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a randomized controlled trial

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RESEARCH PAPER

Pregabalin alleviates clinical signs of syringomyelia-related central neuropathic pain in Cavalier King Charles Spaniel dogs: a randomized controlled trial

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Abstract

Objective We aimed to assess the efficacy and benefit-risk profile of pregabalin (PGN) to reduce the clinical signs of central neuropathic pain (CNeP) as reflected by scratching episodes in dogs with symptomatic syringomyelia (SM).

Study design Randomized, double-blind, placebo-controlled crossover study.

Animals A total of 12 client-owned Cavalier King Charles Spaniels (age, 1.1–7.4 years, bodyweight, 8.2–10.8 kg) with magnetic resonance imaging-confirmed SM and clinical signs of CNeP.

Methods Dogs were randomized to either PGN 150 mg or placebo for 25 days, followed by 48 hour washout period before crossover to the alternate phase of 25 days. The primary outcome was defined as number of scratching events during 10 minutes of video-recorded physical activity. Treatment effect was estimated using a generalized estimation equation model. Benefit-risk and quality of life assessments were obtained through owner interviews focusing on potential adverse events.

Results The treatment effect estimate was an 84% (95% confidence interval = 75–89%) reduction in mean number of scratching events relative to baseline compared with placebo ($p < 0.0001$). Owner-assessed satisfactory quality of life was status quo and rated as 'good' or 'could not be better' in six/11 dogs and improved in four/11 dogs. The most prevalent adverse events were increased appetite in nine/12 dogs and transient ataxia in nine/12 dogs. There was one dog withdrawn by the owner 7 days after crossover to PGN owing to persistent ataxia. No dogs needed rescue analgesia during the trial.

Conclusions and clinical relevance PGN is superior to placebo in the reduction of clinical signs of SM-related CNeP in dogs. At a dose range of 13–19 mg kg^{-1} orally twice daily, the encountered adverse events were acceptable to all but one owner.

Keywords analgesia, canine chronic pain, Chiari-like malformation, clinical pharmacology, neuralgia, spinal cord disorder.

Introduction

Symptomatic syringomyelia (SM) and concomitant Chiari-like malformation (CM) is a neurological syndrome that occurs in up to 15% of Cavalier King Charles Spaniels (CKCS) (Thøfner et al. 2015). The clinical phenotype is diverse and includes both physical and behavioural indicators of hypersensitivity, discomfort and pain (Rusbridge et al. 2007; Rutherford et al. 2012; Hechler & Moore 2018). Common clinical signs are spontaneous and evoked scratching, phantom scratching and paroxysmal pain manifestations with vocalization (Rusbridge & Jeffery 2008; Cerda-Gonzalez et al. 2009). Furthermore, aberrant behaviours including nightwandering, hiding, avoidance of touch and grooming and reluctance to wear a collar or harness are reported by the owners (Rusbridge et al. 2000; Sanchis-Mora et al. 2016; Sparks et al. 2018).

There are no prescription drugs labelled for use in animals with chronic or neuropathic pain. Non-steroidal anti-inflammatory drugs, corticosteroids, opioids, gabapentinoids, the N-

methyl-D-aspartate antagonist amantadine, serotonin-norepinephrine reuptake inhibitors and tricyclic antidepressants have been suggested for the management of chronic and neuropathic pain in general and symptomatic SM in CKCS (Rusbridge 2005; Mathews 2008; Rusbridge & Jeffery 2008; Grubb 2010; Plessas et al. 2012; KuKanich 2013; Epstein et al. 2015; Plessas et al. 2015; Moore 2016; Hechler & Moore 2018).

The antiepileptic compound pregabalin (PGN) is a first-line analgesic in the evidence-based guidelines on pharmacotherapy for neuropathic pain in humans (Finnerup et al. 2015). The primary target is the α2-δ-subunit of the voltage-gated calcium channels in the central nervous system (Gong et al. 2001; Marais et al. 2001). PGN inhibits the calcium-mediated release of excitatory neurotransmitters resulting in analgesic and anticonvulsant effects (Li et al. 2004; Taylor et al. 2007; Bauer et al. 2009).

The pharmacokinetics of 4 mg kg^{-1} PGN administered orally has been investigated in six adult Labrador/Greyhound dogs (Salazar et al. 2009). The maximal plasma concentration was 7.15 (4.6−7.9) μg mL^{-1}, which occurred after 1.5 (1.0−4.0) hours. The elimination half-life was 6.9 (6.21−7.4) hours, and no adverse effects were seen. The extra-label PGN dosage for dogs with neuropathic pain is 2−4 mg kg^{-1} twice to thrice daily at 8 or 12 hour intervals (Plumb 2015; Hechler & Moore 2018). The clinical use of PGN as an add-on anticonvulsant and analgesic has been sparsely reported (Dewey et al. 2009; Plessas et al. 2012; Bhatti et al. 2015).

Up to 25% of symptomatic CKCS with SM are euthanized due to inadequate treatment (Plessas et al. 2012; Thofner et al. 2015). Acknowledging the unmet need of evidence-based treatment recommendations, the primary aim of the study was to assess the efficacy and benefit-risk profile of PGN in CKCS with SM-related central neuropathic pain (CNeP). We hypothesize that the analgesic efficacy of PGN is superior to placebo in reducing the clinical signs of SM-related CNeP.

Materials and methods

The study protocol was approved by the Danish Medicines Agency (11 April 2017, file number 2017020400) and the local Ethics and Administration Committee (20 February 2017, file number 2017-4). Informed consent was obtained from all owners.

Study population

Eligible dogs were client-owned, purebred CKCS, older than 1 year and weighing 8−12 kg, with clinical signs of SM-related CNeP. They were defined as uni- or bilateral spontaneous scratching directed at the cervical or shoulder area. SM was defined as a fluid-filled cavity in the spinal cord parenchyma with a diameter ≥ 2 mm confirmed on T1-weighted magnetic resonance imaging (MRI). Owners had to be willing to administer an ectoparasite prophylaxis (e.g. fipronil, imidacloprid/permethrin or fluralaner) before inclusion. Exclusion criteria were pregnant or lactating bitches, dogs treated with analgesics 48 hours prior to inclusion, dogs with clinical signs of other neurological disorders than SM, dogs that scratched solely at the ears or face, dogs scratching due to other causes than SM and dogs with clinical findings contraindicating anaesthesia.

Pre-inclusion assessment

Pre-inclusion assessments were undertaken by the principal investigator (PI; MST) and a dedicated research veterinary technician. A questionnaire (Rutherford et al. 2012) was used to assess the dog's general health status, medical history, clinical signs and behaviour to confirm eligibility. In addition, the owners were asked to rate their dog's quality of life (QOL) as 'could not be better', 'good', 'fairly good', 'neither good nor bad', 'fairly poor', 'poor', 'could not be worse' or 'do not know'. The dogs were video-documented walking on a predefined route for 10 minutes to confirm the expression of quantifiable spontaneous scratching and to enable retrospective reassessment of the dogs' scratching profiles and quantification of scratching events. All dogs underwent a clinical and neurological examination including otoscopy and ear swab cytology. Urine analysis, haemogram, biochemical and thyroid profile were undertaken before MRI of the neurocranium and cervical spinal cord parenchyma (Thoefner et al. 2019).

Study design

This superiority trial was designed as a two-treatment two-period crossover trial. Dogs were randomly assigned to treatment arm A with sequence 'PGN ➡ placebo' or treatment arm B with sequence 'placebo ➡ PGN' (Fig. 1). The intended allocation ratio was 1:1. The owner was asked to withdraw a random number from a nontransparent envelope. The random number corresponded to a unique trial code on a randomization list previously generated (www.randomization.com). The list was provided in a sealed envelope by the pharmacist who manufactured, packed and labelled the containers with the unique trial code and 'treatment period one' or 'treatment period two'. They contained identical gelatine capsules of either 150 mg of PGN (Lyrica; Pfizer, NY, USA) or placebo. Thus, randomization to treatment arm A or B was blinded to the PI and the owner. The owners were blinded to treatment to eliminate any biased expectation of effect. The trial was continuously followed by an external monitor. The PI, owners, monitor and statistician were blinded to the treatment sequence allocation.

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Intervention and dose rationale

All dogs were administered PGN orally. In treatment arm A, 150 mg of PGN was administered once daily for 2 days increasing to a targeted maintenance dose of 150 mg twice daily for 21 days. This was followed by a tapering phase of 150 mg once a day for 2 days. A 48 hour washout period was followed by crossover to the placebo-treatment period: one capsule once daily for 2 days, one capsule twice daily for 21 days, followed by one capsule once a day for 2 days. In treatment arm B, dogs were administered placebo treatment firstly, followed by PGN using the same dosage protocol as described for treatment arm A. The 150 mg dose twice daily was based on a pilot study and pharmacological data (Salazar et al. 2009).

Discontinuation and rescue analgesia

The owners and PI could withdraw the dogs from the study at any time. Discontinuation was indicated in case of noncompliance to the protocol, failure to respond or deterioration of the dog's QOL. In case of failure to respond or clinical deterioration, rescue analgesia with firocoxib 5 mg kg^{-1} once daily for 48 hours would be provided by the PI. In case of insufficient analgesia, add-on treatment with PGN 75 mg kg^{-1} once daily for 48 hours followed by 75 mg kg^{-1} twice daily for 7 days would be prescribed. A weekly assessment and up-titration with additionally 25 mg kg^{-1} twice daily should proceed. This was continued until a clinically overt reduction in scratching events and other indicators of discomfort and pain were obtained without side effects. Adverse events that indicated discontinuation were anorexia, vomitus or repeated episodes of prolonged deep sedation.

Outcome measures

The outcomes were assessed on five occasions: during the preinclusion assessment, when baseline data were collected, and at four follow-up visits (two in each treatment period) on days 7, 21, 34 and 48 ± 2.

The primary outcome 'number of scratching events during 10 minutes of continuous physical activity' was chosen based on previous reports on the most prevalent clinical signs in symptomatic CKCS with SM (Rusbridge et al. 2000, 2007; Sanchis-Mora et al. 2016; Sparks et al. 2018). The dogs' scratching profiles were documented in standardized videoseries of 10 minute duration and quantified by counting scratching episodes.

Secondary outcome measures for intensity of scratching and pain or discomfort during the preceding 24 hours were assessed by the owner using two separate scales. They consisted of an 11 point numerical rating scale (NRS; 0 = no scratching/no pain or discomfort, 10 = worst scratching/pain or discomfort imaginable) and a modified children's Faces Pain Scale (FPS-M; Fig. 2a) combined with a visual analogue scale (VAS). It consisted of five faces, a colour-intensity scale beneath the faces and a horizontal sliding indicator on the front of the FPS-M (Hicks et al. 2001). On the reverse side was a preprinted 0−100 mm VAS scale (Fig. 2b). The owners were asked to place the sliding indicator on the colour or face that corresponded to their assessment. The PI subsequently read the corresponding VAS score on the reverse side. Finally, the owner was asked to rate the dog's QOL by the same descriptors as listed under the pre-inclusion visit.

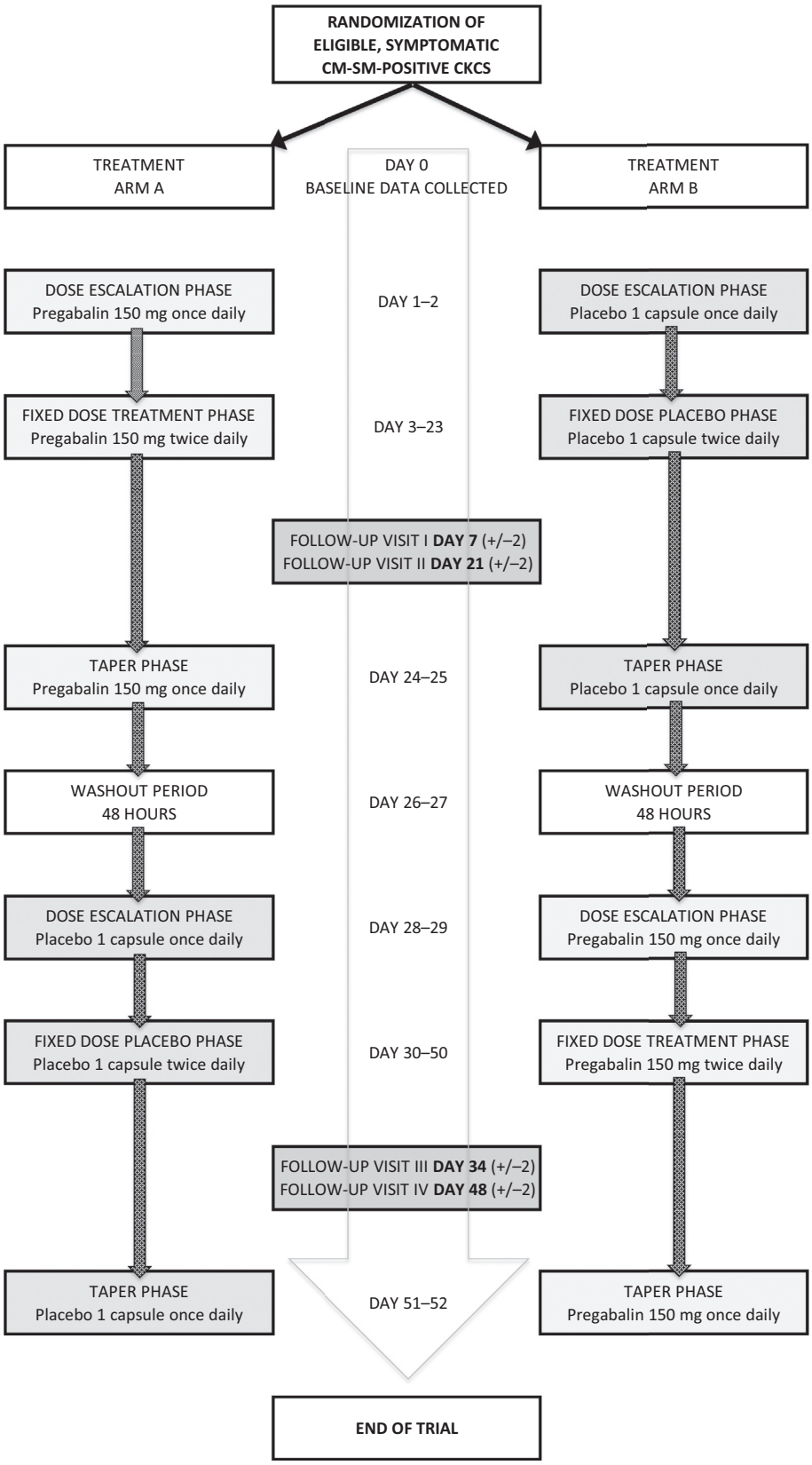
The PI rated the dog's scratching intensity and pain/discomfort, respectively, by means of the same NRS and FPS-M as the owner after each visit. In addition, the PI assessed the dog's QOL by the same descriptors as the owner based on the history, clinical findings and overall subjective impression of clinical efficacy of the treatment on number of scratching events and stress level.

The owners were given a diary at enrolment to log deviations of medicine administration from the predefined time, the daily scratching intensity, SCRATCH/NRS and to document any adverse events and other observations during the trial period. At each follow-up visit, the dogs' body weight was recorded and the owners were asked a series of questions to monitor adverse events. The questions addressed activity level (normal/reduced/hyperactive), aggression (towards other people/animals, yes/no), appetite (normal/increased/decreased), ataxia (yes/no), behavioural changes (yes/no: if yes, please describe), faecal score (normal/hard/moist/watery), food intake (normal/increased/decreased), sleeping pattern (normal/reduced sleeping activity/somnolence), vomiting (yes/no), water intake (normal/increased/decreased) and details on their dog's scratching phenotype (intensity compared with baseline, anatomical localization, phantom scratching yes/no) and if the dog was chewing paws (yes/no).

The remaining capsules were counted at each follow-up visit to account for end-of-trial owner compliance. The proportion of capsules given relative to the expected number of capsules given at each follow-up visit was used to categorize owners as 'satisfactory adherent' (≥90% capsules administered correctly) or 'suboptimal administrator' (≥80% and ≤90% capsules administered correctly) (Pullar et al. 1989; Dodd et al. 2012). The owners were asked for a final preference statement (treatment period one or two) at the end-of-trial visit to assess the efficacy of blinding.

Dimensioning of the study

A minimum sample size of 13 was calculated based on a normal distribution approximation using $\alpha = 0.05$ and $\beta = 0.8$. It was assumed that the mean number of scratching episodes during 10 minutes of exercise would be reduced by 20%



using the placebo (Vasseur et al. 1995; McMillan 1999) and by 75% using PGN (pilot data). To account for drop-outs, capsules with PGN and placebo were prepared for a total of 20 dogs. The calculated sample size was used as a guideline since the applied assumptions were only applicable for a simple *t* test study design. A blinded interim analysis was planned when 13 dogs had completed the trial. The decision was made acknowledging the lack of appropriate sample size calculation tools for the applied repeated measurements design's complex data structure and correlation analysis (Guo et al. 2013). The dataset was completed and locked, and the code was not broken until data analyses were finalized. Accordingly, the last-patient-last-visit defined the end of trial.

Statistical analysis

Data were analysed with SAS Studio version 3.71 (SAS Institute Inc., NC, USA), and $p < 0.05$ was considered significant. Categorical variables are reported as frequencies and proportions and continuous data as medians and ranges. The primary outcome 'number of scratching events' is, however, reported as mean and range. Since 'number of scratching events' is a countable variable, a negative binomial distribution was used to model it, allowing for overdispersion (compared with a Poisson distribution). The effect of treatment of PGN and placebo, period, follow-up visit number and potential carryover was modelled using a log-link (i.e. multiplicative effects), and a generalized estimating equation was applied to account for the correlation of scratching events over time for the same dog (Zeger & Liang 1986). The effect estimates are given as ratios, such as of PGN *versus* placebo. Treatment effect on owner- and PI-assessed SCRATCH/NRS, SCRATCH/VAS, PAIN/NRS and PAIN/VAS was modelled by means of a general linear mixed model as was the effect on body weight after log-transformation (Liang & Zeger 1986). Cross-tabulations were made to assess the agreement between the owners and PI with regards to their assessment of SCRATCH/NRS, SCRATCH/VAS, PAIN/NRS, PAIN/VAS and the dogs' QOL. Data were included in the analysis when dogs had participated in at least three of four consecutive follow-up visits. If owners answered a question with 'do not know', data were excluded from analysis.

Results

A total of 81 potential cases were consecutively assessed for eligibility between March 2017 and June 2018 (Fig. 3). Of these, 12 dogs were included in the analysis ($n = 4$ in treatment arm A; $n = 8$ in treatment arm B). The last follow-up visit was in July 2018. No dogs needed rescue analgesia during the trial.

The 12 participants (six females, one ovariohysterectomized female, four males and one castrated male) were 3.6 (1.1−7.4) years old and weighed 8.7 (8.2−10.8) kg at baseline. The overall mean number of scratching events during 10 minutes of continuous physical activity was 9.1 (2−27). Additional MRI findings were CM in 12/12 dogs, unilateral otitis media with effusion in two/12 dogs and bilateral otitis media with effusion in four/12 dogs.

Treatment effect

The treatment effect of PGN on the mean number of scratching events was estimated to be a factor 0.16 [95% confidence interval (CI) = 0.11−0.25]. It corresponded to an 84% reduction from baseline in the mean number of scratching events during 10 minutes of continuous physical activity compared with placebo ($p < 0.0001$). No significant effect was found of placebo, period, follow-up visit number or carryover on the primary outcome. In addition, the scratching profile changed during treatment with PGN. The phantom scratch stopped in seven/eight dogs (88%) and vocalization when scratching ceased in five/five dogs (100%) compared with baseline.

Efficacy estimates of PGN revealed a significant reduction in owner- and PI-reported scratching and pain intensity (Table 1). Only the effect of PGN on owner-assessed mean PAIN/NRS was not significantly different from the effect of placebo compared with baseline ($p = 0.056$).

Quality of life

The dogs' QOL data are shown in Table 2. There was one owner who was unable to assess the dog's QOL at baseline. Compared with baseline, treatment with PGN resulted in improved QOL in two/four dogs (50%) allocated to arm A (PGN ➡ placebo) and in two/seven (29%) dogs allocated to arm B (placebo ➡ PGN). The status of one dog allocated to arm B changed from 'good' in the first follow-up visit after crossover to PGN to 'fairly good' at the end of trial owing to an owner-assessed increased appetite. After crossover from PGN to placebo, the owner-assessed QOL deteriorated in three/four dogs (75%) compared with baseline in arm A, and remained status quo in four/seven dogs (57%) in arm B from baseline to the end of the placebo period. In the remaining three/seven dogs (43%)

Figure 1 Trial design. The trial was designed as a two-treatment two-period crossover study. Eligible Cavalier King Charles Spaniels (CKCS) expressing clinical signs consistent with Chiari-like malformation (CM) and syringomyelia-related (SM) central neuropathic pain were randomized to treatment arm A [treatment sequence pregabalin (PGN) ➡ placebo] or treatment arm B (placebo ➡ PGN) after baseline data collection. Each treatment period was of 25 days duration separated by a 48 hour washout period. During the dose escalation and taper phase, 150 mg of PGN was administered once daily. In the fixed dose treatment phase, 150 mg PGN was administered twice daily. Primary and secondary outcomes were assessed at baseline and at follow-up visits I−IV (two visits in each treatment period).

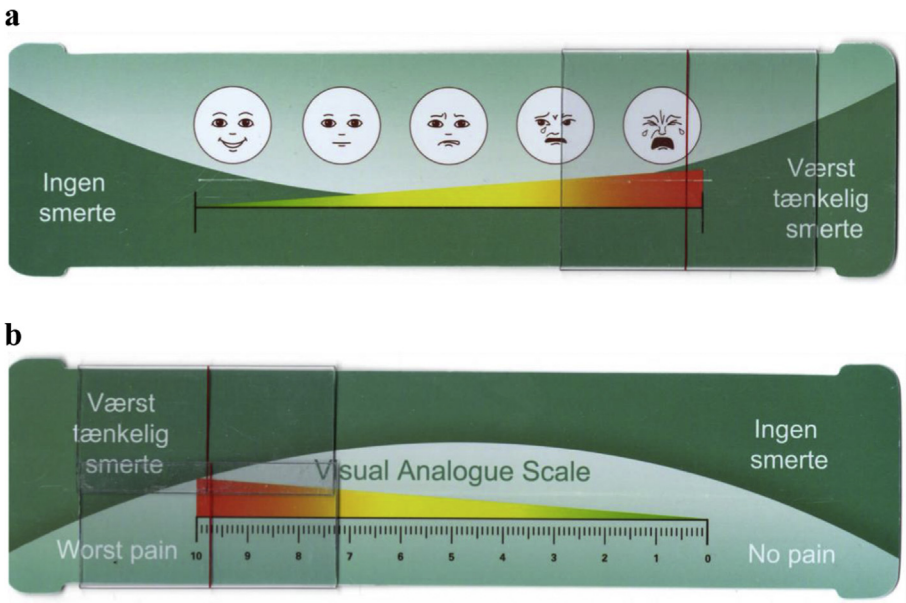


Figure 2 The modified Faces Pain Scale. The scale was used to assess each dog's scratching and pain intensities at baseline and four follow-up visits. The sliding indicator was placed on a face or colour corresponding to the dog's scratching intensity during the last 24 hours by the owner as shown in (a). The SCRATCH/VAS and PAIN/VAS scores were subsequently read from the back side by the principal investigator (b). Translation of the Danish wording: 'Ingen smerte', no pain. 'Værst tænkelig smerte', worst imaginable pain. Depicted and reproduced with permission from MEDshop.dk (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article).

of arm B, the changes were a result of a change in weather. The owners reported a decrease in their dogs' activity level owing to extreme summer heat (the summer of 2018 was the warmest summer for 140 years in Denmark). A cross-tabulated comparison in QOL revealed agreement between the owner and PI in 30/58 assessments (52%). In 21 of the remaining 28 assessments, the owner evaluated a better QOL, which was significantly more often than the PI ($p = 0.016$).

Additional information reported by the owners

According to the owners' diary records, the clinical effect of PGN was observable 48−72 hours after administration. External factors that affected the owners' daily SCRATCH/NRS ratings were wearing a harness or a collar (six dogs) and flea infestation (two dogs), which was promptly treated, in arm B during treatment period two. Increased scratching intensities during oestrus were reported in two females during the trial. Reluctance to take medication was reported in three dogs, and four owners found it difficult to fit the 12 hour dosing interval into their daily routines.

Dose range and adverse events

The administered dose was 13−19 mg kg^{-1} twice daily. The body weight of included dogs ranged from 8.0 to 11.4 kg. Despite the reported increase in appetite and a clinically overt weight gain in four dogs, the 2.1% increase (95% CI = 0.4%−4.6%) in mean body weight during PGN treatment was nonsignificant ($p < 0.099$). The weight gain was more evident in four dogs fed *ad libitum* compared with the other seven dogs whose owners were more attentive to restricted feeding.

The incidences of owner-reported adverse events are presented in Table 3. The most prevalent adverse events following PGN administration were increased appetite and transient ataxia, which resolved between days 1 to 10. A reduced activity level was reported in four/12 dogs (33%), and two/12 dogs (17%) were assessed to be hyperactive. An increased water intake was reported by four/12 owners (33%) at the first follow-up visit after PGN administration was initiated. The water intake was normalized in all dogs at the second follow-up in the PGN treatment period. The reported adverse events were acceptable for all but one owner. This owner withdrew his dog as a result of ataxia and somnolence. No serious adverse events, such as death or hospitalization occurred during the trial.

Compliance

The overall owner compliance was 98% (range 93%−105%). An "over-compliance" of 105% (46 capsules administered in 44 days) resulted from one owner administering the capsules every 12 hours from day 1 (instead of day 3) in period two. All owners in treatment arm B and two owners in treatment arm A (50%) were categorized as 'satisfactory adherent' at all four

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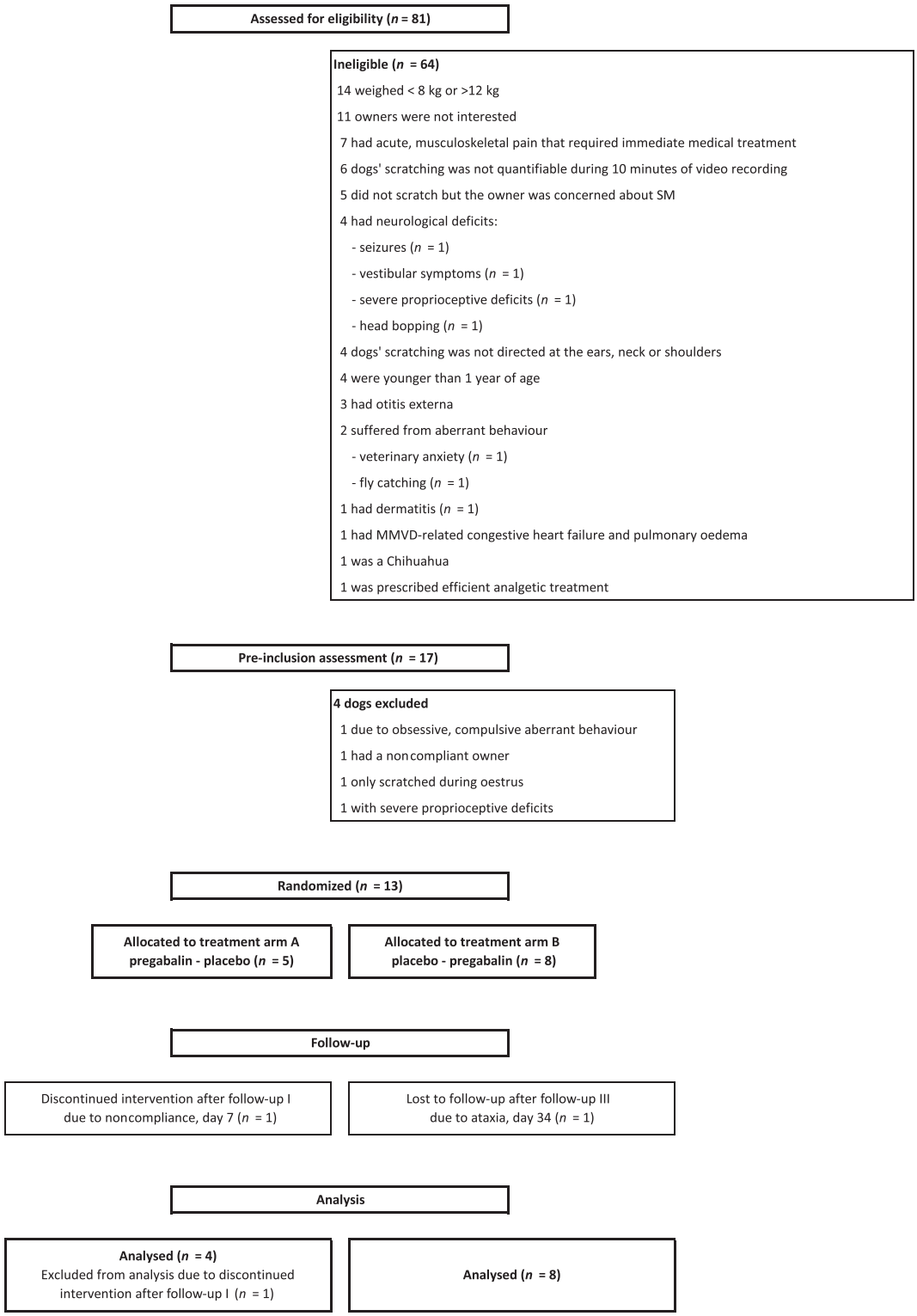

Figure 3 Trial profile. Recruitment was initiated in January 2017. A total of 81 owners and veterinarians responded to the recruitment notices. Of the 81 enquiries, 17 potential cases (21%) were continuously assessed and 13 dogs were included in the study between March 2017 and June 2018. MMVD, myxomatous mitral valve disease; SM, syringomyelia.

Table 1 The effect of pregabalin 150 mg twice daily on scratching and pain intensity in 12 dogs

	Owner-assessed		*p*	PI-assessed		*p*
	Baseline mean	**Treatment effect (95% CI)**		**Baseline mean**	**Treatment effect (95% CI)**	
Scratching intensity						
NRS, 0–10	4.0	−2.7 (−4.4, −1.0)	0.003	5.2	−2.7 (−4.2, −1.1)	0.002
VAS, 0–100 mm	43	−33 (−46, −19)	<0.0001	53	−29 (−46, −12)	0.001
Pain intensity						
NRS, 0–10	2.6	−2.1 (−4.3, 0.05)	0.06	4.2	−4.1 (−5.6, −2.6)	<0.0001
VAS, 0–100 mm	34	−24 (−42, −6)	0.01	44	−44 (−59, −29)	<0.0001

CI, confidence interval; NRS, numeric rating scale; PI, principal investigator; VAS, visual analogue scale.

Table 2 Incidence of quality of life (QOL) descriptors at baseline and during the trial. Data are shown as % and (the number of dogs given the specific QOL descriptor/the total number of dogs allocated to the specific treatment arm in that phase of the study)

Treatment arm A	**Baseline**		**Pregabalin**				**Placebo**			
			Follow-up I		**Follow-up II**		**Follow-up III**		**Follow-up IV**	
	Owner	**PI**	**Owner**	**PI**	**Owner**	**PI**	**Owner**	**PI**	**Owner**	**PI**
QOL descriptor										
Could not be better	25 (1/4)	0	25 (1/4)	25 (1/4)	50 (2/4)	25 (1/4)	25 (1/4)	0	0	0
Good	50 (2/4)	75 (3/4)	50 (2/4)	75 (3/4)	50 (2/4)	75 (3/4)	50 (2/4)	50 (2/4)	25% (1/4)	25% (1/4)
Fairly good	25 (1/4)	0	25 (1/4)	0	0	0	0	25 (1/4)	75% (3/4)	50% (2/4)
Neither good nor bad	0	25 (1/4)	0	0	0	0	25 (1/4)	0	0	0
Bad	0	0	0	0	0	0	0	25 (1/4)	0	25% (1/4)
Treatment arm B	Baseline		Placebo				Pregabalin			
			Follow-up I				Follow-up III		Follow-up IV†	
	Owner *	PI	Owner	PI	Owner	PI	Owner	PI	Owner	PI
QOL descriptor										
Could not be better	28.5 (2/7)	0	0	0	12.5 (1/8)	0	50 (4/8)	50 (4/8)	28.5 (2/7)	57 (4/7)
Good	28.5 (2/7)	12.5 (1/8)	37.5 (3/8)	37.5 (3/8)	37.5 (3/8)	37.5 (3/8)	37.5 (3/8)	37.5 (3/8)	57 (4/7)	28.5 (2/7)
Fairly good	43 (3/7) *	62.5 (5/8)	62.5 (5/8)	37.5 (3/8)	37.5 (3/8)	50 (4/8)	12.5 (1/8)	12.5 (1/8)	14 (1/7)	14 (1/7)
Neither good nor bad	0	12.5 (1/8)	0	12.5 (1/8)	12.5 (1/8)	12.5 (1/8)	0	0	0	0
Bad	0	12.5 (1/8)	0	12.5 (1/8)	0	0	0	0	0	0

*The owner of one dog was unable to assess the animal's QOL.
†After follow-up III, one animal was withdrawn from the trial.

follow-up visits. During the placebo period, two treatment arm A owners (50%) were categorized as 'suboptimal administrators'.

Final preference statement

All 12 owners preferred the period in which their dog had received PGN over the placebo period despite blinding to treatment allocation and the reported adverse events.

Discussion

This study demonstrates that PGN significantly alleviated the clinical signs of SM-related CNeP in CKCS. The treatment effect's relatively wide confidence interval of 75–89% reflects the small sample size and the clinical variation between dogs. This variation may be caused by several factors. According to the owners, scratching was more evident on the day of a follow-up visit. Transportation, often by car, entering the hospital facility and wearing a collar or harness during video recordings are external stressors that may have intensified scratching (Rusbridge et al. 2000; Rutherford et al. 2012). The flea infestation in two dogs probably increased scratching activity as well. Oestrus was reported to increase the scratching intensity and duration in two intact bitches. Aggravation of scratching as a consequence of cycle-dependent intensification of pain and reduced sensory threshold was described in rodent pain models and humans (Iacovides et al. 2015). Whether it was the cause of increased scratching in the entire bitches

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Table 3 Incidence of adverse events recorded during the study. Data are derived from the 12 dogs included in the study

Adverse events	Treatment	
	Pregabalin	Placebo
	Incidence (%)	
Activity level		
Reduced	33 (4/12)	8 (1/12)
Hyperactive	17 (2/12)	8 (1/12)
Aggression	0	0
Ataxia	75 (9/12)	8 (1/12)
Fecal texture: moist	8 (1/12)	8 (1/12)
Food intake		
Hypophagia	8 (1/12)	33 (4/12)
Polyphagia	75 (9/12)	17 (2/12)
Paw chewing	0	0
Sleeping pattern: somnolence	8 (1/12)	0
Vomiting	0	0
Water intake		
Reduced	0	8 (1/12)
Increased	33 (4/12)	8 (1/12)

remains unknown. An initial reluctance among some dogs to accept oral administration of PGN potentially resulted in plasma concentrations below the therapeutic level at the first follow-up visit. This clinical variation may have been reduced by stratification of bitches by neuter status and by avoiding collars and harnesses. By incorporating repeated ectoparasite prophylaxis and a run-in period in the protocol, flea infestations could have been avoided and dogs could have been accustomed to oral administration of capsules.

A clinical challenge is the lack of quantifiable biomarkers of pain and a gold standard of pain assessment in veterinary patients (Mathews 2008). VAS and NRS are accepted in the human pain research community as valid for self-reporting of pain severity (Attal et al. 2010, 2018). Facial coding systems are used for carers to rate pain in babies who are unable to self-report pain (Hicks et al. 2001). Owing to the inherent lack of verbal communication with animals, the FPS-M was used in the present study. No canine facial coding systems or grimace scales are available. This was a limitation of the study since the FPS-M has not been validated for assessment of scratching and pain/discomfort intensities in dogs. Opposed to the PI, owners did not understand their dog's scratching intensity as an indication of pain or discomfort. This could explain the nonsignificant effect of PGN on the owner-assessedPAIN/NRS.

The screening questionnaire published by Rutherford et al. (2012) was used in the present study to assess the eligibility of potential cases before inclusion in the trial. It consists of a 5-point neuropathic pain score (NPS) based on owner ratings in seven clinical manifestations of symptomatic SM: persistent compulsive scratching, facial rubbing, hypersensitivity to touch, unexplained yelping, reluctance to lift the head, reluctance to bend the neck to eat and reluctance or pain when defaecating. The NPS was not developed for and has not been validated to assess treatment effect. The authors of the present study argue that facial rubbing and reluctance or pain when defaecating are not inevitably synonymous with symptomatic SM. The NPS was accordingly deselected as an outcome measure in the present trial.

The ChiMPS-T questionnaire was published after the initiation of the present study (Sparks et al. 2018). This clinical screening and assessment tool addresses the medical history, frequency and severity of symptoms and includes a pain and scratch map to outline the dog's affected body areas. The ChiMPS-T questionnaire was unable to establish an association between the presence of pain or scratching and SM in 30 SM-affected dogs. There was a lack of correlation between the presence of pain determined after neurological examination and the owner-reported presence of pain, pain score and affected body area as indicated on the pain and scratch map. These findings emphasize the need for objective, quantifiable biomarkers of pain in veterinary clinical research.

The use of QOL assessment introduced another limitation to the present study. The dog's physical and mental status, social behaviour and function are among the factors that are entailed in the concept of a good QOL from the owner's perspective. Factors that define a good QOL for some owners are less or not important to others. In the present study, a majority of the owners did not juxtapose their dogs' physical and behavioural indicators of discomfort and pain with a suboptimal QOL. Accordingly, it was only possible to achieve an actual improvement in owner-assessed QOL in one-third of the included dogs.

The dose rationale of the present study was founded on a very careful benefit-risk assessment based on our pilot study and a previous pharmacological study (Salazar et al. 2009). Here, we aimed to identify the dose that resulted in a beneficial clinical effect and at the same time to avoid unwanted adverse events and risks to the dogs. The most frequently occurring side effect in the present study was transient ataxia. The ataxia was subjectively described by all but one owner as acceptable and resolved between days 1 to 10 in 8/12 dogs (66%). By contrast, ataxia was not seen in the dogs included in the pilot study. One possible explanation is the difference in PGN administration dose regimens. Dogs included in the pilot study were initially given the extra-label PGN dosage of 2−4 mg kg^{-1} twice daily (Plumb 2015; Hechler & Moore 2018). Subsequently, PGN was titrated to effect. Hence the concentration was slowly increased over several weeks. Conversely, the PGN dose was up-titrated from 13−19 mg kg^{-1} once daily to twice daily during 48 hours. The plasma concentration increased more rapidly in the present study, which probably explains the initial, transient ataxia. The other frequently occurring adverse

event was an increased appetite and resultant increase in body weight in dogs fed *ad libitum*. When owners became aware of the weight gain, restricted feeding was initiated and no further weight gain was seen.

This is the first double-blind, placebo-controlled crossover study to report that PGN results in a highly significant reduction in clinical signs of SM-related CNeP in CKCS. Treatment with PGN maintained or improved a satisfactory owner-assessed QOL in 10/11 dogs. Transient ataxia and increased appetite were acceptable adverse events to all but one owner. The present study found that the number of scratching events, phantom scratching and vocalization when scratching can be used as pharmacological responsive, quantifiable indirect biomarkers of pain. The results of this short-term study support a positive treatment effect. To assess if long-term administration of PGN is safe in dogs, a longitudinal cohort study with continuous monitoring of effective plasma PGN concentration and potential adverse effects on organ systems is needed.

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Authors' contributions

MST: principal investigator, study design, data acquisition, management and interpretation, statistical analysis, manuscript preparation. LTS: data interpretation, statistical analysis, critical revision of the manuscript. FM: data acquisition, manuscript review. MB: study design, manuscript review. OJB: study design, data interpretation, critical revision of the manuscript. All authors approved the manuscript prior to submission.

Conflict of interest statement

The authors declare no conflict of interest.

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