy could be due to the resumption of a moderate physical activity determined by a better pain control than in dogs treated with tramadol.

Synergic effects were probably associated with (1) anti-inflammatory effect of prednisolone, which promotes improved vascular supply and reduces the compression on nerve roots; (2) motion restraint, to minimize the risk of sudden movements that could cause an excessive stress on the spine; (3) reduction in body weight.

The persistence of abnormal spinal reflexes after 4-week treatment was an expected result because the medical treatment did not solve the underlying problems and the drugs used had an analgesic but not a neurotrophic effect.

This is a pilot study with some limitations: (1) small number of dogs enrolled; (2) lack of measurement of plasma levels of both drugs, useful for a dosing strategy; (3) lack of a randomized controlled arm; (4) lack of a control group treated with corticosteroid alone, however, considered ethically unacceptable, given the initial degree of pain; (5) lack of follow-up, to check for any relapses; and (6) lack of surgical confirm of the correspondence with diagnostic findings.

## Conclusions

DLSS is a multifactorial disease that can cause neuropathic pain of varying degrees, and advanced diagnostics are essential for the final diagnosis.

When surgery is not advisable or possible, a conservative medical treatment is necessary to improve the quality of life. The management of pain requires a continuum of care that includes early intervention and evaluation of response on an individual-patient basis. Oral tramadol should not be relied on as a sole or, perhaps, first-line analgesic in dogs, and gabapentin might be a valid alternative option in an outpatient setting. Because controlled clinical trials are still lacking in animals, further studies should be carried out to confirm the analgesic activity of gabapentin in veterinary neuropathic pain conditions and to rule out eventual adverse effects related to a prolonged administration.

## Conflict of interest

The authors declare no conflict of interest.

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