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FLORIDA SOCIETY OF INTERVENTIONAL PAIN PHYSICIANS

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September 21, 2009

Dear Dr. Corcoran:

As per your inquiry of September 9, 2009, regarding recent publications in the New England Journal of Medicine (NEJM) relating to vertebroplasty and the necessity to reevaluate our local coverage determination, please accept the following statements as the initial formal reply from the Florida Society of Interventional Pain Physicians.

The two studies cited were:

1. A Randomized Trial of Vertebroplasty for Painful Osteoporotic Vertebral Fractures, *Rachelle Buchbinder, Ph.D.*, et al, volume 361:557-568, August 6, 2009. *Conclusions:* We found no beneficial effect of vertebroplasty as compared with a sham procedure in patients with painful osteoporotic vertebral fractures, at 1 week or at 1, 3, or 6 months after treatment. (Australian, New Zealand Clinical Trials Registry number, ACTRN012605000079640).
2. A Randomized Trial of Vertebroplasty for Osteoporotic Spinal Fractures, *David F. Kallmes, M.D.*, et al, volume 361:569-579, August 6, 2009. *Conclusions:* Improvements in pain and pain-related disability associated with osteoporotic compression fractures in patients treated with vertebroplasty were similar to the improvements in a control group. (Clinical Trials.gov number, NCT00068822 [ClinicalTrials.gov]).

The Buchbinder study is flawed from the following perspective. Over 67% of the patients came from a single site. If this paper was being submitted to the FDA it would not qualify as a multi-center trial. The influence of the single site is likely to be dramatic and if the primary investigator at the site was in favor of conservative management, there exists reason to question

the results. Additionally, it appears that the primary variable was the difference in mean pain, not the difference in a clinically relevant response rate (responder analysis). To achieve a difference of 1 (one) point in the mean, would have required over 120 patient participants in each group, not the 35 and 38 that were actually followed. Thus it is a negative trial because the size was likely too small to begin with. The FDA would have required a responder analysis, but this was not accomplished in this study. Because all of the statistical output is in terms of means and confidence intervals it is woefully inadequate to determine the distribution properties. The NEJM should have done a better job of scrutinizing these results. The New York Times media outlet has now dispersed to the public that a valuable procedure performed in the United States for 15 years is no better than a sugar pill.

With respect to the Kallmes paper, the study was also sized on the difference in mean changes in the outcomes, which were analyzed by methods that were based on a normal distribution. The distinction between the differences in means and the differences in responders give reason to believe that the data were also badly asymmetric. If one were to design a study to detect a difference in responders between 64% and 48%, the sample size should be 133 per group for 80% power, not 68 and 63 patient participants as provided by these authors. Thus this study is underpowered leading to a type 2 statistical error (falsely concluding no difference, when one exists). Obviously, the size of the Kallmes trial was very much smaller than that necessary to achieve relevant statistical data. One extra person with a clinically significant change would have produced a P-value less than 0.05. The problem with this observation is that it was probably a secondary endpoint. That being the case, there would have had to be a multiplicity adjustment and the P-value would have to be less than 0.025. If a single additional patient had a favorable response to vertebroplasty or an unfavorable response to the sham procedure, the resultant conclusion of the paper would change.

There are several other perplexing concerns with Kallmes study. Only patients who had fractures of uncertain age were required to have imaging with MRI or bone scan. The need for imaging with MRI prior to vertebroplasty is well documented in the literature. The increased sensitivity of MRI over plain film allows for detection of unsuspected fractures at other levels. It also allows for characterization of fractures as acute or chronic/healed. Furthermore, 36% of fractures in the vertebroplasty group were treated between 27 and 52 weeks after the onset of symptoms, a loosely controlled time frame that questions the varying degrees of fracture age in the groups. The natural history of osteoporotic compression fractures is that they generally heal over a 6-8 week period. In reality, two out of approximately three vertebral compression fractures are non-painful and discovered as incidental findings on radiographs. This publication leaves this phenomenon completely unexplained and provides no correlation to the myriad of literature available supporting vertebroplasty.

Another confounding factor is that 13% (9/68) of patients in the vertebroplasty group were receiving workers compensation. This could provide incentive for these patients to describe continued pain and disability. Would the data change if patients receiving workers compensation were excluded from the study? Moreover, many patients with osteoporosis have co-existing spine disease, spinal stenosis, facet arthropathy and or sacroiliac joint dysfunction that can be contributing sources of pain. Patients who undergo vertebroplasty and complain of persistent spine pain that is different from the original fracture pain require additional intervention or

medical management. The authors fail to address any investigation as to subsequent spine pain in the vertebroplasty group.

Some of the data in Kallmes study seems to support the efficacy of vertebroplasty. It is interesting to note that the crossover rate from sham to vertebroplasty was 43% after "adequate pain relief was not achieved." The crossover rate from vertebroplasty to sham at one month was only 12%. Was there some factor not captured in pain and disability scales to account for this significant difference? Additionally, we question whether any attempts were made to investigate the causes of failed vertebroplasties. Specifically, were any other refractures noted? In, *A Prospective Analysis of Clinical Outcomes after Percutaneous Vertebroplasty for Painful Osteoporotic Vertebral Body Fractures*, Do, et al, reported a 17 % (29/167) rate of refracture in vertebroplasty patients. Likewise, Trout, et al, reported subsequent fractures in 19.9% (86/432) of patients.

Our Society is concerned as to whether the very nature of an invasive study with a sham procedure and a high patient refusal rate, creates a skewed population. The sham procedure, in essence, resulted in a facet block. Consequently, the patients did indeed get therapy, with no untreated control for comparison. Thus the study design is flawed, misinterpreting facet injection as a "sham" procedure. The facet block and marcaine infiltration will provide short term pain relief. Furthermore, it does not require a sophisticated understanding of statistics to realize that the target populations of patients, those with incapacitating pain, are very unlikely to agree to a study with a placebo treatment arm when they have the option of treatment that is likely to help them immediately. The slow accrual of patients and ultimate abandonment of target enrollment despite the high volume of institutions involved argues strongly that there was overwhelming selection bias in patient enrollment.

Finally, The Florida Society of Interventional Pain Physicians stands firm that the results of these studies are not conclusive and that vertebral cement augmentation remains an effective treatment for vertebral compression fractures. I forwarded the *Position statement on percutaneous vertebral augmentation: a consensus statement developed by the American Society of Interventional and Therapeutic Neuroradiology, Society of Interventional Radiology, American Association of Neurological Surgeons, Congress of Neurological Surgeons and American Society of Spine Radiology*, Jensen, et al, *American Journal Neuroradiology*, 28:1439–43, Sept., 2007. This position statement in no uncertain terms maintains that the mortality and morbidity associated with untreated vertebral compression fractures outweighs the risks of not providing the procedure as well as the risks of the procedure itself. FSIPP continues to support this position statement until such time that the foundation of our knowledge is changed by well conducted studies with accurate and reproducible statistics and methodologies. There are hundreds of published papers documenting the dramatic improvement in pain and function in patients who undergo vertebral cement augmentation. Physicians, Societies and Associations in the United States, are left to wonder why the vertebroplasty patients in these studies did not do as well as those that are published in multiple prospective and retrospective case series. There is no thoughtful commentary within these studies on their inherent limitations.

In summary, spine pain is a complex medical condition that requires detailed clinical evaluation by experienced practitioners. Patient selection is principal in considering treatment with vertebral cement augmentation. Randomized controlled studies will often disagree. These

studies have relatively small cohorts of patients and should raise red flags in drawing conclusions as I have outlined above.

Sincerely,



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