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Perils of Intravascular Methylprednisolone Injection into the Vertebral Artery

An Animal Study

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Background: Intravascular injection of particulate steroids during cervical nerve root blocks has been postulated to be a source of catastrophic neurologic complications that might be avoided with the use of non-particulate steroids. The objective of this study was to compare the effects of direct intravascular injection of particulate and non-particulate steroids on the spinal cord and central nervous system.

Methods: Eleven adult pigs underwent direct injection, under fluoroscopic guidance, into the vertebral artery while under general anesthesia. A particulate steroid (methylprednisolone) was injected into four animals (Group 1), whereas seven animals received a non-particulate steroid (dexamethasone in four animals [Group 2] and prednisolone in three [Group 3]). Following injection, the animals were assessed by direct observation of physical activity and with magnetic resonance imaging. After the animals were killed, brain and spinal cord material was retrieved, fixed in paraformaldehyde for one week, and then subjected to histopathologic analysis.

Results: All four animals in Group 1 failed to regain consciousness after the injection and required ventilatory support. The animals in Groups 2 and 3 recovered fully and demonstrated no evidence of neurologic injury. Magnetic resonance imaging revealed upper cervical cord and brain stem edema in Group 1, but not in Groups 2 and 3. Histologic analysis showed early evidence of hypoxic and ischemic damage—specifically, early eosinophilic neuronal necrosis, nuclear condensation, white-matter pallor, and extracellular edema—in Group 1 but not in Groups 2 and 3.

Conclusions: These data suggest that one etiology of neurologic complications following cervical nerve blocks may be inadvertent intravascular injection of particulate steroids, as all animals injected with methylprednisolone had neurologic deficits while none of the controls injected with non-particulate steroids were affected. To our knowledge, this study is the first to demonstrate that particulate steroids cause neurologic deficits and to suggest that use of non-particulate steroids might prevent such complications.

Cervical radiculopathy is a constellation of symptoms, often including arm pain, numbness, weakness, and neck pain. Nonoperative treatment of cervical radiculopathy often incorporates various modalities, including analgesics, physical therapy, traction, orthoses, and epidural or transforaminal cervical nerve root injections[1]. There have been numerous reports emphasizing the efficacy of nerve root injections in delaying and/or preventing the need for surgery in both the cervical and the lumbar spine[2-7]. Some investigators have claimed good outcomes in as many as 80% of patients[8,9].

Although there have been retrospective studies of the safety of these injections, data proving the efficacy and safety of cervical nerve root injections are limited[10].

Given the proximity of the vertebral artery and the robust cervical radicular arteries adjacent to the cervical nerve roots, concerns have been raised about the potential for adverse outcomes from inadvertent intravascular injections. Serious complications that may arise from inadvertent injections include cortical blindness, quadriplegia, and death secondary to infarction of the spinal cord or brainstem[11,12]. Tiso et al.[13] exam-

TABLE I Data on the Pigs					
Pig	Drug	Clinical Effect	Magnetic Resonance Imaging Performed	Findings on Magnetic Resonance Imaging	Histologic Findings*
Group 1					
1	Methylprednisolone, 40 mg/mL	Failure to self-ventilate	No	Extensive signal changes noted in hindbrain and midbrain along with upper cervical cord signal changes	Early neuronal necrosis consisting of neuronal cytoplasmic eosinophilia, nuclear chromatin condensation, serpentine white-matter pallor with vacuolation involving midbrain, brainstem, and temporo-occipital lobes
2	Methylprednisolone, 40 mg/mL	Failure to self-ventilate	No		
3	Methylprednisolone, 40 mg/mL	Failure to self-ventilate	Yes		
4	Methylprednisolone, 40 mg/mL	Failure to self-ventilate	Yes		
Group 2					
1	Dexamethasone, 4 mg/mL	Normal recovery	Yes	No gross abnormalities noted	Normal neuronal nuclei. No evidence of necrosis
2	Dexamethasone, 4 mg/mL	Normal recovery	No		
3	Dexamethasone, 10 mg/mL	Delayed recovery, no neurologic deficits	No		
4	Dexamethasone, 10 mg/mL	Delayed recovery, no neurologic deficits	Yes		
Group 3					
1	Prednisolone, 10 mg/mL	Normal recovery	Yes	No gross abnormalities noted	Normal neuronal nuclei. No evidence of necrosis
2	Prednisolone, 50 mg/mL	Normal recovery	Yes		
3	Prednisolone, 50 mg/mL	Normal recovery	No		
*All animals underwent histopathologic analysis.					

ined various steroids with light microscopy and noted that particulate steroids have a tendency to aggregate, forming large crystals that are more likely than non-particulate steroids to embolize. This embolization has been theorized to be a potential mechanism for the adverse outcomes seen with particulate steroids.

We are not aware of any study in which the investigators specifically examined the potentially devastating outcomes that may result from transforaminal injection of steroids directly into the cerebrovascular system. The purpose of this study was to compare the effects of particulate and non-particulate steroid injections, into the vertebral artery, on the spinal cord and central nervous system. It was designed to be an exploratory pilot study of the use of steroids for cervical nerve root injections.

Materials and Methods

After institutional board review and approval by the university animal studies committee, we obtained eleven adult pigs (York-Landrace crossbreed) for the purposes of this study. All pigs were male and weighed between 50 and 62 kg. None of the pigs had undergone any prior medical intervention.

Surgical Technique

The pigs were premedicated with atropine (0.04 mg/kg given intramuscularly) and a cocktail consisting of Telazol (tiletamine and zolazepam), ketamine, and xylazine (1 mL/50 lb [22.7 kg] of body weight given intramuscularly). They were transported to the animal preparation room, where anesthesia was induced with use of isoflurane (1% to 5%) delivered by mask. The pigs were intubated, an intravenous catheter was placed in the marginal ear vein, and prophylactic antibiotics (15 mg/kg of cefazolin) were administered intramuscularly. The groin was shaved free of hair and prepared with use of Betadine (povidone-iodine) scrub and sterile water. The femoral artery was accessed with use of a vascular cut-down technique. A longitudinal skin incision was made, and the femoral vessels were identified by blunt dissection. Silk sutures were then placed around the femoral artery. An appropriately sized catheter sheath was placed in the artery and secured with use of the silk ties. Contrast angiography with use of Oxilan (ioxilan; 2 to 4 mL/kg/hr given intravenously) was used to identify the vertebral artery under live fluoroscopy. Appropriately sized guidewires and catheters were used to monitor the path toward the vertebral artery.

Fig. 1-A

Fig. 1-B

Fig. 1-A T2-diffusion-weighted sagittal image depicting a diffuse pattern of edema (arrow) with signal changes in the upper cervical spine, hindbrain, and midbrain of an animal in the methylprednisolone group. **Fig. 1-B** T2-diffusion-weighted sagittal image demonstrating no edema in the midbrain, hindbrain, or upper cervical spine of an animal in the dexamethasone group.
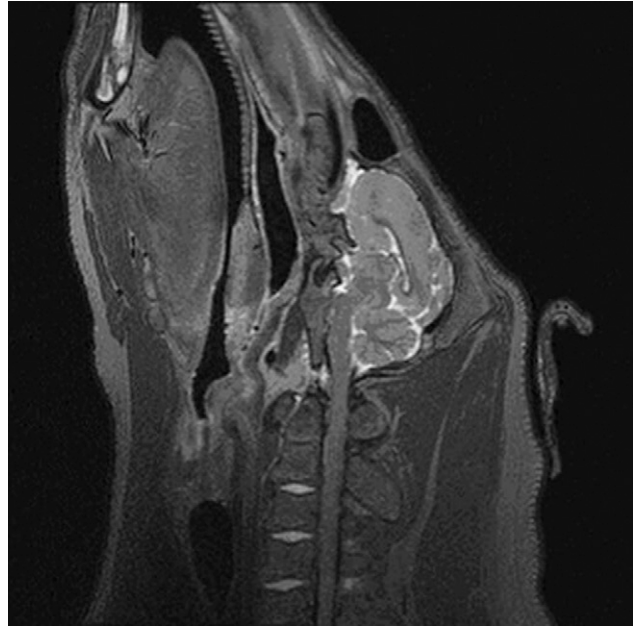
Once the contrast angiography confirmed the localization of the vertebral artery, the animals were injected with one of three drugs. In Group 1, four pigs were injected with 1 mL of methylprednisolone acetate (40 mg/mL). In Group 2, four pigs were injected with 1 mL of dexamethasone sodium phosphate, with two pigs receiving a low dose (4 mg/mL) and two pigs receiving a high dose (10 mg/mL). In Group 3, three pigs were injected with 1 mL of prednisolone sodium succinate, with one pig receiving a low dose (10 mg/mL) and two receiving a high dose (50 mg/mL).

Following injection, the animals were allowed to recover from the anesthesia, if possible, and were taken back to their cages. Animals that could not be weaned from the ventilator were subsequently killed, after magnetic resonance imaging was performed.

All animals that recovered from the injections were monitored closely until full recovery was confirmed. They were then housed overnight.

Technique and Protocol for Magnetic Resonance Imaging
In Groups 2 and 3, one pig treated with each dose concentration (high and low) underwent magnetic resonance imaging twenty-four hours following injection. Two animals in Group 1, which did not recover from the injections, also underwent magnetic resonance imaging, approximately four hours following injection. The animals were sedated and supported by a ventilator prior to transfer to the magnetic resonance imaging facilities. Throughout the process they were kept sedated with the use of isoflurane (1% to 5% in a 1:2 oxygen-nitrous oxide mixture).

Magnetic resonance imaging was carried out with a MAGNETOM Tim Trio 3.0 scanner (Siemens Medical Solutions, Malvern, Pennsylvania) with use of a twelve-channel head array coil. A three-plane localizer was used. Sagittal scans were obtained with use of an MP-RAGE (magnetization-prepared rapid gradient-echo) isotropic 0.9-mm protocol, with a T2-weighted SPACE (sampling perfection with application optimized contrasts) three-dimensional sequence with isotropic 0.9-mm spatial resolution. Axial images were obtained with FLAIR (fluid attenuated inversion recovery) transverse imaging (slice thickness, 2 mm; repetition time, 9000 msec; echo time, 94 msec). Diffusion-weighted spin-echo images were acquired with EPI (echo planar imaging) diffusion-trace-weighted scan-3 direction with b-values of 0, 500, and 1000 s/mm^2 in the slice direction.

Histopathologic Evaluation
All eleven animals in the study were subsequently killed. Dissection was then performed to obtain brain and upper spinal cord neural material. Sharp dissection was carried down to the skull. A saw was used to divide the skull and the upper cervical vertebrae in order to gain access to the neural material. Sharp instrumentation was then used to remove the neural material in whole.
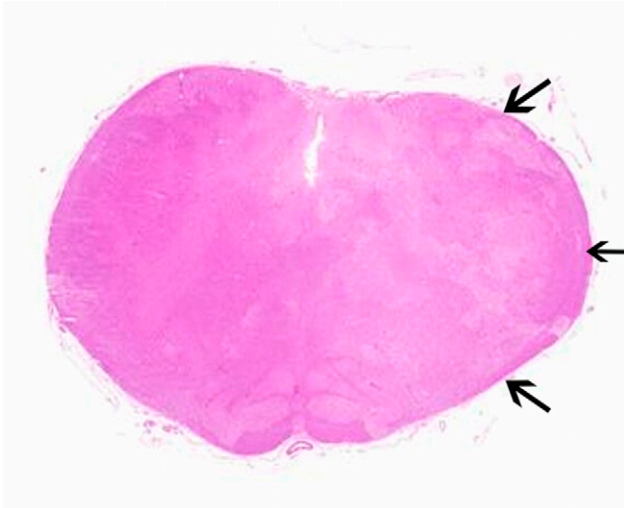
Fig. 2-A

Fig. 2-B

Fig. 2-A Methylprednisolone-group midbrain showing diffuse changes with areas of hypointense staining (arrows) representing edematous regions. These changes are a result of early eosinophilic necrosis and tissue degeneration (hematoxylin and eosin, whole mount). **Fig. 2-B** Neural cells appear eosinophilic with nuclear collapse in this methylprednisolone-group midbrain. Individual cells demonstrate early necrosis (arrow) (hematoxylin and eosin, ×40).
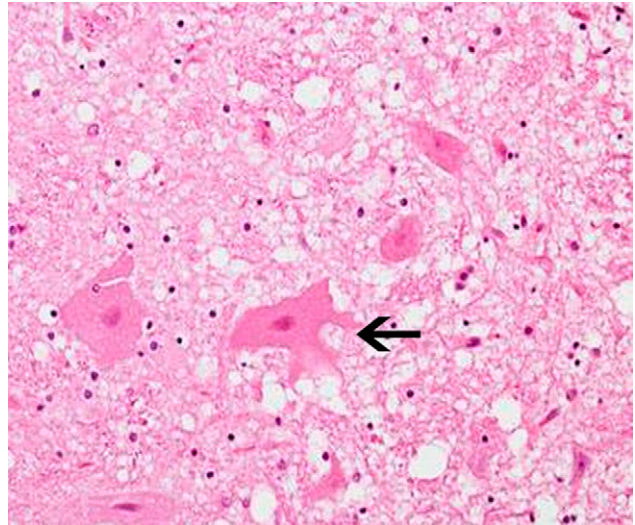

Fig. 2-C

Fig. 2-D

Fig. 2-C A dexamethasone-group midbrain does not demonstrate hypointensity similar to that seen in the methylprednisolone group. Staining is uniform with very subtle hypointensity at the periphery of the sample, representing artifact (hematoxylin and eosin, whole mount). **Fig. 2-D** Neuronal cells appear healthy with no evidence of nuclear collapse in this dexamethasone-group midbrain (hematoxylin and eosin, ×40).
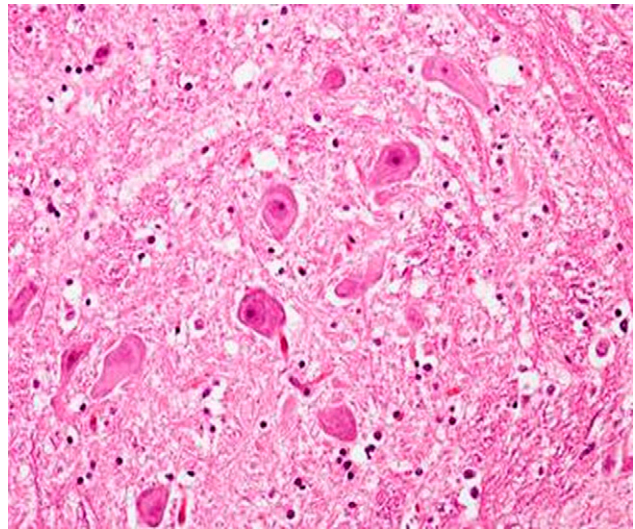
Following harvest of the neural material, each specimen was fixed in 4% paraformaldehyde for approximately one week. The specimens were then individually sectioned with sharp instrumentation, dehydrated in graded alcohols and xylene, embedded in paraffin, and cut into 6-μm-thick sections. Hematoxylin and eosin and periodic acid-Schiff stains were used.

Statistical Analysis

We calculated one-sided 95% confidence intervals with use of the modified Wald method for this study.

Results

Clinical Findings

None of the four animals in Group 1 recovered from the bolus injection of 1 mL of methylprednisolone (estimate of mortality = 1.0; 95% confidence interval = 0.54 to 1.0). They all required ventilatory support after demonstrating no ability to breathe independently. Attempts to wean the animal from the ventilator led to desaturation as no spontaneous, voluntary effort to self-ventilate occurred (Table I). The two Group-2 animals that received the low dose of dexamethasone recov-

ered from the anesthesia without complications and resumed baseline preoperative activities (estimate of mortality = 0; 95% confidence interval = 0 to 0.63). In comparison with this low-dose group, the two Group-2 animals that received the high dose of dexamethasone took 1.5 to two hours longer to show full signs of recovery. Both the high and the low-dose subsets in Group 2 regained preoperative activity levels once recovery from the procedure was complete (estimate of mortality = 0; 95% confidence interval = 0 to 0.63). All three Group-3 animals, both the one that received the low dose of prednisolone and those that received the high dose, recovered fully from the anesthesia without complications and with full recovery of preoperative activity levels (estimate of mortality = 0; 95% confidence interval = 0 to 0.53).

Findings on Magnetic Resonance Imaging

Two Group-1 animals underwent magnetic resonance imaging. Use of the specified diffusion-weighted technique mentioned above revealed distinct areas of signal change in the midbrain and brainstem of both animals (estimate of morbidity = 1.0; 95% confidence interval = 0.37 to 1.0) (Fig. 1-A, Table I). The frontal lobes did not demonstrate any notable edema.

Neither of the two animals that underwent magnetic resonance imaging in Group 2 and neither of the two that underwent it in Group 3 demonstrated any evidence of edema or distinct pathologic change (estimate of morbidity = 0; 95% confidence interval = 0 to 0.63). All aspects of the upper cervical cord and brain were well visualized and appeared to be normal (Fig. 1-B, Table I).

Histopathologic Findings

In Group 1, sections of the midbrain, medulla, and occipital lobe of all four pigs demonstrated evidence of eosinophilic neuronal necrosis (estimate of morbidity = 1.0; 95% confidence interval = 0.54 to 1.0), with condensation of neuronal nuclei, surrounded by vacuolated neurophil and white-matter pallor. There was a distinct serpentine pattern of hypodensity, vacuolation, and edema consistent with early infarction (Figs. 2-A and 2-B, Table I). These findings were in the midbrain, hippocampus, medulla, and temporal-occipital lobe.

The specimens in Groups 2 and 3 did not demonstrate any distinct patterns of infarction or eosinophilic neuronal necrosis (Figs. 2-C and 2-D, Table I).

Discussion

This study demonstrated a dramatic difference between the clinical, magnetic resonance imaging, and histopathologic findings of the group treated with particulate steroids and the one treated with non-particulate steroids. Methylprednisolone is a particulate steroid that is widely used for epidural steroid injections into the cervical and lumbar spine and into joints. The particulate carrier that is used enhances the drug's half-life in order to facilitate its efficacy. However, the effects of this particulate material on the central nervous system have not been fully elucidated. In our study, none of the animals injected with methylprednisolone recovered baseline neurologic func-

tion. All four sustained a clinical cerebrovascular insult, leading to an inability to be weaned from the ventilator.

Historically, both particulate and non-particulate steroids have been used for epidural and nerve root injections. In general, steroids have numerous effects in the body. These include alterations in carbohydrate, protein, and lipid metabolism; maintenance of fluid and electrolyte balance; and preservation of normal function of the immune, musculoskeletal, and other systems[14]. It is the anti-inflammatory effect of steroids that is believed to account for the pain relief that may be seen with cervical nerve root injections[15]. Particulate steroids are delivered by means of a carrier and are thus less soluble than non-particulate steroids. Non-particulate steroids have been demonstrated to dissipate rapidly and therefore may have a limited duration of effect[14]. Methylprednisolone, a particulate steroid, is often the drug of choice for cervical nerve root injections as a result of its long-lasting effects. Other agents may also be used for these injections, including dexamethasone—a non-particulate steroid, triamcinolone—a particulate steroid, and betamethasone—a particulate steroid. To our knowledge, there have been no prospective, randomized controlled studies that have specifically shown an advantage of one steroid preparation over another, but the general consensus is that particulate steroids are longer-lasting[2].

The non-particulate steroids used in this study were dexamethasone and prednisolone. Dexamethasone can also be used for epidural injection, and prednisolone is primarily used in animals and is administered intravenously. The concentration of drugs used in this study were based on the clinical doses of methylprednisolone. Epidural injections of methylprednisolone usually consist of a 1-mL bolus of 40 mg/mL of the drug. The dose equivalent of 4 mg of methylprednisolone is 0.75 mg of dexamethasone, which is equivalent to 5 mg of prednisolone. Dexamethasone is packaged in a low-dose form (4 mg/mL) and a high-dose form (10 mg/mL). A consistent volume of drug (1 mL) was delivered in order to avoid confounding factors that may result from bolus injection of higher volumes into the vertebral artery. The high-dose-dexamethasone group therefore received a higher dose equivalency relative to methylprednisolone (10 mg of dexamethasone is equivalent to 53 mg of methylprednisolone), but it did not experience a similar devastating clinical outcome. Prednisolone is available in 10 mg/mL and 50 mg/mL-dose concentrations. The high-dose form of this drug was essentially equivalent to the 40 mg/mL form of methylprednisolone, yet these pigs recovered with no adverse clinical manifestations. This suggests that the neurologic impact of intravascular injections is affected more by the solubility of the steroid than its dose.

Clinical examination, magnetic resonance imaging, and histologic analysis demonstrated pathologic findings consistent with a cerebrovascular insult in the particulate-steroid group. Clinically, the animals never regained consciousness. Magnetic resonance imaging showed edema in the midbrain and hindbrain. On histopathologic analysis, the cells demonstrated advanced pyknosis, cell membrane degeneration, and nuclear breakdown. Most of these changes were seen in the midbrain

and brainstem. It is these regions that one would expect to be most affected, with clinical evidence of respiratory compromise. In contrast, the animals in Groups 2 and 3 recovered fully, regaining baseline activity levels and demonstrating no notable radiographic or histopathologic abnormalities.

This study may be clinically relevant for humans as transforaminal epidural cervical nerve root blocks are commonly used as part of the management of cervical radiculopathy. Prior case reports have demonstrated complications that may result from the use of these injections. Many of these adverse effects are believed to arise from injection of material into the vertebral or, more commonly, radicular arteries. These complications include cerebellar infarct, brainstem herniation, brainstem infarction, spinal cord infarction, and generalized cerebral edema. In all of these reported cases, particulate steroids (either methylprednisolone or triamcinolone) were administered with use of a transforaminal approach[4,16-19]. Most of the affected patients subsequently died. The model in our study was designed to allow us to examine complications of transforaminal injections. Interlaminar injections have been shown to be safer, as they avoid the radicular arteries and there is a lower chance of inadvertent penetration of the vertebral artery[20]. Additional clinical studies or meta-analyses could shed light onto the comparative safety and clinical efficacy of these two modes of injection.

Weaknesses of this study include the limited number of animals that were used, the limited use of magnetic resonance imaging, and the lack of direct evidence that particulate steroids led to the observed clinical findings. As this study was designed to be an exploratory pilot study, future endeavors involving more animals may provide further support of the findings. Histologically, changes consistent with edema and necrosis were noted in the methylprednisolone group; however, there was no direct evidence of damage mediated by particulate steroids. Nonetheless, as the only difference between Group 1 and Groups 2 and 3 was the presence of particulate steroids, there appears to be a strong relationship between the presence of particulate steroids and the observed clinical findings. Tiso et al.[13] used electron microscopy to study various steroid formulations and noted that particulate steroids form microaggregates of at least 100 μm in size. This finding is in contrast to the 10-μm size of microaggregates of non-particulate steroids. The authors concluded that blockage of smaller vessels by the larger aggregates of particulate steroids leads to ischemic

changes in the brains of affected animals. The findings of our study are consistent with this theory.

Many studies aimed at addressing the specific anatomy of the central nervous system have shown adverse outcomes following injections[21,22]. Fluoroscopic (contrast-enhanced) and computed-tomography-guided imaging have been introduced as techniques to ensure precise placement of needles in these vital regions[5,23-25]. Nonetheless, there have continued to be case reports of devastating complications during selective transforaminal cervical nerve root injections of steroids[16-19,23,26].

Given the catastrophic consequences of inadvertent intravascular injection observed in this study, there should be further research on the relative efficacy of particulate compared with non-particulate steroids. Although the frequency of intravascular complications from particulate injections is low, a well-designed prospective study comparing the clinical efficacy of the two formulations would be beneficial. This will undoubtedly provide a useful risk-benefit analysis that may guide clinicians in their treatment of cervical radiculopathy. ■

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