Editorial Perspective

The Effects of Randomized Controlled Trials on Vertebroplasty and Kyphoplasty: A Square Peg in a Round Hole

Sheri L. Albers, DO[1] and Richard E. Latchaw, MD[2]

Evidence based medicine (EBM) is currently dominated by the randomized controlled trial (RCT). The addition of a placebo arm to the trial in hopes of further elimination of bias in the outcome gives it a higher position in the hierarchy of the levels of evidence, resulting in a higher grade of recommendation for its use and subsequent reimbursement. While such a model works well for medicinal treatments, it is inappropriate for determining the safety and efficacy of a device or a procedure. Using such a model to test a new device or procedure requires the addition of a sham procedure as an analog for the placebo. Along with the sham come all of the ethical implications of a nontreatment arm.

This perspective discusses the formulation of the RCT and its inherent problems with randomization, blinding, and trial size when used to test devices and procedures. These issues are analyzed using recent trials to test vertebroplasty (VP) and kyphoplasty (KP) as examples. The redefining of EBM, and its role in government programs that proclaim lofty goals of improved patient outcomes while they are actually focused on cost containment, is discussed in detail. The implications for our specialty are enormous as this methodology is increasingly used for reimbursement of procedures such as VP and KP. Not only will this deleteriously affect any medical specialty employing devices or procedures, but its effect on patient care will likely be even more detrimental with delayed or limited patient access and delay or attrition in the development of new devices and procedures.

This perspective acts as an introduction to papers both in this issue, in the upcoming issue of the journal, and to ideas forthcoming later this year. Any or all of these papers can be viewed as having a part to play in the ongoing controversies of EBM, forced utilization of RCTs, and the repercussions of negative trials.

It is essential to recognize the validity of non-RCT studies, randomized nonblinded trials, and observational outcomes-related research in the evaluation of devices and procedures. After all, good patient outcomes are the most important goal of any procedure and of any trial or study. A number of papers have demonstrated the equal validity of well-designed non-blinded trials and well-designed observational studies (with either cohort or case-control design) relative to the RCT. Most importantly, as cost containment and regulation exert an ever-tighter hold on the medical profession, we need to take a very sober and sanguine view of how we judge our clinical research on procedures and devices.

From: [1]Radiology Research and Consultation, Sacramento, CA; [2]Department of Radiology, University of California at Davis, Sacramento, CA

Address Correspondence:
Sheri L. Albers, DO
Radiology Research and Consultation
2178 Morley Way
Sacramento, CA 95864
E-mail: Sla2oz@aol.com

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"Safety and efficacy." These are key words that we as physicians have always lived by. Before we can use a new device, or before we can perform a new procedure, the safety and efficacy of that device or procedure must be proven. The Food and Drug Administration will not grant a license for device use, nor will an institutional review board allow its use in a given institution until specific criteria have been met. How are safety and efficacy proven? Sadly, scientific methodology now seems to be "one size fits all." The same

formula that is used to prove the safety and efficacy of a new drug—the RCT --is the same formula used to prove the safety and efficacy of a device or procedure. Allegedly, the best trials are randomized and blinded, to remove "bias" from the evaluation. The "better" the RCT, the higher is the level of evidence, and the higher will be the grade of recommendation for its use. This is EBM today.

The Randomized Controlled Trial and Levels of Evidence

It is with this background that the current conflict over vertebral augmentation for osteoporotic vertebral compression fractures (OVCF) is discussed. The focus in this perspective will be on VP and KP as examples of the difficulties in using methodologies considered to represent current standards of EBM. There have been many trials and studies evaluating these two techniques. Hundreds, even thousands of case studies, case reports, case series, cohort studies, and nonrandomized as well as randomized controlled studies have been performed. Most of these reports have been in support of VP and KP (1-17). But the studies that have received the most attention are the 2 negative, double blind, RCTs by Kallmes et al (19) and Buchbinder et al (18), published in 2009 in the New England Journal of Medicine, that concluded that VP was no better than a sham procedure in reducing pain from OVCF. Since the publication of these trials, the literature has been barraged with articles supporting and refuting the benefits of VP and KP (20-23). This article tennis match has occurred primarily because each study has inherent biases and flaws, depending upon how the clinical trial was structured. Much of this work has been done in an attempt to overcome bias in a testing system, the RCT, made for drugs, not devices and procedures. Why, if initially there was cumulative support for VP and KP, has so much controversy evolved regarding these procedures? The answer can be found by examining a hierarchy of the levels of evidence, an example of which is demonstrated in Table 1 (24-26).

At the top of the list are Level 1 studies comprising systematic reviews or meta-analyses of well-designed RCTs, and RCTs with a high degree of statistical significance which some authors refer to as high quality RCTs. The concept of "high quality" is related to the methods of data collection that the clinical trials use to eliminate bias, e.g., randomization and blinding (27). Randomization and blinding are commonplace for the testing of a new drug. Randomization in creating both a treat-

Table 1. Levels of evidence and grade definitions.

1a	**Systematic reviews of randomized controlled trials (RCTs) with homogeneity** Grade A (high certainty net benefit is substantial) strong recommendation, high-quality evidence
1b	**Individual RCTs with narrow confidence interval** Grade A (high certainty net benefit is substantial) strong recommendation, moderate-quality evidence
2a	**Systematic reviews of cohort studies with homogeneity** Grade B (high certainty net benefit is moderate or moderate certainty that net benefit is moderate to substantial) weak recommendation, high-quality evidence
2b	**Individual cohort studies and low-quality RCTs** Grade B (high certainty net benefit is moderate or moderate certainty that net benefit is moderate to substantial) weak recommendation, moderate-quality evidence
2c	**"Outcomes" research: ecologic studies** Grade B (high certainty net benefit is moderate or moderate certainty that net benefit is moderate to substantial) weak recommendation, low quality or very low quality evidence
3a	**Systematic reviews of case-control studies with homogeneity** Grade B (high certainty net benefit is moderate or moderate certainty that net benefit is moderate to substantial) weaker recommendation, higher-quality evidence
3b	**Individual case-controlled studies** Grade B (high certainty net benefit is moderate or moderate certainty that net benefit is moderate to substantial) weaker recommendation, moderate-quality evidence
4	**Case series and poor-quality cohort and case control studies** Grade C (at least moderate certainty of to be only a small benefit); USPSTF: offer on individual basis
5	**Expert opinion** Grade D (moderate to high certainty that the service has no net benefit or that the harms outweigh the benefits); USPSTF: discourage the use of this service

Combination of Oxford Centre for Evidence-based Medicine and U.S. Preventive Services Task Force (USPSTF). {need to fix referencs.}

ment and a control group (with the addition of a placebo control group considered as an even higher study design) allows the treatment effect to be isolated and studied (28-30). Blinding allegedly removes the possibility of over- or underestimating the treatment effect or distorting the measuring parameters, which supposedly happens if either the patient or the treating clinician (in the case of VP and KP) knows which group they are in. We all are familiar with the scenario where a patient receives either the drug in question or a sugar pill (the placebo). If the patient doesn't know which one they received, the study is blinded. If neither the patient nor the physician knows, the study is double blinded. Double blinding is considered to give the best results in EBM. Without blinding, and assuming the typical lack of equipoise (no preference for either treatment), the physician may produce bias toward his or her preferred treatment in numerous ways, including selection bias (31-33). The patient may produce selection bias if not blinded to the study arms (24). The unblinded patient may also bias the study outcome in an effort to please the physician.

Problems with Blinding, Randomization, and Trial Size

There are significant arguments against both blinding and randomization. One problem with blinding is the use of a placebo (34-36). There is no sugar pill for device testing or procedures, since either the patient or the physician can see the alternative device or its stigmata. Efforts to create a facsimile result in the use of a sham procedure or some other type of physical placebo (37,38). In the case of VP and KP is there really such a thing as a sham? Or must an alternative active control be used (39)? Since it is usually physicians who can distinguish the active from the inactive procedure, or the sham device from the real device, they are the ones faced with participating in deception or fraud. Many papers have been written that focus on the risk-benefit of invasive sham procedures, but underlying this topic are issues of morality, personal integrity, and ethics (40). Moral discomfort can occur when these sham procedures are viewed as unethical (41,42). Questioning whether something is deceptive or unethical opens a door for bias, in part because it affects the patient--physician relationship (43-45). Regrettably, the testing of a device or a procedure using a placebo or sham is difficult, even impossible, to perform, much like trying to fit a square peg into a round hole.

Arguments against the use of placebo-controlled, randomized trials for devices and procedures are valid (46,47). Placebo control can produce devastating results, such as those that occurred in the 1998 PROACT I trial (intra-arterial tissue plasminogen activator versus saline in a blinded RCT) (48). That study was halted early because, in view of the severity of negative outcomes in the blinded control patients who received only saline, the trial was considered unethical.

One problem with randomization concerns issues of generalization (49). Can a highly focused, randomized, placebo-controlled study be generalized to more diverse clinical settings? Randomization also produces problems in recruitment, study length due to difficulties in recruitment, and costs which can increase significantly as studies lengthen (50-52). Problems with recruitment create issues with study validity, in that a small number of patients decreases the power of the study and therefore the impact of its outcome (53-55). Low-powered studies are frequently reported as negative studies, implying that there is "no difference between the treatment and the control" (56-62). However, low-powered studies are better seen as inconclusive because they are unable to detect small differences between the study arms that could be clinically significant (63).

The importance of this concept of statistical power can be seen in the June 2011 Technology Evaluation Center (TEC) assessment of VP and KP for OVCF (64). The TEC assessment reported that the most robust measure of clinical assessments is response or meaningful improvement. Beneficial effects of interest include relief of associated symptoms (e.g., pain) and improvements in the ability to function (i.e., activities of daily living). Relative to the Kallmes et al (19) and Buchbinder et al (18) trials, their conclusions were that these studies were underpowered in the most important measures, which were the secondary aims of the 2 studies. The Buchbinder et al study (18) was felt to be underpowered in its primary outcome as well. Although the TEC assessment did not report that the Kallmes et al trial (19) was underpowered in its primary outcome, other authors have raised this concern. The TEC assessment states that without adequate statistical power, it is not possible to determine if VP was effective or not, and the results of both studies should be interpreted as uncertain (64).

Interestingly, the TEC assessment also reports that the most informative outcome is the proportion of patients that respond. Pain is a continuous outcome and therefore the magnitude of improvement on an individual level is clinically meaningful. The Buchbinder et al trial (18) reported an improvement of 2.5 on the Visual Analog Scale (VAS) for overall pain, and it was

the VP patients who showed a more frequent meaningful response at one month, 3 months, and 6 months. The TEC assessment reported that the Kallmes et al study (19) also showed a trend toward a higher clinically meaningful improvement in pain at one month for the VP group. Additionally, the TEC assessment took notice that significantly more patients in the control group chose to cross over (leave their control arm for the alternative control arm) than in the VP group (43% versus 23%). This was not reflected in the Kallmes et al trial (19) primary outcome since the cross overs occurred after the primary outcome assessment (64).

Since the publication of the Kallmes et al (19) and Buchbinder et al (18) trials, many articles have sought to expose the deficiencies in these 2 RCTs (39,50,65-69). One glaring deficiency was the lack of nonsurgical controls. As a result, the FREE (Fracture Reduction Evaluation Trial) (69) and VERTOS II (10) trials, in efforts to compare current forms of treatment, utilized a nonsurgical medical group, i.e., medical management, as a control and compared this group of patients to those who received vertebral augmentation. Published results of the FREE and VERTOS II trials redeemed the tarnished reputation of KP and VP, respectively (10,70). However, although strict methodology was used in these trials and the data were detailed and critically evaluated, they were not blinded studies and so were judged by many using a levels of evidence hierarchy such as that in Table 1 to be Level 2 at best, which resulted in a grade of recommendation for their use as "B" ("probably useful") at best. Because the FREE (70) and VERTOS II (10) trials did not lend themselves to blinding, by definition they could not meet the requirements of "high quality" Level 1 research as currently defined. The Kallmes et al (19) and Buchbinder et al (18) trials were blinded, but as we will discuss, they were not free from bias, yet they are still considered Level 1 studies by most and their recommendations for use have been given the highest grade. What is the basis of this evidentiary mindset?

The Redefining of Evidence Based Medicine

At the foundation of this mindset is a distorted and manipulated version of EBM. What was the original concept behind EBM? In a 1996 article written by Sackett et al (71), the authors discuss the initial intent of the process. What EBM was intended to be was a conscientious, explicit, and judicial use of current best evidence in decisions about individual health care. Its intention was to integrate the proficiency and judgment that individual clinicians acquire through clinical experience and practice with the best available external evidence from systematic research (i.e., clinically relevant research). EBM was not intended to tyrannize clinical practices by forcing cookie cutter medicine upon them. Its intent was to respect the individuality of patients, their situation, rights, and preferences, and to empower the clinician with the best available treatment options. External evidence was not intended to replace clinical expertise or the clinician's ability to choose, based on the individual patient. In its original intent, EBM would not be restricted to randomized trials and meta-analyses. Originally, EBM recognized that some medical questions can only be answered with nonrandomized trials. Some research would not and should not be able to conform to blinded controls (71).

Somewhere along the way, the original intent was lost. Clouded in efforts to improve the statistical significance of research, "scientists" reshaped EBM. During the course of creating and honing study designs and methodologies created for drug therapy, statisticians, bioethicists, epidemiologists, and other "scientific" researchers decided that variables such as bias could be minimized or eliminated in research on devices and procedures in much the same way it had been in pharmaceutical research (72-74). Unfortunately, as it stands, we have imposed limitations that are being used as ammunition to reduce the clinical validity of studies. An inappropriate research model for drugs and devices has been elevated to the top of the hierarchy of EBM: the RCT (75). Because the revised form of EBM suits monetary and control purposes, the RCT has become the standard by which all research on drugs and devices is judged and by which medical and economic decisions are made.

Evidence-Based Medicine and the Government

The original intent behind EBM was not a financial one. The original intent was to provide the best health care available, regardless of cost (71). Despite this intent, initial fears are coming to fruition that EBM could and would be hijacked by purchasers and managers (including governmental agencies), which leads to serious financial implications for product developers and manufacturers and the users of such goods (76). As we are seeing, EBM has gained momentum over the past 20 years, and with this momentum EBM has spread like wildfire across the health care industry. In fact, EBM, comparative effectiveness research (CER) and guidelines (embodied in the Patient Centered Outcomes Research

Institute, [PCORI]) have become the cornerstones of the Affordable Care Act (ACA) and have become embedded in multiple governmental agencies (77,78). CER is promoted as part of the Effective Health Care Program (EHCP) (79,80). This program funds individual researchers, research centers, and academic organizations to work together with the Agency for Healthcare Research and Quality (AHRQ). The AHRQ's job is to produce CER for clinicians, consumers, and policymakers. The AHRQ is the lead federal agency charged with improving the quality, safety, efficiency, and effectiveness of health care, and is one of 12 agencies within the Department of Health and Human Services. The AHRQ supports health services research that will hopefully improve the quality of health care and promote evidence-based decision making (81). The AHRQ created the Evidence-based Practice Centers (EPCs) in 1997 (82). Their job is to perform in-depth reviews of existing evidence for the EHCP. In August 2012, 5-year contracts were awarded to 11 EPCs. One of the 11 EPCs is TEC, which was discussed earlier. Another EPC is the Oregon Health & Science University in Portland, OR, which is under the leadership of Roger Chou, MD, who led the efforts to produce evidence-based clinical practice guidelines for the American Pain Society (83).

How the research is graded, who decides on the grading system, who judges the research, how the research is used, and linking it with cost-saving measures have tainted our ability to define proper treatment programs (84-86). The Centers for Medicare and Medicaid Services (CMS), an agency of the Department of Health and Human Services, along with the United Kingdom's National Institute for Health and Clinical Excellence, reward physicians and institutions for their cost-saving measures, encouraging them to practice EBM and CER (87-89). The CMS will spend up to $1 billion over 3 years to evaluate and reward projects from across the country. Some of these projects will be designed to rapidly reduce Medicare, Medicaid, and the Children's Health Insurance Program costs in outpatient and postacute settings through the Health Care Innovation Awards (89). The ACA seeks to decrease health care expenditures not only through CER, but also by value-based purchasing, through Accountable Care Organizations and through Section 3403 of the ACA known as the Independent Payment Advisory Board (IPAB) (90). This is a 15-member panel of presidential appointees whose task will be to produce recommendations to hold down Medicare spending (91).

Evidence-Based Medicine Will Affect Reimbursement

The fear is that the Independent Payment Advisory Board and other ACA changes will simply cut provider reimbursements to meet spending targets. The fear that these measures will all eventually lead to restricted access for some patients is apparently justified, as evidenced in a recent letter from California Anthem Blue Cross notifying providers that effective August 1, 2013, prior authorization of "high tech radiology," and "pain management injections and procedures," among other service categories, will be required before they can be provided to members enrolled in Medi-Cal, Managed Care, the Healthy Families Program, the Access for Infants and Mothers Program, and the Major Risk Medical Insurance Program (92). Is this the beginning of a 2-tiered health care system supported by EBM?

Constructing guidelines based on an evidentiary scale created as an exclusion hierarchy for research sets up a situation where clinically relevant, valid research can be dismissed if it does not or cannot fit into Level 1 requirements (93). Conversely, less valid or controversial research can be elevated to a higher level of evidence if it fits the criteria of Level 1 evidence, which has implications for funding. As an example, the California Technology Assessment Forum has recently written a strongly worded paper recommending that funding of endovascular techniques for the treatment of acute stroke be halted after the publication of 3 highly controversial negative articles (IMS-III, MR Rescue and Synthesis Trials) (94). Efforts to decrease or eliminate reimbursement for the use of a device or the performance of an interventional procedure are major problems for practitioners of interventional treatments (95). Few, if any, practitioners will be spared. Complaints regarding the evidentiary hierarchy have been raised by numerous groups, including, for example, the surgical specialties, dentistry, physical therapy, and interventional neuroradiology (38, 96-98). If we do not stand together, the injustices imposed on one of our specialties may eventually become the injustices imposed on all.

Evidence-based Medicine, Vertebroplasty, and Kyphoplasty

Where research falls on the evidentiary scale can affect funding and the survival of a product or a technique. Are VP and KP becoming collateral damage of EBM as a result? Several studies have reported an overall decline in these procedures with a more specific

(and significant) decrease occurring for VP, which declined by 12.9% annually from 2006 to 2010 (99-102). Although KP utilization initially increased from 120 /100,000 Medicare patients to 141 /100,000 from 2007 to 2008, these numbers declined to 135 /100,000 in 2009, with a further decrease to 121 /100,000 in 2010. Part of the reason for the decline in VP utilization may have been the result of the introduction of KP codes in 2006; however, the published results of the Kallmes et al (19) and Buchbinder et al (18) trials are suspected to have played a significant role in the diminished utilization of both VP and KP from 2009 to 2010 (103,104).

Despite the long history of positive clinical outcomes research, national coverage by the CMS has not been established for VP and KP. While it is acknowledged that coverage by the CMS is decided on a state by state basis, the resistance to national coverage stems in large part from the belief that clinical outcomes research and RCTs without placebo controls are inferior (105,106). In their December 2011 article (106), authors Wulff, Miller, and Pearson seem disturbed that coverage wasn't rescinded for VP in light of the negative Kallmes et al (19) and Buchbinder et al (18) trial results. They state that legal advice inside Medicare warned that the lack of precedent for reversing the long history of coverage for VP without new evidence of harms would invite a legal challenge (107). Could this be part of the reason that so many articles concerning a negative risk-benefit ratio for VP and articles referring to or studying potential harm from VP have emerged (108-110)?

Wulff, Miller, and Pearson (106) express their hope that better evidence would be generated by CER through PCORI. They note that the Institute of Medicine in 2009 compiled a list of invasive procedures set as priorities for CER, because invasive procedures are expensive, risky (as well as beneficial), and have gained widespread acceptance based primarily on observational case series and uncontrolled clinical trials. This type of research is now considered as subject to biases leading to overstatement of clinical benefits, as opposed to the rigorous RCTs, performed as part of the evolving concepts of EBM which are the ruling academic approaches to medicine (107).

However, several articles disagree with this belief that observational studies are subject to biases leading to overstatement of clinical benefits (111-113). Concato et al (114) published their article in the New England Journal of Medicine in which they used published meta-analyses to identify randomized clinical trials and observational studies that examined the same clinical topics. They found that the results of well-designed observational studies (with either cohort or case control designs) did not systematically overestimate the magnitude of the effects for treatment when compared with those in RCTs on the same topic (114). Articles such as these are disregarded by other authors when they recommend that insurers (starting with Medicare) should require more rigorous evidence on comparative effectiveness before unrestricted coverage is granted to new interventions.

Authors such as Wulff, Miller, and Pearson (107) have recommended that insurers take the lead at investigating invasive procedures and exercise their power to require at least 2 high-quality randomized trials, at least one of which should include sham procedures in the control arm, before authorizing reimbursement. They recommend that insurance coverage with evidence development be employed since they believe that the payment structure for clinicians in the United States is a problem. According to Wulff et al, "Doing more procedures reaps greater payment"(107) They have suggested changing the payment structure in the United States to increase the appreciation of EBM by clinicians. They have also suggested innovative payment incentives such as bundling of payments or global payments to Accountable Care Organizations (we are experiencing some of these payment processes now). They hope that PCORI will help with the interpretation and verification of negative studies. Their surprise that patients are still undergoing VP despite the negative trials is echoed by their surprise that women aged 40-49 were still getting mammograms despite the USPSTF recommendations. They reminded their readers of the "firestorms" that occurred when the USPSTF tried to move away from universal coverage for breast cancer screening in women aged 40 - 49, and when the Agency for Health Care Policy and Research questioned whether spine surgery was necessary for uncomplicated low back pain (107). The implications of this and other articles on this subject appear to be that the firestorm of outcries following these recommendations were unjustified backlashes from political and advocacy groups. It seems that government-supported research is fertile ground for statisticians, epidemiologists, bioethicists, and general internists with master's degrees in public health. Comments have been made suggesting that breast cancer is a cancer of ageing. But these comments fail to inform the public that breast cancer in younger women tends to be more aggressive. In regard to the astonishment that VP is still being performed, what of

the active 78-year-old woman who suffers an OVCF that significantly alters her lifestyle? If she only undergoes medical therapy, she is at risk for isolation, deconditioning, dependency, depression, thrombophlebitis, stroke, and pulmonary diseases such as emboli and infection. The opioids may make her nauseated and constipated so she may not eat. This is not an uncommon story. Morbidity and mortality risks are real life issues, not just statistics. There may be significant benefits from the expensive and risky interventions that evidence-based researchers, following their rigid methodologies, seek to end.

In their articles, Drs. Kopans (115) and Zuurbier (116) point out serious errors on the part of the USPSTF in its evidence-based research which has led to the effort to remove universal coverage for screening mammography in 40 – 49 year old women. One of the comments made by Dr. Zuurbier (116) pointed to the potential bias in the USPSTF's 16 member panel, which included 4 members having affiliations with health care delivery entities like Kaiser Permanente and Blue Cross/Blue Shield. She also indirectly questioned what credentials these members have to qualify them as experts in breast cancer. Perhaps that is the type of question that should be asked of the members of all governmental health care agencies and panels. What qualifies these members to be experts on the devices, procedures, or services that their recommendations or lack thereof may bury? This question is essential considering that the thrust behind evidence-based health care is cutting costs. "Experts" should have significant hands-on experience.

Dr. David Kallmes, whose INVEST trial was sponsored by the National Institutes of Health (NIH), and Dr. Franklin Miller, who works in the Department of Bioethics at NIH, wrote an article (117) in which they argue that the critical response to the 2 placebo-controlled RCTs (the Kallmes et al (19) and Buchbinder et al (18) trials) was due to physicians being "placebo reactors." This is a psychological dynamic that reinforces the clinicians' belief in the value of the procedure that they recommend or administer and perceive as beneficial. A dissonance is created when clinical experience conflicts with trial results. The remedy to eliminate this perceived bias is to change the culture of medicine and to remove the "clinical mentality" of physicians by strengthening the culture of evidence-based procedural medicine. They believe that it is neither necessary nor desirable that the dissonance be resolved in favor of clinical experience (117). Evidently, physicians believing in what they do or recommend, believing that they do good rather than harm, and that they make a difference (117) are significant negatives in the world of RCTs and EBM.

It is interesting that despite many positive randomized trials performed after the Kallmes et al (19) and Buchbinder et al (18) trials, these supportive articles did not have the same run of news headlines that the negative Kallmes et al and Buchbinder et al trials did. Could this be, in part, due to the activities of the National Initiative for Promoting Evidence-Based Health Information, through which the EHCP disseminates research and related issues through media outreach, national partnership development, and online virtual centers (118)?

Alleviation of Pain with Vertebroplasty and Kyphoplasty

Where does vertebral augmentation go from here? We can continue with the valid argument that needling, with or without lidocaine and bupivacaine, is not a placebo but rather is an active control. Some have even argued that this form of active treatment may be affecting facetogenic pain rather than vertebral body pain, which could explain the rapid pain relief and the lack of statistically significant differences between patients in the Kallmes et al (19) trial in particular (39,119,120). But Kallmes, along with Brinkikji et al, rejected this theory in a follow-up trial (121). So, if we accept the validity of the Kallmes et al (19) and Buchbinder et al (18) trials and if we accept that a placebo was used, then we must understand what a placebo and the placebo effect are, since these trials have linked VP to a placebo with placebo effects. They are not the only studies to raise the possibility that a patient's response to VP is due to the placebo effect.

In the next issue of *Pain Physician*, Liu et al (122) performed a meta-analysis and systemic review of RCTs comparing pain reduction following VP and conservative treatment. They found that VP afforded greater long-term pain relief when compared with conservative treatment. Subsequently, the authors subdivided the conservative treatment group into sham procedures and nonoperative groups. VP continued to demonstrate significantly greater pain relief than the nonoperative group. However, there were no differences between VP and the sham injection groups. Although the authors discuss potential causes for this glaring discrepancy, they include in those causes the possibility that the sham procedure, as well as VP, achieve analgesia by means of a placebo response (122).

In this issue of Pain Physician, Saxena et al (123) discuss the importance of blinding for the reduction of bias and state that in view of the demonstration of outcome equivalence between the blinded augmentation and sham procedure patients in the Kallmes et al (19) trial, the placebo effect as a cause of the patients' responses is suggested. Additional articles have raised this possibility.

Although postulating that the mechanism of action of such a historically well-received procedure as VP could simply be the result of the placebo effect may be repugnant to some physicians, let us examine the concept of placebo effect to see if it warrants consideration or disdain. Part of the confusion with the concept of placebo is the antiquated view that a placebo is an inert substance or procedure. Therefore, if it is inert it cannot elicit an effect. Through a great deal of research, the evidence has forced a shift in this mechanistic understanding of the placebo effect, steering progressive thinkers into recognition that the placebo effect is a genuine psychological phenomenon attributable to an overall therapeutic context. To understand this, we must accept the concept that there are many placebo effects and that these can be broadly divided into neurobiological and psychological categories (41).

Neurobiological mechanisms are under continuous study and have incorporated the use of functional magnetic resonance imaging (fMRI) and positron emission tomography scanning to help understand brain activation centers as can be seen with their use in the study of pain pathways (41,124-129). fMRI provides a window that permits the visualization of centers within the brain such as the diencephalon, hypothalamus, amygdala, anterior cingulate cortex (ACC) as well as the insular and prefrontal cortex (PFC) shown to be active in the mediation of placebo analgesia. These centers contribute to descending influences by eliciting inhibition or facilitation of nociceptive transmission via the brainstem during placebo analgesia. fMRI, illustrates decreased brain activity in the thalamus, insula and ACC (classic pain processing areas) and increased activity in the PFC and periaqueductal grey (PAG) during "anticipation" of pain. The stronger the PFC activation, the greater the placebo induced pain relief and the greater the diminishment in neuronal activity. This correlates with the theory that prefrontal mechanisms trigger opioid release in the brainstem which influences the descending pain modulatory system thereby modulating pain during placebo analgesia (130). In their 2013 article, Lee and Tracey (131) looked at activation within the primary somatosensory, insular and mid ACC regions following reported pain, using an opioid (a fixed remifentanil dose) while modulating pain intensity via expectancy. The effects seen on fMRI were distinguishable because expectancy and remifentanil influenced different areas of the brain without significant interaction. In addition, the analgesic onset effect of expectancy occurred earlier than the onset of remifentanil.

Of the many psychological mechanisms, the two most studied are expectancy, by both the patient and the physician, and conditioning (which are thought to occur in that order). Both can be modified by many factors. An example of a factor that affects patient expectation is the physician's verbal cues. But, it is not just the patient's expectations and conditioning that are important, it is also the physician's. If we recognize that there are many psychosocial issues that surround the patient and the clinician, then perhaps we can employ these factors into facilitating and enhancing clinical practice through placebo effects. When discussed in this fashion, the placebo effect becomes a process of helping the patient to heal himself (132).

The overall response to a treatment is the result of the treatment itself and the context in which the treatment is given (133). This important concept will be discussed later in terms of placebo efficacy versus specific efficacy. The treatment context, including the nature of the treatment and how it is administered, and the therapeutic interaction (the doctor-patient relationship, for example) comprise the treatment environment. Unfortunately, factors comprising the treatment environment are complex (133). The physician as part of the treatment environment can play a positive or a negative role. For example, physician attitude and cues can produce an enhanced patient response or can diminish a patient response. The latter is considered a nocebo effect (i.e., a process where the patient's condition worsens or doesn't change with use of a substance or procedure that is known to be effective) (41). Could lack of enthusiasm or ambiguity by a Kallmes et al (19) trial physician produce a nocebo effect? This discussion points to ways a physician can inject bias into a blinded RCT, even though blinding was intended to negate bias.

If viewed as an interactive process, a placebo no longer seems inert. If we consider just the act of needle placement as producing a placebo effect, as researchers have done in respect to acupuncture, then in regards to VP, could the equivalent patient response to the VP needle and the sham needle be due to a similarity in treatment context (134)? If so, then where they differ is

in the treatment itself: i.e., the intra-osseous placement of cement.

It is important to recognize the difference between placebo efficacy and specific efficacy. In the article, "Vertebroplasty and the Placebo Response," (133), the authors purport that when the patient's response is due to the treatment context and treatment ritual, placebo efficacy is being demonstrated. The patient's response to the inherent pharmacologic or physiologic properties of the treatment refers to specific efficacy. The authors claim that because the VP and the sham intervention had equivalent pain reduction, VP has no specific efficacy. They then go on to question the legitimacy of VP. In the process of denying any specific efficacy VP might have, and relegating it to only placebo efficacy, they question VP's cost effectiveness (105,106,135-137). To worsen the situation, they discuss all of the possible complications of VP, without giving the percentage of those that are clinically significant, and proceed to suggest that VP has an unfavorable risk-benefit ratio. They detail consequences of cment leakage (the most common complication), including the percentage of pulmonary emboli seen within the VERTOS II trial, but give only a glancing statement that the adverse effects have rarely been found to be of clinical significance (9,10,17,138). They bring up incident fractures; however, a cause and effect relationship of incidental fractures to VP has not been proven and remains controversial (2,139-143). All of this paints a negative risk-benefit ratio for VP.

If we accept that at least part of the initial patient response to VP is a placebo response, we do not have to limit the process by accepting that placebo response is the entire response. What if VP is a 2-fold process? What if VP and KP produce both a short-term and a long-term response? What if the initial short-term patient response to VP is at least partly due to a placebo effect (placebo efficacy)? As you will recall, follow-up in the Kallmes et al (19) trial was only for one month. The Buchbinder et al trial (18) was carried out primarily over 3 and up to 6 months. But the FREE (70) and VERTOS II (10) trials demonstrated KP and VP, respectively, to have sustained effects out to one year. Perhaps the demonstration of the specific efficacy of VP and KP requires time. Perhaps in the acute stage, healing after OVCFs is markedly enhanced by employing the placebo effect (144). Could this explain the dramatic decrease in pain following VP compared to natural healing? If the same treatment context is employed, this would also explain why the short-term studies comparing a sham injection and VP have similar patient responses (145,146). If it is possible that pain in the subacute to chronic stage of healing is due to factors not significantly affected by the placebo effect, then the cement deposition in KP and VP may be alleviating pain through a different mechanism which would constitute specific efficacy for both procedures. Pain in this stage of healing may be the result of the inherent mechanical instability of a fractured vertebral body (147-149). Much research has been done to determine how the presence of polymethylmethacrylate (PMMA) affects the biomechanics of the affected vertebral body and its relationship to the remainder of the spine (150). In the normal healing process, most stages of healing benefit from stabilization (151-153). Doesn't the infusion of cement into cancellous bone with its insinuation into fracture lines provide stabilization as a form of internal fixation? Research has shown that PMMA infusion via VP and KP increases vertebral body stiffness which helps to redistribute loading pressures within the spine. It helps to restore more normal intradiscal pressures, and in strengthening the centrum, it redistributes weight from the vertebral walls back to the centrum, helping to normalize force transmission. All of this could be looked upon as VP's and KP's specific efficacy, i.e., treatment.

Although some articles have suggested that this increased stiffness is the source of incident fractures, this has not been proven (154). It has been shown that incident fracture risk is equal to or lower postprocedure when compared with the risk of incident fractures following nonsurgical treatment of an OVCF (108,155). Part of the more chronic pain may also be the result of injury to the paravertebral soft tissues (110). More research will be needed to fully understand the mechanisms of pain and overall spine stability as they relate to vertebral augmentation. As new vertebral augmentation fillers with better bioavailability, mechanical effectiveness, and osteoconductivity are developed, some of the present controversies may become moot (156,157).

Why All the Fuss?

As will be discussed in the current issue of *Pain Physician* (158), osteoporosis continues to be one of the 10 most important diseases in the world according to the World Health Organization. Greater than 75 million people in the US, Europe, and Japan are affected every year. More than 9 million fractures per year worldwide are attributed to osteoporosis with 4 - 5 million of those fractures occurring in the US and Europe. White women are at the greatest risk. Up to 22% of white women

in the US, ages 60 - 69, are affected. This percentage increases to 70% in white women 80 years of age or older. Although white women are primarily affected, men and women of all racial backgrounds are at risk.

Studies on OVCF have demonstrated that pain relief in augmented vertebral bodies equalizes to that in nonsurgical vertebral bodies with time. That assumes normal healing. We are all aware that many people suffer chronic pain and disability after an OVCF. But even assuming a normal, natural (nonsurgical) healing process, it is the difference in quality of life offered by augmentation that is captured in real life. Much of this quality is due to restoration of back function. Koch and Greiner (159) evaluated patients treated with KP compared to those given nonsurgical medical care. These researchers found greater improvement in the European Quality of Life-5 Dimensions Scale and relevant improvement in the Roland-Morris Disability Questionnaire (RMDQ) for KP patients than for the nonsurgical group. Both of these tests are measurements of the quality of life. RMDQ is specific to back function. Earlier and improved reduction in pain and faster restoration of back function increase a patient's positive lifestyle options, leads to quicker reentry into the patient's social or usual life environment, and potentiates an active lifestyle.

The mortality risk has been shown to increase almost as much as 9-fold following a vertebral fracture. In their article, Edidin et al (160) identified 858,978 patients of which 119,253 underwent KP and 63,693 underwent VP, while the rest were treated nonsurgically. Their results after close to 4 years of follow-up demonstrated that patients in the operated cohort had a higher adjusted (for covariates and comorbidities) survival rate of 60.8% compared with the nonoperated cohort rate of 50.0%. The operative cohort patients were 37% less likely to die. The authors suggested that part of this difference in mortality after augmentation may be due to the patient's improved pulmonary function. Death following vertebral compression fractures has been associated with pulmonary disease (161). Medical treatment alone promotes a sedentary lifestyle and can be a factor in the patient's morbidity and mortality (162). A sedentary lifestyle can result in weight gain and obesity. Sedentary patients and those confined to bed rest are more susceptible not only to pulmonary disease and emboli, but also to cardiovascular disease, including stroke (163-165). Not all patients can or will use the back brace recommended for nonoperative medical treatment. Not all patients can tolerate opioids or other pain medications and some are adversely affected by them, which includes becoming addicted to them (166,167). In view of the survival and quality of life statistics, how is extracting VP and KP from treatment options justified when the overall risk of clinically significant complications is less than 1% (9,17)? Oddly enough, this epidemiologic data on the morbidity and mortality issues associated with OVCF is paid little attention in the negative VP and KP articles.

Decreasing the Incidence of PMMA Leakage

Given that there are significant benefits to KP and VP, research has been done to address the more common and alleged complications. In one of the articles in this issue of Pain Physician (168), the issue of intravertebral pressure as a possible cause for PMMA leakage during both procedures is addressed. It has been thought that the formation of a cavity during KP reduces intravertebral pressure and may explain why the percent of PMMA leakage is usually lower for KP as compared with VP. However, this study demonstrated no significant difference in intravertebral pressures during all common phases of KP and VP. They found that pressures are highest for both procedures during PMMA instillation. The authors suggest that leakage and embolic phenomena may be most prone to occur during this phase. Studies are still inconclusive as to whether the higher viscosity of the partially cured PMMA in KP is a factor in decreasing the incidence of leakage (157).

There are many factors to consider when choosing KP versus VP. The choice used to depend on the specialty of the patient's physician, since KP used to be performed primarily by surgeons and VP by radiologists (169). But as more and more interventional physicians have become comfortable with both procedures, patient preference, physician choice, cost, and comorbidities have become more important factors. If KP is chosen, is a unilateral or bilateral approach better? Two of the articles in the next issue of Pain Physician address this question (170,171). Both studies were performed as systematic reviews and meta-analyses of RCTs. Both studies found an equivalence of pain relief between the two approaches. Both found no significant difference in the incidence of PMMA leakage. These papers discuss differences in fracture reduction between the two approaches and the relevance of the differences in PMMA deposition. One of these articles offers suggestions as to factors that may assist in the decision between a unilateral and a bilateral approach.

Vertebroplasty and Kyphoplasty for Metastatic Disease

Although we have concentrated on VP and KP, many of the issues we have touched upon could apply to the other uses of augmentation which include nonvertebral osteoplasty, use in symptomatic vertebral hemangiomas, as well as the use of augmentation in neoplastic vertebral disease (172-177). At the present time the use of augmentation in these conditions is not under as severe scrutiny as VP and KP in OVCF. In providing its readers with innovations in these procedures, 2 studies are presented in this issue of Pain Physician and 2 in the next issue. In their article, Sun et al (178) discuss an alternative approach to VP for metastatic disease at C2 where treatment options are limited. Anselmetti et al (179) discuss the use of the KIVA system as a unique and effective minimally invasive treatment option for patients with severe pain due to osteolytic vertebral metastases, while Otten et al (180) compare the Kiva system with kyphoplasty. Woo et al (181) discuss the use of VP as an option in the treatment of terminally ill patients with epidural and dorsal root ganglion metastatic involvement who have not responded to conservative therapy and who are not surgical or radiation therapy candidates.

In 2 of the last 3 papers to be discussed in this issue of Pain Physician, the authors give detailed discussions, each with a slightly different twist, on the controversies involved between the major RCTs, meta-analyses, and systematic reviews of vertebral augmentation (158,182). One additional article also discusses the controversies of the Kallmes et al (19) trial compared with their single-center findings (123). These articles bring us back full circle into the controversies of the Kallmes et al (19) and Buchbinder et al (18) trials.

Other Controversial Issues Regarding the Kallmes and Buchbinder Trials

As stated at the beginning of this perspective, there have been many articles that have been published questioning the results and methodologies of the Kallmes et al (19) and Buchbinder et al (18) trials. The following discussion is simply to remind the reader that no study is without bias and unintentional flaws. Some of the major controversial issues brought forth in the medical literature of 2010 that resulted from the analyses of the Kallmes et al (19) and Buchbinder et al (18) trials have already been discussed; others are as follows: (39,50,66-69,183)

Fracture Acuity

Fractures of mixed ages (from < 6 weeks up to one year) were used in the Kallmes et al (19) and Buchbinder et al (18) trials with an average age of fracture at 14.7 weeks. Since fracture union usually occurs at approximately 8 weeks, roughly 75% of fractures in these trials were nonacute. Acute fractures (< 6 weeks) that do not respond to conservative care are those that usually receive recommendation for an augmentation procedure. Subacute and chronic fractures do not respond to vertebral augmentation as dramatically as acute fractures. Healing or partial healing may account for the small volumes of PMMA used in these trials (184,185). Otherwise, the volumes of PMMA were not sufficient.

Enrollment

By trial design few inpatients were included. As discussed earlier, the small number of patients affected the power of the studies. Both studies were not sufficiently powered to evaluate their secondary outcomes or to evaluate subgroups of patients such as those with clefts that might have been more likely to show improvement.

The VAS score may have been set low with a wide range to overcome enrollment failures. VAS scores may not be as effective in assessing chronic pain as other forms of evaluation and, as mentioned, the majority of the fractures in these studies were nonacute (186).

Recruitment continued over an extended period of time (4.5 years for the Buchbinder et al [18] trial) with relatively few patients enrolled. In the Kallmes et al (19) trial, 1,812 patients were initially screened but only 131 were enrolled. Patient refusal was the most common reason. The Buchbinder et al (18) trial was described as a multi-center trial but 2 hospitals withdrew early from the trial after only enrolling 5 patients each. One radiologist in one hospital performed 68% of the procedures. Despite using high volume centers for enrollment, Buchbinder et al (18) enrolled only 78 patients. A total of 141 patients refused randomization. In the Kallmes et al (19) trial, 85% of their patients from the US declined to participate. The severity of pain and degree of functional compromise for patients that refused was not reported, nor was the type of treatment they received. Patients with severe pain would be unlikely to risk entering into the sham arm of the study. Shouldn't the patient's willingness to participate or the researcher's decision whom to enroll be considered bias?

Control Groups

Were these sham procedures or alternative therapy? The Kallmes et al (19) and Buchbinder et al (18) reports do not clearly confirm that the origin of the back pain was the OVCF. The significant difference in cross-over rates for the control group (43% vs. 12%) in the Kallmes et al (19) trial suggests patient dissatisfaction with the sham procedure.

Outcomes

There is a lack of documentation as to the origin of the back pain pre- and postprocedure in the Kallmes et al (19) and Buchbinder et al (18) trials, as determined by physical examination. The inadequacy of only a phone call as postprocedure follow-up should have been apparent to the research team.

Questions have been raised as to whether the difference in VAS pain score reduction between the Kallmes et al (19), Buchbinder et al (18), and VERTOS II trials was really as dissimilar as reports would have readers believe.

Other controversies regarding the Kallmes et al (19) trial to be brought forth in Pain Physician 2013:

Workers' compensation

The Kallmes et al (19) trial had a relatively high percentage of workers' compensation patients compared to a typical tertiary academic institution (13% versus < 1%, respectively). Occupational status influences patient response to therapy. Patients getting workers' compensation payments are more likely to have an unsatisfactory surgical outcome (123).

Physical Examination

The lack of sufficiently detailed documentation of pre- and postprocedural physical examination in the Kallmes et al (19) trial has been noted, with these authors questioning the need for further research to document the validity of the need for a periprocedural physical examination (123).

Imaging

The Kallmes et al (19) trial used magnetic resonance imaging or bone scans only for cases in which fracture age was in question. Advanced imaging was not uniformly incorporated into the patient's procedural workup (123).

Conclusions

It will be interesting to see the results of VERTOS IV which is being conducted as a double blind RCT with a sham control (64,187). Regardless of the outcome of VERTOS IV, the controversy will likely continue. The evolved form of EBM has infiltrated all walks of medicine and medical education (188-191). Innumerable books have been written on the subject. Courses have been developed to educate epidemiologists, statisticians, bioethicists, other nonphysician and physician researchers in the concepts and study designs of the RCT.

The need for well-designed research is not in question. However, using research methodologies designed for drug therapies to evaluate devices and procedures is the problem. There might be fewer heated discussions and fewer therapies put at risk if procedures and devices were evaluated under their own statistically significant research conditions.

In these days when the economy is lean and fragile and shortages are rampant, quantity trumps quality, and rewards are extended for money-saving ventures seemingly without an unbiased assessment of the fallout, we should re-evaluate the appropriateness of the current clinical trial design for devices and for both image-guided and open surgical procedures. The outcome of this evidentiary hierarchy affects guidelines, which affect recommendations and ultimately funding for trials as well as reimbursement for treatment. More importantly, the ramifications affect the patient's right to choose and our right as healers to provide our patients with treatment options for the highest quality of care. This fight for VP and KP is only an example of the problems we face.

Currently, health care has become a major battle ground. If we as clinicians lose control of health care, at what point will any treatment of the terminally ill, the elderly, and others with limited life spans or limited funds be considered cost ineffective? At what point might any device or procedure be labeled as having too high a risk/benefit ratio to justify the cost? It becomes very difficult to break an association between a procedure or device and perceived risk once that linkage has been suggested, even if in error. Even more distressing, benefit is now in large part determined primarily by the RCT. Once labeled, recommendations are withheld, access is limited…is this the road we wish to travel? By designing investigative methodologies appropriate for procedures and devices, and revising the levels of evidence scales accordingly, we can change our path. We have a square peg. We need a square hole.

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