Animal Trial

Clinical and Histological Effects of the Intrathecal Administration of Methylprednisolone in Dogs

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Disclaimer: Study supported by Brazil Federal Agency for the Support and Evaluation of Graduate Education (CAPES).
Conflict of interest: None.

Manuscript received: 04/16/2010
Revised manuscript received: 06/007/2010
Accepted for publication: 06/14/2010

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Background: Methylprednisolone is one of the most commonly used steroids for management of chronic back pain via epidural injection. Its inadvertent injection into the intrathecal space is associated with complications such as adhesive arachnoiditis.

Objective: The present study aimed to assess the clinical and histological changes associated with the injection of methylprednisolone into the intrathecal space of dogs.

Study Design: A randomized, double blind, controlled animal trial.

Methods: After approval by the animal research ethics committee, 14 dogs were studied in a randomized double blind controlled trial. They were assigned to one of 2 groups: Group I received 1 mL of 0.9% normal saline; Group II received 1 mL (1.15mg/kg) of methylprednisolone into the intrathecal space. Animals were clinically evaluated for 21 days, and then sacrificed. The lumbar and sacral portions of their spinal cords were removed for histological examination.

Results: In Group I, there were no clinical or histological changes. All animals in Group II showed no clinical changes but all exhibited histological changes in the spinal cord. The main histological changes consisted of meningeal thickening and lymphocytic infiltrates in the blood vessels. In 3 animals, adhesion of pia, arachnoid, and dura matter was noted and the nerve roots were surrounded by fibrosis. In one animal, necrosis of the spinal cord was evident.

Limitations: The limitations of the present study include: small sample of animals (n=14), relative short clinical follow-up (21 days), and use of a commercially available drug solution, which is not preservative free.

Conclusion: The present study demonstrated that the intrathecal administration of commercially available methylprednisolone was responsible for causing histological changes in the spinal cord and meninges of the animals studied.

Key words: Methylprednisolone; intrathecal injection; steroids; adhesive arachnoiditis; low back pain; epidural injection; spinal cord.

Pain Physician 2010; 13:493-501

Chronic low back pain related to radicular compression is the most common spinal pain treated with epidural corticosteroids (1-22). Steroids have enjoyed a relatively safe profile (23-26). However, debate continues about their use in the epidural space (1-22,27-35). The use of epidural steroids in the treatment of back pain was first reported in 1952 and the technique has been widely practiced since that time (36). Even though reports indicated a favorable response to this therapy, debate continues

not only about effectiveness but also safety. Double blind studies also have shown that steroid treatment is beneficial both in short term as well as long term evaluations (2-5,15-22,37,38).

Administration of corticosteroids in the epidural space utilized the anti-inflammatory action relatively close to the nerve roots that are irritated. They then, presumably have less systemic effects. However, there are reports in the literature of Cushing like symptoms and other systemic side effects from epidural steroids (28,39-42). Epidural injection also have their own potential complications such as local discomfort, infection, inadvertent dural puncture, post-dural puncture headache, epidural hematoma, nerve injury, coma, and, in rare cases, death (1-7,41-44). Some of these complications can be due to vasospasm, direct vascular trauma, or embolus from particulate steroids (44-46). Inaccurate placement of epidural needles into the vein occurs in 1.9-11.2% of lumbar epidural injections (44,47,48), while intrathecal injection occurs in 5%-6% of epidural steroid injections when the needle insertion is done under fluoroscopy (49-51).

The use of intrathecal steroids has been associated with severe nervous system complications such as adhesive arachnoiditis (AA). It is more likely to occur when methylprednisolone is used (52,53). Animal experimentation is the first step to establish the safety of intrathecal methylprednisolone injection (54). To our knowledge there are no reports in the literature of untoward clinical and histological effects of intrathecal methylprednisolone injection in the animal model. The objective of this study was to determine the clinical and histological effects of injecting methylprednisolone into the intrathecal space of dogs.

Methods

Animal Model

After approval by the animal research ethics committee, 14 male adult mongrel dogs were obtained from the Experimental Animal Center at the Sao Paulo State University at Botucatu campus. The animals weighed from 7 to 14 kg, and the length of their vertebral column ranged from 54 to 68 cm. All animals were kept under clinical observation in individual cells and were assessed before spinal puncture and had normal neurological function. All tests were performed in accordance with Ethical Guidelines in Conscious Animals (55).

Experimental Groups

The dogs were randomized to one of 2 experimental groups according to the type of solution to be administered into the intrathecal space. Seven dogs were allocated to each group. Group I was defined as the control group, in which saline 0.9% was injected. Group II received methylprednisolone (1.15mg/kg). The dose of the solution was calculated based on the dose epidurally employed to treat radicular pain in a 70 kg adult patient (80 mg methylprednisolone acetate). Both solutions had the same 1 mL volume. All the syringes in our study were covered with sterile opaque white tape to keep the investigator blinded to the solution being injected, as methylprednisolone is a milky solution compared to saline, which is a clear solution.

Spinal Puncture Protocol

The dogs were fasted 12 hours before the procedure, with water ad libitum. All animals were anesthetized with an intravenous administration of etomidate (2 mg/kg) and fentanyl (0.005 mg/kg). A 10 cm area around the site of the spinal puncture at the L6-7 intervertebral space level was washed with water and soap, followed by hair removal and skin cleansing with saline. Finally, the naked skin was disinfected with a 2% chlorexidine gluconate solution and sterile fields were appropriately positioned.

The subarachnoid puncture was performed through the midline, approximately 45^0 to the skin, with a 22-gauge Quincke needle. Any difficulties during the procedure and any changes in the color of the cerebrospinal fluids (CSF) were recorded. When a traumatic spinal puncture was identified, as defined by the presence of hemorrhagic CSF or the need for more than one puncture, the animal was excluded from the study. Once the needle was properly placed and clear CSF could be identified, 1 mL of the randomized solution was injected for approximately 10 seconds through 1mL disposable syringes.

Solution Specification

Preparations of methylprednisolone (Depo-medrol, Pfizer, Puurs, Belgium) contained methylprednisolone 80mg/ml, polyethylene glycol (Macrogol 4000), myristil-gama-picolinine chloride, and saline. The pH of the final product remains within the USP specified rate, between 3.5-7.0. The saline (Baxter Healthcare Corp., Sao Paulo, Brazil) administered to the control group had a pH of 5.0.

Evaluation and outcomes

The animals were evaluated after the recovery from the anesthesia and were followed daily during

the next 21 days by the same researcher every day. Each animal was evaluated regarding the following secondary outcomes: motor deficit, anal sphincter tonus, and painful sensibility. The primary aim of the study was to evaluate the histological changes in the spinal cord and meninges of the dogs 21 days after subarachnoid administration of the methylprednisolone.

The presence of pain was defined by the following: hind limb withdrawal, vocalization, and facial expression. All 3 secondary outcomes (motor deficit, anal sphincter relaxation, and nociception) were classified dichotomously into absent or present. If the slightest deficit in any of these dimensions was observed at clinical assessment, the animal would be classified as positive for the deficit according to the dichotomous classification used. Nociception was assessed by reaction to painful pressure and thermal stimuli. Motor deficit was determined by the inability to walk, jump, and sustain the tail in an upward position. Anal sphincter relaxation was ascertained through visual inspection. Pressure nociceptive stimuli were elicited by the bilateral pinch of a skin fold over sacral, lumbar and thoracic dermatomes, and interdigital membranes of hind limbs. Thermal painful stimuli were provided by thermoalgometer set at 50°C for 10 seconds, touching the interdigital membranes of the hind limbs.

After 21 days, the animals were anesthetized with intravenous sodium pentobarbital and then killed by electroshock. The lumbar and sacral segments of the spinal cord with the surrounding meninges were quickly removed in less than 3 minutes to minimize the risk of ischemia and apoptosis of those tissues. The specimens were fixed in formalin 10% solution for 7 days, and then histological sections were prepared from about 10 cm above the level of the spinal puncture to the end of the cauda equina. The histological sections were stained by hematoxilin-eosin and Masson trichome technique and examined by optical microscopy. Researchers who were blinded to the solutions administered to each of the animals performed all clinical and histological evaluations.

Statistical analysis

To evaluate the effectiveness of the randomization procedure and the comparability of the 2 groups, Student t-test was performed for the animals' weight and the length of their vertebral columns. One-sided Fisher's exact test was selected to compare the frequencies of the findings on the outcomes between the methylprednisolone and the control groups. P values less than 0.05 were considered statistically significant. Prism 4 software (GraphPod Software, La Jolla, CA) was used to perform the statistical analysis.

Results

There were no significant differences between the studied groups with regard to the weight ($p = 0.18$) or spinal length ($p = 0.57$). No animals were excluded due to multiple or hemorrhagic punctures. None of the animals demonstrated any clinical change, such as increased sensitivity to pain, decreased mobility, or anal sphincter relaxation.

There were no histological changes in the spinal cord of the animals from Group I (Fig. 1). However, all seven animals in Group II presented with spinal injury ($p < 0.001$). (Table 1; Figs. 2, 3, and 4). The main histological changes observed in Group II were areas with meningeal thickening and lymphocytic infiltration in the blood vessel. Further histological examination also revealed that in 3 animals there was adherence among the pia, arachnoid, and dura matter and the nerve roots were seen completely encircled by fibrous tissue. One animal also demonstrated necrosis of the dorsal spinal cord.

Discussion

Dogs were selected for this study because other toxicity studies have been successfully performed in this species. The anatomy of the dog also provides easy access to the intervertebral space, and so facilitates lumbar puncture and intrathecal injection (56,57). No animal had to be excluded from the present study due to difficult or traumatic spinal puncture.

The neurotoxic and inflammatory mediator phospholipase A2 (PLA2), which is normally contained in the nucleus pulposus, is released after an annular injury (58). The PLA2 triggers the arachdonic acid cascade that leads to localized inflammation mediated by prostaglandins and leukotrines. Corticosteroids have powerful anti-inflammatory effects because they inhibit prostaglandin synthesis, block PLA2 activity, and stabilize inflammatory cell membranes. Injection of steroid in the epidural space should result in a higher concentration of the steroid in the epidural space compared to oral or parenteral administration. Epidural injection is the only method of drug delivery that does not rely on blood flow and thus is deemed to be beneficial in compressive disc herniation in which blood flow to the region might be impaired (3-6).

Methyprednisolone is one of the commonly used steroids in the treatment of lumbosciatic pain de-

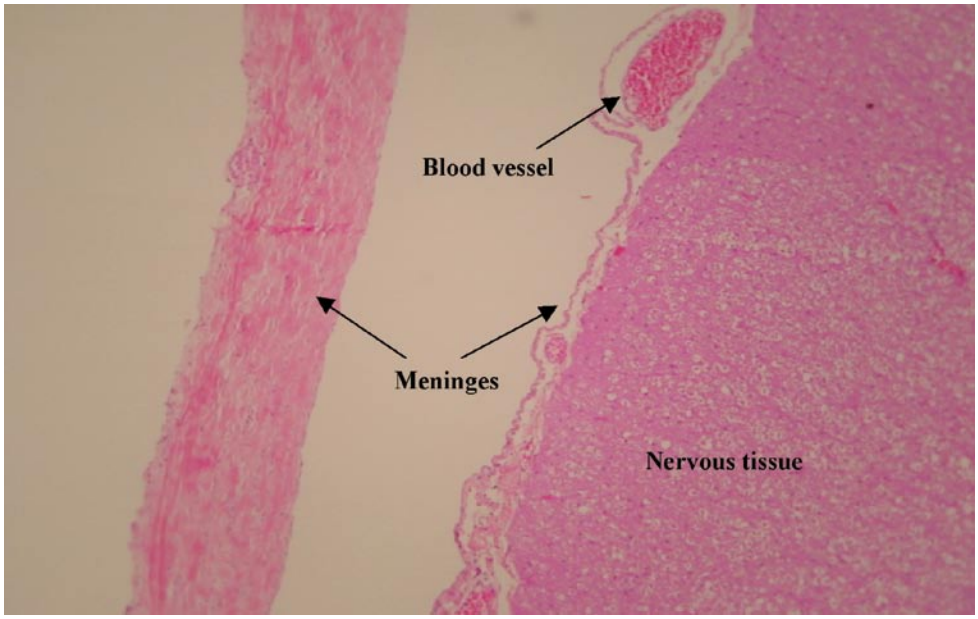

Fig. 1. *Group I (saline). Segment of nerve and lumbar nervous tissues, meninges and blood vessels showing no abnormalities (H&E 100X).*

Table 1. *Findings observed in Group II (methylprednisolone) during the review of histological sections.*

Histological changes	Meninges			Blood vessels		Spinal cord
	Fibrous thickening	Inflammatory infiltration	Trabeculae formation (adherence among pia, arachnoid, and dura matter)	Wall thickening	Inflammatory infiltration	Necrosis
Animal 1	present	present	absent	present	present	absent
Animal 2	present	present	present	present	present	absent
Animal 3	present	present	absent	present	present	absent
Animal 4	present	present	present	present	present	present
Animal 5	present	present	present	present	present	absent
Animal 6	present	present	absent	present	present	absent
Animal 7	present	present	absent	present	present	absent

Animals in Group I (saline) have not presented with any change in the histological sections.

spite its association with adhesive arachnoiditis (AA) (26,27,40). The present study confirms the potential for spinal damage due to the intrathecal administration of methylprednisolone. Arachnoiditis is a severe progressive disorder characterized by an inflammatory process leading to fibrosis of the arachnoid and subarachnoid space (59). The course of this disease can be irregular with 1.8 to 33% of patients presenting a progressive state and 50% to 59% of patients suffering with a static state (25,27,39,44,54,60-62). It can cause bladder and bowel dysfunction, loss of sensation, and motor weakness (53). In the present study, the animals had no clinical changes during the study period, though histological damages were observed in animals of Group II. Different researchers, using different animal models, have reported similar findings, suggesting that clinical findings do not always correlate with the degree of the histological changes (57,63,64). AA has an insidious on-

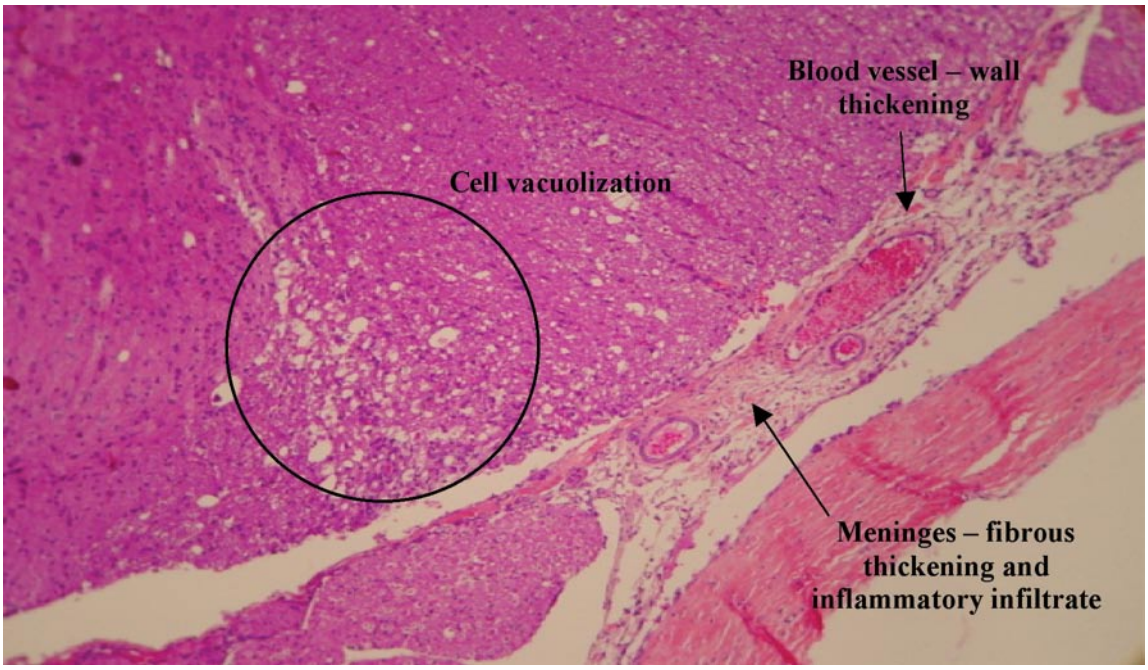

Fig. 2. *Group II (methylprednisolone). Segment of lumbar nervous tissues and meninges, showing thickness of the meninges and of the meningeal blood vessels (arrows). Nerve tissue necrosis with cell vacuolization is highlighted in the figure (H&E 100X).*

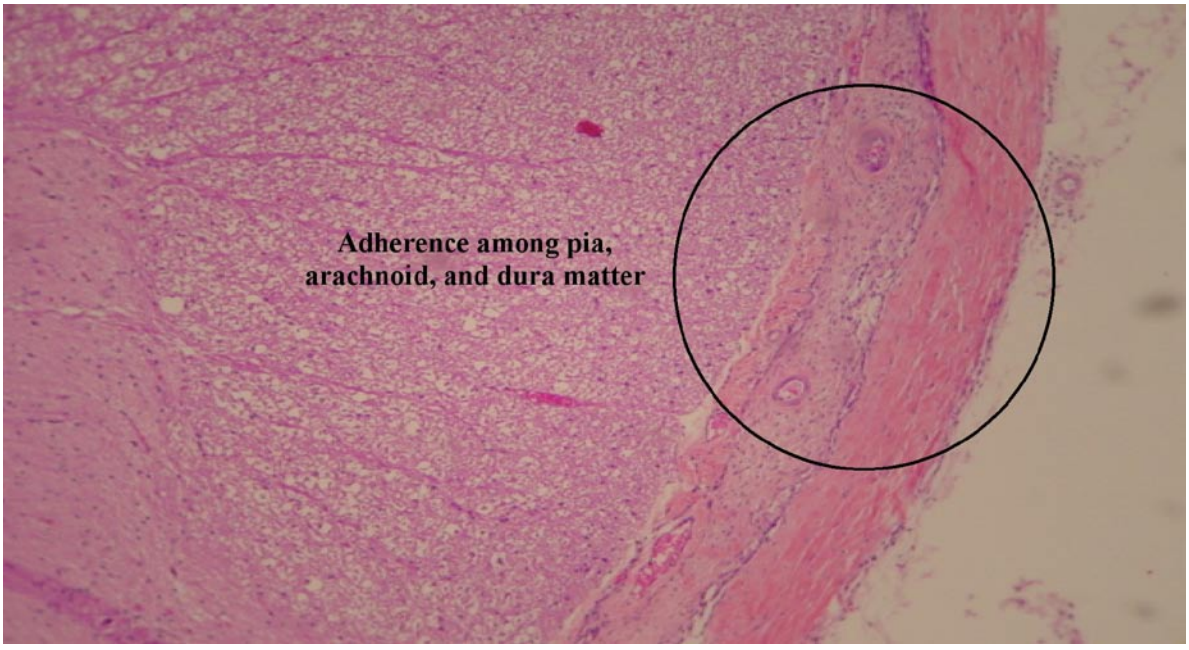

Fig. 3. *Group II (methylprednisolone). Segment of lumbar nervous tissue and meninges, showing adherence among pia, arachnoid, and dura matter (in detail: early stage of adhesive arachinoidits) (H&E 100X).*

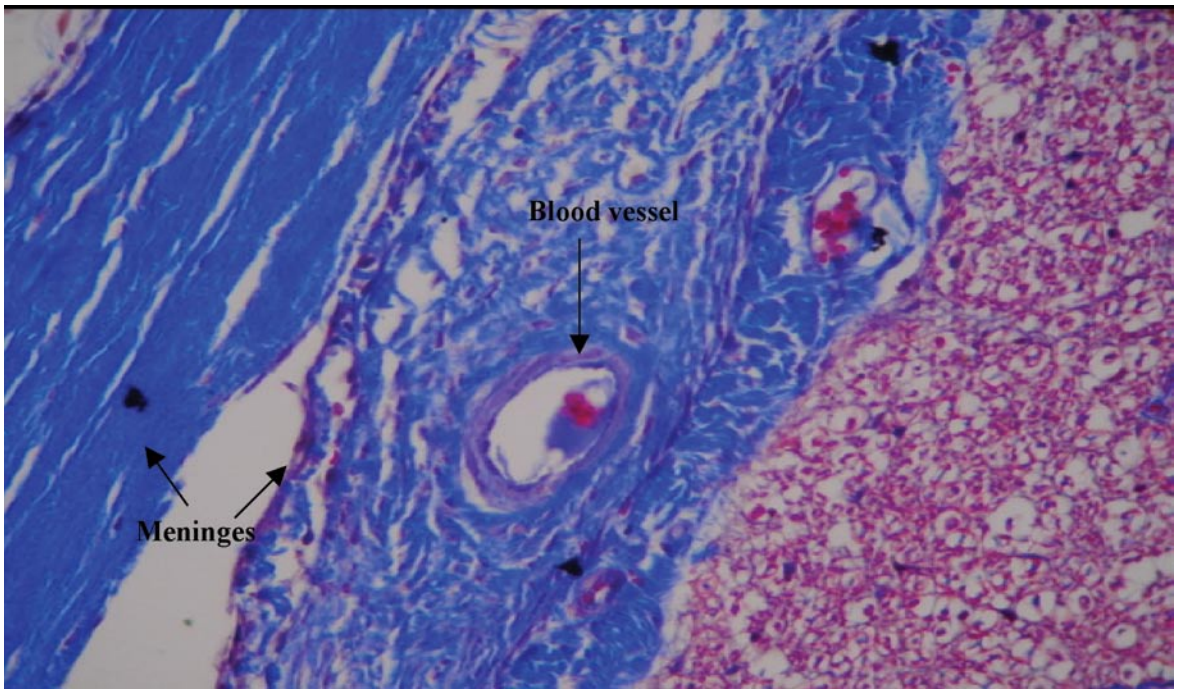

Fig. 4. *Group II (methylprednisolone). Segment of nerve and lumbar nervous tissues with fibrous tissue reaction in the meninges and meningeal blood vessels (Masson's trichrome 400X).*

set and the neurologic symptoms and signs are likely to occur after an extensive period. This could be the reason why the animals in the present study did not manifest any clinical signs during the 21 days of the study. The lumbar puncture technique should not be responsible for the lesions observed in the animals in Group II, since animals in Group I showed no signs of histological abnormality.

Methylprednisolone, as a depo-steroid with a long half-life, will have prolonged contact with the neural tissue and will allow for extensive distribution onto the spinal cord surface. The meningeal thickening and associated vascular inflammation found in the present study might be an indicator of the onset of AA. Goldstein (65), in 1970, performed a clinical study with intrathecal methylprednisolone injection in 38 patients with multiple sclerosis. One of these patients presented with clinical AA. Since the time of this publication, physicians have been concerned about the risk of AA following intrathecal methylprednisolone (49). Based on the many AA cases reported (29,30,52,58,59,63-65), the Australian Physicians Medical Defense Union (New South Wales, Australia) had published a warning recommending that methylprednisolone should no longer be used for epidural steroid injections (66)." Ten years later, the use of depo-steroids in the epidural space was recognized as safe in the review published by the Australian Pain Society, but the authors do not recommend the use of methylprednisolone (67).

Polyethylene glycol (PEG) is used as an excipient for depo-steroid preparation. It is added to the commercially available methylprednisolone solutions and other steroids in order to increase their solubility. PEG might be responsible for the reports associated with AA resulting from such methylprednisolone injections in the intrathecal space (26,40,49,52). Methylprednisolone and triamcinolone contain 3% PEG in their commercially available solutions. Concerns have been raised about the potential neurotoxic effects of 3% PEG injected in the human intrathecal space. Experiments with rabbit nerve preparation has revealed no significant neurolysis or slowed conduction velocities with solutions containing 40% PEG. Histopathological studies were not done to corroborate these findings. Currently, there is

no data on human toxicity with PEG (61). On the other hand, Selby (68) observed immediate demyelization when PEG was injected into the peripheral nerves, optic nerve, nerve roots and spinal cord of rats and rabbits. The drug preparation that we used in this study contained 3% PEG and that might have contributed to the histological changes found in the spinal cord. Exposure of the nerves of a rat's paw to solutions containing PEG for a period longer than one hour resulted in permanent lesions and neuronal degeneration. Remarkably, such lesions occurred with the administration of methylprednisolone with concentration of PEG found in commercial preparations, which was supposed not to cause neurotoxicity (54,69). In our study we have demonstrated that the dose of methylprednisolone we had used has the ability to produce histological changes in the meninges and the spinal cord of dogs. Most antioxidants, preservatives, and excipients are safe for human use. However, a word of caution seems appropriate for such additives when considered for epidural or intrathecal injections (61).

Another important complication related to the epidural injection of particulate corticosteroid, such as methylprednisolone, is brain and/or spinal cord infarct. Several hypotheses have been suggested, but the exact mechanism is not yet known. The leading hypothesis is that the inadvertent intra-arterial injection of particulate corticosteroid creates an embolus, causing a distal infarct (31-34). Derby et al (35) showed in their study that methylprednisolone particles were smaller than red blood cells, but the particles were densely packed and few aggregations were observed. The risk of the densely packed particles suggests that they are capable of forming an embolus that could occlude a small arteriole. A study performed by Okubadejo et al (70), comparing intravascular injection of particulate and non particulate steroids in pigs (methylprednisolone vs. dexamethasone vs. prednisolone), demonstrated that all animals injected with methylprednisolone had neurologic deficit and histological changes consistent with edema and necrosis, while none of the controls with non-particulate drug were affected (70). The occlusion of small arterioles should not be ignored as a reasonable explanation for the spinal cord damages found in the present study.

It is clear that the present study has some limitations. First, the small sample of animals can limit the applicability of the results. Second, we performed the clinical follow-up for a short period (21 days). The present 21-day time course of the study might not be adequate to detect the complete extent of the spinal damage caused by the methylprednisolone, since AA has an insidious onset and can take longer to produce clinical symptoms. Third, the drug used in the present study was not preservative free. Consequently, we can not assure that the spinal injuries observed were due to the methylprednisolone by itself or due to the other components of the presentation such as PEG. We decided to use the same preparation that is used clinically to treat spinal pain (i.e., with preservatives) because we believe it has a higher clinical relevance. However, further studies including intrathecally PEG solution injection might help to elucidate the role of the preservative in the development of histological changes observed in the present study.

Conclusion

In this study we were able to show that intrathecal injection of commercially available methylprednisolone is capable of producing histological changes in the spinal cord and meninges of dogs. Further studies are necessary to elucidate the mechanism of the meningeal toxicity observed and to evaluate the clinical long-term outcome in dogs and in different animal models.

Acknowledgments

The authors wish to thank the editorial board of *Pain Physician* for review and criticism in improving the manuscript.

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