Letters to the Editor

Digital Subtraction Angiography is Not the Answer for Safe Epidural Injections

To the Editor:

We read with great interest the recent publication of El Abd et al (1) regarding the intraarterial detection rates identified during transforaminal epidural steroid injections (TFESI). The authors sought to define the rate of detection of arterial uptake observed by using digital subtraction angiography (DSA) that is missed by traditional safety precautions, including that provided by real-time, live fluoroscopy. They enrolled 150 consecutive patients and performed 222 TFESI at the cervical, lumbar, and sacral levels. Live fluoroscopy with contrast medium detected 46 intravascular flow patterns and DSA identified an additional 5 venograms not identified using live fluoroscopy. Interestingly, all 5 of these vascular injections were venous and were found while performing sacral TFESI. These results are similar to those of a prospective study of vascular flow detection rates in lumbosacral TFESI. Lee et al (2) performed 60 lumbar and 20 S-1 TFESI and found 20 cases of intravascular injection (11 at S-1 and 9 in the lumbar spine) utilizing DSA. Real-time fluoroscopic guidance with contrast medium injection predicted 12 of the 20 instances (60%). These authors did not distinguish between arterial versus venous contrast medium uptake, but concede that "the majority of these vascular injections were venous" with a statistically significant higher injection rate at S-1 (2).

In a retrospective analysis by Mclean et al of 134 patients that underwent 177 cervical TFESI, intravascular injection was detected in 18% using real-time fluoroscopy vs. 32.8% when DSA was used (P = 0.0471). Notably, all of the vascular flows identified by both live fluoroscopy and DSA were venous and none were arterial (3).

The results of the Lee et al (2) and El Abd et al (1) studies are consistent with what is known about the rich venous plexus in the sacral epidural space, and are supported by previous data in detecting intravascular injections during lumbo-sacral TFESI. Furman et al (4) looked at 761 TFESI and concluded that "There was a statistically significant higher rate of intravascular injections (21.3%) noted with transforaminal ESIs performed at S-1 (n = 178), compared with those at the lumbar levels (8.1%, n= 583)."

These studies suggest that while DSA may detect unintentional venous injection at a higher rate than does live fluoroscopy, there is less robust evidence (case reports) that DSA enhances recognition of arterial injection and thus may not be useful for preventing the most catastrophic adverse events associated with TFESI.

We agree with these authors that DSA is not a panacea for preventing adverse outcomes during the performance of neuraxial procedures. DSA will not prevent other serious complications including intracord injection or hematoma formation. DSA is limited by motion artifacts and the images are subject to human interpretation. Any motion between the initial scout film and subsequent images will be detected as a change, impeding the subtraction process and causing degradation of image quality. Thus, utilization of this technology does not negate the potential for human error nor the potential for patient injury. The false negative rate of live fluoroscopy is unknown, but has been observed in one study to be 0.75%, with a calculated sensitivity of 99.25% and specificity of 100% to detect unintentional vascular injections (5). DSA may provide greater sensitivity and specificity, but the exact limits of detection are unclear and the safety profile is neither fully characterized nor validated.

While the magnitude of differences in radiation exposure associated with DSA versus fluoroscopy has not yet been quantified, extrapolation from the interventional vascular literature suggests that DSA may substantially increase exposure to ionizing radiation, comparable to computed tomography angiography (CTA). Manninen et al (6) compared patient radiation exposure during diagnostic CTA and biplanar DSA ex-

aminations for both cerebral and cervicocerebral vessels. This study demonstrated that for the cerebral vessels and cervicocerebral vessels, the effective dose for DSA was 5 and 3 times greater respectively than CTA.

We applaud the authors for their meticulous performance of the procedure but disagree with the authors' conclusions that "we recommend the use of DSA to observe dynamic contrast [medium] flow during TFESI (1)." Considering the volume of interventional spine procedures performed annually, routine use of DSA may have a poor risk/benefit ratio due to escalated radiation exposure to patients and staff, particularly when rates of preventing rare catastrophic outcomes may reliably be averted by employing other safety measures. Among these, primarily, would be ceasing the use of particulate steroid injections during TFESI. Concerns for efficacy have been recently addressed by Kennedy et al (7) in a multi-center double-blind prospective, randomized trial demonstrating similar efficacy between dexamethasone and triamcinolone for lumbar TFESI.

Conclusion

The routine use of DSA is not warranted based on current medical evidence. DSA use increases exposure to ionizing radiation, yet the current best literature does not demonstrate that it provides additional detection of arterial injection beyond that provided by traditional live fluoroscopy. The occasional exposure of an individual patient to this increased radiation exposure is still undetermined, yet for a practitioner performing hundreds of procedures/month or year, the cumulative exposure may have grave consequences. Practitioners should consider using dexamethasone as a first line agent in all TFESI.

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In Response

We read your points with particular interest and attention. We share with you the same concerns. In this response we will attempt to answer these lingering questions. The focus of the study was to identify missed vascular flow with traditional methods that is subsequently identified by digital subtraction angiography(DSA). We were able to identify venous vascular flow missed by traditional methods in 5 of 222 injections (2.25%) (1). Since the DSA step was dependent on the prior steps, i.e., if there was vascular flow detected with any method then the needle was repositioned, thus we were unable to compare the rates of vascular detection by the different methods statistically.

Adding an extra 2.25% improvement in vascular

penetration detection is procedurally relevant. The fact that vascular flow was missed using traditional methods and only picked up on DSA is also significant. We suspect that arterial injection of particulate steroids can lead to spinal cord or cerebral infarcts. The gravity of these complications dictates that we exert maximum efforts for prevention. On the other hand, reports of these complications are considered rare with the total number of transforaminal epidural injections performed as the denominator and the argument as well can be made whether these complications are statistically significant.

Nonetheless, the only reported case of spinal cord infarct after using DSA for transforaminal epidural steroid injections (TFESI) (2) presented some procedural flaws, such as using particulate steroids and no reported use of live fluoroscopy. We advocate always using nonparticulate steroids such as dexamethasone for TFESI. DSA should be performed after a negative vascular flow on live fluoroscopy injection for 2 reasons. First, live fluoroscopy contrast medium injection gives a better anatomic view of the flow. Second, it reduces chances of having to repeat DSA as the majority of the vascular flow can be visualized by live fluoroscopic injection. Technically, with regular use of DSA, operators gain experience to reduce the motion artifact, become more familiar with the images generated, and the identification of vascular flow becomes easier. We also don't believe that the cost of adding a DSA unit to an existing or new fluoroscopy unit is prohibitive.

In regards to visualization of sacral vascular flow detection, the S1 level should not be underestimated since Houten and Erico (3) reported spinal cord infarction after an S1 transforaminal injection.

In regards to patients' and operators' exposure to radiation, there is no argument that the addition of DSA increases the exposure rate. We are not aware of specific studies that evaluated complications of exposure to operators using DSA over a long duration with variable shielding options. Cerebral angiography, vascular, cardiac interventions, and biplanar DSA are very different in duration from TFESI. We use pulsed (8 pulses/s) for live fluoroscopy and low dose continuous mode for DSA. It is unknown if the extra 3 - 10 seconds of exposure would be harmful to patients. Also, it is our experience that adding DSA only after negative vascular flow detection using other methods is a way to keep the radiation dose as low as reasonably achievable. Since we can detect most of the vascular flows with traditional methods, one would have to reposition the needle and repeat the DSA step in only 2.25% of the cases.

Conclusion

The gravity of complications dictates that we exert maximum effort for preventing intravascular injection. We advocate the use of DSA after a negative contrast medium injection on live fluoroscopy and the use of nonparticulate steroids.

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Use of Topical Lidocaine, Diphenhydramine Hydrochloride, Nystatin, and Gabapentin Swish in Treatment for Post-Radiation Neuropathy and Oral Mucositis

To the Editor:

The pain caused by cancer treatment-related oral mucositis is often described as the most excruciating symptom (1). Frequently, it leads to reduced ingestion, malnutrition, and sometimes postponement or withdrawal of the therapy (1). For health care providers, adequate pain treatment is a major challenge. Treatments that have varying degrees of success include antibiotics, antifungal, antivirals, opioids, benzydamine oral rinse, and palifermin (2,3). Topical pain management is invariably administered in most patients due to its favorable risk-benefit profile and adjuvant role (2,3). However, topical treatment of mucositis pain today is based on empiricism and not on scientific evidence (2,3). We report the use of a novel topical mixture of lidocaine, diphenhydramine hydrochloride, nystatin, and gabapentin along with a course of oral opioids for radiation-induced intractable oral pain.

Case Presentation

A squamous cell carcinoma of the right base of the tongue was diagnosed in a 76-year-old woman. She underwent initial chemotherapy and radiotherapy leading to temporary remission. However, 2 years later the tumor reoccurred and temporary brachytherapy was provided for 3 days which led to a full remission. A recent magnetic resonance image showed no reoccurrence. But 2 months after the above treatment,{which one of the 2 treatments "listed above"?} the patient began to experience significant pain in the throat, the base of the tongue, and jaw causing difficulty in swallowing. It became chronic and progressively worse. At the time of the initial presentation to the pain clinic, the patient scored her pain as 7 of 10 on a "0 to 10" pain scale{did you use the actual Numeric Rating Scale?} with frequent occurrences of maximal pain (10 of 10). Pain was burning and sharp. The most significantly aggravating factors appeared to be swallowing, coughing, or speaking. Difficulty in swallowing prevented adequate nutrition and the patient reported a loss of 40 pounds despite a normal appetite. Her pain medicine regimen consisted of meperidine hydrochloride 600 mg/d and lidocaine 2% daily swish every 4 hours. In addition she was using a nystatin swish and swallow for her oroesophageal fungal infection.

The patient was extremely slender to emaciated but pleasant and cooperative. Her facial appearance was normal in color and appearance except for a mild to moderate fullness over the anterior aspect of the neck and over the area below and above the hyoid bone. Her voice sounded soft and muffled, which the patient reported as a change since her radiation therapy. Neck palpation revealed induration of the inframandibular area but without evidence of adenopathy. External surface motility of the laryngeal structures was normal and deep palpation of the jaws or neck did not reveal significant tenderness. Examination of her oral cavity revealed an edentulous maxilla and mandible. Thrush was seen over the dorsal aspect of the tongue and redness of the tongue and mouth floor, but no lesions on the tongue, gums, inner cheeks, or mouth floor were observed. Her diagnosis was oropharyngeal postradiation neuropathy and mucositis with secondary oral thrush.

A mixture of lidocaine 1 g, diphenhydramine hydrochloride 63 mg, nystatin 2.5 megaunits, and gabapentin 10 g in a total of 100 mL total volume (final concentration of the mixture: lidocaine 10 mg/mL, diphenhydramine hydrochloride 0.63 mg/mL, nystatin 25,000 U/mL, gabapentin 100 mg/mL) was prescribed. The patient was recommended to do swish-and-swallow with this mixture 4 times a day. In addition, due to the ineffectiveness of the maximal dose of meperidine, we switched her to an equianalgesic combination of morphine sulfate sustained release 20 mg by mouth twice a day. Oxycodone hydrochloride (5 mg) and acetaminophen (325 mg) one tablet by mouth every 8 hours as needed were also prescribed.

At the 20-day follow-up visit the pain in her jaw had been completely eliminated. She reported some residual pain due to swallowing. Physical examination

revealed the thrush on her tongue was improved from the initial presentation and palpation of the mandible and throat failed to reveal significant tenderness. The patient was advised to continue the swish-and-swallow of the lidocaine, diphenhydramine hydrochloride, nystatin, and gabapentin. Morphine sulfate sustained release was decreased to 10 mg by mouth every 12 hours and oxycodone hydrochloride and acetaminophen was continued. The oral cavity biopsy indicated no recurrence of malignancy with subsequent surgery to partially remove/debulk the postradiation scar tissue. A pathology examination of the discarded tissue revealed only necrosis. A significant and consistent improvement in the level of her pain with the swish-and-swallow treatment was maintained. At 2 months follow-up it was possible to discontinue the swish-and-swallow as well as her opioid therapy and the patient's symptoms of sharp burning pain resolved without reoccurrence during the one year follow-up period.

Discussion

This case describes a patient with severe chronic pain of the mandible and anterior neck following brachytherapy for carcinoma of the base of the tongue that persisted for several months. Standard postradiation treatment failed to provide adequate pain relief, so we added a novel topical mixture of lidocaine, diphenhydramine hydrochloride, nystatin, and gabapentin to a course of oral opioids. This unique regimen provided rapid and effective pain relief, demonstrating that new topical mixtures may be useful in alleviating pain secondary to radiation therapy. The causes of pain secondary to radiotherapy include painful mucosal thinning and ulceration (e.g., oral mucositis, esophagitis, gut pain, perianal pain); myelopathy; fibrosis of the neural plexus (e.g., brachial or lumbar); and peripheral nerve tumors. Among the factors that may determine the occurrence of postradiation pain are the amount of delivered rads, therapy fractionation, prior irradiation, infection, and the degree of tissue vascularization (4).

Mucositis usually appears toward the end of the second week of treatment, reaches a plateau during the fourth week, and may persist for 2 or 3 weeks after the completing treatment (1). Initially, the mucosa of the mouth becomes reddened and swollen, then it becomes covered with a fibrous exudate as the treatment continues. Typically the patient complains of a burning sensation, while the examination of the mouth reveals erythema. Management involves the aggressive use of analgesics (e.g., patient-controlled analgesia) and, eventually, antimicrobial agents (3). This aggressive approach can become counterproductive if the symptoms become unremitting and chronic.

Radiotherapy results in chronic inflammation and subsequent fibrosis of connective tissue that may induce unremitting chronic pain by exerting pressure upon the axons of peripheral nerves (4,5). It is not clear yet what the pathological changes of radiation-induced neuropathy in the peripheral nerves are (5). In every instance, associated occluded or necrotic blood vessels were found. The vascular lesions included acute and chronic vasculitis, fibrinoid necrosis, and telangiectasia.

Opioid therapy alone was not sufficient to treat her symptoms. A combination therapy was needed to facilitate the ability to swallow which was thought to be attainable by the described mixture. A topical ointment mixture of amitriptyline, gabapentin, and lidocaine has previously been used as a treatment for postherpetic neuralgia; diphenhydramine hydrochloride has also been used as a topical treatment for itching in the form of a cream, gel, or spray. To our knowledge, the current report is unique due to the demonstration of a successful nonconventional topical treatment in combination with standard opioid therapy for radiotherapy-induced oral mucositis and peripheral neuropathic pain. Further applications may be useful in treating other patients with this distressing syndrome.

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Tramadol Article Conclusion Troubling

To the Editor:

The meta-analysis by Chung et al (1) is a useful evaluation of the currently utilized drug treatments for chronic low back pain. However, we do not agree with their conclusion that tramadol shows no statistically significant effect on pain relief. The authors included 3 studies (Peloso et al [2], Ruoff et al [3], and Vorsanger et al [4]) in their meta-analysis. Chung et al (1) used the visual analog scale (VAS) pain intensity as a primary efficacy measure for their meta-analysis for the studies by Ruoff et al (3) and Vorsanger et al (4). It seems that for the study by Peloso et al (2) they used the mean and standard deviation (SD) values for change from baseline of the short form McGill Pain Questionnaire/present pain index instead of the VAS pain intensity, which is available as well. In addition, we were unable to deduct from the study by Ruoff et al (3) the SD values for the change from baseline reported by Chung et al (1).

We conducted 2 meta-analyses with datasets D1 and D2. Dataset D1 consists of data reportedly used by Chung et al (1). Dataset D2 differs from D1 in that from the study by Peloso et al (2) the change from baseline in VAS pain intensity has been taken and that the SD value s_C for the study by Ruoff et al (3) was calculated in the same way as it was calculated for the other 2 studies as follows (Table 1):

$$s_C = \sqrt{s_0^2 + s_1^2 - 2rs_0s_1}$$

where s_0 and s_1 are the observed standard deviations of pain intensity scores at baseline and end-of-treatment, respectively, and r is the correlation between pain intensity scores at baseline and end-of-treatment. Since this correlation is not reported, we have assumed $r = 0.8$ in all studies following what Chung et al (1) presumably did for the study of Vorsanger et al (4). Peloso et al (2) and Ruoff et al (3) did not report s_1; therefore we have assumed that $s_1 = s_0$.

Our results for dataset D1 are identical to those of Chung et al (1). The results for dataset D2 showed a statistically significant difference (estimated overall effect -1.18; 95% confidence interval -1.65 to -0.71; $P < 0.0001$) between tramadol and placebo (Table 2).

We conclude that there is persuasive evidence for a benefit of tramadol alone or in fixed dose combination with acetaminophen in the management of chronic low back pain. This is important to report because, in contrast to nonsteroidal anti-inflammatory drugs and Cox II inhibitors, long-term use of tramadol is not associated with an increased risk of gastrointestinal, renal, and cardiovascular organ damage and, in contrast to strong opioids, the risk of respiratory depression, addiction, and abuse is lower.

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Table 1. *Change in pain intensity from baseline. Pain scale is VAS 0 – 100 mm for all studies. Length of follow-up is 12 weeks for all studies. SD = standard deviation; n = number of subjects; PE = primary endpoint.*

Study	Source	Tramadol			Placebo			Dataset	
		Mean	SD	n	Mean	SD	n	D1	D2
Peloso 2004	Chung 2013	-1	1.2	167	-0.4	1.2	171	X	
	Peloso 2004, PE revised	-20.5	9.46	167	-4.7	9.82	169		X
Ruoff 2003	Chung 2013	-26.7	2.66	161	-16.5	2.63	157	X	
	Ruoff 2003, SD revised	-26.7	9.17	158	-16.5	9.42	153		X
Vorsanger 2008	Chung 2013	-20	14.36	128	-8	14.36	129	X	X

Table 2. *Results of the meta-analysis for each dataset. Heterogenity: Tau^2=total amount of heterogeneity; Chi^2=statistic for the test of heterogeneity; I^2=ratio of total heterogeneity to total variability. Overall effect: Est=estimated value; 95% CI=95% confidence interval; Z = test statistic of no effect. Weights of each study in the meta-analysis: S1 corresponds to Peloso et al (2004); S2 to Ruoff et al (2003); S3 to Vorsanger et al (2008).*

	Heterogeneity				Overall effect			Weights (%)		
Dataset	Tau^2	Chi^2 (df)	*P*-value	I^2	Est. (95%CI)	Z	*P*-value	S1	S2	S3
D1	2.32	243.5 (2)	<0.0001	99.18%	-1.72 (-3.45, 0.01)	-1.95	0.0518	33.5	33.1	33.4
D2	0.156	21.67 (2)	<0.0001	90.77%	-1.18 (-1.65,-0.71)	-4.94	<0.0001	33.32	33.54	33.14

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