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REVIEW ARTICLE

Intra-arterial injection of particulate corticosteroids: mechanism of injury

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Abstract

Mechanism of neurologic complications after epidural spinal injections (ESI) of particulate steroids at the cervical spine include intrathecal injection, epidural hematoma, direct spinal cord injury, and brain stem or cord infarction due to an arterial spasm or inadvertent intra-arterial injection of particulate steroids. At the lumbar spine, there is evidence that a spinal cord infarction secondary to an inadvertent intra-arterial injection of particulate steroids through a transforaminal approach is the leading mechanism.

Variations in the arterial supply of the spinal cord help to understand how a lumbar ESI may lead to a spinal cord infarction at the thoracic level. A radiculomedullary artery arising from the lumbar or sacral spine may participate to the supply of the spinal cord. All radicular and radiculomedullary arteries penetrate the spinal canal through the intervertebral foramen. Therefore, its catheterization carries a risk of inadvertent intraarterial injection. An ex vivo animal study has shown that particulate steroids injected in the blood stream produce an immediate and unexpected change of red blood cells into spiculated cells which aggregate and cause arterioles obstruction, while no particulate steroid macroaggregates or vascular spasm were observed. Rare instances of neurologic complications also occurred after ESI performed through a posterior approach. All occurred in previously operated on patients suggesting a pathologic role for the epidural scar.

Keywords Spine injections · Complications · Lumbar spine · Herniated discs · Interventional radiology · Lumbar spine · Interventional radiology · Complications

Introduction

Concerns have been raised concerning severe neurologic events reported after epidural steroid injections. Ninety such events were reported to the FDA Adverse Event Reporting System (FAERS) between 1997 and 2014 [1]. At the cervical spine, there are several mechanisms which can lead to neurologic complications after spinal injections of suspension of particulate steroids including intrathecal injection, epidural hematoma, direct spinal cord injury, and brain stem or cord infarction due to an arterial spasm or a vascular obliteration after inadvertent intra-arterial injection of particulate steroids [1].

At the lumbar spine, the spinal cord cannot be damaged directly by the puncture as at the cervical level and the main mechanism of the neurologic deficits is a spinal cord infarction secondary to an arterial occlusion. The review of the reported cases of lumbar spinal injections leading to such complications combines two technical features: a transforaminal approach and the use of particulate steroids [2].

In the following review, we will first recall anatomic notions concerning the vascularization of the spinal cord, which are key features to understand how a steroid injection at the lumbar level may lead to a spinal cord infarction at the thoracic level, and will then discuss the respective role of the transforaminal approach and of the particulate steroids.

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The vascularization of the spinal cord

The spinal cord is supplied by three longitudinal arterial axes, the anterior spinal artery (ASA), a single midline artery which runs all along the anterior aspect of the spinal cord and supplies the two anterior third of the spinal cord, and two posterolateral arteries.

At around 1.5 cm from the termination of the conus medullaris, the ASA and the two posterolateral arterial axes form an anastomosing circle, similar to the Willis polygon at the inferior aspect of the brain, to protect the vascularization of the conus medullaris (Fig. 1). The ASA is prolongated below the conus medullaris by the artery of the filum terminale, which is anterior to the vein and the filum itself [3].

Nerve roots are vascularized by 32 pairs of metameric radicular arteries. Among these radicular arteries, only a small number (6 to 12), either right or left, also supply the spinal cord in addition to their nerve root. They reach the spinal cord and supply the ASA and, therefore, are named the radiculomedullary arteries. Among these radiculomedullary arteries, the Adamkiewicz artery supplies the ASA at the level where the spinal cord is responsible for the lower limb innervation.

In 75% of cadaveric dissections, the Adamkiewicz artery arises from a T9 to T12 radicular artery, from the left side more frequently. When the Adamkiewicz artery arises above T9, there is, in most instances, an additional radiculomedullary artery (Desproges-Gotteron artery), which participates to the supply of the ASA, and may arise at any of the lumbar or sacral levels [3]. A radiculomedullary artery arises from a level below L1 in 1.6% of the cases [4], and as low as the L4-5 foramen in 3 out of 4000 spinal angiograms [5]. Cadaveric studies suggested even a higher frequency of radiculomedullary artery of lumbosacral origin. Desproges-Gotteron found such arteries in 3 out of 10 cadaveric specimens [6, 7]. Such lumbosacral radiculomedullary arteries could originate from either the ilio-lumbar, primary iliac, or sacral arteries which are not currently explored in spinal cord angiographic studies. Therefore, there is a small probability that any lumbar or sacral foramen contains a radiculomedullary artery participating to the vascular supply of the conus medullaris and put the cord at risk in case of inadvertent catheterization of this artery in the foramen.

The role of the transforaminal approach

A first argument suggesting that the transforaminal approach has a responsibility in the occurrence of the neurologic deficits is the gross time concomitance between the reports of the severe neurological events following spinal injections and the dissemination of this technical approach to the spine for steroid injections [8].

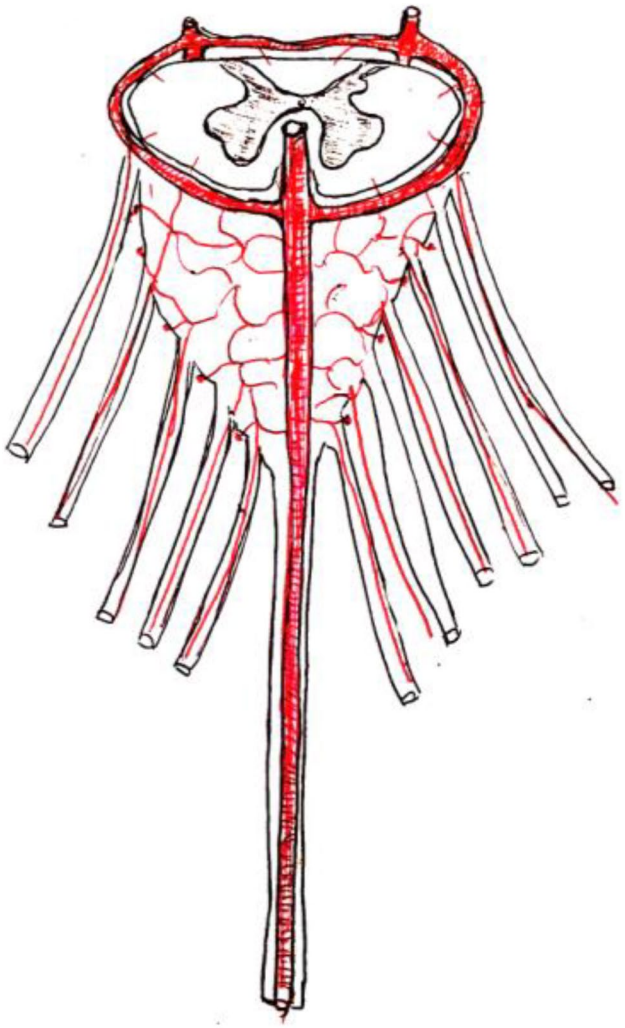

Fig. 1 Drawing showing the arterial circle around the conus terminalis by the anterior spinal artery on the midline and the two posterolateral spinal arteries

A second argument is based on the vascularization of the spinal cord which is exclusively provided by radiculomedullary arteries as mentioned above. All radicular and radiculomedullary arteries enter the spinal canal and subdural space through the intervertebral foramen.

Usually, lumbar radicular and radiculomedullary arteries and a superior foraminal venous network run in the upper part of the foramen along the corresponding nerve root with an almost parallel orientation, on the anterior aspect of its dural sheat within the narrow foraminal space [7, 9]. Therefore, an injection needle directed toward the nerve sheat may injure and sometimes penetrate a radicular artery, which, in a small percentage of cases, is a radiculomedullary and such an inadvertent intra-arterial injection may reflux up to the arterial circle insuring the vascularization of the conus medullaris.

Two different methods of lumbar transforaminal epidural steroid injections have been reported to access to the lumbar intervertebral foramen (Fig. 2). In the lower infraneural "Kambin's triangle" technique the needle is directed toward the inferior part of the foramen in order to avoid the exiting nerve root which is usually located in the upper part of the foramen [10, 11]. This technique should also theoretically avoid the incurring radicular artery. In the upper supraneural "safe triangle" technique, the needle is directed to the upper part of the foramen superiorly and laterally to the exiting nerve root. More precisely, the needle is targeted laterally and inferiorly to the junction between the transverse process and the inferior zygoapophyseal process (Fig. 2).

However, the position of the radicular artery into the foramen appears to be variable. Simon et al. retrospectively evaluated the precise location of arterial vessels into the intervertebral foramen from L1 to L4 in patients who underwent abdominopelvic CT angiograms for aortic vascular diseases [12]. They found that the location of the radicular artery was quite variable and was crossing either the supraneural "safe triangle" (50.39% of the cases) or the infraneural "Kambin's triangle" (20.31% of the cases), which theoretically put the supraneural catheterization of the foramen more at risk than the infraneural approach.

Another anatomic issue may also play a role: to target the "Kambin's triangle", the needle tip must be placed inferiorly and medially to the nerve root and ganglion, within the tighter part of the foramen through a posterolateral approach, while the supraneural "safe triangle" can be targeted through the strictly anteroposterior approach used by anesthesiologists for nerve block tests, placing the needle tip just below and laterally to the junction between the transverse process and the inferior zygoapophyseal process, at the lateral opening of the foramen. It may be hypothesized that catheterizing the intervertebral foramen, especially its middle and narrowest part, puts more at risk the radicular artery than placing the needle at its outer enlarging hole where the artery has more room to escape the needle tip.

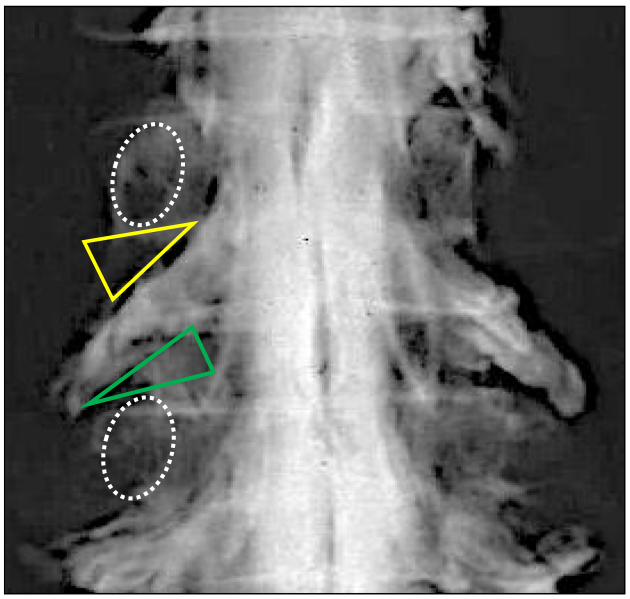

Fig. 2 Location of the supraneural safe triangle (yellow triangle) and infraneural Kambin triangle (green triangle) for foraminal needle approach drawn on a lumbar epidurography

The role of the particulate steroids

The clinical sequence of the neurological events at the lumbar level, namely the very acute and rapid onset of the motor deficit in the minutes following the injection together with the MR findings in the following hours or days, show that the dominant cause of the neurologic deficit is a spinal cord infarction related to the action of the needle tip on an artery supplying the spinal cord into the intervertebral foramen [2, 13–18].

Several mechanisms have been discussed to account for the arterial obliteration including compression by a hematoma, an intimal flap or arterial dissection, a vasospasm, and an embolism of the steroid particulates or aggregates of particulates.

Experimental works confirmed that the intravascular injection of particulate steroids may result in brain or spinal cord infarction. Okubadejo et al. studied the effect of a bolus of particulate steroid, methylprednisolone acetate, and two non-particulate steroids, dexamethasone sodium phosphate and prednisolone sodium succinate in the vertebral artery of pigs [19]. They reported that all the animals in the methylprednisolone acetate group required mechanical ventilation and had brain lesions at MRI and brain and spinal cord ischemia and necrosis at pathological examination. In contrast, no lesions or MRI abnormalities were found in the two non-particulate steroid groups. Dawley et al. also reported neurologic deficit and histological brain lesions in rats injected with methylprednisolone acetate whereas no deleterious effect was found with dexamethasone sodium phosphate [20].

Mechanism of vascular obliteration leading to spinal cord infarction

As discussed above, the most frequently suggested mechanism to explain the neurologic ischemia is the obliteration of feeding arteries by macroaggregates of steroid particles which have a tendency to coalesce [13, 21]. It has been suggested that the size of their final aggregates, which

differs among the different types of particulate steroids, may influence the risk of arterial embolization [22]. This mechanism is supported by in vitro light microscopic studies demonstrating that particulate steroids are sometimes large enough or tend to form aggregates large enough to occlude small arteriolar capillaries [22, 23]. While dexamethasone sodium phosphate contains only small particles, methylprednisolone acetate, triamcinolone acetonide, and betamethasone sodium phosphate-betamethasone acetate tend to amalgamate in large aggregates, well above 100 µm in size, suggesting that they could form an embolus and occlude small arterioles [22, 23].

However, the experimental work by Laemmel et al. favors a different mechanism for cord infarction [24]. It shows that particulate steroids injected in the blood stream are causing an immediate and unexpected aggregation of RBC responsible for the obstruction of arterioles [25]. These authors used an in vivo animal preparation allowing the direct observation of the effects of an intra-arterial injection of particulate steroids on microvascular perfusion. In their study, three of the particulate steroids implicated in most of the case reports of severe and permanent neurologic deficits following spinal injections, namely methylprednisolone acetate, triamcinolone acetonide, and prednisolone acetate, as well as a dexamethasone sodium phosphate solution were tested. Intra-arterial administration of 20 µL of pure prednisolone acetate or triamcinolone acetonide suspension completely stopped blood flow in all arterioles and venules and decreased the functional capillary density to zero. Methylprednisolone acetate sharply decreased perfusion as well, although some blood flow was maintained. In contrast, intra-arterial administration of dexamethasone sodium phosphate solution did not alter microvascular blood flow [24]. All three particulate steroids also induced in vitro red blood cell (RBC) agglutination with total human blood whatever the donor blood group. Results were unchanged with mononuclear cells-depleted blood as well as with washed RBC indicating that the particulate steroids have the ability to directly interact with the RBC, without mediation by white blood cells or plasma proteins [24]. Vascular obliteration by macro-aggregates of particulate steroids or arterial spasms was not observed in Laemmel et al. animal experiments. The same direct effect of the steroids on human RBC was also demonstrated in vitro [24]. Scanning electron microscopy provided some insight into the mechanism of RBC agglutination, showing RBC with a deformed shape and their transformation into spiculated cells with prednisolone acetate, triamcinolone acetonide and methylprednisolone acetate administration (Fig. 3). More than 28% of the RBC changed into spiculated cells with these 3 corticosteroid suspensions [24]. Once deformed, the spiculated red cells fit together, leading to vascular occlusion.

However, the exact mechanisms by which steroids induce RBC shape alteration as well as the role of drug concentration, osmolarity and viscosity remain to be elucidated. In addition, the reason why some particulate steroids induce the altered red cell shape and finally vascular occlusion while cortivazol, another particulate steroid, does not, remains to be explained.

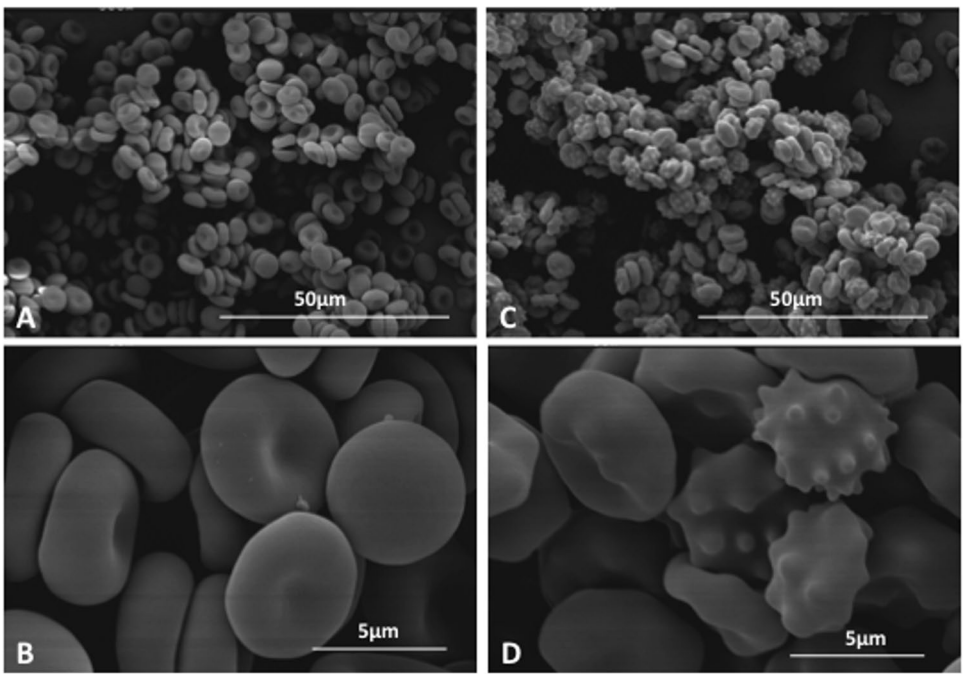

Fig. 3 Scanning electron microscopy images showing normal human red blood cells (**A**, **B**) and spiculated red blood cells (**C**, **D**) after contact with particulate steroids. Reprinted with permission from Laemmel E, Segal N, Mirshahi M, Wybier M, Vicaut E, Laredo JD. Deleterious effects of intra-arterial administration of particulate steroids on microvascular perfusion in a mouse model. Radiology 2016; 279: 731–40 [24]

Other possible routes to the vascular supply of the spinal cord?

Since all the arterial vascularization of the spinal cord is exclusively provided by the radiculomedullary arteries which enter the spinal canal through the intervertebral foramens, the occasional occurrence of spinal cord infarction following a steroid injection performed through a posterior route raises the question of its mechanism.

A typical example of such situations is provided by the reports of paraplegia following an epidural steroid injection through a posterior route in patients with a dural arteriovenous fistula [26–28].

One tentative explanation is that an intravenous injection of steroid in the venous plexus present in the posterior epidural space could reach the arterial supply of the spinal cord through arteriovenous communications.

Veins that drain the spinal cord and conus terminalis cross the dura matter to join the epidural venous network. The epidural venous network is arranged in four main anterior longitudinal venous channels located in the anterior epidural space and peridural membrane with horizontal anastomoses receiving the basivertebral veins which drain the vertebral body. There is also a smaller venous network in the posterior epidural space which communicates with the anterior channels. At each intervertebral level, the epidural veins are drained toward the lumbar ascending veins through the intervertebral foramens where they are arranged in two main channels, one superior accompanying the radicular artery and the nerve root and one inferior, at the level of the intervertebral disc [3].

Epidural and intradural veins belong to a low-pressure network with very few antireflux system. Only minute valves are present at the origin of the radicular veins [29]. Narrowing of the veins where they cross the dura serves as the main antireflux process [30]. Therefore, an inadvertent intravenous injection of particulate steroid under a relatively high pressure may force the blood flow backward toward the conus medullaris.

Physiological arteriovenous anastomoses present in the normal subject may also constitute a pathway for steroids injected intravenously. According to Parke, numerous and relatively large normal arteriovenous anastomoses throughout the length of each root protect the functional integrity of the radicular circulation in the event of focal compressions [30]. It is not known whether such small physiological arteriovenous communications may account for some of the reports of spinal cord infarction following particulate steroid injections.

Possible role of the epidural scar in patients previously operated on

Eight out of the 12 cases of neurological complications following particulate steroid injections reported or reviewed by Wybier et al. occurred in patients who had previous spine surgery involving a posterior approach to the spinal canal [2, 31–33]. Since the percentage of operated on patients in their epidural steroid injection recruitment was much lower, these authors suspected that a history of previous surgery at the level of the steroid injection was a risk factor for spinal cord infarction [2]. Since the epidural scar tissue has abundant vasculature resulting from neo-angiogenesis [34], these authors hypothesized that the rich vascularization of postoperative epidural scar could contain abnormal arteriovenous communications which could constitute a pathway toward the arterial spinal cord supply [31]. The high pressure delivered by the syringe into the small epidural scar vessels may push steroid particles up to the conus terminalis arterial network, possibly via a sudden enlargement of nonfunctional arterial anastomoses [2].

In conclusion, injections of particulate steroids into the intervertebral foramens carry a rare risk of severe neurological adverse events. Inadvertent injection of particulate steroids into a radiculomedullary artery during a transforaminal approach is one of the explanations at the cervical level and the leading mechanism at the lumbar level. Particulate steroids injected in the blood stream produce an immediate and unexpected change of red blood cells into spiculated cells which aggregate and cause arterioles obstruction. In addition, a previous history of surgical posterior approach to the spinal canal is a risk factor for such neurological events even in case of posterior interspinous or interlaminar particulate steroid injections at an operate on level.

Declarations

Conflict of interest The authors declare no competing interests.

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