Letters to the Editor

Vertebral Augmentation of Osteoporotic and Malignant Compression Fractures: Our Viewpoint and Experience in Preventing Cement Leakage

To the Editor:

It is with great interest that we read the article by Georgy et al, "Feasibility, Safety and Cement Leakage in Vertebroplasty of Osteoporotic and Malignant Compression Fractures Using Ultra-Viscous Cement and Hydraulic Delivery System", published in the 2012 May/June issue of Pain Physician (1).

Nowadays, percutaneous vertebroplasty (VP), and kyphoplasty (KP), are valid therapeutic options in the management of severe back pain caused by vertebral compression fractures (2-4). They are minimally invasive, radiologically guided interventional procedures, which involve the injection of polymethylmethacrylate (PMMA) into the fractured vertebral body. Major complications arising from VP or KP are related to leakage of cement beyond the confines of the collapsed vertebral body (1).

This is a thoughtful and well-designed retrospective article which evaluated the safety and feasibility of VP performed for both osteoporotic and malignant vertebral compression fractures using ultraviscous cement injected by a hydraulic delivery system. The results of this evaluation show that highly viscous cement injected by a hydraulic delivery system in VP can be potentially beneficial to decrease the leakage rate when treating osteoporotic and malignant vertebral compression fractures (1). The article also suggests that the hydraulic cement injection device has many advantages and convenience over the most commonly used mechanical injectors. The viewpoint of the author is right, but we have some concern about forcefully injecting cement by the hydraulic injection device used in VP.

It is known that higher viscosity cements used in VP and KP could result in significantly lower cement leakage rates (5-7). However, the increased in situ pressures in the vertebral body generated by the hydraulic injection device during VP may induce unexpected extravasations, especially for malignant vertebral compression fractures which often have high frequency of cortical breakdown by metastatic tissue (5). The degree of cortical disruption determines the viscosity of the cement that can be safely injected. The more extensive the bony disruption, the greater the viscosity of the cement is recommended since this will decrease the risk of unwanted extravasation (8). Our viewpoint is that low pressure fill of higher viscosity cement into the fractured vertebral body may result in significantly lower extravasation rates of PMMA.

The most important advantage of KP over VP is the ability to create a cavity into the vertebral body by using the inflatable balloon for the injection of a very viscous cement with very low pressure into the cavity, significantly reducing the probability of cement leakage (Fig. 1.). The application of cement during KP is done via a bone filler device and not through a syringe or injector system (5,9). Another advantage for KP is the compression of cancellous bone during the intravertebral expansion of the balloon which creates a condensed spongiosa layer surrounding the void which may close possible cortical breakdown of the vertebral body, thus further reducing the risk of subsequent cement leakage, and allows bone repair to occur on the surface of the PMMA cement (5,10). For patients with damage to the vertebral wall, leakage of PMMA through cortical defects is very high. In our experience, the leakage can be avoided with good technique. We first insert 1 mL of viscous cement after expanding the intravertebral space and removing the balloon. Next, we reinsert the balloon into the cement and reinflate it, in order to expand the surrounding cement until it abuts the compromised vertebral wall. At this stage, we

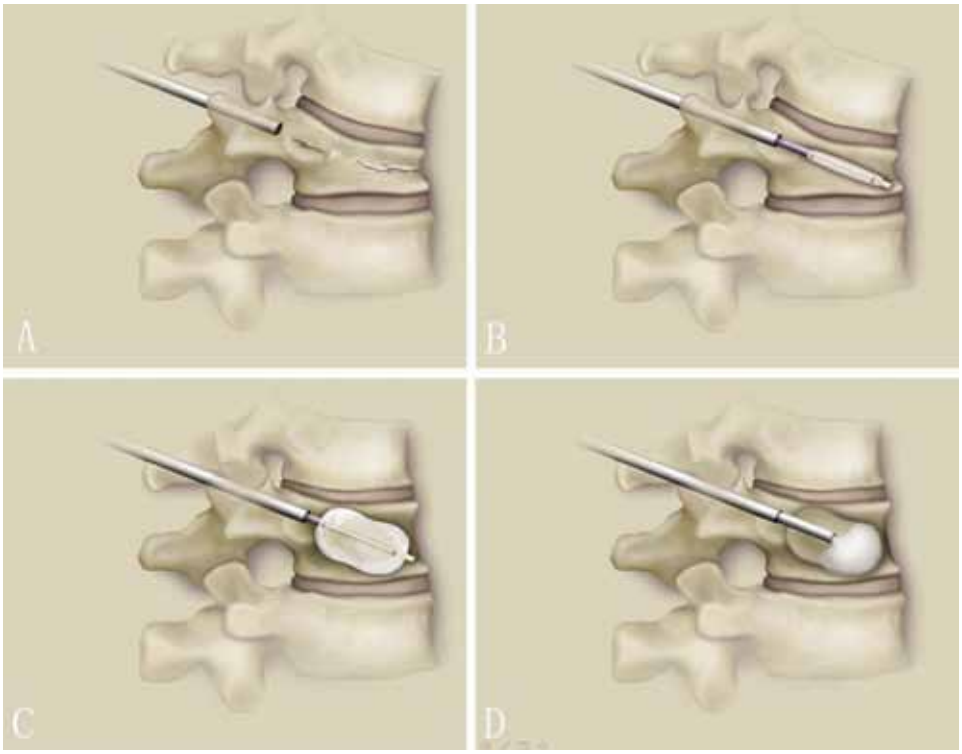

Fig. 1. *Kyphoplasty technique. (A) Vertebral compression fractures cause vertebral body collapse; (B) An inflatable balloon is advanced through a cannula placed in transpedicular fashion; (C) The balloon device is inflated in an attempt to create a cavity into the vertebral body; (D) The cavity created by the balloon is filled with very viscous cement under very low pressure, significantly reducing the probability of cement leakage.*

allow the cement to harden. Then we remove the balloon and proceed with conventional cement filling. As a result of using these techniques, no symptomatic cement leakage occurred among our patients (5).

In summary, KP is considered a "low-pressure" injection and VP is considered a "high-pressure" injection technique. To patients with osteoporotic and malignant compression fractures, we also advise using highly viscous cement in the vertebral augmentation process, however, the creation of a bony void and subsequent low pressure in the vertebral body are recommended to reduce extravasation rates of PMMA.

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Response

We appreciate the author's thoughtful and constructive critique for the article. Although the authors agree on the benefit of high viscosity cement, they are concerned about using a hydrolic injection device that can potentially create high pressure inside the vertebral bodies with subsequent increased risk of extravasation. The authors then describe kyphoplasty as an alternative technique that allows low-pressure injection of highly viscous cement. Furthermore they describe what is known as an "egg-shell" technique to further reduce the extravasation rates in cases with severe cortical disruption.

The hydrolic system is designed to generate enough force to allow movement of the high viscous cement through small caliber needles and not to apply high-pressure inside the vertebral body. Pressure is first applied to water that then is transmitted to the cement container before it enters the needle into the vertebral body. Needles are designed with a relatively larger inner diameter than the standard sizes to allow for the highly viscous cement to flow under lower pressure.

Although kyphoplasty allows injection of cement under low pressure, we should not ignore the fact that high pressure had been already applied inside the vertebral body when the balloon was first inflated before cement injection. Considering the very high pressure that sometimes is required to elevate a depressed end plate, kyphoplasty is not a low-pressure technique. The compressed cancellous bone created by balloon inflation theoretically can decrease leakage but also can decrease cement interdigitation especially if combined with high viscosity cement.

We are also concerned about using a balloon and creating high pressure inside tumors with the theoretical risk of displacement of tumor cells outside the compromised boundaries of the vertebral body. There is no theoretical benefit of height restoration, cavity creation and compression of "cancellous" bone in malignant metastatic lesions.

The elegant "egg-shell" technique described by the authors is definitely useful to decrease leakage however, this is technically demanding and some operators may not be comfortable performing it, especially those with little experience. It could be difficult to perform with severely compressed vertebrae in high thoracic lesions. I am not sure if this technique can be the standard for treating compression fractures.

Regardless of the technique used, vertebroplasty or kyphoplasty,I believe we need to emphasize for the readers that using good basic rules and habits are essential to prevent leakage during vertebral augmentation procedures. Good fluoroscopy and injections of cement under real time fluoroscopy are essential. Once the operator feels increased pressure or recognizes a start of the extravagation,, injection should be stopped and the needle tip repositioned.

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Suspected Respiratory Depression Associated with Use of a Transdermal Fentanyl Patch

To the Editor:

Transdermal fentanyl has been proved as being effective in the long-term management of chronic non-cancer pain (1,2). Besides its efficacy, the transdermal route is also safe, since with it the plasma concentration of fentanyl can be adequately maintained at a steady level. However, when the patch is exposed to heat, it may lead to increased blood fentanyl levels that can cause dangerous respiratory depression (3,4). We report a patient who had respiratory depression suspected of resulting from the use of a transdermal fentanyl patch while warming his upper body with a heater.

A 60-year-old man had pain and numbness in his back and legs secondary to lumbar canal stenosis at the L1-S1 level for which he had previously undergone laminotomy. Two years postoperatively, he had pain and numbness in his legs for which he was prescribed loxoprofen (180 mg orally), pregabalin (300 mg orally), oxycodone (15 mg orally) and rescue oxycodone (5 mg, 2 – 3 times a day). However, despite this medication, his visual analog scale (VAS) score for pain at rest was 82 mm. He also suffered from constipation. Therefore, the 15 mg oral oxycodone dose was changed to transdermal fentanyl (Durotep MT patch, JANSSEN, Japan; 2.1 mg every 3 days). Due to inadequate pain relief with this dose, however, the dose of the transdermal fentanyl patch was increased from 2.1 mg to 4.2 mg. This led to decreased pain in his legs and an improvement in VAS score for pain at rest to 55 mm. The patient was also a known hypertensive for which he was being medicated with the calcium channel blocker cilnidipine (20 mg orally) for 2 years.

Three months after switching to transdermal fentanyl therapy, the patient complained of difficulty in breathing and respiratory depression when warming his upper body with a heater and in the bath. He visited the emergency department where he was diagnosed with respiratory depression associated with the fentanyl transdermal patch. Therefore, he was prescribed morphine sulfate (40 mg orally) instead of the transdermal fentanyl patch (4.2 mg). With this, his respiratory depression decreased, but did not completely improve. Hence, suspecting that his difficulty in breathing was caused by myocardial ischemia, we recommended that he undergo coronary computed tomography, which led to a diagnosis of 90% stenosis of the distal left circumflex coronary artery. Finally, the patient underwent percutaneous coronary intervention with a bare metal stent, which resulted in a decrease in his respiratory symptoms.

Transdermal fentanyl provides sustained analgesia for 72 hours; long-term treatment with transdermal fentanyl is generally well tolerated, particularly in view of the low incidence of potentially serious side effects, such as respiratory depression (5). However, when the patch is exposed to heat, it may lead to increased fentanyl blood levels that can cause dangerous respiratory depression (3,4). Hence, in this case, since our patient complained of difficulty in breathing when warming himself with a heater or while in the bath, we believed that increased blood fentanyl levels were the cause of his respiratory depression. Furthermore, fentanyl is metabolized by P450 3A4, P450 3A4 inhibitors (e.g., ketoconazole, erythromycin and calcium blockers) and may lead to an increase in blood fentanyl concentration (6,7). Our patient was being treated with calcium channel blockers. Hence, it is possible that the calcium blocker might have led to the increased fentanyl blood concentration and respiratory depression. Although discontinuation of fentanyl led to an improvement in our patient's respiratory depression, his symptoms did not completely disappear. As demonstrated by coronary computed tomography, his symptoms could also have resulted from myocardial ischemia. Thus, our patient's respiratory difficulties probably resulted from a combination of causes and mechanisms.

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Heart Failure Associated with Pregabalin Use

To the Editor

Pregabalin is a widely used antiepileptic drug that is also approved for the treatment of neuropathic pain. However, pregabalin may cause some adverse events, such as dizziness, somnolence, peripheral edema and weight gain (1). Moreover, we previously reported patients who developed muscle rigidity while taking oral pregabalin (2). Pregabalin has also been reported as causing deterioration of chronic heart failure (3-5). We report here a patient with no previous history of chronic heart failure who developed heart failure while on long-term oral pregabalin.

A 64-year-old male patient who had undergone rectal amputation 6 months previously presented with gradual onset of pain and paresthesia in his urethra after the operation. He had been implanted with a DDD pacemaker for complete atrioventricular block 2 years prior to his symptoms. His cardiothoracic ratio (CTR) on chest x-ray was 52%, with no evidence of pulmonary congestion. Echocardiography showed normal biventricular function and an estimated left ventricular ejection fraction of 68%.

The patient was prescribed loxoprofen (180 mg orally), tramadol (100 mg orally), oxycodone (40 mg orally) and duloxetine (40 mg orally) for the pain. He was also prescribed pregabalin for the paresthesia, at a dose of 150 mg orally, which is the recommended starting dose based on the value of Glomerular Filtration Rate (GFR) (his GFR at this time was 81.8 mL/min/1.73 m2). A week later, the dose of pregabalin was increased to 300 mg/day, which resulted in a decrease in the urethral pain and paresthesia.

Over a period of 3 months, however, the patient started developing peripheral edema, with the gradual appearance of facial edema and symptoms of volume overload, including a weight gain of 6 kg in one week. Hence, pregabalin was discontinued. Despite this, however, he was admitted to our hospital in a state of unconsciousness, with lip cyanosis, wheezing and orthopnea. At this time, his blood pressure was 124/66 mmHg, heart rate was 100 bpm and peripheral oxygen saturation was 80%. Despite immediate administration of 100% oxygen via a face mask with the maintenance of spontaneous respiration, he continued to have difficulty breathing. Arterial blood gas analysis showed

a pH of 7.271, arterial carbon dioxide tension of 68.9 mmHg and arterial oxygen tension (PaO2) of 35.8 mmHg. Chest X-ray demonstrated cardiomegaly (CTR 60%) with a butterfly shadow, suggestive of congestive cardiac failure and pulmonary edema. The patient was administered 100% oxygen via a face mask at a flow rate of 10 L/min, and intravenous furosemide 20 mg/day. With this therapy, he showed a good response by the next day. Over 7 days, he lost the weight he had acutely gained and there was an improvement in his peripheral and facial edema and heart failure.

Pregabalin is a calcium channel blocker that binds with high affinity to the alpha 2 delta subunits of voltage-gated calcium channels (6). Gong and colleagues (7) reported that human calcium channel alpha 2 delta mRNA subtypes have a high level of expression in the brain, heart and skeletal muscle. Murphy and colleagues (3) suggested a mechanism for heart failure induced by pregabalin. They hypothesized that pregabalin binds to the alpha 2 delta subunits of L-type calcium channels causing potassium-evoked attenuation of calcium ion influx, thus exerting a deleterious effect on myopathic ventricles. They also suggested that pregabalin directly promotes salt and water retention by the kidneys, which may also contribute to its potential to cause congestive heart failure (3). Our patient, who had normal biventricular function and a left ventricular ejection fraction of 68%, although with a DDD pacemaker, had worsening of ventricular function after therapy with pregabalin. Further, pregabalin also possibly caused a deterioration of his kidney function, resulting in his GFR of 60.1 mL/min/1.73 m2 3 months after taking pregabalin.

We describe the development of heart failure in a patient taking pregabalin. Although pregabalin-induced deterioration of cardiac function has been previously reported in patients with chronic heart failure, this is the report describing pregabalin-induced heart failure in a patient without a previous history of chronic heart failure.

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Unclear Mechanism of Cardiopulmonary Arrest Following Cervical Epidural Steroid Injection

To the Editor

We read with much interest the case report titled 'Cardiopulmonary Arrest Following Cervical Epidural Steroid Injection' by Stauber et al (1) in the March/April 2012 issue. The case report highlighted a cardiopulmonary arrest which occurred within 5 seconds after the injection of epidural steroid in 1% lidocaine. The quoted amount of betamethasone was 12 mg in a total volume of 4 mL. Assuming a standard concentration of 6 mg per milliliter, this would indicate two milliliters of 1% lidocaine were injected into the epidural space. The authors maintain that the cardiopulmonary arrest was caused from the blockade of sympathetic cardiac accelerator fibers immediately following the injection at C6-C7. It was also postulated that the pneumocephalus that was later found on CT scan was the result of a similar "pump" mechanism proposed by the Imanishi article (2) which describes the finding of air in intracranial veins after CPR.

A more likely cause that would account for the case details is intrathecal administration of lidocaine as the culprit for subsequent cardiac arrest. The fact that the pneumocephalus found on CT was subarachnoid and that loss of resistance to air was the method used to locate the epidural space leads me to believe that it is more probable that the air entry site was also subarachnoid. Imanishi's article explains the rare finding of air in intracranial veins after external cardiac massage but does not adequately explain the finding of subarachnoid air.

It would be instructive to see the fluoroscopy images after the 2 mL of iodinated contrast agent had been injected. Depending on the patient's body habitus and the fluoroscopy views used, it is certainly possible that there was either an inadvertent rent in the dura matter or even intrathecal spread of contrast which was not recognized. These findings would explain not only the pneumocephalus but also the rapidity of which cardiovascular collapse occurred after injection.)

This case report also highlights one of the rare but potential dangers for even "routine" procedures. Although it has not been our standard practice to start a peripheral intravenous line in all patients undergoing cervical procedures, our practice may change in the future.

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Response:

In response to "Unclear mechanism of Cardiopulmonary Arrest Following Cervical Epidural Steroid Injection," the author brings to light a very plausible mechanism to explain the aforementioned cardiac arrest. While we had considered the mechanism of an intrathecal injection (and in fact touched on this in terms of phrenic nerve involvement in our discussion), we ultimately shied away from this conclusion. The most compelling reason was the almost immediate onset of the cardiopulmonary arrest following the injection. To the

best of our knowledge, such an injection, even with 2ml of lidocaine, would not cause such a profound reaction with 5 seconds. However we believe this mechanism to certainly be plausible and aside from the time factor, have no reason to dispute it.

We agree that the fluoroscopy images would have indeed been helpful. Unfortunately they are not available to us for review. The authors of the manuscript took over care of this patient after she presented to the emergency department, while the patient's original procedure occurred at an outside surgical center. We thank the author for the interest in our manuscript.

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