Causes of pain in degenerative bone and joint disease: a lesson from vertebroplasty

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Abstract

Pain in degenerative bone and joint disease is usually attributed to sensitized nociceptors in inflamed periarticular soft tissues. Here we draw attention to the potential contribution of intrinsic bone innervation. The structure and innervation of articular bone ends is analogous to that of teeth. Although some dental pain derives from inflamed periodontal soft tissue, a more important source is the dentine and root canal. By analogy, pain on weight bearing in osteoarthritis and related conditions may be due to compressive forces applied to the innervation of subchondral bone exposed by erosion of the overlying cartilage. Pain relief obtained by injecting acrylic cement into the bone interior during percutaneous vertebroplasty is consistent with this concept. The development of a new family of pain relief options based on “marrow canal treatment” may be a realistic possibility.

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Keywords: Bone innervation; Bone pain; Marrow canal treatment; Osteoarthritis; Subchondral bone; Vertebroplasty

1. Introduction

Pain and resulting disability characterizes most conditions involving degenerative changes in bones and joints, including the arthritides, osteoporosis, spondylolysis, and bone metastases. Among these, degenerative arthritis (osteoarthritis, OA) rates along with back pain and headache as the most prevalent of all chronic pain conditions. OA is also among the most costly in terms of quality of life for the sufferer and his/her family, and in terms of financial burden to society. Mainly affecting people in the later years of their lives, the burden of degenerative diseases of bones and joints is very likely to increase substantially as the population ages.

Remarkably, almost nothing is known with confidence about the mechanisms of pain in degenerative arthritis and related conditions (Felson et al., 2000). This contrasts with the more advanced state of knowledge on pain mechanisms in inflammatory (rheumatoid) arthritis. Most contemporary research on OA focuses on the cellular processes responsible for cartilage erosion, rather than on pain. The long-term goal is ‘disease modification’, i.e. slowing or reversing joint degeneration. The presumption is that if the joint heals, the pain will go away. Whether or not this presumption is justified, there is no cure for OA in sight, and so it makes sense to consider OA pain as a problem in its own right, not ‘just’ as a disease symptom.

2. Causes of bone pain

2.1. Pain sensation depends on tissue innervation

A great deal of elegant work has been carried out over the last few decades to characterize the nociceptive afferents that innervate joint tissue, and to identify changes induced by inflammation (Schmidt, 1996). However, virtually all of this work has focused on the innervation of periosteal and capsular soft tissues of the joint. Very little is known about the functional properties of hard tissue innervation; nerve endings in the articular surfaces and underlying subchondral bone, the bone–marrow interface, afferents in bone marrow,
or innervation of corresponding tissues along the bone shaft away from the joint.

There are tantalizing hints that the afferent innervation of the cortex and interior (medulla) of bones may be primarily nociceptive in function and may play an important role in chronic pain in degenerative bone and joint disease. We know, for example, that although articular cartilage itself has no innervation, cancellous (spongy) and compact bone below the cartilage (subchondral bone) is invested with endings of small diameter axons (Serre et al., 1999; Mach et al., 2002). These axons, which gain access to the inner bone surface from the marrow (medullary) canal, tend to label with immunohistochemical markers that are characteristic of nociceptors elsewhere in the body, such as substance P and CGRP. There are also functional indications that this innervation can support pain sensation. For example, the injection of irritants such as alcohol into the medullary canal is painful, as is needle aspiration of bone marrow, a routine procedure for harvesting stem cells. The pain of aspiration is distinctly different from the pain that occurs as the aspiration needle is inserted through the periosteum. Similarly, an epidemiological study has associated lesions in the bone marrow with pain in OA (Felson et al., 2001). Finally, in recent experimental studies in which tumor cells were injected into the sealed medullary cavity of long bones in rodents, the animals showed clear behavioral signs of pain when the tumor expanded, generated intramedullary hypertension, and mechanically compressed marrow and bone matrix. Stimulation by pro-nociceptive chemical mediators released in the process of osteoclastic bone resorption, and/or from the malignancy itself, may also have contributed (Clohisy and Mantyh, 2003; Wacnik et al., 2003).

2.2. Chew on this

Thinking ‘outside of the box’, we draw an analogy between the articular surfaces of bones and the occlusive surfaces of teeth. The cartilage at the articular surfaces of the joint is analogous to the enamel at the occlusive surfaces of teeth. Likewise, subchondral bone is analogous to dentine, bone marrow is analogous to tooth pulp, and synovial and periosteal soft tissue is analogous to gingiva (Fig. 1). This analogy is potentially helpful because the causes of tooth pain have been extensively studied, and this information can shed light on pain mechanisms in bones and joints. Tooth enamel, like articular cartilage, is not innervated. However, when enamel is removed from a tooth, even weak stimulation of the underlying dentine (mechanical or thermal) evokes pain. The pain is due to activation of nociceptor endings that fill dentinal cannuliculae. These axons enter the dentine along nerve bundles that travel within the tooth pulp (Byers, 1994). Pursuing our analogy, erosion of articular cartilage in OA uncovers the dentine-like subchondral bone. Nociceptor endings in the bone are now subject to activation by biomechanical forces associated with weight bearing. This, we propose, is a major cause of pain in OA. Similarly, in other degenerative bone diseases, fractures or osteoporotic bone softening may bring abnormal mechanical forces to bear on sensitive nociceptive endings within the formerly hard, compact bone matrix.

Inflammation is not a prerequisite for tooth pain; exposed dentine is tender even in entirely healthy teeth (dentists often drill into healthy teeth to anchor bridgework). However, dentinal and pulp inflammation when present also makes a contribution (Byers, 1994). By analogy, in bone and joint disease, inflammatory mediators in the synovial fluid and/or bone interior may well exacerbate pain by sensitizing nociceptor endings in subchondral bone. Inflammation is probably not an essential factor, however. Note that dentinal pain is different from pain arising from the gingiva. By analogy, nociceptive signals that arise in the external soft tissue of the joint capsule, articular synovium and periosteum, are expected to yield a qualitatively different pain than those due to bone marrow afferents that form nociceptor endings within the bone matrix.

3. Evidence from pain relief in vertebroplasty

Percutaneous vertebroplasty (PVP) is a relatively new interventional procedure performed under radiologic guidance in which bone cement, usually polymethyl methacrylate (PMMA), is injected into a cavitated vertebral body that has partially collapsed or is at risk of collapsing. The primary goal is to refill and ‘inflate’ the vertebral body with cement which, when it hardens, increases the mechanical

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Fig. 1. The structural analogy between teeth and joints may provide useful insights into the possible causes of pain in degenerative bone and joint disease. As illustrated in this schematic diagram, tooth enamel is analogous to articular hyaline cartilage (note that neither is innervated), dentine is analogous to subchondral bone, the tooth pulp is analogous to bone marrow, and the external soft tissues of the tooth (gingiva) are analogous to synovial soft tissue and periosteum of the joint. Just as the rich internal nociceptive innervation of the tooth contributes to dental pain, the intrinsic nociceptive innervation of bones may contribute to pain in degenerative bone and joint disease.
strength of the bone. The procedure was first developed by Galibert et al. (1987) to treat aggressive spinal hemangioma, but other indications have been added since. These include osteoporotic vertebral collapse, compression fractures, lytic lesions due to bone metastases, and multiple myeloma. Needless to say these conditions are often associated with severe pain that may be medically intractable. In vertebroplasty stability of the spine, rather than pain relief, is the primary treatment objective. However, in most published studies pain is also an outcome measure.

The matter is relevant to the sensory role of nerve endings within compact bone for two reasons. First, increasing the rigidity of the bone through the injection and subsequent hardening of PMMA cement is expected to reduce bone deformation during weight bearing, and hence to reduce the mechanical forces applied to nociceptive endings within the bone. Secondly, since the cement itself is toxic for nerve tissue, vertebroplasty causes at least partial denervation of the bone matrix. Our working hypothesis therefore predicts that vertebroplasty should yield pain relief. In contrast, if the pain of vertebral bone disease is due exclusively to inflamed, sensitized nociceptor endings in peri-spiral soft tissues, there is no special reason to predict that filling an intravertebral cavity will reduce pain. On the contrary, inflation of the vertebra might activate periosteal nociceptors exacerbating pain, as might small amounts of cement that are frequently extravasated into the surrounding soft tissues. What are the facts?

We performed a Medline search of the English language literature for humans within the period 1/1994–4/2003 using the search terms vertebroplasty or cementoplasty. The search yielded 179 citations which were checked individually and sorted by type: 26 were case series and clinical trials (none was a randomized controlled trial (RCT)), and the remainder were reviews, individual case reports, radiological or biomechanical studies, commentaries and editorials, or papers not directly related to vertebroplasty. All 26 clinical trials of PVP included pain as a key outcome measure, and all reported significant pain relief (Table 1). Typically, authors reported that 60–100% of their patients had at least 50% reduction in pain within 1–2 days of cement injection. Relief usually persisted for at least several months, a remarkable result given the progressive nature of the underlying disease in many cases. The analgesic effect was not much affected by the volume of PMMA used or the precise injection protocol (Cotten et al., 1996; Levine et al., 2000). Interestingly, despite the unequivocal effect on pain, many of the authors remained uncertain about the reliability of vertebroplasty at achieving bone stabilization and preventing future vertebral fracturing.

4. Potential for application to pain relief in OA and other degenerative bone and joint diseases

Although the mechanism of pain relief has not been studied directly, inferences can be drawn from our knowledge of the intrinsic and extrinsic innervation of bone (above). Whereas vertebral collapse, like deflation of a balloon, is expected to unload nociceptors investing the periosteal soft tissue envelope that surrounds the bone, it is expected to bring compressive forces to bear on nociceptor endings within the bone matrix. Intravertebral injection of cement might relieve some of these forces by increasing the bone’s rigidity. Probably a more important mode of analgesia, however, is destruction of sensitive nerve endings within the matrix by the PMMA cement itself. Neurotoxicity is a direct effect of PMMA, perhaps enhanced by free oxygen radical production (Vale et al., 1997; Moreau et al., 1998) and heating during cement polymerization (Nelson et al., 1997).

Because of the good reputation of vertebroplasty for pain relief among orthopedists, there are several clinical reports of percutaneous injection of PMMA cement where there was no intention in the first place to strengthen bones. Dehdashti et al. (2000), for example, used this approach to obtain relief from pain due to metastatic lesions in the sacrum. The same end is accomplished by injecting ethyl alcohol as a neurolytic agent into the lesion (Gangi et al., 1994; Cotten et al., 1999; Doppman et al., 2000). Finally, Khan et al. (2002) reviewed the literature on cemented vs. uncemented hemiarthroplasty for displaced intracapsular fractures of the hip. In cemented hemiarthroplasty PMMA is injected into the opened marrow canal of the femur to help stabilize the prosthetic joint. The majority of studies reported less ongoing pain in the thigh, and less pain on weight bearing, in patients with a cemented prosthesis. This may well be due to cement-induced denervation of the bone matrix that supports the prosthetic.

3.1. Implications for pain mechanism in bone and joint disease

The analgesic effect of vertebroplasty appears to be reliable, with the caveat that no RCTs are available. Although the mechanism of pain relief has not been studied directly, inferences can be drawn from our knowledge of the intrinsic and extrinsic innervation of bone (above). Whereas vertebral collapse, like deflation of a balloon, is expected to unload nociceptors investing the periosteal soft tissue envelope that surrounds the bone, it is expected to bring compressive forces to bear on nociceptor endings within the bone matrix. Intravertebral injection of cement might relieve some of these forces by increasing the bone’s rigidity. Probably a more important mode of analgesia, however, is destruction of sensitive nerve endings within the matrix by the PMMA cement itself. Neurotoxicity is a direct effect of PMMA, perhaps enhanced by free oxygen radical production (Vale et al., 1997; Moreau et al., 1998) and heating during cement polymerization (Nelson et al., 1997).

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4. Potential for application to pain relief in OA and other degenerative bone and joint diseases

There is nothing conceptually radical about the suggestion that nociceptive nerve endings in marrow and bone matrix contribute significantly to pain sensation in diseases in which noxious stimuli are brought to bear on these tissues. Nonetheless, this concept has rarely been raised until recently, and it plays little role in pain management. Rather, emphasis is placed on innervation of external soft tissues, notably peristium and synovial membranes. The blinkered emphasis on soft vs. hard tissue innervation may have prevented the development of potentially effective treatment options for pain in degenerative bone and joint disease. Returning to our dental analogy, suppose that dentists focused only on pain associated with the periodontal soft tissue, the gingiva, and ignored the intrinsic innervation of the tooth itself!

What we propose, therefore, is the application to bones and joints of a new family of therapies analogous to root canal treatment of teeth. For example, it might be possible to
<table>
<thead>
<tr>
<th>Authors</th>
<th>Type</th>
<th>Pathology</th>
<th>n</th>
<th>Synopsis of pain outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amar et al. (2001)</td>
<td>R</td>
<td>OP, Mts</td>
<td>97</td>
<td>Analgesics use decreased in 63% of patients. Mobility improved in 51%; 74% believed vertebroplasty improved quality of life. In patients with osteoporotic fractures VAS dropped from 10 to 0–3 in 63% and to 4–6 in 32%. Four of eight patients with Mts had significant pain relief.</td>
</tr>
<tr>
<td>Barr et al. (2000)</td>
<td>R</td>
<td>OP, Mts</td>
<td>47</td>
<td>VAS decreased from 8.2 ± 1.5 to 3.7 ± 2.2 at 24 h and was 3.2 ± 1.9 at 1 month (both ( p &lt; 0.05 )). All patients could return to their previous activities.</td>
</tr>
<tr>
<td>Chen et al. (2002)</td>
<td>P</td>
<td>OP</td>
<td>50</td>
<td>VAS decreased from 8.2 ± 1.5 to 3.7 ± 2.2 at 24 h and was 3.2 ± 1.9 at 1 month (both ( p &lt; 0.05 )). All patients could return to their previous activities.</td>
</tr>
<tr>
<td>Cortet et al. (1999)</td>
<td>P</td>
<td>OP</td>
<td>16</td>
<td>VAS decreased from 7.2 ± 1.5 to 2.9 ± 1.6 (( p &lt; 0.0005 )) and McGill score decreased from 3.4 ± 0.8 to 1.7 ± 0.9 (( p &lt; 0.005 )), especially on pain, mobility, emotion and energy scales.</td>
</tr>
<tr>
<td>Cortet et al. (1997)</td>
<td>P</td>
<td>Mts, MM</td>
<td>37</td>
<td>VAS decreased from 7.2 ± 1.5 to 2.9 ± 1.6 (( p &lt; 0.0005 )) and McGill score decreased from 3.4 ± 0.8 to 1.7 ± 0.9 (( p &lt; 0.005 )), especially on pain, mobility, emotion and energy scales.</td>
</tr>
<tr>
<td>Cotten et al. (1996)</td>
<td>CS</td>
<td>Mts, MM</td>
<td>37</td>
<td>Partial or complete pain relief was sustained in 36 of 37 patients.</td>
</tr>
<tr>
<td>Cyteval et al. (1999)</td>
<td>CS</td>
<td>OP</td>
<td>20</td>
<td>Mean VAS decreased from 8.5 to 3.3. Analgesics were stopped in 70% of patients.</td>
</tr>
<tr>
<td>Evans et al. (2003)</td>
<td>R</td>
<td>OP</td>
<td>245</td>
<td>Mean pain score decreased from 8.9 to 3.4 (( p &lt; 0.001 )). Substantially impaired ambulation decreased from 72 to 28% of the patients (( p &lt; 0.001 )).</td>
</tr>
<tr>
<td>Fourney et al. (2003)</td>
<td>R</td>
<td>Mts</td>
<td>56</td>
<td>VAS decreased from 7.2 ± 1.5 to 2.9 ± 1.6 (( p &lt; 0.0005 )) and McGill score decreased from 3.4 ± 0.8 to 1.7 ± 0.9 (( p &lt; 0.005 )), especially on pain, mobility, emotion and energy scales.</td>
</tr>
<tr>
<td>Gangi et al. (2003)</td>
<td>CS</td>
<td>OP, Mts, MM</td>
<td>663</td>
<td>Satisfactory results (pain score fell &gt; 2 points) in 73–87% of patients depending on type of pathology; 25–50% reduction of analgesic doses postoperatively.</td>
</tr>
<tr>
<td>Grados et al. (2000)</td>
<td>R</td>
<td>OP</td>
<td>25</td>
<td>Preoperative VAS of 8.0 ± 1.6 decreased to 3.7 ± 2.4 at 1 month and 3.4 ± 2.8 at mean 48 months (both ( p &lt; 0.05 )).</td>
</tr>
<tr>
<td>Heini et al. (2000)</td>
<td>CS</td>
<td>OP, Mts</td>
<td>17</td>
<td>VAS (mean) was 7.5 preoperatively, 3.2 1 day postoperatively, 2.7 after 12 weeks and 3.2 after 1 year (( p &lt; 0.01 )).</td>
</tr>
<tr>
<td>Hodler et al. (2001)</td>
<td>P</td>
<td>OP, Mt, HA</td>
<td>152</td>
<td>Complete pain relief in 9% of patients, partial relief in 28%, no change in 14%.</td>
</tr>
<tr>
<td>Jensen et al. (1997)</td>
<td>CS</td>
<td>OP</td>
<td>29</td>
<td>VAS fell from 9.7 ± 1.0 to 1.7 ± 1.9 (( p &lt; 0.0001 )); analgesics use fell significantly.</td>
</tr>
<tr>
<td>Kallmes et al. (2002)</td>
<td>R</td>
<td>OP</td>
<td>41</td>
<td>VAS fell from 9.7 ± 1.0 to 1.7 ± 1.9 (( p &lt; 0.0001 )); analgesics use fell significantly.</td>
</tr>
<tr>
<td>Kaufmann et al. (2001)</td>
<td>R</td>
<td>OP</td>
<td>75</td>
<td>VAS fell from 9.7 ± 1.0 to 1.7 ± 1.9 (( p &lt; 0.0001 )); analgesics use fell significantly.</td>
</tr>
<tr>
<td>Kim et al. (2002)</td>
<td>R</td>
<td>CF</td>
<td>49</td>
<td>VAS fell from 9.7 ± 1.0 to 1.7 ± 1.9 (( p &lt; 0.0001 )); analgesics use fell significantly.</td>
</tr>
<tr>
<td>Martin et al. (1999)</td>
<td>CS</td>
<td>OP, Mts, MM, HA, BL</td>
<td>40</td>
<td>Ca. 80% ‘success’ for pain relief, reduced pain medication, and increased mobility.</td>
</tr>
<tr>
<td>McGraw et al. (2002)</td>
<td>P</td>
<td>OP, Mts, OI</td>
<td>100</td>
<td>Significant pain relief in 97% of patients after 24 h; 93% still improved 24 h post procedure; ambulation after surgery compared with ( p &lt; 0.0001 ). Special pain relief improved; decreased pain medication and increased mobility.</td>
</tr>
<tr>
<td>Nakano et al. (2002)</td>
<td>P</td>
<td>OP</td>
<td>17</td>
<td>VAS scores decreased in all patients after surgery, with relief maintained.</td>
</tr>
<tr>
<td>Peh et al. (2002)</td>
<td>P</td>
<td>OP</td>
<td>155</td>
<td>At 11 month follow-up pain relief was complete in 47%, partial in 50%, and unchanged in 3%.</td>
</tr>
<tr>
<td>Perez-Higuera et al. (2002)</td>
<td>P</td>
<td>OP</td>
<td>13</td>
<td>VAS fell from 9.1 to 2.1 by the third day postoperatively; was 1.1 after 3 months, and 2.2 at 5 years.</td>
</tr>
<tr>
<td>Peters et al. (2002)</td>
<td>P</td>
<td>OP</td>
<td>42</td>
<td>VAS decreased in all patients after surgery, with relief maintained.</td>
</tr>
<tr>
<td>Tsou et al. (2002)</td>
<td>P</td>
<td>OP</td>
<td>16</td>
<td>VAS fell from 9.1 to 2.1 by the third day postoperatively; was 1.1 after 3 months, and 2.2 at 5 years.</td>
</tr>
<tr>
<td>Weill et al. (1999)</td>
<td>CS</td>
<td>Mts</td>
<td>37</td>
<td>VAS decreased in all patients after surgery, with relief maintained.</td>
</tr>
<tr>
<td>Zoarski et al. (2002)</td>
<td>P</td>
<td>OP</td>
<td>30</td>
<td>VAS fell from 9.7 to 1.7 after 2 weeks; 29 patients reported durable pain relief at 15–18 months.</td>
</tr>
</tbody>
</table>

P, prospective trials; R, retrospective study; CS, case series. BL, bone lymphoma; CF, compression fracture (cause not indicated); HA, hemangioma; MM, multiple myeloma; Mts, metastatic lesion; OI, osteogenesis imperfecta; OP, osteoporosis; n, number of patients.
eliminate pain associated with weight bearing in osteoarthritic knees and hips by denervating the relevant bone ends (epiphyses). The procedure would be to make a small angled hole through the bone shaft near the epiphysis and apply a neurolytic procedure internally. As a diagnostic trial, a local anesthetic such as bupivacaine might be infiltrated into the epiphysis. For a prolonged effect, suction might be used to remove the marrow of the epiphysis (presumably after infiltrating with a local anesthetic), on alcohol or another neurolytic agent might be injected, or the epiphysis might be filled with bone cement. In addition to destroying residual innervation of the subchondral bone, this would prevent nerve regeneration. In the first instance such ‘marrow canal treatment’ might be offered to patients who would otherwise be candidates for surgical joint replacement but who for one reason or another turned down this option. If accumulating experience were favorable, the procedure might be adopted to postpone or even to replace whole knee or hip replacement.

Potential risks include structural weakening of the denervated bone end, or exacerbation of cartilage erosion, although there is little a priori reason to expect such consequences. Neuropathic pain due to deafferentation or neuroma formation is a highly unlikely complication as it is not known to occur when equivalent intraosseous nerve injury is induced during the course of hemiarthroplasty of the femur in hip joint replacement therapy. The preservation of periosteal and synovial innervation should insure against Charcot-like changes in the joint. In any event, the ‘marrow canal’ approach if planned carefully would not foreclose the possibility of proceeding to conventional treatment options, including the joint replacement surgery that is currently the gold standard for treatment of advanced OA.

The concept of attacking the nociceptive nerve supply of the bone marrow and bone matrix has a range of potential applications beyond the treatment of pain in OA. In malignant disease, for example, it might be possible to denervate the bone interior by lysis of nerve bundles as they enter the bone at mid-shaft or near the epiphysis. Likewise, the innervation of bone interior might be blocked using any of the range of one-time neurolytics, or continuous nerve block procedures currently applied to the innervation of other tissues (Niv et al., 2000). The possibilities are limited only by the imagination.

References


