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Vertebroplasty and kyphoplasty as treatment for osteoporotic vertebral fractures

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Summary
Over the last decade vertebroplasty and kyphoplasty have become popular as therapeutic options for the treatment of vertebral fractures. In fact, numerous non-controlled studies have indicated that both procedures are very efficacious for the control of pain associated with fractures. However, some recently published randomised trials have cast doubt on the true effectiveness of these procedures. On the other hand, certain observations have suggested that the increase in the rigidity which is produced by the injection of metacrylate into a vertebral body could facilitate the collapse of the adjacent vertebra. Therefore, vertebroplasty and kyphoplasty should not be considered as a routine theraputic measure, but should be limited to carefully selected patients, in whom the potential benefits surpass the risks and costs of the procedure. In any case, the patients should be put on a global treatment programme which includes pharmaceutical measures and non-pharmaceutical care to reduce the risk of future vertebral and peripheral fractures.
Various clinical trials have recently been published which were supposed to be an important contribution to knowledge regarding the effectiveness of vertebroplasty. The results have been rather contradictory both within themselves, and with earlier observational studies. For this reason it is worth reviewing this questions with the intention of helping clinicians who need to take decisions on the treatment of patients with osteoporotic fractures. We have not dealt with the possible utility vertebroplasty in other processes, such as fractures caused by tumours or by trauma.

Key words: *Vertebroplasty, Kyphoplasty, Vertebral fractures, Osteoporosis.*

Non-controlled studies

In the last decade vertebroplasty has been popularised for the treatment of acute or sub-acute vertebral fractures. This technique consists of the injection of a mixture of polymethacrylate (PMMA) and radio-opaque contrast by means of metallic trocars which are introduced through one or both vertebral pedicles (Figure 1). This compound, initially liquid, later solidifies in the interior of the vertebral body. It is assumed that this augments the resistance and provides mechanical stability to the fractured vertebral body, thereby avoiding its progressive collapse. In addition, since the initial studies it has been observed that many patients report a notable improvement in pain immediately after the procedure, due to a mechanism which is unclear, perhaps related to the chemical or thermal ablation of the nerve endings. These factors resulted in the establishment of the technique in many centres. The procedure requires a general anaesthetic or deep sedation. It is a demanding technique, which needs to be carried out by trained persons and with high resolution fluoroscopic equipment. Generally it is well tolerated and has few secondary effects. The main complication in the short term comes from the escape of PMMA into adjacent structures. If this happens in the direction of the intervertebral disc it may cause pain and result in a lesion in the adjacent vertebra. But if it is a small amount it does not usually have consequences. More serious is an escape towards the medullar canal or towards the foramens, causing medullar or radicular compression which may require surgical decompression[1]. Escapes into the venous blood flow may provoke local problems, pulmonary embolisms or arrhythmias[2].

Later, a modification in the initial technique arose, called kyphoplasty (Figure 2). With this, the injection of material is not made directly into the spongy vertebral bone, rather, a cavity is first created by inflating one or two balloons in the central region of the vertebral body[3,4].

In a search of Pubmed carried out in September 2009, 1,100 works were found on vertebroplasty or kyphoplasty. In the initial studies, with series of patients with osteoporotic or tumorous vertebral fractures, very favourable results were seen, such that 80% of patients had a significant improvement in pain. The refractory pain due to medical treatment was precisely the principal indication for treatment. However, in some patients the indication was prophylactic, that is to say, with the intention of "strengthening" a vertebra which had a small loss of height, and thereby avoiding the progression of its collapse. It has been suggested that the presence of bone oedema in the magnetic resonance (as a marker for acute or sub-acute fracture) is associated with a higher clinical efficacy of this procedure. However, a study by Voormolen et al. observed an improvement in pain in 94% of patients who had oedema, and 71% in those whom it was not present[5]. This suggests that the presence of oedema is associated with a greater efficacy of vertebroplasty, but that its absence does not exclude its use. However, it being a non-controlled study, means it is difficult to assess the influence the results could have on the spontaneous evolution of pain after fractures, which means that it is not possible to draw definitive conclusions.

It is notable that the growing establishment of vertebroplasty took place in the absence of appropriate clinical trials which demonstrate its efficacy. Hence, although observational studies suggested that the procedure was highly efficacious, it remains unclear up to what point the natural history of the disease is modified, nor what was the placebo effect component of the intervention. Also, it must not be forgotten that the pain of vertebral fractures tends to improve after a few weeks in the majority of patients, even in the absence of treatment. On the other hand, there have been doubts as to the long term safety of the procedure, since some authors have observed a higher rate of appearance of new fractures in adjacent vertebrae[6]. In fact some biomechanical models predicted that the increased rigidity of a vertebra increased the stress to which the neighbouring vertebrae were subject, which in theory increased the risk that they would fracture. Subsequently, in various series of cases, a higher incidence of new fractures in patients treated with vertebroplasty or kyphoplasty than in those subject to non-invasive treatment, has been found[7]. However, these not being randomised trials, the two groups are not necessarily comparable, which means that these studies do not allow definitive conclusions to be drawn in this respect.

Although the widespread use of vertebroplasty in the absence of trials which have demonstrated its efficacy may have been facilitated by some aggressive commercial practices, it should be taken into account that it is very difficult to carry out randomised blind trials with this type of treatment, in which invasive interventions are analysed. Fortunately, some researchers have made a serious effort in recent years to establish controlled studies which try, better, to assess the real efficacy of the intervention.

Non-randomised controlled trials

Between the years of 2003 and 2005 4 controlled, but not randomised, studies have been published. This is to say, patients were offered the possibility of having vertebroplasty (or kyphoplasty) and the development of those who accepted the procedure was compared with those who rejected it (which became the control group).

One of these studies (published preliminarily in 2003 and then in 2005), included patients with recent osteoporotic fractures, of less than 6 weeks standing. In comparison with the control group, the group treated with vertebroplasty experienced an improvement in pain from the following day and after 6 weeks. However, at the end of 6-24 months there were no differences[8,9].

A Spanish group, Alvarez et al.[10], carried out a similar study, but with patients with fractures and

pain of longer standing, between 6 weeks and 12 months. They also found that the group treated by vertebroplasty reported less pain than the control group on the following day, and after 3 to 6 months. Again, at the end of a year there were no differences between them. On the other hand, the treated group had a higher rate of new vertebral fractures.

On their part, Kasperk et al. assessed the usefulness of kyphoplasty in patients with vertebral fractures of more than 1 year's standing. They found that the procedure was associated with less pain and a better quality of life in the measures taken during the 6 months of follow up. They found no differences in the risk of suffering new vertebral fractures[11].

The assignment to the treatment groups not being randomised in these studies, the two groups, treated and control, are difficult to compare. In various cases the authors show that there are no differences in their baseline characteristics (one exception is the work of Alvarez in which the group subject to vertebroplasty had more serious characteristics of disease than the control group). But this means that it is impossible to say to what degree the patients were comparable on account of aspects related to their perception of the disease, their aversion to risk or tolerance of pain, all of these very important when the measure of the results is essentially subjective, such as it the case with pain and quality of life. On the other hand, the fact that there is no masking, means it is difficult to know the extent to which the result may have some involuntary bias, originating from the patients or the evaluators. In addition, it is certainly not possible to separate the real effect from the placebo effect.

Figure 1. Fracture of L3 treated by vertebroplasty

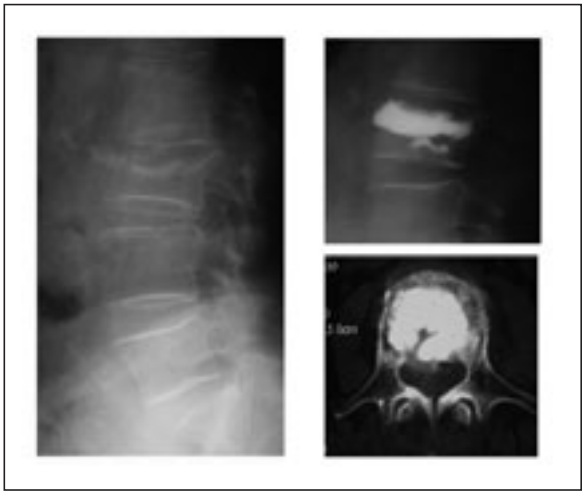
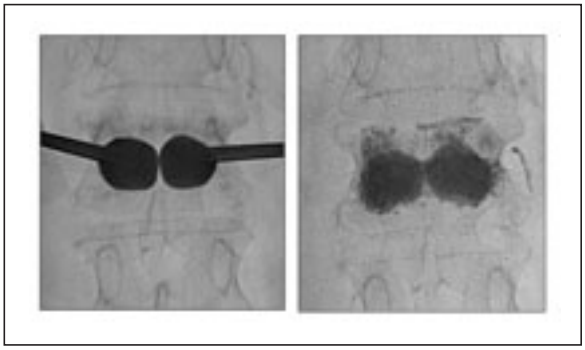


Figure 2. Kyphoplasty. Balloons inflated in the interior of the vertebral body (left) and control at the end of treatment (right)



Randomised controlled trials

The first randomised trial was published by Voormolen et al., who compared the evolution of a small group of patients with osteoporotic fractures, which had developed over between 6 weeks and 6 months[12]. From the day following the procedure the intensity of the pain was significantly less in those treated with vertebroplasty than in the controls. At 2 weeks there continued to be a definite trend in the same direction, but the difference was not statistically significant. However, given the small number of patients, the power of the study was limited. Interestingly, in this brief follow up period, two new fractures appeared in the treated group and none in the control group.

Another randomised study of 49 patients with recent osteoporotic fractures and refractory pain found similar results: the group subject to vertebroplasty had less pain 24-48 hours after the procedure, but the differences had disappeared after 3 months[13].

More recently, Wardlaw et al. published a randomised trial on the effect of kyphoplasty in 149 patients, who were compared with 151 patients subject to non-invasive treatment[14]. Differently from other studies, these authors included both osteoporotic and tumorous fractures (although the latter only made up 2% of cases). All these were relatively recent (according the indication of the presence of oedema in the RM), but which had been developing over more than 3 months. During the 12 months of follow up the patients who had received kyphoplasty had less pain, and higher points on the quality of life scale, than those subject to medical treatment. The differences were established early and then later tended to decrease a little. Although they did not reach statistically significant levels, the incidence of new morphometric vertebral fractures was higher in the kyphoplasty group than in the control group (33% against 25%). Similarly, 14% of this group presented new clinical fractures (against none in the control group).

Compared with those covered earlier, these three studies present the advantage of being controlled, which tends to ensure the comparability of the treated and control groups. However, in not being masked, it is difficult to know if the subjectivity of the patients or the evaluators has an influence in the analysis of the development. So, this means that other studies published more recently

are especially interesting, in which for the first time an effort was made to mask the treatment applied. One of these, published by Kallness et al., included 131 patients with fractures of more than one year in development. Of these, 68 were randomly allocated to have vertebroplasty and 63 to have medical treatment, preceded by a simulation of vertebroplasty, including sedation and the injection of a local anaesthetic in the periosteum[15]. There were no differences between the two groups in terms of pain or in the quality of life scales during the 3 months follow up. This was the case independently of the period of development of the fracture. However, the study's protocol allowed the patients to request another intervention in cases where significant symptoms persisted: which 43% of those in the control group and 12% of the group treated with vertebroplasty ($p< 0.001$), requested.

In a similar study, Buchbinder et al., compared 38 patients treated with vertebroplasty with 40 controls, in whom the procedure was simulated. Again, no differences were found between the two groups with respect to pain or quality of life scales, neither in the group as a whole, nor in the sub-groups resulting from dividing the patients according to their period of development (more or less than 6 weeks). Neither were there differences in the incidence of new fractures[16].

Vertebroplasty, kyphoplasty and biomaterials

In theory, kyphoplasty can present some advantages over simple vertebroplasty. On the one hand, it reduces the escape of material from the vertebral body. On the other, the inflation of the balloons lifts the vertebral platelets, which, to a greater or lesser extent, recovers the vertebral collapse, so, attempting to correct the angle of vertebral kyphosis. Although, theoretically, the re-establishment of the height of the vertebral body is beneficial, its practical clinical repercussions continue to be unclear. In a systematic review of 69 studies, Hulme et al. did not find clear differences in the degree of correction of the height of the vertebral body obtained with vertebroplasty and kyphoplasty, but the escapes of material from the vertebral body were less frequent with kyphoplasty (9% against 41%)[17]. However, it should be taken into account that only a small number of studies carried out a direct comparison between the two techniques, and there were no randomised studies. It has been suggested that that the higher number of escapes of cement towards the intervertebral disc which happens with vertebroplasty could be associated with a higher frequency of fractures in adjacent vertebrae[18]. In the controlled studies on which we have commented earlier, there seems to be a tendency to better results in those in which a kyphoplasty has been carried out than in those which assessed vertebroplasty. This question has also been analysed in another review of 168 studies of vertebroplasty and kyphoplasty, in which a lower rate of escape of cement was observed with kyphoplasty (7% against 20%), as well as a lower rate of new fractures (14% against 18%), although paradoxically, the improvement in pain was somewhat higher after vertebroplasty 18. However, most of the studies reviewed did not carry out a direct comparison between the two procedures, and as a consequence, the patients included are not necessarily comparable. This, therefore, makes a recent study by Lui et al. very interesting, in which they randomly assigned 100 patients with fractures of the thoracic-lumbar union to vertebroplasty or kyphoplasty. In the latter, an improvement in vertebral height and of angle of kyphosis was observed, but no differences were found between the two groups in terms of pain over 6 months of follow up[19]. Similar results (lower incidence of escape of cement and improvement in kyphosis, but without differences in terms of pain) were found after another study which compared kyphoplasty with vertebroplasty, after an assignation by suitability, not randomly[20].

There have scarcely been any studies carried out into the cost-effectiveness of these procedures[21]. But, in all cases, it is necessary to take into account the fact that the cost of materials for kyphoplasty are notably higher than those for vertebroplasty.

In recent years, biomaterials based on calcium phosphate (CaP) have been used as an alternative to PMMA. Some authors have suggested that these materials are reabsorbed over time and could induce a powerful osteogenic response. Our personal experience does not support this idea and neither do the studies of other authors. Thus, Grafe et al. studied a series of patients treated by kyphoplasty and compared the results of an injection with PMMA with that of CaP (20 patients in each group). They found no significant differences at 6, 12 and 36 months with respect to pain, physical function, the restoration of the height of the vertebral body, or the frequency of new fractures[22]. On the other hand, Blattert et al. analysed the effects of kyphoplasty with PMMA or CaP in a prospective study of 60 osteoporotic fractures with randomised assignment. They found a higher rate of failure in cement based on CaP in burst fractures, which suggests that its biomechanical properties do not make it recommendable for this type of fracture[23]. However, it has been suggested that biomaterials based on CaP would be preferable to PMMA in young patients, with traumatic fractures and good bone quality, in whom are expected a good bone-forming response, and who wish to avoid the presence of an inert foreign substance in the long term.

Conclusions

In view of the these studies it is evident that we still have significant gaps in our knowledge around the real benefits of vertebroplasty and kyphoplasty in terms of their capacity to modify the natural history of vertebral fractures. However, it is possible to draw some, at least provisional, conclusions, which go towards defining the role of these procedures in the therapy for vertebral fractures, and to guide clinical practice:

Table 1. Summary of controlled studies. VP: vertebroplasty. CP: Kyphoplasty

Author, year	Promoted by industry	Inclusions	Period of evolution	Randomised	Masked	Groups (n)	Results
Buchbinder 2009	no	Recent fractures (oedema or linear frx in RM) Average age: 76 Sex: 80% women	< 1 year	yes	yes	VP (n=38) Puncture (n=40)	• No differences in pain or quality of life at 1 week, 1, 3 o 6 months. • No differences in new fractures
Kallmes 2009	no	Clinical fractures with bad response to analgesics (VAS > 3/10) Average age: 74 Sex: 75% women	< 1 year	yes	yes	VP (n=68) Puncture (n=63)	• No differences in pain or quality of life at day 3, 14, 30 or 90. • More changes to the other intervention in the control group (43 against 12%)
Rousing 2009	no	Recent fractures with refractory pain Average age: 80 Sex: 82% women	< 2 months	yes	no	VP (n=25) Control (n=24)	• Less pain in VP at 24 hrs, without differences at 3 months. • 3 new fractures in VP and 1 in control
Wardlaw 2009	yes	Recent fractures (oedema in RM), primary or secondary, with intense pain (VAS > 4/10) Average age: 73 Sex: 77% women	> 3 months	yes	no	CP (n=149) Control (n=151)	• Less pain and improvement in quality of life in CP at 1 and 12 months. • Tendency to more frx in CP (clínical 14 vs 0%; Rx 33 vs. 25%)
Voormole 2007	¿	Recent fractures (oedema in RM), with refractory pain Average age: 73 Sex: 82% women	6 weeks-6 months	yes	no	VP (n=18) Control (n=16)	• Less pain in VP at day 1; no significant trend at day 14 • 2 new fractures in VP
Kasperk 2005	yes	Fractures Average age: 69 Sex: 82% women	< 1 year	no	no	CP (n=40) Control (n=20)	• Less pain at 3 and 6 months and quality • No difference in new fractures
Diamond 2006	no	Recent fractures Refractory pain Average age Sex	< 6 weeks	no	no	VP (n=88) Control (n=38)	• Less pain at day 1 and 6 weeks, but not at 6, 12 and 24 months. • No difference in new fractures
Álvarez 2006	no	Recent fractures with refractory pain Average age: 72 Sex: 80% women	6 weeks-1 year	no	no	VP (n=101) Control (n=27)	• Less pain day 1, month 3 and 6, not at end of 12 months. • Initial functional improvement, but not later. • More fractures in VP

• The pain of vertebral fractures tends to improve with time, independently of the treatment applied.

• The trials with higher methodological quality with random assignment and masking, do not demonstrate a clear benefit of vertebroplasty as against conventional treatment in the treatment of osteoporotic fractures. Therefore vertebroplasty should not be recommended as a standard treatment. These patients should receive appropriate treatment with analgesics, education on activities to be undertaken, measures for the prevention of falls, and drugs aimed at increasing bone resistance. On occasions they may benefit from physiotherapy or orthosis which limit flexion, with the aim of allowing early mobility for the patient, this avoiding secondary bone loss through being bedridden.

• In two randomised but not masked trials, promoted by the industry, kyphoplasty has shown symptomatic benefits in patients with osteoporotic fractures, together with a tendency to an increase in the number of new fractures. As a consequence, neither is it possible, at this moment, to recommend kyphoplasty, generally, as a standard treatment.

• In comparison with vertebroplasty, kyphoplasty improves the angle of kyphosis and presents a lower risk of escape of contrast, but there is no evidence that it brings a clear benefit from a clinical point of view.

• There is no definitive evidence as to whether these procedures increase, or not, the incidence of new fractures. Neither are there studies which demonstrate their preventative value. Therefore, at present, there is no justification for their use with the sole objective of preventing the progression of vertebral collapse in patients without significant pain.

• Numerous observational studies (in addition to the personal experience of many doctors, including the authors of this article) indicate that in some patients these procedures achieve a rapid and acute alleviation of symptoms. As a consequence, we think that they can be a therapeutic alternative for some specific patients, such as:

- Those who have recent fractures, with intense pain which persist for more than 6 weeks despite appropriate analgesic treatment (including opiates).

- Those who have intolerance or contraindications to powerful analgesics

- Those who have concomitant diseases which make immobilisation or the limitations of respiratory excursions especially inadvisable.

- In pseudoarthrosis of vertebral fractures of more than three months standing in which is progressive and painful kyphosis is confirmed.

• Vertebral fractures are a well known marker for a heightened risk of other fractures. As a consequence, invasive treatment should always be accompanied by other therapeutic measures which reduce the possibility of suffering new vertebral or peripheral fractures.

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