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Health Policy Opinion

Epidural Steroid Injections Safety Recommendations by the Multi-Society Pain Workgroup (MPW): More Regulations Without Evidence or Clarification

Laxmaiah Manchikanti, MD[1], Frank J.E. Falco, MD[2], Ramsin M. Benyamin, MD[3], Christopher G. Gharibo, MD[4], Kenneth D. Candido, MD[5], and Joshua A. Hirsch, MD[6]

From: [1]Pain Management Center of Paducah, Paducah, KY, and University of Louisville, Louisville, KY; [2]Mid Atlantic Spine & Pain Physicians, Newark, DE, and Temple University Hospital, Philadelphia, PA; [3]Millennium Pain Center, Bloomington, IL, and University of Illinois, Urbana-Champaign, IL; [4]NYU Langone - Hospital for Joint Diseases, NYU School of Medicine, New York, NY; [5]Advocate Illinois Masonic Medical Center and University of Illinois College of Medicine, Chicago, IL; and [6]Massachusetts General Hospital and Harvard Medical School, Boston, MA;

Address Correspondence:
Laxmaiah Manchikanti, MD
2831 Lone Oak Road
Paducah, Kentucky 42003
E-mail: drlm@thepainmd.com

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The regulations of the Food and Drug Administration (FDA) are crucial to the entire population of the United States. Since its establishment in 1906, however, a myriad of governmental agencies and nongovernmental organizations have openly criticized numerous controversial actions and regulations of the FDA (1-4). Contemporary critics of the FDA claim that the FDA possesses an excessive regulatory authority that is ever expanding, and that its decisions and actions are often lacking in both evidence and consistency (1-10). In contrast to these critiques, a 2006 Institute of Medicine (IOM) report found major deficiencies in the FDA system for ensuring the safety of drugs in the American market, calling for an increase, instead of a decrease, in the regulatory powers, funding, and independence of the FDA (11,12). A recent action by the FDA in the management of chronic, persistent, intractable pain has elicited widespread criticism, namely, the unprecedented warning related to corticosteroid epidural injections that was without scientific analysis of the evidence or even reliance on consensus (2,4,13). The controversy beleaguering the FDA on this issue revolves around the inaccuracies of this warning, the inadequate literature review and subsequent faulty conclusions drawn from these reviews, all of which have been extensively discussed (2,4).

Despite an official appeal by the American Society of Interventional Pain Physicians (ASIPP) and an appeal letter with signatures of 1,040 practicing interventional pain physicians (14), the FDA continued its misguided efforts culminating in a favorable decision and approval by a self-appointed "consensus" organization called the Multi-Society Pain Workgroup (MPW) (15). The major participant of this workgroup, the American Society of Anesthesiologists (ASA), proposed a set of approximately 20 regulations and potential publication of manuscripts (16-18). Subsequently, the FDA, setting its Safe Use Initiative Committee aside, obtained nominal approval by the MPW without an evidence assessment or even consensus of the society members that was announced on August 1, 2014 (15,19,20). The International Spine Intervention Society (ISIS) stated that they felt the alert was misleading in its message regarding the safety of epidural steroid injections and contained inaccuracies regarding the effectiveness of this procedure (19). However, they have approved 17 safety recommendations identical to those considered by the Safe Use Initiative, and were basically rejected and not based on evidence and even more inaccurate than the FDA warning itself.

The MPW also issued a misleading statement. They stated that the FDA Safe Use Initiative worked with physician experts from multiple organizations, including several ISIS leaders, over the past 2 years to help create a set of expert recommen-

dations for the safe administration of epidural steroid injections (19). ASA statements also provided similar information as ISIS that ASA leaders have been creating a set of expert recommendations for the safe administration of epidural steroid injections (16-18). They also stated that it is important to note that the release of the April 23, 2014 statement by the FDA regulatory branch was unilateral and unbeknownst to the panel experts working with the Safe Use Initiative on epidural steroid injections (18). Further, they stated that following the release of the statement, the Safe Use Initiative expert panel, in collaboration with the FDA staff supporting the Safe Use Initiative, decided to involve the 14 societies represented on the MPW to craft a set of consensus recommendations for the safe administration of epidural steroid injections. The statement may not be accurate since these recommendations were not crafted by the MPW, but rather they were approved by the MPW. The recommendations were already proposed unilaterally, and unable to get through the Safe Use Initiative, and were supported by some organizations in the MPW that opposed them in the Safe Use Initiative.

In its press release, the MPW claimed that it was originally formed to assist Medicare contractors in developing more consistent local coverage determinations (LCDs) through multisociety consensus recommendations (19). Furthermore, the MPW also claimed that based on its track record in generating consensus and producing multisociety recommendations on interventional pain management issues, the MPW was selected by the Safe Use Initiative leaders as the logical body to develop recommendations on the safe use of epidural steroid injections. They failed to disclose the unfavorable results of these determinations that were developed without proper evidence assessment (21-36). No reasons have been given why they have adopted the same ASA recommendations which were rejected by an expert panel of the Safe Use Initiative. They further claimed that the MPW process, which results in majority consensus recommendations, is entirely democratic, transparent, and collaborative with no single society having more influence than any other participating society—a fact that has been vigorously argued. The societies represented on the MPW are:

1. American Academy of Neurological Surgeons (AANS)
2. American Academy of Pain Medicine (AAPM)
3. American Academy of Physical Medicine and Rehabilitation (AAPM&R)
4. American College of Radiology (ACR)
5. American Pain Society (APS)
6. American Society of Anesthesiologists (ASA)
7. American Society of Neuroradiology (ASNR)
8. American Society of Regional Anesthesia (ASRA)
9. American Society of Spine Radiology (ASSR)
10. Congress of Neurological Surgeons (CNS)
11. International Spine Intervention Society (ISIS)
12. North American Neuromodulation Society (NANS)
13. North American Spine Society (NASS)
14. Society of Interventional Radiology (SIR)

As shown in its own statement, upon its inception ASIPP was involved in the MPW. In fact, although this is partially accurate, ASIPP subsequently resigned from participation. The MPW includes 4 surgical societies [American Academy of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS), North American Spine Society (NASS), North American Neuromodulation Society (NANS)]; 4 radiology societies: [American College of Radiology (ACR), American Society for Neuroradiology (ASNR), American Society of Spine Radiology (ASSR), Society of Interventional Radiology (SIR)]; 2 anesthesiology societies: [American Society of Anesthesiologists (ASA) and American Society of Regional Anesthesia and Pain Medicine (ASRA)]; 2 pain management societies, [American Pain Society (APS) and American Academy of Pain Medicine (AAPM)]; one physiatry society: American Academy of Physical Medicine and Rehabilitation (AAPMR); one international society: International Spine Intervention Society (ISIS). The fifteenth society was ASIPP, which has since withdrawn due to dissatisfaction with the process and inability to convince any of the members to look at the balance of evidence other than what was presented by ISIS and approved by Noridian's executive carrier medical director. In addition, it is interesting to note that a congressional investigation was initiated on this process leading to significant improvement and consensus from other organizations and CAC representatives.

Table 1 shows the 17 safety recommendations approved by the MPW that may be either fully or partially adopted by the FDA. Consequently, ASIPP has filed an official appeal with the FDA, based on the essential requirement that appeals may be filed only by nonparticipating organizations (37). Although ASIPP was not a participant in the MPW, it did participate on the expert panel on the Safe Use Initiative. As a result of this panel, these recommendations were not approved and

Table 1. *Epidural steroid injections safety recommendations passed by the MultiSociety Pain Workgroup (MPW).*

1. Cervical interlaminar (IL) ESIs are associated with a rare risk of catastrophic neurologic injury.
2. Transforaminal (TF) ESI using particulate steroid is associated with a rare risk of catastrophic neurovascular complications.
3. All cervical interlaminar (IL) epidural steroid injections should be performed using image-guidance, with appropriate AP, lateral or contra-lateral oblique views, and a test- dose of contrast medium.
4. Cervical transforaminal ESIs should be performed by injecting contrast medium under real-time fluoroscopy and/or DSA, in a frontal plane, before injecting any substance that may be hazardous to the patient.
5. Cervical interlaminar epidural steroid injections are recommended to be performed at C7-T1, but preferably not higher than the C6-C7 level.
6. No cervical interlaminar epidural steroid injection should be undertaken, at any segmental level, without reviewing, before the procedure, prior imaging studies that show there is adequate epidural space for needle placement at the target level.
7. Particulate steroids should not be used in cervical TF injections.
8. All lumbar IL ESIs should be performed using image-guidance, with appropriate AP, lateral or contralateral oblique views, and a test-dose of contrast medium.
9. Lumbar TF ESIs should be performed by injecting contrast medium under real-time fluoroscopy and/or DSA, in a frontal plane, before injecting any substance that may be hazardous to the patient.
10. A non-particulate steroid (e.g. dexamethasone) should be used for the Initial injection in lumbar transforaminal epidural injections.
11. There are situations where particulate steroids could be used in the performance of lumbar TF ESIs.
12. Extension tubing is recommended for all TF ESIs.
13. A face mask and sterile gloves must be worn during the procedure.
14. The ultimate choice of what approach or technique (IL vs. TF ESI) to use should be made by the treating physician by balancing potential risks vs. benefits with each technique for each given patient.
15. Cervical and lumbar IL-ESIs can be performed without contrast in patients with documented contra-indication to use of contrast (e.g. significant history of contrast allergy or anaphylactic reaction).
16. TF ESIs can be performed without contrast in patients with documented contraindication to use of but in these circumstances, particulate steroids are contraindicated and only preservative free, particulate free steroids should be used.
17. Moderate to heavy sedation is not recommended for epidural steroid injections, but if light sedation is employed, the patient should remain able to communicate pain or other adverse sensations or events.

ESI = epidural steroid injection; AP = anteroposterior; DSA = digital subtraction angiography

ASIPP withdrew from the formation of MPW. These recommendations apply to cervical and lumbar interlaminar epidural injections and cervical and lumbar transforaminal epidural injections. It seems that these do not include thoracic interlaminar epidural injections, caudal epidural injections, or thoracic transforaminal epidural injections. Thus, these published recommendations may be divided into 6 categories:

1) Recommendations 4 and 7 specifically related to cervical transforaminal epidural injections;
2) Recommendations 9, 10, and 11 specifically related to lumbar transforaminal epidural injections;
3) Recommendations 2 and 16 applicable to both cervical and lumbar transforaminal injections other than the specific recommendations include;
4) Recommendations 1, 3, 5, 6, and 15 related to cervical interlaminar epidural injections;
5) Recommendations 8 and 15 related to lumbar interlaminar epidural injections and;
6) Recommendations 12, 13, 14, and 17 related to all epidural injections.

1. Cervical Transforaminal Epidural Steroid Injections

The recommendations for cervical transforaminal epidural steroid injections may be the only accurate set of recommendations based on the available evidence. The risks of cervical transforaminal epidural injections have been described in multiple manuscripts and in an FDA warnings and were also discussed in the FDA Safe Use Initiative panel meetings (2,4,13,14,21,37-42).

The FDA drug safety communication contained 17 references supporting their stance, of which 6 were related to cervical transforaminal epidural injections or nerve root blocks (40,43-47). Manchikanti et al (2),

in discussing controversies related to epidural steroid warnings, provided many other references. As described in the FDA document (20), an editorial (48) in 2009 led to the Safe Use Initiative. This editorial was in response to a manuscript describing potential intraarterial flow patterns in 15% of cervical transforaminal injections (49). Multiple manuscripts before and after the publication of the above manuscript (49), however, have described increased intravascular flow patterns in transforaminal epidural injections, specifically in the cervical spine (1,2,50-56). Consequently, digital subtraction technology was offered as a response to curb this untoward incidences during cervical transforaminal epidural injections (48).

In the review of the epidural steroid warning (2), all the cases reported in the FDA safe advisory report were reviewed, including the letters to the editors. In short, Scanlon et al (38), in a survey of 287 pain physicians, reported 78 overall complications, including 16 vertebrobasilar brain infarcts, 12 cervical spinal cord infarcts, and 2 combined brain/spinal cord infarcts. Of these 30 major complications involving infarcts, 13 cases resulted in fatal outcomes with brain infarcts in 5 patients, combined brain/spinal cord infarct in one patient, high spinal anesthesia in one case, associated seizures in one case, and unspecified etiology in 5 other patients. In all of the 4 cases resulting in either cerebral infarcts or posterior cerebral territory infarct, methylprednisolone was the corticosteroid injected. In another review of the literature (57), 16 cases of spinal cord and posterior circulation ischemia were identified, with 2 cases having had transient symptoms and having had long-term sequelae, with 4 resulting in death. In a recent review (39), it was shown that there were 13 deaths and many catastrophic neurological injuries. This review (39) combined the results from the previous review (38), with the addition of 10 fatal events and 53 other serious consequences (39).

The mechanism of brain injury and spinal cord infarction have been suggested to account for the brain and spinal cord infarctions with a leading hypothesis that vascular disruption or inadvertent intraarterial injection of corticosteroid creates an embolus, causing a distal infarct (2,38,39,41,44,45,58-61). A variety of vascular mechanisms of injury including arterial dissection, vasospasm, mechanical arterial disruption, ischemic events, cortical blindness, high spinal anesthesia, and seizures have been proposed and reported. The vascular theories are based on published literature, including factors suggesting that there is a lower margin of safety because of the proximity of arteries supplying the brain and the spinal cord itself; the random nature of the location of the vascular feeder arteries to the spinal cord within the cervical foramen and the lack of strategy for avoiding them while performing procedures. Complications following cervical procedures appear to be related to the injury or transection of these arteries or embolism from injection into them. In contrast, the arterial supply to the thoracolumbar spinal cord follows a more consistently reliable pathway along the vertebrae and within the thoracic and lumbar foramen (59,62-67). In the cervical spine, the internal carotid artery in the carotid sheath and vertebral artery may be encountered by the needle or injectate during the procedure; there is close proximity of the vertebral artery to the foramen, pedicle, and vertebral body; and passage of the vertebral artery through the foramen, thus increasing the risk of intraarterial penetration. Furthermore, the radicular arteries supplying the arterial supply to the spinal cord, posteriorly and anteriorly, have been found running along both the anterior and posterior nerve roots. Thus, the high risk associated with transforaminal procedures in the cervical spine are based on the fact that medullary arteries may be found anywhere in cervical foramen.

The embolic theory of vascular injury may be flawed (68-71). The embolic theory is based on multiple suppositions that it is feasible to perform safe and atraumatic cannulation and then decannulation of an artery, and following cannulation of the artery, the injection of a particulate steroid leads to embolism distally, which then leads to infarction. The assumption underlying these theories regarding the protective effect of detecting intravascular uptake rests on the belief that these small arteries can be entered and exited without any sequelae or damage to that artery. This assumption may not be accurate based on the fact that some of these cases involve delayed and gradual development of nerve injury as well as anatomic studies that reveal that the diameters of these radicular and medullary arteries are smaller than a 22-gauge or 25-gauge needle. Thus, while this theory appears very attractive, it is virtually impossible to assess the efficacy of identifying intraarticular flow and in the process, avoiding the injection. Embolic phenomena may be only one of the multiple mechanisms responsible for these devastating complications.

The other logical mechanisms of injury to be considered include transection of the artery, creating arterial intimal flaps, traumatic arteries dissection, arte-

rial smooth muscle spasms, and embolization of fresh thrombus after arterial dissection, local pressurization by the injectate that exceeds the perfusion pressure at the local radiculomedullary artery and air embolism. Any of the above mechanisms of injury or combination of them may lead to gradual or immediate cessation of arterial flow resulting in infarction, and may better explain the range of temporal onset reported that ranges from sudden to delayed. These mechanisms may also be explained by the fact that contrast flow appeared normal and lacked vascular uptake during many of these procedures even though catastrophic vascular and neurological complications resulted following the injection. As a result, multiple modifications for the detection of intravascular uptake have been proposed, including contrast medium injection under live fluoroscopy, use of digital subtraction angiography, injection of local anesthetic test doses with an appropriate waiting period to monitor the patient for side effects associated with intraarterial injection of local anesthetic, injection of nonparticulate steroids, use of blunt needles, utilizing a posterior approach, utilizing a TRUCATH® (Smith & Nephew, London, United Kingdom), and finally using a cervical interlaminar approach with a steerable catheter to reach the appropriate nerve root (2,40,72-94). Reports documenting the performance of the procedures utilizing alternate techniques are extremely limited and are not part of the standard of care, and thus remain unproven. The major issue in the cervical spine is the lack of a regular anatomical pattern of the radicular and segmental arteries within the foramen, which makes it impossible to ensure that they can be avoided with any modifications of the technique.

Specific MPW recommendations for cervical transforaminal epidural injections included that cervical transforaminal epidural steroid injection should be performed by injecting contrast medium under real-time fluoroscopy and/or DSA, in a frontal plane, before injecting any substance that may be hazardous to the patient. This recommendation essentially states that contrast medium injection or local anesthetic injection is hazardous to the patient. This statement is onerous in that no physician would ever intentionally inject any substance that the evidence shows to be hazardous to the patient. Since cervical transforaminal epidural injections do not always utilize steroids, one may consider that these recommendations apply only when steroids are utilized. Injecting contrast media under real-time fluoroscopy may somewhat improve the safety of this procedure, although this will not avert all the associated complications through alternative mechanisms of injury. In addition, the accuracy of DSA has not been proven, requires additional expensive equipment and most importantly exposes the patient and the clinician to excessive doses of ionizing radiation(90). These recommendations also mandate that a nonparticulate steroid such as dexamethasone should be used for the initial injection as the efficacy of nonparticulate steroids for long-term improvement has not been proven. Dexamethasone injections may be associated with a higher number injections to get to and maintain the desired effect over a span of time, thus increasing the overall number of required injections and risk to the patient. One may presume, then, that if a particulate steroid is not injected none of these standards apply.

Above all, the recommendations state that the injection must be carried out in the frontal plane. Among the multiple reviews available on imaging planes in radiology, only some of them describe using the frontal plane (95). "Frontal plane" is the term used to describe the coronal plane or vertical plane dividing the body into anterior and posterior. An anteroposterior (AP) view of a chest x-ray uses the frontal plane, wherein the central ray (CR) portion of the x-ray beam emitted from the x-ray tube is posterior to anterior. Essentially, the frontal plane describes the front side of the body, also known as anterior or ventral. Thus, a cervical transforaminal epidural injection can be performed in the frontal plane since these are mostly performed with the patient supine. If the injection is performed with the patient prone, however, the patient should be turned into the supine position prior to injecting any solution, including contrast medium.

Other recommendations combining cervical and lumbar transforaminal epidural injections are related to recommendations 15 and 16. This states that transforaminal epidural steroid injections using a particulate steroid are associated with the rare risk of catastrophic neurovascular complications, which is acceptable based on the present evidence for cervical transforaminal epidural injections; however, the risk is less for thoracic transforaminal epidural injections (2), and significantly less for lumbar transforaminal epidural injections (59). The second recommendation in this category is 16, which provides the ability to perform transforaminal epidural steroid injections without first injecting contrast medium in patients with a documented contraindication to contrast medium. It is redundant and repet-

itive as particulate steroids are prohibited based upon the recommendation 7.

Other recommendations are applicable to all procedures include the use of extension tubing, a face mask, and sterile gloves. The ultimate choice of what approach or technique to use (interlaminar versus transforaminal) is to be made by the treating physician as is the decision whether or not to use sedation.

None of these recommendations are based on evidence. Extension tubing has no basis in evidence, but could increase the mechanical risk to the patient due to the rotational effect of the extension tubing on the needle where the needle tip may enter and exit the arterial lumen. A face mask is recommended for all procedures and is mandated by the Centers for Disease Control and Prevention (CDC) (96).

2. Lumbar Transforaminal Epidural Injections

As shown in Table 1, specific recommendations related to lumbar transforaminal epidural injections include 9, 10, and 11. These are related to injecting contrast media under real-time fluoroscopy or DSA in a frontal plane before injecting any substance that may be hazardous to the patient; injecting a nonparticulate steroid for the initial injection in lumbar transforaminal epidural injections; and are based on the opinion that there are situations where particulate steroids could be used in performing lumbar transforaminal epidural steroid injections.

As described above, there is no proof for the accuracy of real-time fluoroscopy and/or DSA. This recommendation, if approved by the FDA, essentially states that a contrast medium injection or local anesthetic injection is hazardous to the patient, which has not been proven in the literature. Moreover, as all procedures in the lumbosacral spine are performed with the patient prone, a patient may have to be turned into the supine position in order to inject in the frontal plane as defined by these recommendations. These recommendations also mandate that a nonparticulate steroid such as dexamethasone should be used for the initial injection in lumbar transforaminal epidural injections despite the unproven efficacy of nonparticulate steroids for long-term improvement. Thus, one may presume that if a particulate steroid is not injected, none of these standards apply. In addition, recommendation 11 also states that in certain situations particulate steroids could be used in lumbar transforaminal epidural steroid injections, however, these circumstances are not defined or described.

The recommendations described for cervical and lumbar transforaminal epidural injections in combination include recommendations 2 and 16. Recommendation 2 states that transforaminal epidural steroid injectionsusing a particulate steroid is associated with a rare risk of catastrophic neurovascular complications putting all transforaminal injections into one category, but in fact, thoracic transforaminal injections are associated with a lower risk if appropriate precautions are observed with the use of alternative techniques and lumbar transforaminal injections are associated with even less risk with the use of alternative techniques (59). Recommendation 16 provides a support to perform these procedures, lumbar transforaminal and cervical transforaminal epidural injections without contrast medium injection in patients with a documented contraindication to contrast medium, but particulate steroids are contraindicated and only preservative-free, particulate-free steroids should be used. While this is not an ideal recommendation, and not based on evidence, the recommendation is not nearly as onerous as the other recommendations.

The recommendations applicable to all epidural injections include 12, 13, 14, and 17. These recommendations, as described above in the cervical transforaminal epidural section, are not based on evidence, are inaccurate, are redundant, and are not factual contradicting the other recommendations while also interfering with recommendations by other agencies.

None of the recommendations mentioned alternative approaches, such as utilizing an inferior triangle approach, which could reliably eliminate each of the risks associated with lumbar transforaminal epidural injections. In fact, Atluri et al (59) reviewed the literature and analyzed the reported cases of paralysis from lumbar transforaminal epidural steroid injections, establishing a causal relationship leading to possible prevention of this complication, with a description of alternate techniques. They concluded that in light of the anatomical and radiological evidence in the literature, radicular arteries dwell in the superior part of the foramen along the traditional needle position. Therefore, they recommended that the traditional technique of placing the needle in the superior and anterior part of the foramen be re-examined (59,63-65). They concluded that ischemic complications seem to occur in cases of needles placed in the superoanterior part of the foramen where the radicular artery usually resides. Using the traditional safe triangle technique is associated with good reported and observed contrast medi-

um spreads. Thus, based on an analysis of the available anatomical studies and radiological studies and thorough review of the literature, it appears that placing the needle in the inferior triangle appears to be the safest. Furthermore, replacing particulate steroids with nonparticulate dexamethasone might avoid an embolization event may be correct, would not avert an injury from needle trauma, dissection, or spasm of the artery. Avoiding the artery seems more prudent than using nonparticulate steroids.

In contradistinction to the cervical spine, the arterial supply to the thoracolumbar spinal cord follows a consistently reliable pathway along the vertebrae and within the thoracic and lumbar foramen. A critical knowledge of the vascular contents of the foramen cannot be ignored, as understanding these will reduce disastrous complications in the thoracic and lumbar spine. In the majority of cases, the artery is located in the superior part of the triangle, occasionally it is located in the middle part of the triangle, and extremely rarely it is located in the inferior part. However, placement of the needle in the lower 1/3 of the foramen occurs at the level of the intervertebral disc and is therefore associated with a higher incidence of intra-discal entry, while the lower 1/3 of the foramen may provide better vascular safety, such placement may increase the incidence of infectious risk such as discitis.

Complications related to lumbar transforaminal epidural injections are focused on the embolic theory of particulate steroids being injected. As discussed in the cervical spine section, there are various other mechanisms to consider and fortunately, alternate techniques could provide near elimination could potentially eliminate of any such complications in the thoracic and lumbar spine.

3. Cervical Interlaminar Epidural Injections

The recommendations related to cervical interlaminar epidural injections are incorporated in recommendations 1, 3, 5, 6, and 15. The recommendations specific to cervical interlaminar epidural injections exceed the recommendations provided for any other procedures. Specifically in combination these recommendations state that cervical interlaminar epidural steroid injections are associated with a rare risk of catastrophic neurologic injury which is similar to either cervical or transforaminal epidural injections; they should be performed using image guidance, with appropriate AP, lateral, or contralateral oblique views and a test dose of contrast medium. They are recommended to be performed at C7-T1, but preferably not higher than the C6-C7 level. No cervical interlaminar epidural steroid injection should be performed without prior imaging studies showing adequate epidural space for needle placement at the target level. Also, cervical and lumbar interlaminar epidural steroid injections can be performed without contrast medium in patients with a documented contraindication to use of contrast medium.

The issues with these recommendations are that cervical interlaminar epidural steroid injections are provided with numerous recommendations, more than any other procedure, and the statement shows that they are associated with a rare risk of catastrophic neurologic injury which is similar to the recommendation stating that transforaminal epidural steroid injections using a particulate steroid is associated with a rare risk of catastrophic neurovascular complications. This recommendation differs from the FDA warning only in that particulate steroids are not implicated in neurovascular complications related to cervical interlaminar epidural injections. The FDA warning cited 2 reports related to cervical interlaminar epidural injections (13,97,98). These case reports and inaccuracies were described previously (2,4,99). Based on correspondence and analysis (99), these 2 cases of cervical interlaminar epidural injections had no proven causal relationship to steroid injections. Thus, including cervical interlaminar epidural injections is not justifiable and the statement in reference to rare catastrophic complications, which is very similar to cervical transforaminal or lumbar transforaminal epidural injections, is not based on available evidence and current standards of practice.

The third recommendation is in reference to using image guidance, with appropriate AP, lateral, or contralateral oblique views and a test dose of contrast medium. As described above, while image guidance is mandatory for all epidural injections, mandating AP, lateral, or contralateral oblique views is unnecessary and encroaches upon physician independence. The recommendation to obtain multiple images should be reworded to reflect that this is "as deemed appropriate" and not to be deemed mandatory. Requiring mandatory multiple views prolongs procedure time and patient anxiety and increases time that the needle in the patient adding complications specifically as a result of attempting to adhering to a burdensome and counterproductive set of mandates. Furthermore, while the AP description may be confusing as in the prone position, the procedure may be described as a PA view instead of AP view. Lateral or contralateral

oblique views and their importance have not been demonstrated to be superior in the literature. In addition, while an AP or PA view is always utilized, lateral or contralateral oblique views are rarely utilized. The mandating of these steps during injection essentially increases radiation exposure to all concerned including the patient and staff and may even increase the risk as it is extremely difficult to identify the targeted structures in the lateral view, and even more so in the contralateral oblique view including the epidural space prior to injection of contrast medium. Furthermore, lateral images in the cervical spine at the level of C7-1 are commonly not achievable. Often, the trunk obscures the visibility of the needle tip at the level of C7-1 on lateral views. At times this may be addressed by pulling down on the patients arms and shoulders, which often has the effect of pulling out the needle from the epidural space due to traction combined with the high elastin content of the ligamentum flavum requiring a needle repositioning and advancement and subjecting the patient to additional risk thereof.

What is the value of a lateral image if there is a good epidurogram in an AP view? Requiring the use of lateral images is overly simplistic for additional reasons and may result in false assessments specifically due to their incorporation. Overreliance on lateral images that only show the bony anatomy does not account for ligamentum flavum hypertrophy, present in many of these patients and which requires further advancement of the needle into the spinal canal to gain loss of resistance and appropriate needle placement. Furthermore, interlaminar injections are often performed far lateral or ipsilaterally on the side of the pain instead of using a purely midline approach. Therefore, quite frequently, with a proper epidural placement proven by an epidurogram, the lateral image will show the needle to be well within the spinal canal while being appropriately placed. Under these circumstances, a lateral image lacks technical and clinical purpose while potentially contributing to lack of effect or complications due to needle exit from the epidural space and a superficial injection.

The next recommendation is related to entry into the epidural space. Entry is recommended at C7-T1, and preferably no higher than the C6-C7 level. While this may be based on the anatomical gaps in the ligamentum flavum in the cervical spine (100,101); however, it is not based on any type of evidence or reported complications (102-108). Due to difficulty in following recommendation 3 suggesting that lateral or contralateral oblique views must be obtained, this recommendation increases the risk of radiation exposure as well as the risk of dural puncture because excessive manipulations are carried out due to the inability to visualized targeted structures in the lateral view at C7-T1 and potentially at C6-7. Multiple reports have been published regarding performing procedures at C5-6 without additional adverse consequences compared to C7-T1 or C6-7 (102-106), whereas multiple reviews on cervical epidural injections have not provided any evidence to support these recommendations (103-108).

The next recommendation is 6, which describes that no cervical interlaminar epidural steroid injection should be undertaken without appropriate imaging studies indicating an adequate epidural space for needle placement at the target level, which essentially mandates that each patient must have pre-procedural magnetic resonance images or at least a computed tomography scans prior to these procedures. However, there is no literature supporting these suppositions that imaging guidance somehow prevents the occurrence of rare complications from steroid injections. Imaging guidance is appropriate in the case of cervical spinal central canal stenosis to avoid injecting at severely stenotic levels in order to avoid loculation-related complications. However, imaging guidance may not be mandated in young patients without central canal spinal stenosis or in major disc herniation without neurological effects.

The next recommendation is related to 15, which essentially supports the ability to perform cervical and lumbar interlaminar epidural injections without contrast medium in patients with a documented contraindication to contrast medium.

The recommendations applicable to all procedures, disadvantages, and lack of evidence have been described above.

4. Lumbar Interlaminar Epidural Injections

The specific recommendations for lumbar interlaminar epidural injections appear to be a combined recommendation inclusive of cervical interlaminar injections, and the common recommendations for all procedures. However, the FDA's advisory has not provided any references in relation to the complications associated with lumbar interlaminar epidural injections, which are the most widely utilized epidural modality in interventional pain management. The substantial body of literature promoting transforaminal epidural injections has, of course, changed these dynamics, even though there is

no demonstrated superiority of transforaminal epidural injections compared to interlaminar or caudal epidural injections (109-112). In fact, in previous reviews, we have reported that lumbar interlaminar epidural injections constituted 74% of the epidural injections performed during 2000, whereas, they decreased to 40% in the fee-for-service Medicare population during 2011 (113).

Recommendation 8 specifically mandates that all lumbar epidural injections be performed using image guidance, with appropriate AP, lateral, or contralateral oblique views, and a test dose of contrast medium. However, there is no specific proven advantage to viewing the procedural anatomy in lateral or contralateral oblique views. This recommendation may increase the unnecessary radiation exposure to all concerned; increase the cost of the procedure, and the duration of the procedure resulting in complications with additional allocation of precious resources, which is not based on evidence.

The other recommendation is 15 which states that lumbar interlaminar epidural steroid injections, along with cervical epidural injections, can be performed without contrast medium in patients with a documented contraindication to contrast medium.

Unfortunately, these recommendations classify lumbar interlaminar epidural injections, which are widely performed for surgical and obstetric anesthesia purposes to the same degree as cervical interlaminar epidural injections. In fact, the FDA affirmed the safety of these injections (114).

Comments

Since the formation of the MPW, there has been a great deal of misinformation, conjuncture, innuendos, debate, and controversies being promulgated by the International Spine Intervention Society (ISIS) and subsequent responsive defensive measures provided by ASIPP. The same stance, similar to MPW, has been taken, by the American Society of Anesthesiology (ASA) in October of 2013.

Both ASA and ISIS continue to argue that safety standards are essential. However, they do not request the removal of the FDA statement of April 23, 2014, which implicitly acknowledges that these recommendations are in addition to the already issued FDA Safe Use Initiative warning. They also state that the evidence has been considered and a consensus has been obtained. However, they are not willing to share any such evidence or even the applied principles in arriving at consensus.

The MPW statement alluded to the "facts" that the process resulting in majority consensus recommendations and is entirely democratic, transparent, and collaborative with no single society having more influence than any other participating society. This description may be considered to be patently false and misleading. The process essentially was in our opinion quite undemocratic. Indeed, rather than transparent it was confidential, and even though "collaborated by multiple societies", a single society, or 2 societies control the entire process. A democratic process is defined as the process of allowing individuals in a group or society (stakeholders) to be involved in the decision-making process. Eight of the 14 societies of the MPW represent surgical fields and radiology fields and perform less than 10% of epidural injections or other interventional pain procedures (113). Thus, these societies tend to automatically support one of the sponsoring major societies. ASIPP was the only society having objections to the process that ultimately resigned from MPW.

Transparency, as used in scientific circles implies openness, communication, and accountability. Thus, transparency is operating in such a manner that it is easy for others to see what actions are performed. The 3 important aspects of transparency relevant to scientific practice include: a) information disclosure, b) clarity, and c) accuracy. In fact, the lack of transparency has been a major issue (115-122). There has been a lack of transparency with the MPW all throughout the development of the primary recommendations, with stakeholders unable to provide input, and with the consensus development process itself.

The MPW also describes its efforts as collaborative, with no single society having more influence than any other participating society. This is inaccurate as one or 2 societies dominated the entire process and others followed passively along. Even opinions which differ from them are passed with slim majorities and are provided as recommendations.

Finally, none of the recommendations provided by MPW seem to have been based on evidence. Rather, they were based solely on consensus and lacked both a transparent process and clear understanding of the issues. It is unfortunate that a large proportion of the membership of these societies on the MPW may not agree with many of the recommendations. This was reflected in the letter sent to the FDA with 1,040 signatures, with members drawn from multiple societies who are also members of ASIPP.

Conclusion

The authors of this manuscript and signatories of the letter to the FDA and appeal recommend that the FDA withdraw the April 23, 2014 statement and replace it with the statement provided in the appeal which is based on evidence and consensus of the overwhelming majority of practicing interventional pain physicians. The recommendation is as follows: The FDA requires label changes to warn of rare but serious neurologic problems after epidural corticosteroid injections for "pain" and "injection of corticosteroids into the epidural space of the spine that may result in rare but serious adverse events, including loss of vision, stroke, paralysis, and death" and replace it with a warning emphasizing the off-label use of epidural steroids can cause rare, but serious neurologic problems following cervical and thoracic transforaminal epidural injections and may be associated with an increased risk with lumbar transforaminal epidural injections when performed without appropriate precautions; and that all procedures must be performed by well-trained providers in appropriate settings under fluoroscopy or other appropriate proven imaging modalities.

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Author affiliations

Dr. Manchikanti is Medical Director of the Pain Management Center of Paducah, Paducah, KY, and Clinical Professor, Anesthesiology and Perioperative Medicine, University of Louisville, Louisville, KY.

Dr. Falco is Medical Director of Mid Atlantic Spine & Pain Physicians, Newark, DE; Director, Pain Medicine Fellowship Program, Temple University Hospital, Philadelphia, PA; and Adjunct Associate Professor, Department of PM&R, Temple University Medical School, Philadelphia, PA.

Dr. Benyamin is Medical Director, Millennium Pain Center, Bloomington, IL and Clinical Assistant Professor of Surgery, College of Medicine, University of Illinois, Urbana-Champaign, IL.

Dr. Gharibo is Medical Director of Pain Medicine and Associate Professor of Anesthesiology and Orthopedics, Department of Anesthesiology, NYU Langone-Hospital for Joint Diseases, NYU School of Medicine, New York, NY.

Dr. Candido is Professor and Chair, Department of Anesthesiology, Advocate Illinois Masonic Medical Center, Chicago, IL, and University of Illinois College of Medicine, Chicago, IL and Professor of Clinical Anesthesiology, University of Illinois College of Medicine, Chicago.

Dr. Hirsch is Vice Chief of Interventional Care, Chief of Minimally Invasive Spine Surgery, Service Line Chief of Interventional Radiology, Director of NeuroInterventional Services and Neuroendovascular Program, Massachusetts General Hospital; and Associate Professor, Harvard Medical School, Boston, MA.

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