Comparative analysis of neurological recovery and adverse effects in chondrodystrophic dogs with thoracolumbar intervertebral disc herniation treated with methylprednisolone versus non-steroidal anti-inflammatory drugs

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Received December 10, 2022
Accepted October 25, 2023

Abstract

Thoracolumbar intervertebral disc herniation is a common neurological disease presented to the small-animal practitioner. The use of methylprednisolone sodium succinate (MPSS) as an adjunct to surgical decompression in cases of acute spinal cord injury following intervertebral disc extrusion is controversial. A prospective study was undertaken to compare the perioperative use of MPSS and non-steroidal anti-inflammatory drugs (NSAIDs) in 40 chondrodystrophic dogs presenting with similar signs and undergoing spinal decompressive surgery. Twenty dogs received MPSS and 20 had NSAIDs administered preoperatively. Dogs were administered with either MPSS intravenously 20 min before surgery (30 mg/kg) or NSAID (meloxicam 0.2 mg/kg or carprofen 4 mg/kg) subcutaneously 20 min before surgery. Dogs were evaluated by neurological examination of gait 24 h postoperatively, at time of discharge, and then at 8 weeks. The neurological recovery was similar in both groups, but the frequency of side effects such as vomiting (MPSS group: 90% vs NSAIDs group: 55%), and anorexia within the first three days (present in all 20 dogs pretreated with MPSS) was significantly different, with complications being more prevalent in the MPSS group. This study showed that side effects were significantly more evident with the MPSS treatment group than with the NSAID group, with a neurological recovery similar in both groups.

Analgesics, chondrodystrophy, disc disease, steroid

Medical and surgical treatments for intervertebral disc herniation (IVDH) have been described extensively (Griffin et al. 2009a; Griffin et al. 2009b). One of the effects of acute spinal cord injury (ASCI) is reduction in blood flow to the neural tissue. As reperfusion occurs, highly reactive free radicals are liberated. These free radicals induce lipid peroxidation and damage to the cellular plasma membrane. Ischaemia/reperfusion injury is key in irreversible tissue loss following spinal cord trauma and ischaemia (Sharp and Wheeler 2005). The potentially beneficial mechanism of action of glucocorticoids in ASCI is inhibition of this lipid peroxidation as well as hydrolysis of lipids, processes that lead to damage of both neuronal and microvascular membranes (Bracken et al. 1990). This inhibition is postulated to be due to the steroids' high lipid solubility and ability to intercalate into artificial membranes between the hydrophobic polyunsaturated fatty acids of the membrane phospholipids and limit the chain reaction of lipid peroxidation throughout the phospholipid bilayer (Demoupoulis et al. 1980; Hall 1992; Hall and Springer 2004). In addition to the primary action of glucocorticoids at physiological doses, some formulations, such as methylprednisolone sodium succinate (MPSS) can exert a number of other actions on the spinal cord, including maintenance of tissue blood flow, maintenance of aerobic energy metabolism, improved reversal of intracellular calcium accumulation, reduction of neurofilament degradation, and enhanced neuronal excitability and synaptic transmission (Bracken et al. 1990; Hall 1992; Bracken et al. 1997).

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Another effect of methylprednisolone is inhibition of phospholipase A2 formation, inhibiting arachidonic acid release as well as prostaglandin F2α and thromboxane A2, which can produce anti-inflammatory effects (Fingeroth and Thomas 2015). The use of MPSS evolved during the 1990s, through the results obtained from the National Acute Spinal Cord Injury Studies –NASCIS II and III–, as a standard treatment in acute spinal injury (Sayer et al. 2006), and it remains a drug used for ASCI worldwide. The potential beneficial effect of high-dose MPSS was initially reported in a series of NASCIS trials in 1990s (Bracken et al. 1990; Bracken et al. 1997).

Following the publication of the NASCIS trials, the pre-operative treatment was adopted worldwide; and, MPSS treatment became the standard of care in human adults (Caruso et al. 2017). However, the subsequent debate over the efficacy and safety of high-dose MPSS treatment (Short et al. 2000; Sayer et al. 2006) has led to serious differences of opinion in the medical community, and variations in practice (Rozet 2008). An increased overall complication rate was observed after high-dose MPSS treatment (Matsumoto et al. 2001; Suberviola et al. 2008; Ito et al 2009). Pneumonia, infection, and gastrointestinal bleeding are the most common complications reported in human patients receiving high-dose MPSS (Rozet 2008; Chikuda et al. 2014). In any case, MPSS, as a steroid, is the only drug approved by the U.S. Food and Drug Administration for the treatment of spinal cord injury in humans (Mirzaei et al. 2020). The results of the human NASCIS trials cannot be directly extrapolated to our veterinary patients. When examined closely, the benefit perceived in humans was very slight, with the result being minimal motor improvement. It is hard to discern what function that would correlate to in our patients, and if that effect would even be perceptible (in some humans there was increased digital motor function; such a benefit in dogs would be clinically insignificant) (Fingeroth and Thomas 2015). Currently there is a lack of studies comparing MPSS and non-steroidal anti-inflammatory drugs (NSAIDs) in the treatment of dogs with ASCI. Thus, this study details the perioperative use of MPSS in a cohort of similar dogs undergoing spinal decompressive surgery and compares the use of MPSS to NSAIDs.

Materials and Methods

The prospective study involved 40 consecutive cases of intervertebral disc disease (IVDD) treated preoperatively with MPSS and NSAIDs that have undergone spinal decompressive surgery at a single private hospital. Twenty cases were selected for every group. Dogs with confirmed IVD extrusions were included in this study.

All animal procedures were done in accordance with the national Research Council Guide for the Care and Use of Laboratory Animals using protocols approved by the Institutional Animal Care and Use Committee at the University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca, Romania. All the methods used in the study were carried out in accordance with the ARRIVE guidelines (Animal Research: Reporting of *In Vivo* Experiments).

Animals

Forty client-owned dogs with acute onset of thoracolumbar (T3-L3) acute IVDH Hansen type I were admitted to the clinic and examined. The median age at the time of surgery was 3.9 years (range, 1–7 years). There were 23 males and 17 females. The breeds included 18 Dachshunds, 7 Jack Russel Terriers, 6 Shih Tzu, 4 French Bulldogs, 2 Pugs, 1 Pembroke Welsh Corgi, 1 Pekingese, 1 Lhasa Apso. Data were collected from the cohort of animals that underwent hemilaminectomy and were treated preoperatively with two different medications: MPSS (group 1) or NSAIDs (group 2). Pain sensation was present preoperatively in all dogs (all dogs had a modified Frankel score of grades 3 or 4, similar between the two groups). Results of haematology, basic liver, and kidney biochemistry were unremarkable.

Data on the nature and progression of signs, patient signalment, history and duration of paralysis, preoperative neurological status, cross-sectional imaging findings, surgical details, details of drugs used for anaesthesia and pain management, and postoperative care were recorded (Table 1). Dogs were evaluated by neurological examination of gait 24 h postoperatively, at the time of discharge, and then at 8 weeks (using modified Frankel score system). Inclusion criteria for the trial were: chondrodystrophic dogs weighing < 20 kg with acute onset of hindlimb paralysis with intact deep pain sensation (within 72 h of admission), no prior treatment with corticosteroids or with NSAIDs before referral, no systemic comorbidities and diagnosis of acute thoracolumbar intervertebral disc herniation (TL-IVDH) that was treated surgically (Fig. 1). The diagnosis was established by

Table 1. Baseline characteristics of dogs in the study.

No.	Group 1			Group 2		
	Breed	Age (years)	Sex	Breed	Age (years)	Sex
1	Dachshund	2	F	Dachshund	3	M
2	Dachshund	5	M	Dachshund	6	F
3	Dachshund	3	M	Dachshund	3	M
4	Dachshund	7	M	Dachshund	4	M
5	Dachshund	3	M	Dachshund	2	F
6	Dachshund	5	F	Dachshund	5	M
7	Dachshund	5	F	Dachshund	6	F
8	Dachshund	3	F	Dachshund	3	M
9	Dachshund	2	M	Pembroke Welsh Corgi	6	F
10	Dachshund	4	M	Shih Tzu	3	M
11	French Bulldog	4	M	Shih Tzu	2	M
12	Pekingese	5	F	Shih Tzu	5	F
13	Pug	7	F	Jack Russel Terrier	4	F
14	Shih Tzu	2	M	Jack Russel Terrier	5	M
15	Shih Tzu	1	M	Jack Russel Terrier	3	M
16	Shih Tzu	4	F	Jack Russel Terrier	4	F
17	Lhasa Apso	7	F	French Bulldog	1	M
19	Jack Russel Terrier	6	M	French Bulldog	2	M
19	Jack Russel Terrier	3	F	French Bulldog	1	F
20	Jack Russel Terrier	5	M	Pug	7	M

F- female; M - male

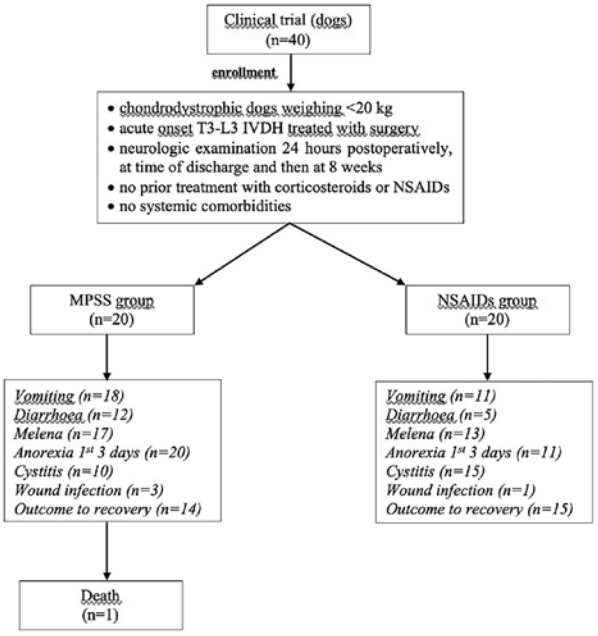

Fig. 1 Consort flow diagram. This flowchart illustrates the recruitment, study groups and complications.

IVDH - intervertebral disc herniation; MPSS - methylprednisolone sodium succinate; NSAIDs - non-steroidal anti-inflammatory drugs

myelography and MRI scan (Siemens Magneton 0.3 T). T1-weighted (T1W), T2-weighted (T2W), 3D T2, short tau inversion recovery (STIR), and contrast studies were performed. Findings to confirm disc extrusions were: extradural compressive material hyperintense to the spinal cord parenchyma on T2W, signal voids in epidural space associated with the compression, suggesting the presence of haemoglobin breakdown products (T2W), increased conspicuity of intervertebral disc-associated extradural compression with STIR and enhanced herniated intervertebral disc material on T1W after administration of gadolinium-based contrast medium. No hyperintensity of the spine was recorded to be compared with the length of L2.

Perioperative management

Dogs were administered either MPSS (n = 20) intravenously 20 min before surgery (30 mg/kg) or NSAID (n = 20) (meloxicam 0.2 mg/kg or carprofen 4 mg/kg) subcutaneously 20 min before surgery. This was in combination with 30 min preoperative antibiotics (cephalexin 25 mg/kg) and analgesia (buprenorphine 0.02 mg/kg or methadone 0.6 mg/kg). Premedication consisted of medetomidine and either methadone or buprenorphine. Induction was performed with propofol and anaesthesia was maintained with isoflurane in oxygen. Methadone or buprenorphine injections were given for three postoperative days plus either prednisolone (2 mg/kg for 3 days, then 1 mg/kg for 4 days) or NSAID (carprofen 2 mg/kg or meloxicam 0.1 mg/kg) orally for 7 days. All dogs underwent hemilaminectomy.

Postoperative follow-up

Drug administration was initiated once the diagnosis of IVDH was confirmed and all dogs underwent hemilaminectomy. The only difference in treatment between the groups was the medication administered. Side effects were recorded and compared using Fisher's test. Diarrhoea was considered because the loose stools were watery. Melena was established based on the dark reddish brown to black colour of the faeces. Vomiting was observed based on digested material eliminated. Anorexia was considered when a dog totally refused to eat for the first three days after surgery. Neurological function was assessed 8 weeks postoperatively (using modified Frankel score system) to assure the outcome of the surgical procedure. Physiotherapy started from postoperative day 1, consisting of assisted standing, flexion/extension, and massage of affected limb muscles. The assisted standing water treadmill started with day 3. Bladder emptying by manual expression was performed every 8 h.

Data analysis

Fisher's exact test was used to compare between the two medication groups. Fisher's test was preferred to Chi-square test, sometimes used for this type of data, due to the size of the two samples. All analyses were compared between the two medication groups. The differences were considered significant when P values were < 0.05. Certain outcomes were binary (e.g., diarrhoea, vomiting).

Results

Postoperative outcome and follow-up

The results indicated significant differences in the occurrence of both vomiting and anorexia within the first three days between two medication groups. Both of these two complications were more prevalent in the MPSS group (Table 2). There was also some evidence that diarrhoea was more common in the MPSS group - 12/20 (60%) versus 5/20 (25%) in the NSAIDs group - although this difference was only of borderline significance ($P = 0.05$) (Table 2). In the MPSS group, there was one death due to unknown causes,

Table 2. Comparison of complications between medication groups.

Complication	Steroid (MPSS) n (%)	NSAIDs n (%)	P value
Vomiting	18 (90%)	11 (55%)	0.03*
Diarrhoea	12 (60%)	5 (25%)	0.05
Melena	17 (85%)	13 (65%)	0.27
Anorexia first 3 days	20 (100%)	11 (55%)	0.001*
Cystitis	10 (50%)	15 (75%)	0.19
Wound infection	3 (15%)	1 (5%)	0.61
Neurological recovery	14 (70%)	15 (75%)	1.00

MPSS - methylprednisolone sodium succinate; NSAIDs - non-steroidal anti-inflammatory drugs; n - number; *$P < 0.05$.

thus, the animal was eliminated from the study. Necropsy was not performed. Twenty-five dogs developed urinary tract infections: 10/20 (50%) in the MPSS group, and 15/20 (75%) in NSAIDs group without significant differences ($P = 0.19$) (Table 2). Thirty animals developed melena: 17/20 (85%) pre-treated with MPSS and 13/20 (65%) with NSAIDs, also without significant differences ($P = 0.27$). Further 3/20 (15%) dogs from the MPSS group suffered wound infection versus 1/20 (5%) dog from the NSAIDs group ($P = 0.61$). Neurological recovery was similar in both groups with no significant differences (Table 2).

Discussion

The use of MPSS as an adjunctive therapy to surgical decompression in dogs with acute spinal cord injury following IVD extrusion is still controversial. Side effects of vomiting and anorexia were more prevalent in the MPSS group in our study, with statistically significant differences in the occurrence compared to the NSAID group. We considered vomiting and anorexia as consequences of gastrointestinal ulceration, because these signs were not present preoperatively. Gastric mucosal lesions were concluded to be common in dogs with acute degenerative disc disease treated with corticosteroids in a previous study also (Neiger et al. 2000).

Renal function analyses were performed only preoperatively to assure no comorbidity was present (an inclusion criteria request). In humans, spinal cord injury is associated with increased risk of gastroduodenal ulceration, but the mechanism is not completely understood (Kewalramani 1979). Also, after high-dose MPSS treatment in patients with acute cervical spinal cord injury (Miekisiak et al. 2014), the authors observed that patients receiving high-dose MPSS had a significantly increased risk of major complications (gastrointestinal ulceration and bleeding). The treatment was not associated with an increase in mortality. In two studies, 100% of healthy dogs that received high dose MPSS had endoscopic evidence of gastric bleeding (Rohrer et al. 1999a; Rohrer et al. 1999b). Concurrent treatment with gastrointestinal protectant drugs did not ameliorate this adverse effect, as was found also in another study (Neiger et al. 2000). We did not use any gastrointestinal protectant drugs for the dogs in the study. In another study, 90% of dogs undergoing spinal surgery with adjunctive MPSS treatment had evidence of gastrointestinal bleeding assessed by faecal occult blood tests (Hanson et al. 1997). Olby et al. (2016) did not find any benefit of MPSS or polyethylene glycol in the therapy of severe acute thoracolumbar IVDH when used as adjunctive treatments administered to dogs in the first 24 h of the onset of paralysis. Boag et al. (2001) found that Dachshunds with acute IVDD treated with decompressive surgery and receiving MPSS had a significantly higher incidence of postoperative gastrointestinal complications, an increased use of gastrointestinal protectants, and also higher financial costs. We consider gastrointestinal bleeding and/or ulceration to be responsible for vomiting, anorexia, and melena, with vomiting and anorexia significantly more prevalent compared to the NSAID group in our study.

Urinary bladder dysfunction is an important and common problem in perioperative cases of thoracolumbar IVDD (Kerwin et al. 2018). It was not possible to accurately determine preoperatively the urinary status of the population of dogs in our study due to the acute nature of the condition and the short amount of time spent in the hospital before the surgery. Ten dogs in the MPSS group and 15 in the NSAID group developed postoperative cystitis without significant differences between the groups. This is not very consistent with what has been reported in the literature. In a study conducted on 161 dogs with surgically confirmed IVDD (Levine et al. 2008), a dexamethasone group of dogs was 11.4 times more likely to have a urinary tract infection and 3.5 times more likely to have diarrhoea compared to the other glucocorticoid and untreated groups of dogs. No differences in neurological function

at discharge or re-evaluation were detected among the groups. In another study there was a strong significant association between not administering NSAIDs after diagnosis and a higher risk of faecal incontinence (Mari et al. 2019). In that study, dogs that were administered NSAIDs (81 cases) were compared to dogs that did not receive NSAIDs (106 cases). The latter group included both dogs that received no anti-inflammatory treatment (93 cases) and dogs that received corticosteroids (13 cases). Comparing dogs that received corticosteroids to those that did not, no significant association with faecal incontinence was found (Mari et al. 2019). In any case, the low number of cases receiving corticosteroids and the lack of randomization, any direct comparison between the effect of these two classes of anti-inflammatory drugs on the occurrence of urinary infection or faecal incontinence was difficult to establish. The neurological grade at referral was also a predictor of urinary and faecal incontinence. This suggests that further prospective randomized studies are necessary to investigate NSAID treatment in dogs with acute nucleus pulposus extrusion. As in our population, detrimental wound-healing effect and increased infection with the use of glucocorticosteroids both in humans and dogs were observed (Levine et al. 2007; Nishida et al. 2016).

There were no statistically significant differences regarding neurological recoveries of dogs in our groups. Recently, it has been shown that MPSS therapy in 50 dogs with surgically treated Hansen type-I TL-IVDH significantly reduced the swelling of the spinal cord, although it failed to provide any significant advance in the recovery rate or length in time (Nishida et al. 2016). A study evaluating 233 dogs treated medically for presumptive thoracolumbar intervertebral disc herniation showed successful treatment (complete or substantial improvement without recurrence) in 55% of the dogs, with recurrence of paraspinal hyperesthesia, ataxia, or weakness in 31%; 14% of dogs were classified as therapeutic failures (decline in or lack of improvement after completion of medical therapy, or necessity for surgery or euthanasia within 1 month) (Moore et al. 2016). In that study, owners completed proxy quality of life scores for their dogs. Although the duration of cage rest was not associated with outcome, administration of corticosteroids was negatively associated with both outcome and quality of life in a multivariate model that controlled for initial severity of spinal cord injury. Administration of NSAIDs was more likely to result in improved quality of life scores. In another retrospective study of 105 dogs with neurological injury, the authors evaluated the type and prevalence of complications of high-dose prednisolone sodium succinate treatment. Thirty-five (33.3%) cases developed complications including diarrhoea, melena, vomiting, haematochezia, haematemesis, anorexia, or a combination and all complications were minor and resolved without additional treatments after termination of the therapy (Culbert et al. 1998).

The small population of dogs in our groups together with the lack of any specific quality of life questionnaire for owners do not allow us to draw any major conclusion regarding the quality of recovery.

The temporal effects of steroid administration limit how the results of human trials can be extrapolated to veterinary patients. Human studies routinely showed either no benefit or even worsened outcomes when patients received steroids more than 8 h after spinal cord injury. Unfortunately for veterinarians, it is not always possible to identify the precise time of the onset of disc-induced spinal cord injury in our patients, so we may find ourselves treating dogs with steroids well beyond any time frame where they might have had any potential benefit. Until we have prospective, blinded, large-scale studies in our patients with naturally occurring spinal cord injury, we cannot advocate using high-dose MPSS in our patients (Fingeroth and Thomas 2015).

Many veterinary clinicians continue to use corticosteroids such as prednisone or dexamethasone routinely at lower, anti-inflammatory doses for the management of canine IVDH (Moore et al. 2016). The question of whether treatment with NSAIDs or steroids

is most appropriate represents a somewhat polarizing issue in veterinary medicine and is highly clinician-dependent (Moore et al. 2020).

Limitations of the study reported here included a small population in the two groups, lack of a control group, and subjective assessment of anorexia and melena in the treated dogs. Future studies with larger groups, ensuring that vomiting and anorexia are clearly due to anti-inflammatory drugs, with dogs having additional risk factors for gastrointestinal injury and bleeding, such as older age and presence of comorbidities, would better represent the clinical population of dogs receiving MPSS and NSAIDs. Any conclusions made in this study cannot be solely attributed to a single dose of MPSS preoperatively. As the dogs were treated postoperatively with prednisolone *per os*, we are not completely sure whether prednisolone on its own rather than methylprednisolone could be the cause of the side effects.

Although such additional studies are warranted, the results of our study lead us to believe that the benefit of preoperative treatment with MPSS in chondrodystrophic patients does not support the use of this drug over NSAIDs prior to spinal surgery.

The findings of this study are in line with the ACVIM consensus statement on the diagnosis and management of acute canine thoracolumbar intervertebral disc extrusion, regarding the anti-inflammatory medication: "Corticosteroids are not recommended for routine use in medical management of the acute phase of presumptive TL-IVDE. In the chronic phase, a short course of anti-inflammatory doses of corticosteroids may be of benefit for some dogs" (Olby et al. 2022).

In conclusion, this study showed that dogs suffering SCI following acute IVDH treated surgically have similar neurological outcomes when they receive methylprednisolone versus NSAIDs. However, there was a significant difference between the groups with regard to side effects, with a higher percentage of dogs having side effects in the MPSS group compared to the NSAIDs group.

Acknowledgements

The publication was supported by funds from the National Research Development Projects to finance excellence (PFE)-14 (ID 546) granted by the Romanian Ministry of Research, Innovation and Digitalization.

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